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Renal Denervation for Resistant Hypertension

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of the McGill University Health Centre (MUHC)**

by

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PRINCIPAL MESSAGES

Renal denervation is a technology that uses radio frequency energy to ablate the nerves surrounding the renal arteries in order to reduce blood pressure in patients whose hypertension is resistant to medical therapy. There is evidence, based mainly on observational data that this procedure results in a clinically significant reduction in blood pressure at 6 months. Weaker evidence suggests that the effect is sustained up to 2 years of follow-up. Some side-effects, none unmanageable or permanent, are reported.

It is recommended that this technology receive temporary (two-year) and conditional approval for use only in the context of a formal research study to be supported by the manufacturer as specified.

List of abbreviations

AHA	American Heart Association
ANZHSN	Australia and New Zealand Horizon Scanning Network
AVALIA-T	Axencia de Avaliacion de Tecnoloxias Sanitarias de Galicia
BP	Blood Pressure
CADTH	Canadian Agency for Drugs and Technologies in Health
ESC	European Society of Cardiology
HTA	Health Technology Assessment
JNC	Joint National Committee
LBIHTA	Ludwig Boltzmann Institute for Health Technology Assessment
NICE	National Institute for Health and Clinical Excellence
RCT	Randomized Controlled Trial
RF	Radio Frequency
SBP	Systolic Blood Pressure
SD	Standard Deviation
TAU	MUHC Technology Assessment Unit

EXECUTIVE SUMMARY

Background

Renal denervation is used to control blood pressure in patients with resistant hypertension. The objective of this report is to summarize the literature on efficacy, effectiveness and safety of renal denervation for treatment of resistant hypertension, and to estimate the budget impact of this technology from the perspective of the MUHC.

Method

We searched for peer-reviewed systematic reviews (in EMBASE (Ovid), MEDLINE (PubMed) and the Cochrane Library) and for HTA reports (in the CRD database and websites of CADTH, INESSS, NICE and INAHTA) of the use of renal denervation in patients with resistant hypertension. We summarized the evidence base used and the conclusions of previous HTAs. We reviewed in detail one systematic review published in English, and one RCT and one cohort study cited by previous HTAs.

Results

A recent and comprehensive systematic review concluded that the available evidence indicates that renal denervation lowers BP in patients with resistant hypertension, but there is a need for larger, long-term studies to confirm these results and to improve assessment of safety.

We reviewed the largest RCT published to date, the Symplicity HTN-2, and the cohort study with the longest follow-up, Symplicity HTN-1; both sponsored by the manufacturer. The RCT randomized 106 participants to receive either the renal denervation intervention plus drug treatment or to maintain drug treatment alone. At six month follow-up the intervention group had a mean reduction of -33/-12 mm Hg compared to the control group; this reduction was statistically significant (two sample t-test; $p < 0.0001$). The authors reported that no serious complications were related to the device or procedure.

The cohort study included 153 patients and measured BP at 6 time points including at 24 months. The mean reduction in systolic BP remained between -20 to -32 at follow-up, while the mean diastolic BP remained between -10 to -14 mm Hg. Mean BP reduction was sustained to 24 months. By the time the study was published only 12% of patients completed the 24-month follow-up period. Four patients (2.6%) experienced procedure related complications (3 aneurysms and one renal artery dissection) or were managed without sequelae.

Four HTAs by other organizations also concluded that additional evidence of high quality is needed with a longer follow up and outcomes that reflect clinically meaningful reductions in cardiovascular adverse events.

Budget impact

The technology requires use of a generator costing \$30,000 and single-use catheters costing \$6,000 each per patient. The company has offered to cover the cost of the generator as long as the catheters are purchased from them and will subsidize the cost of each catheter for a two-year period by \$2,000 for every patient enrolled in an ongoing registry study. Thus, if each patient is enrolled the equipment cost to the MUHC for this initial period would be \$4,000 per procedure. The estimated cost of MUHC resource use for each renal denervation procedure is \$85. Therefore, the total cost of each procedure is \$4,085. Assuming 20 renal denervation procedures are carried out per year at an anticipated cost of \$4,085 per procedure, the budget impact to the MUHC would be \$81,700.

CONCLUSIONS

- The evidence reviewed in this report was largely derived from a comprehensive systematic review, one RCT, and one cohort study.
- The available evidence consistently demonstrates that in patients with resistant hypertension, renal denervation is followed by a lowering (not necessarily a normalisation) of blood pressure for periods of at least 6 months and possibly up to 2 years. Longer term results are not yet available.
- A few manageable complications are reported, but the number of observations is still too small to be able to evaluate the frequency and severity of complications.
- Four HTAs have recommended the acquisition of additional evidence of high quality with a longer follow up and outcomes that reflect clinically meaningful reductions in cardiovascular adverse events.
- There is therefore a need for further research to verify the expected benefits of this procedure, to establish that they are long-lasting, and to better estimate the rate and severity of complications. Such research is reported to be taking place.

RECOMMENDATIONS

It is recommended that this technology receive *temporary* and conditional approval as follows:

- There is agreement by the applicant and the divisional head that this technology be only applied in the context of a formal research study designed to further evaluate its efficacy or effectiveness and safety. The study should meet associated requirements of ethics committee approval and informed consent of subjects.

- Although this research is partly sponsored by the manufacturer, the applicant should retain the rights of publication of any data generated.
- Renal denervation procedures should be limited to a maximum of 20 per year and subsidized by the manufacturer as indicated above.
- The question of permanent approval be reconsidered at a maximum of two years after the first procedure is completed.

SOMMAIRE

Contexte

La dénervation rénale est une technique utilisée pour régulariser la tension artérielle chez les patients souffrant d'hypertension artérielle résistante. Les objectifs de ce rapport sont de résumer la littérature concernant l'efficacité potentielle, l'efficacité réelle et l'innocuité de la dénervation rénale utilisée pour le traitement de l'hypertension artérielle résistante et d'estimer l'impact budgétaire de cette technologie dans le contexte du CUSM.

Méthodologie

Une recherche documentaire a été effectuée dans diverses banques de données indexées (EMBASE (Ovid), MEDLINE (PubMed) *Cochrane Library*) ainsi que des rapports d'évaluation des technologies de la santé (ETS) (base de données du Center for Review and Dissemination et les sites internet de l'ACMTS, de l'INESSS, de NICE et de l'INAHTA) afin de trouver des revues systématiques ou des rapports d'évaluation portant sur l'utilisation de la dénervation rénale pour le traitement de l'hypertension artérielle résistante. Nous avons examiné en détail une revue systématique publiée en anglais, un essai clinique randomisé (ECR) et une étude de cohorte. Nous avons résumé la base de preuves utilisées et les conclusions de l'ETS précédentes.

Résultats. Revue de la littérature

Dans l'ensemble des publications identifiées, une revue systématique publiée en anglais, un essai clinique randomisé (ECR) et une étude de cohorte ont été sélectionnés. Ces données probantes sont résumées ci-dessous.

Basés sur les données probantes disponibles, les auteurs d'une revue systématique récente et exhaustive ont conclu que la dénervation rénale diminue la tension artérielle (TA) chez les patients atteints d'une hypertension artérielle résistante. Toutefois, des études supplémentaires de plus grandes envergures sont requises afin de déterminer l'efficacité à long terme de cette technique et d'améliorer l'évaluation de l'innocuité.

L'étude *Symplcity HTN-2*, la plus grande étude publiée à ce jour, a été examinée. Dans cette étude commanditée par l'industrie, un total de 106 sujets atteints d'hypertension résistante ont été aléatoirement assignés à recevoir soit une dénervation rénale avec une intervention pharmacologique ou une intervention pharmacologique seule. Après un suivi de 6 mois, une diminution moyenne de leur TA de -33/-12 mm Hg (systolique/diastolique) a été observé chez les sujets ayant eu une dénervation rénale avec intervention pharmacologique comparativement aux sujets du groupe contrôle ($p < 0,0001$). Aucune complication majeure reliée à la dénervation rénale n'avait été constatée.

L'étude de cohorte *Symlicity HTN-1*, évaluant l'efficacité à long terme de la dénervation rénale, a également été évaluée. Cette étude, commanditée aussi par l'industrie, a inclus un total de 153 sujets présentant une hypertension artérielle résistante traitée par dénervation rénale. Les sujets ont été suivis jusqu'à 24 mois suivant l'intervention chirurgicale. La réduction moyenne de la TA systolique lors du suivi a variée de -20 mm Hg à -32 mm Hg tandis que la réduction moyenne de la TA diastolique variait de -10 mm Hg à -14 mm Hg. Les réductions observées de la TA se sont maintenu jusqu'à 24 mois suivant l'intervention. À la fin du suivi, 88 % des sujets avaient abandonnés l'étude. Aucune explication n'a été rapportée par les auteurs pour expliquer ce taux élevé d'abandons. Au total, 4 personnes (2,6 %) ont présenté des complications sans séquelles en lien avec la procédure de dénervation rénale (3 pseudo-anévrismes de l'aîne et 1 dissection de l'artère rénale).

Quatre rapports d'évaluation des technologies ont été trouvés. Ceux-ci ont conclu que des données probantes additionnelles appuyées sur une durée d'observation à plus long terme et des indicateurs d'efficacité reflétant une réduction cliniquement pertinente des événements indésirables cardiovasculaires étaient requises.

Analyse des coûts

La dénervation rénale effectuée par la technologie *Symlicity* nécessite l'utilisation d'un générateur (30 000 \$) et d'un cathéter à usage unique (6 000 \$ par personne). La compagnie détenant cette technologie propose de couvrir le coût associé à l'achat du générateur tant et aussi longtemps que les cathéters à usage unique seront achetés de leur compagnie. Le coût d'achat des cathéters pourrait être réduit de 2 000 \$ par personne pendant deux ans si celle-ci sont incluses dans une étude clinique. Ainsi, le coût d'acquisition de l'équipement par le CUSM pour la période initiale de deux ans est de 4 000 \$ par intervention. Le coût associé à l'utilisation des ressources du CUSM pour chaque procédure de dénervation rénale est estimé à 85 \$. Au total, pour la période initiale de 2 ans, le coût de chaque procédure de dénervation rénale est estimé à 4 085 \$ par personne. Pendant la période initiale de 2 ans, en supposant que 20 procédures de dénervation rénale seront effectuées par année, l'impact budgétaire pour le CUSM serait 81 700 \$/an. .

CONCLUSIONS

- **Les données examinées dans ce rapport est en grande partie issu d'une revue systématique, un ECR, et une étude de cohorte.**
- **Les preuves que nous avons recueillies indiquent que la pression artérielle diminue pour des périodes de 6 mois jusqu'à 2 ans pour les patients souffrant d'hypertension résistante traitée au moyen du système de dénervation rénale. Des résultats à long terme ne sont pas encore disponibles.**

- **Les études que nous avons examinées ont déclaré quelques complications gérables mais pour l'instant il n'y a pas assez d'observations pour déterminer la fréquence et la sévérité des complications.**
- **Quatre ETS ont recommandé la nécessité d'études de haute qualité et à long suivi et des résultats qui démontrent la réduction des effets aderses cardiovasculaire qui sont cliniquement significative.**
- **Il existe un besoin d'approfondir les recherches afin de vérifier les avantages attendus de cette procédure, d'établir que les bénéfices vont durer longtemps, et pour mieux estimer la fréquence et la gravité des complications. Ce type de recherche est aux premiers stades.**

RECOMMANDATIONS

Considérant les données probantes disponibles, il est recommandé que la dénervation rénale reçoive une approbation temporaire et conditionnelle. :

Qu'avec l'accord du demandeur et du chef de division, la dénervation rénale ne soit utilisée que dans le cadre d'une étude clinique formelle visant à évaluer davantage l'efficacité et l'innocuité de cette technique; Cette étude devra répondre aux exigences du comité d'éthique et ne devra inclure que des sujets ayant consentis à y participer.

- **Les droits de publications de toutes les données générées par cette étude sont conservés par le demandeur même si l'étude est partiellement financée par l'industrie.**
- **Qu'un maximum de 20 dénervations rénales par an soient effectuées et subventionnées selon les conditions budgétaires proposés par le fabricant.**
- **que la question de l'approbation permanente de cette technologie soit réexaminée dans un délai maximal de deux ans suivant l'exécution de la première dénervation rénale.**

Renal Denervation for Resistant Hypertension

BACKGROUND

Resistant hypertension is defined by most guidelines as blood pressure (BP) that remains above goal (>140/90 mm Hg; JNC and NICE guidelines^{1, 2}) with the concurrent use of 3 antihypertensive drugs (or with best tolerated doses of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, plus a calcium channel blocker; NICE guideline²), including one diuretic¹⁻⁴.

True resistant hypertension is difficult to diagnose because of secondary factors such as non-adherence to medication, inaccurate measurement of BP (white coat effect and cuff related artefacts), and lifestyle factors^{3, 5, 6}. As a result, it is difficult to estimate its true prevalence^{3, 6}. In a recent systematic review the prevalence was found to range anywhere from 8% to 20% among hypertensive patients⁷. At the MUHC, strict criteria will be applied for identifying resistant hypertension patients and the prevalence is more likely to be around 2% of the hypertensive population (Dr. S. Dandona, personal communication).

Data from small clinical studies and observational cohorts suggest that patients with resistant hypertension may have an increased cardiovascular risk, increased risk of vascular morbidity, and increased stroke incidence, as compared to patients with more easily controlled hypertension⁸⁻¹⁰. Resistant hypertension may also lead to target-organ damage and cardio- and cerebro-vascular morbidity and mortality⁸⁻¹⁰.

The current diagnostic and treatment recommendations of the American Heart Association include confirming true treatment resistance, excluding pseudo-resistance, and identifying and reversing contributing lifestyle factors (such as obesity, physical inactivity, diet, alcohol). In addition, patients should be screened for secondary causes of hypertension (such as sleep apnea, chronic kidney disease) and pharmacologic treatment should be optimized^{3, 5}.

Renal denervation is a technique that uses an endovascular catheter with a radio frequency (RF) energy electrode tip to deliver RF energy to the renal arteries to ablate the nerves in the renal arteries, thereby reducing sympathetic nerve drive and lowering blood pressure⁸. The first renal denervation device to be marketed and the only one currently approved in Canada is the Symplicity Renal Denervation System (Medtronic Inc, Mountainview, CA)¹¹.

OBJECTIVE(S)

- The objective of this report is to review the literature and summarize evidence on the efficacy, effectiveness and safety of renal denervation for treatment of resistant hypertension, and to estimate the budget impact to the MUHC of this technology.

METHODS

We searched medical literature databases (EMBASE (via Ovid), MEDLINE (via Pubmed), Cochrane Library) for peer-reviewed systematic reviews. We also searched for Health Technology Assessment (HTA) reports via the CRD database and on the websites of some of the internationally recognized HTA organizations (NICE, CADTH, INESSS). We retained HTA reports that published at least an abstract in English or French allowing us to extract their conclusions. If the report was not in English or French, we used Google Translate to identify the evidence on which the report was based. The key words used in the search were ("denervation" OR "renal denervation") AND "resistant hypertension". The last date of the search was April 30, 2013.

Based on the results of one systematic review and a number of the HTAs, we chose two peer-reviewed articles for more detailed review. The first study was a randomized controlled trial (the Symplicity HTN-2 trial by Esler et al, 2010¹²) with a 6-month follow-up. We chose not to review the only other RCT published so far because it was smaller, it included a subset of the patients from Esler et al.¹² and had a shorter follow-up of 3-months. The second study selected for review was the largest cohort study published so far. This study also had the highest percentage of patients followed beyond the 12-month period, as well as the longest follow-up period with the last measurement being at 24 months. (We found additional results on the manufacturer's website regarding follow-up up to 3 years, but we chose not to include them in our review as they were published only in abstract form.) Thus we expected the RCT to provide evidence of efficacy of renal denervation in the short term and the cohort study to provide evidence of effectiveness over a longer term.

We estimated the budget impact of renal denervation from the point of view of the MUHC. We also searched the online registry of ClinicalTrials.gov to determine if renal denervation is the subject of ongoing research studies.

LITERATURE REVIEW: EFFECTIVENESS

Evidence from the systematic review

One recent systematic review (2013)⁷ assessed the efficacy and safety of renal denervation in resistant hypertensive patients.

Gosain et al⁷ (2013) carried out a systematic review of the literature up to June 2012 that included 19 studies¹²⁻³⁰ with a total of 683 participants (range 11 to 153). Of these, 2 were RCTs^{12, 26} (the second²⁶ RCT included some patients from the first RCT, Symplicity HTN-2), 1 was a large cohort¹⁷, 4 were case-control studies^{14, 18, 20, 21}, and 12 were case series^{13, 15, 16, 19, 22-25, 27-30}. The authors reported that the standard definition of resistant hypertension was used in all studies. They reported that the method of measuring BP varied between studies. Follow-up ranged from 2 weeks to 24 months. Six^{12, 17-20, 30} of the 19 studies were funded by the manufacturer and 11 studies^{13, 14, 16, 22-29} did not declare a funding source. The average age of the patients ranged from 50 to 70 years.

The systematic review found that all studies “reported significant reductions in systolic and diastolic pressures”, that a “sustained benefit” of blood pressure reduction at 12 months was seen in five studies.” Eight studies reported the average change in BP (systolic/diastolic) at 6 months to be between -22 to -34/ -8.8 to -15 mm Hg following renal denervation. Three studies that included a control group on continued medical therapy reported the mean change at 6 months in the control group to be between -4.4 to +14/-3 to +9 mm Hg. Four studies reported change in BP measurements at 1 year following renal denervation – mean values ranged from -23 to -33/-9.7 to -19 mm Hg.

Among 683 patients studied in the systematic review, the reported adverse events included pseudoaneurysm (2 patients in 2 studies), renal artery dissection (2 patients in 2 studies), back and/or flank pain (12 patients in 3 studies), intraprocedural bradycardia requiring atropine (7 patients in 1 study), and hypotension (6 patients in 2 studies). They concluded that data from short-term studies suggest that renal denervation is a safe and effective therapeutic option in carefully selected patients with resistant hypertension, but that long-term studies with large patient populations are needed to study whether the benefit is sustained with a demonstrable difference in cardiovascular event rates.

Evidence from the Symplicity HTN-2 randomized controlled trial

The Symplicity HTN-2 was a multicenter randomized controlled trial sponsored by the manufacturer that compared the antihypertensive efficacy of renal denervation plus previous drug treatment with drug treatment alone¹². The manufacturer monitored, collected and managed the data. In total, 106 participants (N=52 intervention group, N=54 control group) with a systolic BP (SBP) greater than 160 mm Hg despite taking at least 3 antihypertensive drugs were enrolled (Table 2).

Randomization was blinded using sealed envelopes, but patients and outcome assessors were not blinded to treatment-group assignment. Patient adherence was monitored during the two-week screening period before the start of the trial. During the screening period patients recorded twice daily automated home blood pressure measurements and completed drug compliance diaries. Baseline anti-hypertensive doses were to be maintained unless an adjustment was medically necessary. All analyses were done per-protocol on the participants that completed the trial (N=49 intervention group and N=51 control group). Three patients in each group were lost to follow-up at 6 months (withdrawal of consent or missed visit).

The intervention and control groups were comparable on most baseline characteristics; however, there were more males with Type 2 diabetes and coronary heart disease in the intervention group than the control group. The primary outcome was office BP (averages of triplicate measurements) at 6 months measured with an automated monitor. The intervention group had a mean change in BP of -32/-12 mm Hg (SD 23/11) from the average baseline value of 178/96 mm Hg, to a final average BP of 146/84 mm Hg (Table 2). The control group had an average change in BP of +1/0 mm Hg (SD 21/10) from an average baseline value of 179/97 mm Hg. The difference between intervention and control groups was 33 / 12mmHg. This difference was statistically significant (two-sample t-test; $p < 0.0001$). Ten intervention patients vs. 3 control had drug reductions and 4 intervention vs. 6 control patients had drug increases during the 6 month follow-up. The BP decrease for patients initially randomized to the renal denervation group was maintained at one year follow-up (-28.1/-23.7 mm Hg)³¹.

No serious complications related to the device or procedure were reported. In the intervention arm, five minor periprocedural events occurred and seven patients had transient intraprocedural bradycardia requiring atropine-none had any sequelae. Serious adverse events requiring hospital admission in the intervention group included: one patient with nausea and oedema, one patient with hypertension crisis, one transient ischemic attack, one hypotensive episode, one patient receiving a coronary stent for angina. In the control group, two patients had transient ischemic attacks and one received a coronary stent for angina.

The RCT concluded that a significant reduction in BP can be achieved with catheter-based renal denervation in patients with resistant hypertension. A reduction in BP of 10 mm Hg or more occurred in 84% patients in the renal denervation arm. However, the average post intervention systolic BP remained over 140 mm Hg, which is the cut off used to define resistant hypertension.

Limitations of the RCT include not blinding the data analysers, having the primary outcome of office BP instead of ambulatory BP (white-coat effect), and a short follow-up of 1 year. However, efforts were made to control for medication non-adherence and a more stringent BP cut off was used for patient inclusion (>160 mm Hg SBP).

Evidence from the Symplicity HTN-1 cohort study

The largest cohort study to date is the Symplicity HTN-1 with 153 patients¹⁷. BP measurements were taken at 1, 3, 4, 6, 12, 18, and 24 months (Table 2). The article was published prior to all participants completing the study; only 18 participants completed the 24 month follow-up period. At 6, 12, and 24 months, data was available on only 56.2%, 41.8%, and 11.8% of the 153 patients, respectively. (Information on the manufacturer's website suggests that more data may now be available for more patients with results being reported for 94.1% patients at 6 months, 86.3% patients at 1 year and 68.6% patients at 2 years). The mean reduction in systolic BP remained between -20 to -32 at follow-up, while the mean diastolic BP remained between -10 to -14 mm Hg.

Of the 153 patients 8 experienced procedure-related adverse events: 1 patient suffered renal artery dissection during the placement of the catheter, 3 patients developed a pseudoaneurysm/hematoma in the femoral access site, 1 patient had a 6-month post procedure renal artery stenosis (stenosis was away from site of RF energy application) and 3 patients reported pitting edema. In addition 4 patients experienced continuous or intermitted bilateral flank pain and 2 patients died of causes unrelated to the procedure. The study concluded that reduction in BP was sustained to 24 months with few, if any, adverse effects directly related to the renal denervation procedure. This study was sponsored by the manufacturer and two members of the writing committee were employees of the manufacturer.

Conclusions of HTA reports

We identified 4 reports³²⁻³⁵ from HTA organizations that were written after the publication of the Symplicity HTN-2 RCT (Table 2). Three³³⁻³⁵ of them relied on the same two studies (the Symplicity HTN-1 trial and the Symplicity HTN-2 RCT) (discussed above). Most reports concluded that renal denervation, while promising, requires further research to determine its long term safety and the clinical impact on reducing cardiovascular outcomes. Two HTAs^{32, 35} explicitly stated that they did not recommend renal denervation for routine use. The NICE HTA^{33, 36} emphasized the role of clinicians in collecting and submitting patient data to a national register.

MUHC BUDGET IMPACT

The renal denervation Symplicity device requires a generator that costs \$30,000. Each single-use catheter costs \$6,000. It is proposed that the manufacturer will cover the cost of the generator as long as the MUHC continues to buy catheters from them. In addition, the company will subsidize the catheter costs by \$2,000 for a 2-year period, resulting in the net cost of the catheter being reduced to \$4,000 per patient. The estimated MUHC personnel cost for each renal denervation procedure is \$85 (1 hour in the catheterization lab with 1 nurse and 1 technician (\$63), followed

by 4 hours in a recovery room (\$22)). Therefore, the total cost of the procedure is \$4,085. Based on input from Dr. Dandona it is anticipated that 20 renal denervation procedures could take place annually. Therefore, under this proposal, the annual budget impact to the MUHC would be $20 \times \$4,085 = \$81,700$. The long-term budget impact after the 2-year subsidization period will be \$121,700 ($20 \times \$6,085$).

ONGOING CLINICAL TRIALS

A large number of research studies of renal denervation are ongoing. A search on www.ClinicalTrials.gov revealed that currently 14 RCTs (4 single blinded, 4 double blinded, 6 open label), 17 prospective cohorts, 1 registry, and 1 non-RCT single blinded trial are ongoing and due to be completed during the next eight years. The RCTs plan to recruit between 30 and 530 participants, and the cohort studies between 20 and 500 participants (two cohorts have 500 planned participants). The planned follow-up time ranges from 3 months to 10 years, with the majority of studies having 6 months follow-up. About half of the studies are sponsored by the industry and do not follow a standard definition of resistant hypertension based on guidelines. Most studies are based in Europe, with only 3 studies being US-based. 70% of studies are planning to measure reduction in BP as the primary outcome and about 23% are planning to look at safety and adverse events as the primary outcome. One study of coronary heart disease patients will be assessing whether renal denervation can reduce all-cause mortality and the risk factors for coronary heart disease.

In addition, there are two ongoing European RCTs with 50 and 130 participants and 6 months of planned follow-up that are comparing renal denervation to increment of drug therapy (spironolactone+baseline drug treatment). One study will also look at cost effectiveness of renal denervation and difference in scores of quality of life between the two groups.

CONCLUSIONS

- The evidence reviewed in this report was largely derived from a comprehensive systematic review, one RCT, and one cohort study.
- The available evidence consistently demonstrates that in patients with resistant hypertension, renal denervation is followed by a lowering (not necessarily a normalisation) of blood pressure for periods at least 6 months and possibly up to 2 years. Longer term results are not yet available.
- A few manageable complications are reported, but the number of observations is still too small to be able to evaluate the frequency and severity of complications.

- Four HTAs have recommended the acquisition of additional evidence of high quality with a longer follow up and outcomes that reflect clinically meaningful reductions in cardiovascular adverse events.
- There is therefore a need for further research to verify the expected benefits of this procedure, to establish that they are long-lasting, and to better estimate the rate and severity of complications. Such research is reported to be taking place.

RECOMMENDATIONS

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- There is agreement by the applicant and the divisional head that this technology be only applied in the context of a formal research study designed to further evaluate its efficacy or effectiveness and safety. The study should meet associated requirements of ethics committee approval and informed consent of subjects.
- Although this research is partly sponsored by the manufacturer, the applicant should retain the rights of publication of any data generated.
- Renal denervation procedures should be limited to a maximum of 20 per year and subsidised by the manufacturer as indicated above.
- The question of permanent approval be reconsidered at a maximum of two years after the first procedure is completed.

TABLES

Table 1 Summary of primary outcomes of RCTs and observational studies

Reference	Total no. patients	Avg BP medications at baseline	Mean baseline BP (mm Hg) systolic/diastolic \pm SD	Mean change in BP (mm Hg) systolic/diastolic \pm SD
Symplicity HTN-2 RCT, 2010 ¹² 6 month study	106‡	5.2	Intervention: 178 \pm 18/96 \pm 16 Control: 178 \pm 16/97 \pm 17	Intervention @6 mos -32 \pm 23/-12 \pm 11 Control @6 mos 1 \pm 21/0 \pm 10
Symplicity HTN-2 One year follow-up study, 2012 ³¹	82 (47intervention; 35 crossover¥)	5.2	Intervention: 178 \pm 18/96 \pm 16 Crossover group: 183 \pm 16/99 \pm 17	Intervention @12 mos -28 \pm 25/-10 \pm 11 Crossover group @6mos -24 \pm 27/-8 \pm 12
Symplicity HTN-1, 2011 ¹⁷	153	5.1	176 \pm 17/98 \pm 15	@6mos -23/-11* (n=86) @24 mos -32/-14* (n=18)

RCT Randomized Controlled Trial; ‡100 (49 intervention; 51 control) patients were included in the analysis based on per-protocol analysis; ¥Cross over of control group to renal denervation group occurred 6 months post randomization; SD: Standard Deviation; * SD estimates not available

Table 2 Conclusions of HTA reports of renal denervation for resistant hypertension

HTA Organization	No. included studies	Total no. patients (range)	Follow-up range	Conclusions
AVALIA-T, 2013 ³²	10 ^{12, 14, 15, 17, 18, 20, 21, 26, 30, 37}	594 (10-153)	3-24months	<ul style="list-style-type: none"> • "In view of the uncertainty surrounding the efficacy, efficiency, effectiveness, safety and therapeutic utility of radiofrequency sympathetic renal-nerve ablation in the treatment of resistant arterial hypertension, its incorporation into the health service portfolio is not recommended at the present time." • "There is a need: for RCTs, aimed both at assessing the technique in the long term and its impact on the reduction of cardiovascular morbidity and mortality, and comparing the different existing renal denervation methods; and for cost-effectiveness studies."
CADTH, 2013 ³⁴	2 ^{12, 17}	259 (106, 153)	6-36 [€] months	<ul style="list-style-type: none"> • "There is evidence that the Symplicity renal denervation device significantly decreases blood pressure in patients with treatment-resistant hypertension and that this reduction can be sustained up to three years." • "Whether the reductions in blood pressure reported in clinical trials translate into clinically meaningful reductions in cardiovascular morbidity and mortality remains an important question that will have to be evaluated with much larger and longer clinical trials. " • "Confirmatory evidence to support procedural safety, patient selection, and therapeutic durability will determine the uptake of renal denervation into clinical practice for treatment-resistant hypertension."
NICE, 2012 ^{33, 36§}	3 ^{12, 17, 18}	303 (50-153)	6-24months	<ul style="list-style-type: none"> • Inadequate evidence on efficacy and safety in the long term. • Further research, data collection and publication of outcomes is needed. • Clinicians should submit data on all patients having this procedure to the national register when it becomes available. • "Clinicians should inform the clinical governance leads and ensure that patients understand the uncertainty about the procedure's safety and efficacy, and provide them with clear written information."
LBIHTA, 2011 ³⁵	2 ^{12, 17}	259 (106, 153)	6-24months	<ul style="list-style-type: none"> • "Given the current paucity of evidence renal denervation in essential hypertonia can currently not be recommended for the Austrian hospital services catalog."

AVALIA-T: Agencia de Avaliacion de Tecnologias Sanitarias de Galicia; CADTH: Canadian Agency for Drugs and Technologies in Health; NICE: National Institute for Health and Clinical Excellence; LBIHTA: Ludwig Boltzmann Institute for Health Technology Assessment; §NICE conclusions based on a supporting guideline document ³⁶; €36 month follow-up data available at <http://www.medtronicrdn.com/intl/healthcare-professionals/symplicity-rdn-system/symplicity-clinical-trial-data/index.htm> and <http://www.whichmedicaldevice.com/editorial/article/249/renal-sympathetic-denervation-a-rapidly-evolving-field>

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