EUnetHTA WP5 Joint Action 2 (2012-2015) Strand B, Rapid assessment of other health technologies such as medical devices, surgical interventions or diagnostics

RENAL DENERVATION SYSTEMS FOR TREATMENT-RESISTANT HYPERTENSION

Pilot rapid assessment of other health technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment

Assessment

Pilot ID: WP5-SB-12

Version 1.3, 18 December 2013
Final version

DOCUMENT HISTORY

Version	Date	Description
V1.0	04 10 2013	First draft
V1.1	28 10 2013	With input from dedicated reviewers (review period: 7-21October 2013)
V1.2	04 12 2013	With input from manufacturers, Strand B members, patient representative and external clinical experts (review period: 28 October – 18 November 2013)
V1.3	18 12 2013	Final version with input from medical editing (review period: 4-11 December 2013)

This assessment was produced by experts from the institutions below and was reviewed by members of Work Package 5 (WP5) Joint Action 2 of the EUnetHTA network; the entire process was coordinated by the Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA).

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Stakeholder involvement

1) Project Plan

SAG:

Comments received from:

- Eucomed
- Covidien
- St. Jude Medical
- Association Internationale de la Mutualité (AIM)
- Johnson & Johnson

Answered but no comments:

- Caisse Nationale d'assurance Maladie (CNAMTS)
- Siemens AG
- Standing Committee of European Doctors (CPME)

Public Consultation:

Comments received from:

- Johnson & Johnson
- European Organisation for rare diseases (EURORDIS)
- Beaumont Hospital
- St. George's NHS Trust
- University of Milano-Bicocca
- University of Valencia
- University of Barcelona
- Hauptverband der österreichischen Sozialversicherungsträger (HVB)

Manufacturers:

Comments received from:

- Medtronic Vascular
- Boston Scientific
- Covidien
- St. Jude Medical

2) Pilot Rapid Assessment

Patient representative(s):

- European Organisation for Rare Diseases (EURORDIS)

Manufacturer(s):

- Medtronic Vascular
- Boston Scientific
- Covidien
- St. Jude Medical
- Johnson & Johnson Medical BV/Biosense Webster
- ReCor Medical
- Eucomed Hypertension Working Group

Conflict of interest:

One external reviewer declared a conflict of interest, but as it was deemed irrelevant per the Procedure Manual for WP5 Strand B, the respective reviewer was not excluded from the pilot process. All authors and other reviewers who were involved in the production of this pilot assessment have declared that they have no conflicts of interest in relation to the technology that has been assessed, per the EUnetHTA conflicts of interest (COI) statement form.

TABLE OF CONTENTS

SUMMARY OF RELATIVE CLINICAL EFFECTIVENESS OF RENAL DENERVATION SYSTEMS

The assessment element ID codes in brackets (e.g. A0001) refer to the result cards in Appendix 1, which give details on the relevant results.

Scope

Population	Patients with treatment-resistant arterial hypertension (defined as persistent hypertension despite administration of at least 3 antihypertensive drugs in adequate doses, including a diuretic) with blood pressure ≥ 140/90 mm Hg (Calhoun 2008; Mancia 2013) and without secondary cause of hypertension.
Intervention	Renal nerve ablation and denervation systems This intervention entails the destruction of efferent sympathetic nerves and afferent nerves in the wall of the renal arteries to reduce sympathetic nerve traffic, thereby reducing blood pressure.
Comparator(s)	Standard of care (which includes here: no treatment, additional pharmacological treatment, device-based therapy for hypertension and sham treatment) All patients continue treatment with at least 3 hypertensive drugs. Any additional intervention or comparator is administered as add-on therapy.
Outcome(s)	Primary outcomes: Overall mortality Cardiovascular mortality Cardiovascular morbidity (stroke, myocardial infarction, heart failure) Blood pressure (changes in systolic and diastolic blood pressure) Complications during or after treatment Secondary outcomes: Left ventricular hypertrophy/systolic and diastolic cardiac function Kidney function Quality of life Effect on daily living
Study design	Efficacy/effectiveness: Systematic reviews (SRs)/Health Technology Assessments (HTAs), randomised controlled trials (RCTs) and, if data from RCTs are lacking or insufficient, prospective, controlled studies Safety: Same as for efficacy and including all prospective studies
Languages	English, Spanish, French, German, Swedish, Danish, Norwegian

Introduction

Health problem

The target population comprises patients who suffer from resistant hypertension, a condition that is linked to sympathetic nervous system overactivity, involving the kidneys. Patients who are eligible for the intervention can be treated with catheter-based renal denervation. The goals of the treatment are to prevent hypertensive end-organ damage and decrease cardiovascular morbidity and mortality **(A0007)**.

Treatment-resistant hypertension is a condition for which conventional/traditional treatments are inadequate – this condition is also described as true resistant hypertension. The traditional/standard treatment is based primarily on medical treatment and lifestyle interventions. Resistant hypertension develops when the appropriate treatments, including lifestyle measures and 3 antihypertensive drugs (1 of which is a diuretic), fail to lower systolic blood pressure (BP) and diastolic BP values to 140 and 90 mm Hg, respectively. All drug agents should be prescribed at the optimal doses. Any secondary causes (due to other diseases, primarily renal disease) must also be ruled out **(A0002)**.

Risk factors for treatment-resistant arterial hypertension are older age, lifestyle factors (e.g. obesity or large weight gains, excessive alcohol consumption, high sodium intake), chronic intake of vasopressors or sodium-retaining substances, obstructive sleep apnoea, undetected secondary forms of hypertension and advanced and irreversible organ damage, particularly when it involves renal function or markedly increases the arteriolar wall–lumen ratio or reduces large artery distensibility **(A0003)**.

The natural course of resistant hypertension has been inadequately examined. If untreated, hypertension will increase the risk of cardiovascular disease, stroke and renal failure. Patients frequently encounter associated cardiovascular risk factors, such as diabetes, obstructive sleep apnoea and left ventricular hypertrophy **(A0004)**. Normally, the patient does not experience symptoms that are associated with resistant hypertension. Some patients might experience fatigue, headache or nosebleed – symptoms that are related to higher BP **(A0005)**.

Overall, the exact prevalence of resistant hypertension is unknown. It is, however, assumed to be a common clinical condition. Based on the aforementioned risk factors, the prevalence is expected to increase in the older and more obese population. The prevalence of resistant hypertension ranges from 5% to 30% of the overall hypertensive population but is likely below 10%. The prevalence of all cases of hypertension is approximately 30% to 45% of the general population, also rising with older age **(A0006)**.

In diagnosing resistant hypertension, one must first consider that most cases of resistant hypertension originate from multiple factors and rarely have a single cause. Evaluation should verify the diagnosis of hypertension – excluding pseudoresistant patients (e.g. white-coat hypertension) – uncover any causes of secondary hypertension and clarify any cardiovascular risk, organ damage and related clinical conditions. A medical history should be included in the clinical evaluation, along with the family history with regard to hypertension, a physical examination, laboratory investigations and further diagnostic tests. The evaluation of patients with resistant hypertension should focus on confirming actual treatment resistance **(A0024)**.

As stated in an expert consensus document on catheter-based renal denervation that was published in 2013 by the European Society of Cardiology, patients should comply with a set of criteria before renal denervation is considered, as follows: i) office-based systolic BP ≥ 160 mm Hg (≥150 mm Hg for those with type 2 diabetes) despite use of ≥ 3 antihypertensive drugs at adequate dosages and combinations (including diuretics); ii) treatment resistance to lifestyle modification when changes in lifestyle fails to alter the BP; iii) exclusion of secondary hypertension; iv) exclusion of pseudo-resistance by monitoring ambulatory BP (average BP > 130 mm Hg or mean daytime BP > 135 mm Hg); v) preserved renal function (glomerular filtration rate ≥ 45 ml/min/1.73 m^2) and vi) eligible renal arteries: no polar or accessory arteries, no renal artery stenosis and no prior revascularization **(B0002)**.

The uncertain prevalence and potential number of candidates, based on the indications/ contraindications for the surgical procedure, render it difficult to calculate a reasonable estimate on the expected annual utilisation of catheter-based renal denervation. Existing data indicate many potential candidates for renal denervation. More experience with the procedure in relevant candidates will clarify the relevant annual use of renal denervation **(A0011)**.

Description of technology

Renal denervation is a treatment for treatment-resistant hypertension that uses low-level radio frequency energy or ultrasonography to disrupt renal sympathetic nerves to reduce blood flow and thereby decrease hypertension by de-activating hyperactive nerves, without affecting other abdominal, pelvic or lower-extremity nerves **(B0001)**.

Most systems are catheter-based and introduce the catheter through the femoral artery, which is threaded into the renal artery lumen **(B0001)** under fluoroscopic control. Renal denervation should be performed in a catheterisation laboratory, for cardiovascular interventions and in a setting that specialises in hypertension treatment **(B0004)**.

The current treatment regimen consists of a combination of at least 3 antihypertensive agents. Renal denervation is intended to be add-on therapy to pharmaceutical treatment **(B0001, B0002)**.

Of the renal denervation systems that use radiofrequency energy, the Symplicity® (Medtronic, Ardian Inc.), OneShot™ (Covidien), EnligHTN™ (St. Jude Medical), Vessix V2™ (Boston Scientific) and Iberis™ (Terumo) systems are CE-marked in Europe. Of the ultrasonography devices that are under development, the PARADISE™ system (ReCor) has received the CE mark. None of the systems is FDA-approved, but all .are seeking this status Medtronic's Symplicity® system is the first system to be reviewed in the U.S. in a parallel review program of the FDA and Centers for Medicare and Medicaid Services from 2014 **(B0003)**.

Methods

'Health problem' and 'Description of technology' Domains

The 'HTA Core Model for Rapid Relative Effectiveness Assessment for Pharmaceuticals' was the only source that was used to select the relevant assessment elements. Overall, a basic search (which was the same for all domains) was used as the springboard for answering research questions. Additional searches were performed for nearly all research questions using PubMed and Google. Google was also used for locating specific information on each renal denervation (RDN) system.

'Safety' and 'Clinical effectiveness' Domains

The 'HTA Core Model for Rapid Relative Effectiveness Assessment for Pharmaceuticals' was the principal source that was used to select the relevant assessment elements. In addition, assessment elements from 'HTA Core Model for Medical and Surgical Interventions 1.0r' and 'HTA Core Model for Diagnostic Technologies 1.0r' were included for the 'clinical effectiveness' domain. Domain results were based on a basic systematic literature search and on information from the manufacturers. The sources of information were Embase (Ovid), Ovid MEDLINE, ISI Web of Knowledge, Cochrane Library, Cochrane Reviews, Centre for Reviews and Dissemination and WHO ICTRP (International Clinical Trials Registry Platform).

For 'safety', all prospective studies that were published in peer review journals were considered – i.e. randomised controlled trials (RCTs), non-randomised controlled trials (non-RCTs) and case series. Conference abstracts and proceedings, editorials, opinion papers and unpublished data were excluded. Data were extracted independently by 2 investiga-

tors (discrepancies were resolved through discussion). Data were analysed qualitatively. Quality was assessed using the Cochrane risk of bias checklist and GRADE, and information was aggregated into evidence tables and displayed in plain text format.

For 'clinical effectiveness', the relevant literature was selected by 2 people independently, as with 'safety', and discrepancies were discussed until a consensus was reached. In terms of study design, systematic reviews (SRs)/Health Technology Assessments (HTAs), RCTs and, if data from RCTs were lacking or insufficient, prospective, controlled studies were selected to answer questions that were related to this domain. To assess the quality of the SRs, the Norwegian Knowledge Centre for the Health Services (NOKC) checklist for SRs, adapted from the Cochrane Effective Practice and Organisation of Care (EPOC) group appraisal list for SRs, was used. The quality of the included individual studies was analysed using the Cochrane risk of bias checklist and GRADE. The quality of the evidence was classified and defined as high (i.e. "We are very confident that the true effect lies close to that of the estimate of the effect"), moderate (i.e. "We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different"), low (i.e. "Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect") and very low (i.e. "We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect"). Like for 'safety', the characteristics of the included SRs and single trials with quality assessments and of ongoing studies that were identified from the trial registry searches are presented in evidence tables and plain text format. When appropriate, meta-analyses were performed using RevMan5.2. All data were reported per the PRISMA Statement.

Results

Available evidence

The evidence for the safety assessment came from 3 RCT publications, 3 non-RCT publications and 16 case series, comprising a total of 904 patients (however, 91 patients were included in more than 1 study), with follow-up periods ranging from 3 months to 2 years. In 2 of the 3 RCTs, all non-RCTs and 11 of the 16 cases series, the RDN procedure involved the administration of radiofrequency ablation (RF) with the Symplicity® catheter system (Medtronic) (784 patients in total.) One RCT of 13 patients performed the intervention using the Navistar® ThermoCool® Irrigated Tip Catheter, designed for cardiac ablation (Biosense Webster). One case study with 30 patients used the Marinr® RF ablation catheter (also typically used for cardiac ablation), 1 with 46 patients used the EnligHTN® multi-electrode renal denervation system and 1 with 9 patients used the OneShot™ (Covidien) RDN system. Another case series included 11 patients who underwent RDN with Paradise™ technology (ReCor Medical), which uses a catheter that emits ultrasonographic energy, and 1 trial with 11 patients did not specify the type of system that was used (see Appendix 1).

In the evaluation of clinical effectiveness, 3 SRs and 4 controlled studies – 3 RCTs and 1 non-RCT in a total of 158 patients with a follow-up period of 3 months to 1 year – were included. In assessing changes in BP and based on the SR that was included, studies were excluded if there was an overlap in patients with another study in the same analysis (in which case the largest sample size of the 2 studies was selected). Thus, overlaps in patients were avoided; ultimately, 190 patients from 3 controlled trials were included for this outcome.

In general, the SRs had slightly different inclusion criteria, but all searched for controlled trials. Irrespective of how the individual studies were identified, all reviews included patients with resistant hypertension, and renal denervation was compared with no treatment or sham procedure. Moreover, all patients continued with their usual pharmaceutical treatment for hypertension. Included SRs were rated as high-quality. Individual studies were assessed using risk of bias and scored well with regard to bias within their study type (see Appendix 1).

Upcoming evidence

Searches in WHO ITRP (International Clinical Trials Registry Platform), performed in October 2013, identified 26 ongoing controlled studies that used various RDN systems, which primarily examined changes in BP. None of the ongoing studies in this rapid assessment is assessing overall mortality or cardiovascular mortality as the primary outcome. Feedback from the manufacturers includes information that 1 study will evaluate the EnligHTN™ System and its ability to reduce the risk of major cardiovascular events, such as heart attack, stroke, heart failure and cardiovascular death. Manufacturers also state that mortality data are collected routinely during clinical trials. Supplementary documentation from the manufacturers (Boston Scientific, St. Jude Medical, Covidien and Medtronic) indicates that they either plan their first randomised trial or an additional randomised trial or that they plan to reportresults from RCTs in the next 1 or 2 years (see Appendix 1).

Safety

Of the 22 studies that were included in the safety assessment, 13 reported procedure-related complications. The most commonly reported procedure- and device-related complications were of a mild to moderate nature.

Table 1 below provides an overview of harms in terms of total and major adverse events.

Major procedure-related complications were reported in 4 studies. Three studies noted renal artery dissection on placement of the catheter (0.65% to 9.09%), 1 study reported a psoas hematoma that was secondary to placement of the catheter (9.09%) and 1 study described 1 case of respiratory and cardiocirculatory depression due to analgosedation (1.89%) and 1 case of severe artery spasm that resulted in residual stenosis that had no hemodynamic relevance (1.89%). Overall, the frequency of major complications was 0.551%. No intervention-related mortality was reported in any study **(C0001)**.

Six studies (n=315) reported major complications during the follow-up period, that ranged from 3 months to 2 years. The complications that were considered to be major were hypertensive episodes that required hospitalisation (5% to 33.3%), hypotensive events that required hospitalisation (2% to 2.86%), angina (2.04%), transient ischaemic attacks (2.04%), progression of existing stenosis (0.65% to 2.17%) and hypertensive renal disease progression (2.17%). None of the studies reported aortic stenosis, thrombosis or significant structural abnormalities of the renal arteries.

In the Symplicity HTN-2 RCT, major complications appeared during the 6-month follow-up in 8 of the RDN treated patients (15.4 %) and 5 of the patients that received only pharmacological medication (9.3%). One RDN patient and 2 control patients suffered a transient ischaemic attack, and 1 patient from each group developed angina. Additional serious events that required hospitalisation in patients who underwent RDN included 1 case of nausea and oedema, 1 hypotensive episode, 3 hypertensive emergencies that were unrelated to non-persistence and 1 hypertensive crisis after clonidine was halted. Two patients of the control group presented with hypertensive emergencies.

In the RCT with 27 patients that assessed the impact of RDN using the Navistar® ThermoCool® catheter plus pulmonary vein isolation (PVI) versus PVI alone, no acute adverse events or renal artery stenosis were reported at 6 months in either group; the study did not comment on other post-procedural adverse events **(C0001, C0008)**.

Clinical effectiveness

The most recent high-quality SR that assessed overall mortality reported no deaths during the follow-up periods and none of the publications in this rapid assessment reported any cardiovascular mortality **(D0001)**.

Table 1 below provides an overview of the main health benefit based on the evidence currently available.

The SR that assessed cardiovascular morbidity from coronary heart disease, stroke, peripheral arterial obstructive disease and heart failure found no relevant studies, and among the RCTs and non-RCTs that were identified, none examined these outcomes **(D0002)**. One SR included 1 non-RCT that examined left ventricular hypertrophy in 64 patients 6 months following renal denervation using the Symplicity® system. The mean difference in left ventricular mass was 23.8 g/m^2 (95% CI, 7.4–40.2 g/m^2). This result significantly favored renal denervation, but the quality of this evidence was very low. Further, 1 non-RCT (prospective controlled trial) of 46 patients analysed left ventricular hypertrophy 6 months after renal denervation using Symplicity® but measured left ventricular mass differently. The mean difference was 3.6 g/m$^{1.7}$ (95% CI, -3.6–10.8 g/m$^{1.7}$), but not significant, and the quality of this evidence was very low.

Finally, 1 RCT with 27 patients assessed left ventricular hypertrophy after 6 months but used the Navistar® ThermoCool®. Left ventricular mass (formula not indicated) was 15.4 g/m lower in patients who had undergone renal denervation (95% CI, 10.8–20.1 g/m). The mean difference was significant, but the quality of this evidence was very low **(D0005)**.

According to the SR, 3 controlled studies analysed changes in systolic and diastolic BP at 6 months (2 RCTs and 1 non-RCT). The studies included 158 patients in total and used different types of catheters (1 RCT used the Navistar® ThermoCool®, and the other RCT and non-RCT used Symplicity®). With renal denervation, there were significant decreases in systolic BP (mean difference 29.8 mm Hg; 95% CI, 20.6–37.2 mm Hg) and diastolic BP (mean difference 11.0 mm Hg; 95% CI, 5.7–16.4 mm Hg), and the quality of this evidence was low. However, on re-analysing the data and grouping studies by catheter type, we noted that pooling the 2 studies that used the Symplicity® system (131 patients) resulted in a mean difference in systolic BP of 33.6 mm Hg (95% CI, 25.9–41.3 mm Hg) and a mean difference in diastolic BP of 13.8 mm Hg (95% CI, 7.3–20.3 mm Hg), both of which were significant. Here, the quality of the evidence was moderate. The study that used the Navistar® ThermoCool® in 27 patients reported mean differences in systolic and diastolic BP of 23 mm Hg (95 % CI, 16.8–29.2 mm Hg) and 7.0 mm Hg (95% CI, 2.5–11.5 mm Hg), respectively, which were also significant, but the quality of the evidence was very low **(D0006)**.

One SR identified an RCT with 100 patients that measured changes in renal function in terms of estimated glomerular filtration rate (eGFR) after 6 months of follow-up using the Symplicity® system. The mean difference was 0.7 ml/min/1.73m^2 and not significant (95% CI, -5.2–3.8 ml/min/1.73m^2). The quality of this evidence for this outcome was low. This RCT also examined changes in renal function, based on serum creatinine levels, after six 6 of follow-up using the Symplicity® system. The mean difference in serum creatinine was 1.3 µmol/L and not significant (95% CI, -4.4–7.0 µmol/L); the quality of this evidence was also low **(D0011)**.

Applicability of the evidence

A summary table that characterises the applicability of the body of evidence is presented in Appendix 1, Table 24. Briefly, regarding the population, the inclusion criteria of the studies appeared to target the intended patient population with treatment-resistant hypertension, but many patientswho were included had higher BP than our inclusion criteria, and it is possible that real-life use may differ from use in the studies. Moreover, normal renal nerve anatomy/access is necessary, depending on how the procedure is performed. Further, with regard to the intervention, the procedure entails the delivery of radiofrequency or ultrasonographic energy along the renal arteries to effect denervation, and there is no immediate method of determining whether the ablation has been successful. The Symplicity® catheter has been used in most controlled studies, but other systems are currently being implemented.

Notably, surrogate outcomes were assessed in the studies, whereas clinically relevant endpoints (i.e. overall mortality, cardiovascular mortality and major events, such as stroke, myocardial infarction and heart failure) have not been analysed. At this stage, no con-

trolled studies have focused on how RDN affects such outcomes as patient satisfaction, quality of life and activities of daily living – thus, the full clinical benefit remains unknown.

Reimbursement

RDN is reimbursed in 13 countries in Europe, and in most cases regardless of the type of device. In the majority of countries, this has been a formal reimbursement decision, i.e. based on (national) policy. In 1 country, Medtronic's Symplicity® received conditional coverage. In 5 countries a decision on reimbursement is in process, 2 countries do not reimburse RDN, and in 3 countries the reimbursement status is unknown **(B0003)**.

Table 1: Summary of relative effectiveness of renal denervation systems

Treatment-resistant hypertension					
	Main health benefit*			Harm	
	Change in SBP at 6 months (mm Hg)	**Change in DBP at 6 months (mm Hg)**	**Change in eGFR at 6 months (ml/min/1.73m²)**	**Total AEs (%)**	**Major AEs (%)**
RDN	MD = -29.8 [-37.2 - (-20.6)] ***(continuous outcome)***	MD = -11.0 [-16.4 - (-5.7)] ***(continuous outcome)***	MD = -0.7 [-5.21-3.81] ***(continuous outcome)***	*40.4% in the RDN group* *9.3% in the control group*	*15.4% in the RDN group* *9.3% in the control group*
Standard of care	***D0006*****	***D0006***	***D0011***	*C0001*	*C0001*
Quality of body of evidence	***LOW***	***LOW***	***LOW***	***LOW***	***LOW***

NA = not applicable; SBP = systolic blood pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; AEs = adverse events; MD = mean difference. ** The assessment element ID codes (e.g. D0001) refer to the result cards in Appendix 2, which gives details on the relevant results.

* This table provides data from the evidence currently available.

Discussion

The published data suggest that RDN is a safe procedure in the short to medium term. Although RDN can cause visceral pain during the procedure, the pain can be controlled with sedatives and narcotics, and the technique can be applied without major complications. The reported rate of major procedure- or device-related complications is low, most of which are resolved without major complications.

Nevertheless, the reporting of adverse events varies – for example, safety was not included as an endpoint, or complications or adverse events were not adequately reported. One of the main post-procedural complications of RDN are hypotension or hypertension that can require hospitalisation. These or other indirect complications, such as the appearance of respiratory and cardiocirculatory depression, related to the control of analgesia and sedation, are underestimated in the included studies.

The follow-up time was inadequate to analyse long-term complications. The detrimental effects of this invasive procedure on the anatomy of the renal arteries are unknown. Moreover, information is limited regarding the use of this procedure in patients with impaired renal function, and whether these patients are candidates for RDN should be examined in future studies.

No conclusion could be drawn from the available evidence regarding overall mortality, as none of the ongoing studies in this rapid assessment defined mortality as its main research goal. Because none of the studies in this rapid assessment addressed cardiovascular mortality, no conclusion could be drawn for this outcome, either. Moreover, there was no evidence on cardiovascular morbidity, except for left ventricular hypertrophy. Although 2 of the 3 studies reported less left ventricular hypertrophy in patients who had undergone renal denervation using the Symplicity® and Navistar® ThermoCool® systems compared with patients who had not, the sample sizes were small, and it was not possible to pool the studies, because left ventricular mass was measured disparately. The poor quality of the evidence did not allow any definitive conclusions to be drawn.

All 3 controlled studies in the SR included for this outcome recorded significant decreases in systolic BP (SBP) and diastolic BP (DBP) after 3 (171 patients) and 6 months (158 patients) of follow-up, thus favouring renal denervation. The quality of the evidence, however, varied when assessed using GRADE, ranging from very low (1 study of 27 patients who used the Navistar® ThermoCool® system) to moderate (2 studies of 144 patients after 3 months of follow-up and 131 patients after 6 months of follow-up using the Symplicity® system).

According to 1 RCT with 100 patients in the SR included for this outcome, there was no change in kidney function, based on eGFR and creatinine levels, following renal denervation at the 6-month follow-up, but no definitive conclusion could be drawn, because the quality of the evidence was low.

Conclusion

The published data suggest that RDN is a safe procedure in the short to medium term. However, because safety was not considered the main endpoint, it can not be dismissed that some complications were not adequately reported.

In terms of clinical effectiveness, renal denervation using the Symplicity® system appears to decrease BP, whereas the effects of other systems on BP are uncertain, because they have only been examined in trials that included very few patients. The assessment of other outcomes, including mortality and cardiovascular morbidity, remains inconclusive.

Current RDN experiences are based primarily on the Symplicity® catheter (Medtronic). The other RDN systems and new versions of RDN systems that have only been assessed in early trials might differ with regard to ablation mechanisms and catheter size, which in turn might generate disparate risk profiles, necessitating further research to establish their safety. There are several ongoing studies in RDN; thus, more data are expected in the next several years.

With regard to its budgetary impact, renal denervation will be an add-on therapy, leading to additional health care resource expenditures in the form of the cost of the system, the training of staff specialists, and the use of hospital radiology services during the procedure.

LIST OF ABBREVIATIONS

AEs	Adverse events
AHA	American Heart Association
AHTAPol	Agency for Health Technology Assessment in Poland
AIM	Association Internationale de la Mutualité
Avalia-t	Galician Health Technology Assessment Agency
BP	Blood pressure
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CNAMTS	Caisse nationale de l'assurance maladie des travailleurs salariés
COI	Conflict of interest
CPME	Comité Permanent des Médecins Européens (Standing Committee of European Doctors)
CR.DK	Central Region Denmark
CRD	Centre of Reviews and Dissemination
CT	Controlled trial
DARE	Database of Abstracts of Reviews of Effects
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
EPOC	Effective Practice and Organization of Care Group
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FDA	Food and Drug Administration
FinOHTA	Finnish Office for Health Technology Assessment/National Institute for Health and Welfare
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GYEMSZI	Gyógyszerészeti és Egészségügyi Minöség- és Szervezetfej le sztési Intézet (National Institute for Quality and Organisational Development in Health Care and Medicine)
HTA	Health technology assessment
HVB	Hauptverband der Österreichischen Sozialversicherungsträger (Association of Austrian Social Insurance Institutions)
ICD	International classification of diseases
ICTRP	International Clinical Trials Registry Platform
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISI	Institute of Scientific Information
LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment
MD	Mean difference
mm Hg	Millimeter mercury
NHS	National Health Service

NOKC	Norwegian Knowledge Centre for the Health Services
Non RCT	Non randomised controlled trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
RDN	Renal denervation
REA	Relative effectiveness assessment
RF	Radiofrequency
SAG	Stakeholder advisory group
SBP	Systolic blood pressure
SR	Systematic review
WHO	World Health Organisation
WP	Work package

1 SCOPE

Description	Project scope
Population	Patients with treatment-resistant arterial hypertension (defined as persistent hypertension despite administration of at least 3 antihypertensive drugs in adequate doses, including a diuretic) with blood pressure ≥ 140/90 mm Hg (Calhoun 2008; Mancia 2013) and without secondary cause of hypertension. ICD-10 code: Hypertensive diseases I10–I15 MeSH terms: Hypertension; Blood Pressure Intended use of the technology: treatment
Intervention	Renal nerve ablation and denervation systems The intervention involves the destruction of efferent sympathetic nerves and afferent nerves within the wall of the renal arteries to reduce sympathetic nerve traffic, thereby causing a reduction in blood pressure. MeSH terms: Denervation; Catheter Ablation; Sympathectomy
Comparison	Standard of care (which includes here: no treatment, additional pharmacological treatment, device-based hypertension therapy and sham treatment) Mesh terms: Not used in the search strategy and thus not indicated Rationale: Currently, there is no standard comparator for this new intervention; thus, we use standard care as the comparator. It should be noted that all patients continue their treatment with at least 3 hypertensive drugs. Additional intervention or comparator is considered add-on therapy.
Outcomes	Primary outcomes: Overall mortality Cardiovascular mortality Cardiovascular morbidity (stroke, myocardial infarction, heart failure) Blood pressure (changes in systolic and diastolic blood pressure) Complications during or after the treatment Secondary outcomes: Left ventricular hypertrophy/systolic and diastolic cardiac function Kidney function Quality of life Effect on daily living Mesh terms: Not used in the search strategyand thus not indicated Rationale: The outcomes included here are those that arecommonly used in studies assessing hypertension. All outcomes, except ‘complications’, which is reported in the ‘safety’ domain, are reported in the ‘clinical effectiveness’ domain. Renal function is reported in both the ‘safety’ and ‘clinical effectiveness’ domains.
Study design	Efficacy/effectiveness: Systematic Reviews (SRs)/Health Technology Assessments (HTAs), randomised controlled trials (RCTs) and, if data from RCTs are lacking or insufficient, prospective, controlled studies Safety: As with efficacy and including all prospective studies
Languages	English, Spanish, French, German, Swedish, Danish, Norwegian

Deviations from project plan

The following deviations from the final version of the project plan (available on the EUnetHTA homepage) were made:

1) In response to the manufacturers' comments, BP was redefined from a secondary outcome to a primary outcome, because the currently acknowledged primary outcomes are those that are known to be associated with a reduction in BP.
2) In light of comments from the Stakeholder Advisory Group (SAG) and the public consultation, all available systems for renal denervation/renal nerve ablation were included, and research questions were changed accordingly.
3) In response to comments from the SAG and the public consultation, 'no renal denervation' was removed as a comparator. Both renal denervation and other interventions have been clarified as add-on therapies.
4) In addition to the reviewer who was suggested by the authors, a second external reviewer who was appointed by the SAG was added.
5) The comparison, the Rheos® System™/baroreceptor stimulation was removed as a comparator per a suggestion from the public consultation. This comparator was described as inappropriate, because it is an experimental therapy that is less developed than RDN.
6) Although they were initially included in the project plan, the authors decided, after further consideration, that ethical, organisational, social and legal aspects were beyond the scope of this rapid assessment on renal denervation systems. Training is necessary to perform the procedure, which will be administered in specialist centres that have access to the proper facilities – a programme that not all hospitals may want to prioritise. Even if it is not among the most resource – consuming of technologies, some sort of re-allocation of resources might be necessary. The procedure could alter the follow-up of patients and shift them between primary and secondary care.

   Because organisational and ethical considerations are setting-specific, they should be considered as part of a local adoption plan rather than in a joint European setting.

2 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

2.1 Methods

Domain framing

No deviation was required from the general scope of the project, according to the final project plan.

Research questions

Element ID	Research question
A0002	What is the precise definition of treatment-resistant arterial hypertension, and which diagnosis is given according to ICD-10?
A0003	What are the known risk factors for treatment-resistant arterial hypertension?
A0004	What is the natural course of treatment-resistant arterial hypertension?
A0005	What is the burden of treatment-resistant arterial hypertension for the patient?
A0006	What is the burden of treatment-resistant arterial hypertension for society in terms of prevalence, incidence and costs?
A0007	What is the target population in this assessment?
A0001	For which indication or for what purposes is renal denervation used, and are there any contraindications?
A0011	What is the expected annual utilisation of renal denervation?
A0024	How is treatment-resistant arterial hypertension currently diagnosed according to published guidelines and in practice?
A0020	What is the marketing authorisation status of renal denervation systems?
A0021	What is the reimbursement status of renal denervation systems?

Sources

Overall, a basic search was used as the starting point for answering the research questions. Additional searches were performed for nearly all research questions in PubMed and Google, and reference lists were searched. Guidelines were searched, as was the WHO website, with regard to ICD-10. (The following sources were used: Andersson 2013, Calhoun 2008, Giles 2012, International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2010, Jentzer 2013, Mahfoud 2011a, Mahfoud 2013a, Mancia 2013, Schmieder 2012, Persell 2011.)

Analysis

No analysis was performed. The aforementioned sources were found to be sufficient to answer the questions. No formal quality assessment of the literature was performed, other than a critical appraisal of the publisher/institutions behind the literature.

Synthesis

The research questions were answered in plain text/narrative format. Also, figures were used to answer some questions.

2.2 Main results

Target population of this assessment (A0007)

The target population is patients who suffer from resistant hypertension, a condition that is linked to sympathetic nervous system overactivity, involving the kidneys (Schmieder 2012). Patients who are eligible for the intervention can be treated with catheter-based renal denervation. The goals of the treatment are to prevent hypertensive end-organ damage and reduce cardiovascular morbidity and mortality (Mahfoud 2011a).

The criteria for having the surgical procedure that identify the actual target population are presented under the 'Indications and contraindications for renal denervation' section.

Definition of treatment-resistant arterial hypertension and diagnosis according to ICD-10 (A0002)

Treatment-resistant hypertension describes a condition in which conventional/traditional treatment measures are inadequate in treating a patient's hypertension – this condition is also described as true or real resistant hypertension. The standard treatment is based primarily on medical treatment and lifestyle interventions. Resistant hypertension develops when the appropriate treatment, including lifestyle modifications (regarding, for example, obesity and sodium intake) and 3 antihypertensive drugs (1 of which is a diuretic), fails to lower systolic blood pressure (SBP) and diastolic BP (DBP) values to 140 and 90 mm Hg, respectively. All drug agents should be prescribed at the optimal doses (Calhoun 2008). Further pseudoresistance (e.g. white-coat hypertension) and secondary causes (caused by other diseases, primarily renal disease) must be ruled out. With regard to the definitions and classification of office blood pressure (BP) levels (mm Hg), guidelines from the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) (Mancia 2013) present the following criteria:

Table 2: Classification of office BP levels (mm Hg)

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140-159	and/or	90–99
Grade 1 hypertension	160–179	and/or	100–109
Grade 1 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

The BP category is defined by the highest systolic or diastolic BP. Isolated systolic hypertension should be graded 1, 2 or 3 according to SBP values in the indicated ranges.

In the WHO ICD-9 coding system, which was replaced by ICD-10 in 1998, "resistant hypertension" was coded 997.91. This classification was omitted in the ICD-10 coding system, and now, 'resistant hypertension' is classified in the category 'I99: Other and unspecified disorders of circulatory system' using ICD-10 online, version 2010 (WHO 2013).

The diagnosis and criteria of resistant hypertension with regard to surgical intervention are described below.

Known risk factors for treatment-resistant arterial hypertension (A0003)

Resistant hypertension can be real or merely apparent. Apparent or pseudoresistant hypertension is caused, for example, by nonadherence to medication. The ESH and ESC have divided risk factors for real, or true, resistant hypertension into 5 categories (Mancia 2013):

- Lifestyle factors: obesity or large weight gains, excessive alcohol consumption, high sodium intake
- Chronic intake of vasopressors or sodium-retaining substances
- Obstructive sleep apnoea
- Undetected secondary forms of hypertension
- Advanced and irreversible organ damage, particularly when it involves renal function or leads to a marked increase in arteriolar wall–lumen ratio or a reduction in large artery distensibility

The American Heart Association (AHA) has identified older age and obesity as the strongest risk factors for resistant hypertension (Calhoun 2008). Other characteristics that are associated with resistant hypertension, as identified by the AHA, are:

- High baseline BP
- Excessive dietary salt ingestion
- Chronic kidney disease
- Diabetes
- Left ventricular hypertrophy

Natural course of treatment-resistant arterial hypertension and the burden on the patient (A0004, A0005)

The natural course of resistant hypertension has been inadequately appraised. If untreated, hypertension will increase the risk of cardiovascular disease, stroke and renal failure. Patients must frequently face associated cardiovascular risk factors, such as diabetes, obstructive sleep apnoea and left ventricular hypertrophy (Calhoun 2013).

Normally, the patient does not experience symptoms that are associated with resistant hypertension (Calhoun 2008). Some patients might experience fatigue, headache or nosebleed – symptoms that are related to higher BP.

The burden of treatment-resistant arterial hypertension on society with regard to prevalence, incidence and costs (A0006)

Overall, the exact prevalence of resistant hypertension is unknown (Calhoun 2008, Persell 2011). It is, however, assumed to be a common clinical condition. Based on the aforementioned risk factors, the prevalence is expected to rise in the older and more obese population (Jentzer 2013). Jentzer et al. reported in an American population that 5% to 10% of patients with inadequately controlled hypertension have resistant hypertension, defined as BP above the goal, despite the use of ≥3 antihypertensive drugs at adequate dosages and combinations (including a diuretic) (Jentzer 2013).

The ESH and ESC report that the prevalence of resistant hypertension ranges from 5% to 30% of the overall hypertensive population but that it is likely less than 10% (Mancia 2013). Persell reports that among U.S. adults with hypertension, 8.9% meets the criteria for resistant hypertension (Persell 2011). The prevalence of hypertension (all cases) is estimated to be 30% to 45% of the general population, which increases with older age. Definitions of BP differ between countries, which should be noted when examining the prevalence of resistant hypertension (Mancia 2013).

No study exists on the specific treatment costs or consequences of resistant hypertension for the health care system or society.

Current diagnostic approach according to published guidelines and in practice (A0024)

In diagnosing resistant hypertension, attention must first be paid to the finding that most cases of resistant hypertension originate from multifactorial factors – rarely from a single cause (Calhoun 2008; Mahfoud 2013a). The evaluation should verify the diagnosis of hypertension, excluding pseudoresistant patients (e.g. white-coat hypertension), uncover any causes of secondary hypertension and clarify the cardiovascular risk, organ damage and related clinical conditions. A medical history should be included in the clinical evaluation, as should a family history with regard to hypertension, a physical examination, laboratory investigations and further diagnostic tests (Mancia 2013). The evaluation of patients with resistant hypertension should be directed toward confirming actual treatment resistance (Galhoun 2008).

Indications and contraindications for renal denervation (A0001)

An expert consensus document, with contributions from 11 European countries, that was published in 2013 from the ESC on catheter-based renal denervation is the basis for the following criteria with which patients should comply before renal denervation is considered (Mahfoud 2013a):

- Office-based systolic BP ≥ 160 mm Hg (≥150 mm Hg for those with type 2 diabetes) despite use of ≥ 3 antihypertensive drugs at adequate dosages and combinations (including a diuretic)
- Treatment resistance to lifestyle modification
- Exclusion of secondary hypertension
- Exclusion of pseudoresistance, based on ambulatory BP (average BP > 130 mm Hg or mean daytime BP > 135 mm Hg)
- Preserved renal function [(glomerular filtration rate (GFR) ≥ 45 ml/min/1.73 m^2)]
- Eligible renal arteries: no polar or accessory arteries, no renal artery stenosis, no prior revascularisation

A position paper from the ESH that was published in 2012 (Schmieder 2012) describes the criteria that are generally consistent with those above. Patients are eligible as follows:

- They have "…(severe) treatment-resistant hypertension defined by office SBP at least 160 mm Hg (> 150 mm Hg in type 2 diabetes) despite treatment with at least 3 antihypertensive drugs of different types in adequate doses, including 1 diuretic, which is equivalent to stage 2 or 3 hypertension"
- Pseudoresistance is excluded
- No adherence to drug therapy must be refuted
- Persisting high office BP in spite of drug treatment (is) confirmed with home and most importantly with 24-h ambulatory BP monitoring, since up to one-third of treatment-'resistant' hypertensive patients have normal BP outside the office (false resistant hypertension due to persisting white-coat effect during treatment)
- Contributing lifestyle factors are identified, and secondary causes of hypertensionare screened to attempt to control BP by removal

The following contraindications are described in the papers above:

- Previous renal artery intervention (balloon angioplasty or stenting)
- Evidence of renal artery atherosclerosis (defined as renal artery stenosis > 50%)

- Presence of multiple main renal arteries in the kidneys or main renal arteries < 4 mm in diameter or < 20 mm in length

Patients should be in stable clinical condition (renal denervation is not an emergent condition), thus ruling out patients with recent myocardial infarction, unstable angina pectoris or a cerebrovascular accident within the past 3–6 months (Mahfoud 2013a; Schmieder 2012).

What is the expected annual utilisation of renal denervation? (A0011, A0020, A0021)

The uncertain prevalence and potential number of candidates, based on indications/contraindications for renal denervation, render it difficult to estimate its expected annual utilisation. The data indicate many potential candidates for renal denervation. More experience with the procedure in relevant candidates will facilitate calculation of theannual use of renal denervation **(A0011)**.

Questions regarding the marketing authorisation status and reimbursement status of renal denervation systems will be answered in the next domain, 'Description and technical characteristics of technology', specifically in **B0003 (A0020, A0021)**.

2.3 Discussion

The number of candidates for renal denervation is potentially significant. Estimating the expected utilisation is challenging, possibly due in part because the ICD-10 coding system has no designation for 'resistant hypertension', despite the increasing recognition of resistant hypertension as a major clinical entity (Giles 2012). Lacking such a category allows for variations in the definition, understanding and categorisation of resistant hypertension. Giles et al. have noted the unfortunate development that resistant hypertension can no longer be classified as it should be with regard to its complexity. Giles continues to recommend that resistant hypertension must be addressed by adding 'complexity' to the illness codes, making it possible to code 'resistant hypertension'.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF THE TECHNOLOGY

3.1 Methods

Domain framing

No deviation was required from the general scope of the project, based on the final project plan.

Research questions

Element ID	Research question
B0001	What is renal denervation and what are the treatment alternatives?
B0002	What are the approved indications and claimed benefits of renal denervation and the treatment alternatives?
B0003	What is the phase of development and implementation of renal denervation systems and the treatment alternatives?
B0004	Who performs or administers renal denervation and the treatment alternatives?
B0005	In what context and level of care are renal denervation systems and the treatment alternatives implemented?
B0008	What kind of special premises are needed to use renal denervation systems and treatment alternatives?
B0009	What materials are needed to use renal denervation systems and the treatment alternatives?
B0010	What kind of data and records are needed to monitor renal denervation systems and the treatment alternatives?
B0011	What kind of registry is needed to monitor the use of renal denervation systems and treatment alternatives?

Sources

The research questions were answered by using sources from the main search and supplemented by searches in Google for specific information on each RDN system. (The following sources were used: Andersson 2013, CADTH 2013, Caulfield 2012, Fornell 2013, Gaffney 2013, KONA medical 2013, Mafeld 2013, Mahfoud 2013a, Mancia 2013, Medlatest 2013, Medtronic 2013, Wojakowski 2012).

Analysis

No additional analysis was performed on the resulting information.

Synthesis

The research questions were answered in plain text format.

3.2 Main results

Description of RDN Systems (B0001)

Most renal denervation systems use low-level radio frequency energy to modulate the output of nerves that lie in the renal artery wall and lead into and out of the kidneys, decreasing blood flow and thereby reducing hypertension by deactivating hyperactive nerves, without affecting other abdominal, pelvic or lower-extremity nerves (CADTH 2013). There are, however, other systems that use ultrasonography for ablation.

The mechanism by which renal sympathetic denervation improvesthe management of BP is complex and involves the following factors (Wojakowski 2012):

- Decreasing efferent sympathetic signalling to kidneys
- Reducing norepinephrine spillover
- Natriuresis
- Increasing renal blood flow
- Lowering plasma renin activity
- Decreasing afferent renal signalling and central sympathetic activation

The system's energy, through radiofrequency (RF) or ultrasonography, increases the local temperature in a limited area of the vascular wall and effects the ablation of afferent and efferent sympathetic nerves (Wojakowski 2012).

Currently, there are a number of RDN systems that use various treatment strategies, as shown in Table 3 below.

Table 3: Renal denervation systems and their manufacturers and regulatory status

Device	Manufacturer	CE-marked	FDA review
Radiofrequency			
Symplicity®	Medtronic	Y	N
Marinr®	Medtronic	N	N
EnligHTN™	St. Jude Medical	Y	N
Vessix V2™	Boston Scientific	Y	N
OneShot™	Covidien	Y	N
Iberis™	Terumo	Y	N
ThermoCool®	Biosense Webster	N	N
Ultrasound			
PARADISE™	ReCor Medical	Y	N

Y = yes; N=no

Most of these systems use RF energy to target sympathetic renal nerves; the ReCor Paradise™ system uses ultrasonography (Mahfoud 2013a).

Description of the various procedures (B0001)

The catheter is introduced through the femoral artery and, under fluoroscopic control, threaded into the renal artery lumen. Once the catheter is in place, a series of 4 to 6 RF treatments are applied in each renal artery to ablate the sympathetic nerves that course along the outside of the artery (CADTH 2013). The procedure takes 40-60 minutes (Mahfoud 2013a). The technology behind the delivery of RF ablation, however, is evolving, with the introduction of devices that improve time efficiency (Mahfeld 2012).

Ultrasonography is being investigated as an alternative to radiofrequency energy that provides more targeted nerve ablation without the need for direct vessel contact. Currently, of the ultrasonographic devices, only the PARADISE™ system is CE-marked. Noninvasive ultrasonography systems are being developed for RDN. A transducer that is positioned outside of the body delivers targeted ultrasonographic energy that 'surrounds' the artery and treats the nerves in the vicinity of the vessel. The rationale behind creating a focused energy field around the outside of the artery is that it should effect greater and more effective ablation that does not impact the arterial walls (KONA medical 2013).

Catheters that are designed to inject therapeutic agents directly and non-systemically through the renal artery wall, such as the Cricket™ and Bullfrog® micro-infusion catheters (Mercator MedSystems), are also in development for RDN. The Mercator micro-infusion catheters are CE-marked in Europe and have been approved by the FDA.

Current practice and other developments for treatment of resistant hypertension (B0001)

The Task Force for the Management of Arterial Hypertension of the ESH and ESC (Mancia 2013) describes in their guidelines that most patients with resistant hypertension require more than 3 drugs. In current practice, this drug combination comprises a thiazide diuretic, a long-acting calcium channel blocker, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a beta-blocker in patients aged under 60 years (CADTH 2013).

An alternative to drug treatment is carotid baroreceptor stimulation, which entails chronic electrical field stimulation of carotid sinus nerves by implanted devices. However, it is recommended that renal denervation and carotid baroreceptor stimulation should be restricted to resistant hypertensive patients who are at particularly high risk, based on the inefficacy of additional antihypertensive drugs in controlling BP (Mancia 2013).

Approved indications and claimed benefits (B0002)

The ESC's consensus document states that per existing evidence, patients are eligible for renal denervation if they have (severe) treatment-resistant hypertension, defined as office SBP ≥160 mm Hg (≥150 mm Hg in type 2 diabetes), despite treatment with at least 3 types of antihypertensive drugs at adequate doses, including a diuretic (Mahfoud 2013a). In certain centres, uncontrolled BP values 140/90 mm Hg are taken as the reference (Mahfoud 2013a). Table 4 below details the criteria that patients should meet before renal denervation is considered (Mahfoud 2013a):

Table 4: Criteria patients should meet before renal denervation is considered

– Office-based SBP ≥ 160 mmHg (≥150 mm Hg diabetes type 2)
– ≥3 antihypertensive drugs in adequate dosage and combination (incl. diuretic)
– Lifestyle modification
– Exclusion of secondary hypertension
– Exclusion of pseudo-resistance using ABPM (average BP 130 mm Hg or mean daytime BP 135 mm Hg)
– Preserved renal function (GFR ≥45 ml/min/1.73m2)
– Eligible renal arteries: no polar or accessory arteries, no renal artery stenosis, no prior revascularisation

Renal denervation is claimed to decrease systolic and diastolic BP. The risk of cardiovascular death is halved with every 20-mm Hg decline in systolic BP. Existing RDN trials have reported an average reduction of approximately 25 mm Hg (Fornell 2013).

Phase of development and implementation (B0003)

One issue with the original Symplicity® catheter was that it necessitated multiple ablations, each one requiring the catheter to be rotated to create a continuous lesion. To simplify this procedure, St. Jude, Covidien and Boston Scientific developed a new catheter that was designed to simplify and shorten the procedure. Medtronic is also investigating a next-generation Symplicity® system that is intended to reduce treatment time (Marinr®) (CADTH 2013).

Of all renal denervation systems, the Symplicity®, OneShot™, EnligHTN™, Vessix™ V2 and Iberis™ systems are CE-marked in Europe. None of the systems is FDA-approved, but all are seeking such status (Medlatest 2013). Of the ultrasonography devices that are in development, only the PARADISE™ system (ReCor Medical) has received the CE mark.

Medtronic's Symplicity® renal denervation device has a lead of several years over the other CE-marked systems and was accepted for parallel review in the US in March 2013. This program allows the Centers for Medicare and Medicaid Services (CMS) to begin considering its use for national coverage while the FDA completes its review of safety and efficacy. The parallel review will be based primarily on the results of the Symplicity HTN-3 trial (Gaffney 2013).

Table 5 shows that in 13 countries in Europe, RDN is reimbursed and in most cases regardless of the type of device. Reimbursement is in the majority of countries decided upon through formal processes, i.e. described in national policy. In one country, Medtronic's Symplicity® received conditional coverage. In 5 countries a decision on reimbursement is in process, 2 countries do not reimburse RDN, and in 3 countries the reimbursement status is unknown.

Table 5: Reimbursement status of renal denervation in Europe

Country	Reimbursement Yes/No	technology-specific vs. non-technology-specific reimbursement
Austria	Yes (temporary, formal)	All devices
Belgium	- (formal: submissions to the authorities)	All devices
Croatia	No	-
Denmark	Yes (formal)	All devices
England	- (Commissioning through evaluation; reimbursement planned to start in 2014)	All devices
Estland	- (application under process)	unknown
Finland	Yes (as part of hospital fees)	All devices
France	- (formal: process waits for STIC results)	All devices
Germany	Yes (formal)	All devices
Hungary	Unknown	unknown
Greece	Unknown	unknown
Italy	Yes (formal)	All devices
Ireland	Yes (decision at local hospital level)	All devices
Lithuania	Yes (formal)	All devices
Malta	No	-
Netherlands	Yes (Conditional Coverage)	Currently onlyMedtronic Symplicity® Flex For other technologies, discussion is on-going
Norway	Yes	All devices
Poland	- (formal: submissions to the authorities)	All devices
Portugal	Yes (formal)	All devices
Serbia	Unknown	unknown
Slovakia	Yes (formal)	EnligtHTN™ and Symplicity® reimbursed from 01.01.2014
Spain	Yes (formal)	All devices
Sweden	Yes (formal)	All devices
Switzerland	Yes (formal)	All devices

Source: Information on reimbursement status was kindly provided by the EUCOMED Hypertension Working Group and Medtronic. The information has been cross-checked and updated from WP5 Strand B members. Answers were received from Croatia, England, Finland, Germany, Hungary, Ireland, Italy, Lithuania, Malta, Poland and Slovakia.

STIC: Support Programme for Innovative and Costly Techniques

Pharmaceutical therapy

Several new pharmaceutical therapies for hypertension are being investigated in phase 2 and 3 clinical trials, including drugs with new pharmacological targets (such as dual vasopeptidase inhibitors, a dual-acting angiotensin receptor neprilysin inhibitor, endothelin antagonists, nitric oxide donors and angiotensin vaccines) and novel, fixed-dose drug combinations (CADTH 2013).

Personnel and technical requirements (B0004, B0005, B0008, B0009, B0010, B0011)

Renal denervation can be performed in a catheterisation laboratory for cardiovascular interventions (Andersson 2013; CADTH 2013) by interventional cardiologists or radiologists and angiologists. The ESC recommends that the procedure should be performed by staff that has been trained in the therapy and is qualified to manage potential complications, such as acute dissection of renal arteries by stent implantation. Renal denervation is performed under analgesic or conscious sedation (CADTH 2013). During the procedure, vital signs must be monitored. The presence of an anaesthesiologist is generally unnecessary but is required in certain countries (Mahfoud 2013a) **(B0004)**.

Andersson et al. recommend that primary care physicians and specialists in internal medicine, nephrology, interventional cardiology and radiology should be involved in the selection of patients (Andersson 2013). Centres that perform >25 renal interventions per year can be assumed to have the appropriate expertise **(B0005, B0008)**.

The long-term follow-up of RDN-treated patients is similar to the usual care of hypertensive patients and can be performed by specialists in cardiology, internal medicine or nephrology, as well as primary care physicians (Andersson 2013).

There will be a slight increase in the demand for functional and morphological diagnostic procedures of the renal arteries (MRI, CT, Doppler-ultrasonography), because they are part of the routine protocol prior to RDN (Andersson 2013). The CADTH assessment (2013) concluded that RDN is associated with additional health care expenditures in terms of the cost of the system, the training of specialist staff, and the use of hospital radiology services during the procedure, as RDN is currently used as an adjunct to existing therapies for hypertension **(B0009)**.

The Joint UK Societies' consensus statement on RDN for resistant hypertension (Caulfield 2012) opines that any institution that performs this procedure should have the commitment and ability to include data in a national registry. This stipulation will allow procedural success to be analysed acutely and at the long-term follow-up (Mahfoud 2013a) **(B0010, B0011)**.

3.3 Discussion

Mahfoud et al. note that BP rarely changes immediately after RDN. It often takes several weeks to months before a significant decrease in BP occurs, suggesting that sympathetic neural regulation resets slowly and progressively (Mahfoud 2013a). Further, as currently implemented, renal denervation is designed to improve BP control in patients whose BP is resistant to conventional drug therapy. In this regard, renal denervation is unlikely to significantly reduce pill burden in most patients and is not a cure for hypertension. It is an add-on therapy, thus leading to additional health care resources to be consumed in the form of costs of the system, training of specialist staff, and use of hospital radiology services during the procedure (CADTH 2013).

Although BP has been the primary outcome variable in these studies, several reports suggest that there are beneficial effects in patients with diabetes mellitus, metabolic syndrome, cardiac arrhythmias, sleep apnoea and heart failure. In the U.S., once RDN systems gain FDA market approval, physicians are predicted to begin using them off-label for con-

ditions other than hypertension (Fornell 2013). In Europe, broadening the indications might also become an issue, where the devices are only CE-marked and not fixed to a certain indication.

4 SAFETY

4.1 Methods

Domain framing

No deviation was required from the general scope of the project, per the final project plan.

Research questions

Element ID	Research question
C0001	What are the minor and major adverse events in patients treated with renal denervation?
C0002	Are there any dose relationships with the adverse effects (e.g. intensity, length of treatment)?
C0004	What are the potential short- and long-term harms, their frequency and differences according to setting?
C0005	Are there any susceptible patient groups that are more likely to be harmed?
C0007	Can adverse events be caused by the behaviour of the patients, professionals or manufacturers?
C0008	What is the safety of renal denervation in relation to the standard of care (which includes additional pharmacological treatment, device-based therapy for hypertension and sham treatment)?

Sources

The search domain results were based on a basic systematic literature search (Appendix 1) and information from the manufacturers. The following sources were used:

- Embase (Ovid)
- Ovid MEDLINE
- ISI Web of Knowledge
- Cochrane Library; Cochrane Reviews
- Centre for Reviews and Dissemination
- WHO ICTRP (International Clinical Trials Registry Platform).

For this domain, all prospective studies that were published in peer review journals were considered RCTs, non-RCTs and case series. Conference abstracts and proceedings, editorials, opinion papers and unpublished data were excluded.

The studies were selected by 2 independent investigators who were responsible for reviewing the abstracts and applying the inclusion/exclusion criteria to determine their eligibility (see Appendix 1).

Analysis

The sources were sufficient to answer 3 of the questions. No data were available to answer C0002, C0005 or C0007.

Data were extracted by 2 independent investigators, and discrepancies between studies were resolved by discussion. Data were analysed qualitatively. Risk of bias was assessed using the Cochrane risk of bias checklist. The characteristics of the included SRs and single trials with quality assessments, along with ongoing studies that were identified from the trial registry searches, are presented in Appendix 1.

Synthesis

The information was synthesised into evidence tables and displayed in plain text format. Evidence tables and GRADE profile tables are provided in Appendix 1.

4.2 Main results

Included studies (C0001)

The evidence for the safety domain is derived from 3 RCT articles, 3 non-RCT articles and 16 case series studies in 904 patients. For 91 patients, the information could be partially duplicated. Twenty-six patients in the Mahfoud study (Mahfoud 2011b), 28 patients in the Ukena study from 2011 (Ukena 2011) and 18 subjects in the Ukena study from 2012 (Ukena 2012) were part of the Symplicity HTN-2 trial (Symplicity HTN-2 2010), and 19 patients in the Mahfoud study (Mahfoud 2012) were included in the Symplicity HTN-1 and Symplicity HTN-2 trials.

In 2 of the 3 RCTs, all of the non-RCTs and 11 of the 16 cases series, the RDN procedure involved RF ablation that was applied with the Symplicity® catheter (Medtronic, Ardian Inc.). A total of 784 patients underwent RDN using this system. One RCT of 13 patients performed the intervention using a Navistar® ThermoCool® Irrigated Tip Catheter (Biosense Webster) (Pokushalov 2012). One case series with 30 patients used the Marinr® RF ablation catheter (typically used for cardiac ablation) (Prochnau 2012a), 1 with 46 patients used the EnligHTN® multi-electrode renal denervation system (EnligHTN I trial) (Worthley 2013) and 1 with 9 patients used the OneShot™ (Covidien) RDN system (RHAS trial) (Ormiston 2013). One case series with 11 patients administered RDN with Paradise™ technology (ReCor Medical), which uses a catheter that emits ultrasonographic energy (Mabin 2012), and 1 trial with 11 patients did not specify the type of system that was used (Voskuil 2011).

Frequency of adverse events (C0001)

Of the 22 studies in this assessment, 13 (Symplicity HTN-2 2010, Mahfoud 2011b; Mahfoud 2012; Symplicity HTN-1 2011; Esler 2012; Mabin 2012;Ukena 2012; Vase 2012; Fontenla 2013; Kaltenbach 2013; Ormiston 2013; Scheurig-Muenkler 2013; Worthley 2013) reported procedure-related complications. The frequency of complications in each of these studies is listed in Tables 6 and 7. Complications were classified as procedural or device-related (Table 6 below) and postprocedural (Table 7 below) and further categorised as major and minor. This classification is based on the original definitions in the studies.

Adverse events related to the procedure or device

Although it has not been quantified in most studies as an adverse event, RDN frequently causes diffuse visceral abdominal pain during the procedure that can be adequately controlled with narcotics or anaesthesics (Mahfoud 2011b; Symplicity HTN-1 2011; Hering 2012; Mabin 2012; Prochnau 2012a; Simonetti 2012; Vase, 2012; Fontenla 2013; Worthley 2013). The most commonly reported procedure- or device-related complications were mild to moderate: hypotensive episodes (1.92% to 55.5%) (Symplicity HTN-2 2010; Esler 2012; Vase 2012; Worthley 2013), femoral artery pseudoaneurysms/hematomas at the access site (1.5% to 44.4%) (Symplicity HTN-2 2010; Mahfoud 2011b; Mahfoud 2012; Symplicity HTN-1 2011; Ukena 2012, Fontenla 2013; Ormiston 2013; Worthley 2013), bradycardias (4.35% to 18%) (Symplicity HTN-2 2010; Symplicity HTN-1 2011; Fontenla 2013; Worthley 2013), series of renal artery spasms (5% to 26%) (Vase 2012; Kaltenbach 2013; Worthley 2013), transient vagal reactions (3.9% to 11.1%) (Symplicity HTN-1 2011, Ukena 2012; Ormiston 2013; Worthley 2013) and vomiting (2.17% to 11.1%) (Ormiston 2013; Worthley 2013).

Other minor periprocedural events in the isolated studies were: haematuria (4.35%) (Worthley 2013), dizziness (3.92%) (Symplicity HTN-1 2011), urine infections (Symplicity HTN-2 2010), paraesthesia (1.92%) (Symplicity HTN-2 2010) and allergic reactions to contrast medium (1.14%) (Mahfoud 2012). Several studies noted the appearance of minor focal renal artery irregularities that were not flow-limiting that were attributed to minor spasms and oedema, but they were not recorded as complications (Symplicity HTN-1 2011; Mabin 2012; Prochnau 2012a; Simonetti 2012; Scheurig-Muenkler 2013).

Major complications that were related to the procedure or device were reported in 4 studies. Three studies accounted for renal artery dissection on placement of the catheter (0.65% to 9.09%) (Symplicity HTN-1 2011; Esler 2012; Mabin 2012), 1 study reported a psoas haematoma that was secondary to placement of the catheter (9.09%) (Fontenla 2013) and 1 study described 1 case of respiratory and cardiocirculatory depression due to analgosedation (1.89%) and 1 case of severe artery spasm that resulted in residual stenosis that had no haemodynamic relevance (1.89%) (Scheurig-Muenkler 2013). No intervention-related mortality has been reported.

Follow-up adverse events

Nine studies (Symplicity HTN-1 2011; Symplicity HTN-2 2010; Mahfoud 2011b; Mahfoud 2012; Brinkmann 2012; Esler 2012; Mabin 2012; Kaltenbach 2013; Worthley 2013) reported on complications during the follow-up period (maximum of 2 years).

The most common minor complication was decreased BP to below target BP or the development of hypotensive symptoms (18.2% to 35.1%) (Mahfoud 2011b, Mahfoud 2012, Mabin 2012). Other minor complications included oedema (1.92% to 5%) (Symplicity HTN-1 2011; Symplicity HTN-2 2010; Kaltenbach 2013) and flank pain (2.6%) (Symplicity HTN-1 2011).

Six studies reported major adverse events during the follow-up (n=315 patients) (Symplicity HTN-2 2010; Esler 2012; Brinkmann 2012, Kaltehbach 2013, Worthey 2013). The complications that were considered to be major were hypertensive emergencies and crisis (frequency, 5% to 33.3%) (Symplicity HTN-2 2010; Esler 2012; Brinkmann 2012; Kaltenbach 2013), hypotensive events that required hospitalisation (2.0% to 2.86%) (Symplicity HTN-2 2010; Esler 2012; Worthley 2013), angina (2.0%) (Symplicity HTN-2 2010), progression of existing stenosis (0.65% to 2.17%) (Symplicity HTN-2 2010; Symplicity HTN-1 2011; Worthley 2013), transient ischaemic attacks (2.0%) (Symplicity HTN-2 2010) and hypertensive renal disease progression: (2.17%) (Worthley 2013). None of the studies reported aortic stenosis, thrombosis or important abnormalities.

Susceptible patient groups (C0005)

Patients with chronic renal disease might be more susceptible to RDN-related complications. All initial RCTs and other included studies restricted the inclusion criteria to patients who had an estimated GFR (eGFR) ≤45 ml/min/1.73 m^2. Only 1 of the included studies (Hering 2012) evaluated patients with moderate to severe renal disease (stage 3-4), finding no significant alteration in renal function, based on GFR according to serum creatinine or cystatin C levels and per plasma creatinine, cystatin C or urea levels. Scheurig-Muenkler et al. reported 2 patients with end-stage renal disease and 1 patient with chronic renal failure who received RDN and did not show any exacerbation in renal function (Scheurig-Muenkler 2013). In the series by Prochnau et al, serum creatinine and proteinuria, used as markers of renal function, remained unchanged in 4 patients with chronic renal insufficiency (Prochnau 2012a).

Comparison with standard care (C0001, C0008)

The Symplicity HTN-2 RCT (Symplicity HTN-2 2010) reported that 40.3% of patients (n= 21) who were treated with RF ablation suffered minor and major complications versus 9.26% of those who received only pharmacological medications (n=5). The majority of adverse events in the RDN group was related to the procedure or device. During the 6-month follow-up, major complications appeared in 16.3% (n=8) and 9.8% (n=5) of patients, respectively. One RDN patient and 2 control patients suffered a transient ischaemic attack, and 1 patient from each group developed angina. Additional serious events that required hospitalisation in RDN-treated patients included 1 case of nausea and oedema (n=1), 1 hypotensive episode (n=1), 3 hypertensive emergencies that were unrelated to nonpersistence with drugs and 1 hypertensive crisis after clonidine was halted. Two control groups presented with hypertensive emergencies. Renal function, as assessed by serum creatinine, eGFR, and cystatin C concentrations, were unchanged from baseline in both groups at 6 months.

In the extension of the Symplicity HTN-2 trial (Ukena 2011), the authors reported that RDN was performed without any major adverse events in all patients (37 interventions and 9 controls) but did not provide results on overall complications. Mahfoud (Mahfoud 2011b) observed that 1 patient from the RDN-treated group (n=37) developed a pseudoaneurysm of the femoral artery site (2.7%) and that after 3 months, 13 patients experienced hypotension that was associated with symptoms (35%). Two patients who received only pharmacological medication (n=13) presented with signs or symptoms that were consistent with hypertension (15.4%).

In 2012 (Mahfoud 2012), Mahfoud noted that RDN was performed without any complications in 97% of patients (n=110) – 2 patients developed a pseudoaneurysm of the femoral artery site (2.27%), and 1 experienced an allergic reaction to the contrast medium (1.14%). During the 6-month follow-up, the antihypertensive drug regimens had to be reduced in 18 patients (18%) and increased in 7 subjects due to the development of symptoms. Mean cystatin C, eGFRand urinary albumin excretion remained unchanged after RDN in all studies. No abnormalities of the renal arteries (significant artery stenosis or aneurysms) were observed during the study period.

In the RCT that assessed the impact of renal artery denervation (Navistar® ThermoCool® catheter) that was added to pulmonary vein isolation (PVI) versus PVI alone, no acute adverse events or renal artery stenosis was reported in either group at 6 months; the study did not comment on other postprocedural adverse events (Pokushalov 2012).

Table 6: Frequency of procedure- or device-related adverse events in the included studies

Author, date	Study type	N	Minor adverse events, n (%)							Major adverse events, n (%)					Total adverse events n (%)
			Hypo-tensive events	Femoral artery pseudo-aneurysm/ Haematoma	BC	Renal artery spasms	TVR	Other	Total	Renal artery dissection	Psoas haematoma	Respiratory and CP depression	Severe artery spams	Total	
Symplicity HTN-2 2010	RCT	52	1 (1.92%)	1 (1.92%)	7 (13.46%)	0	0	3 (5.77%)	12 (23.08%)	0	0	0	0	0	12 (23.08%)
Ukena 2011	RCT	37	0	0	0	0	0	0	0	0	0	0	0	0	0
Pokushalov 2012	RCT	13	0	0	0	0	0	0	0	0	0	0	0	0	0
Mahfoud 2011b	Non RCT	37	0	1 (2.70%)	0	0	0	0	1 (2.70%)	0	0	0	0	0	1 (2.70%)
Brandt 2012a	Non RCT	110	0	0	0	0	0	0	0	0	0	0	0	0	0
Mahfoud 2012	Non RCT	88	0	2 (2.27%)	0	0	0	1 (1.14%)	3 (3.41%)	0	0	0	0	0	3 (3.41%)
HTN1 2011	Case series	153	0	3 (1.96%)	15 (9.80%)	0	6 (3.92%)	0	24 (15.69%)	1 (0.65%)	0	0	0	1 (0.65%)	25 (16.34%)
Voskuil 2011	Case series	11	0	0	0	0	0	0	0	0	0	0	0	0	0
Brinkmann 2012	Case series	12	0	0	0	0	0	0	0	0	0	0	0	0	0
Esler 2012*	Case series	35	1 (2.86%)	0	0	0	0	0	1 (2.86%)	1 (2.86%)	0	0	0	1 (2.86%)	2 (5.71%)
Hering 2012	Case series	15	0	0	0	0	0	0	0	0	0	0	0	0	0
Mabin 2012	Case series	11	0	0	0	0	0	1 (9.09%)	1 (9.09%)	1 (9.09%)	0	0	0	1 (9.09%)	2 (18.2%)
Prochnau 2012a	Case series	30	0	0	0	0	0	0	0	0	0	0	0	0	0
Simonetti 2012	Case series	5	0	0	0	0	0	0	0	0	0	0	0	0	0
Ukena 2012	Case series	136	0	2 (1.47%)	0	0	8 (5.88%)	0	10 (7.35%)	0	0	0	0	0	10 (7.35%)
Vase 2012	Case series	9	5 (55.56%)	0	0	1 (11.11%)	0	0	6 (66.67%)	0	0	0	0	0	6 (66.67%)
Zuern 2012	Case series	11	0	0	0	0	0	0	0	0	0	0	0	0	0
Fontenla 2013	Case series	11	0	1 (9.09%)	2 (18.18%)	0	0	1 (9.09%)	4 (36.36%)	0	1 (9.09%)	0	0	1 (9.09%)	5 (45.45%)
Kaltehbach 2013	Case series	20	0	0	0	1 (5%)	0	0	1 (5%)	0	0	0	0	0	1 (5%)
Ormiston 2013**	Case series	9	0	4 (44.44%)	0	0	1 (11.11%)	4 (44.44%)	9 (100%)	0	0	0	0	0	9 (100%)
Scheurig-Muenkler 2013	Case series	53	0	0	0	0	0	2 (3.77%)	2 (3.77%)	0	0	1 (1.89%)	1 (1.89%)	2 (3.77%)	4 (7.55%)
Worthley 2013	Case series	46	3 (6.52%)	8 (17.39%)	2 (4.35%)	12 (26.09%)	3 (6.52%)	4 (8.70%)	32 (69.57%)	0	0	0	0	0	32 (69.57%)

* Only crossover group patients included. **Article refers to adverse events and specifies that they were mostly periprocedural.

BC: bradycardia; CP: cardiopulmonary; RCT: randomised controlled trial; TVRs: transient vagal reactions

Table 7: Frequency of follow-up adverse events in the included studies

Author, date	Study type	N*	Follow up (months)	Minor complications, n (%)			Major complications, n (%)								Total n (%)
				Hypotensive events	Other	Total	Nausea and/or oedemas	Hypertensive episodes (hospital admission)	Hypotensive episodes (hospital admission)	Angina	Transient ischaemic attack	Progress of existing stenosis	Progress of renal disease	Total	
Symplicity HTN-2 2010	RCT	I:49	6	0	0	0	1 (2.0%)	4 (8.2%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	0 (0%)	9 (18.3%)	9 (18.3%)
		C:51		0		0	0	2 (3.92%)	0 (0%)	1 (1.96%)	2 (3.92%)	0 (0%)	0 (0%)	5 ((9.8%)	5 (9.8%)
Ukena 2011	RCT	I:37	3	0	0	0	0	0	0	0	0	0	0	0	0
		C:9		0	0	0	0	0	0	0	0	0	0	0	0
Pokushalov 2012	RCT	I:13	12	0	0	0	0	0	0	0	0	0	0	0	0
		C:14		0	0	0	0	0	0	0	0	0	0	0	0
Mahfoud 2011b	Non RCT	I: 37	3	13 (35.1%)	0	13 (35.1%)	0	0	0	0	0	0	0	0	13 (35.1%)
		C:13		0	0	0	0	0	0	0	0	0	0	0	0
Brandt 2012a	Non RCT	I:110	6	0	0	0	0	0	0	0	0	0	0	0	0
		C: 10		0	0	0	0	0	0	0	0	0	0	0	0
Mahfoud 2012	Non RCT	I:88	6	18 (20.4%)	0	18 (20.4%)	0	0	0	0	0	0	0	0	18 (20.4%)
		C:12		0	0		0	0	0	0	0	0	0	0	0
HTN1 2011	Case series	153	24	0	4 (2.61%)	4 (2.61%)	0	0	0	0	0	1 (0.65%)	0	1 (0.65%)	5 (3.3%)
Voskuil 2011	Case series	11	1	0	0	0	0	0	0	0	0	0	0	0	0
Brinkmann 2012	Case series	12	6	0	0	0	0	4 (33.3%)	0	0	0	0	0	4 (33.3%)	4 (33.3%)
Esler 2012	Case series	35	12	0	0	0	0	2 (5.7%)	1 (2.86)	0	0	0	0	3 (8.57%)	3 (8.57%)
Hering 2012	Case series	15	12	0	0	0	0	0	0	0	0	0	0	0	0
Mabin 2012	Case series	11	3	2 (18.2%)	0	2 (18.2%)	0	0	0	0	0	0	0	0	2 (18%)
Prochnau 2012a	Case series	30	12	0	0	0	0	0	0	0	0	0	0	0	0
Simonetti 2012	Case series	5	2	0	0	0	0	0	0	0	0	0	0	0	0
Ukena 2012	Case series	136	6	0	0	0	0	0	0	0	0	0	0	0	0
Vase 2012	Case series	9	1	0	0	0	0	0	0	0	0	0	0	0	0
Zuern 2012	Case series	11	24	0	0	0	0	0	0	0	0	0	0	0	0
Fontela 2013	Case series	11	6	0	0	0	0	0	0	0	0	0	0	0	0
Kaltehbach 2013	Case series	20	6	0	2 (10%)	2 (10%)	0	1 (5%)	0	0	0	0	0	1 (5%)	3 (15%)
Ormiston 2013	Case series	9	12	0	0	0	0	0	0	0	0	0	0	0	0
Worthley 2012	Case series	46	6	0	0	0	0	0	1 (2.17%)	0	0	1 (2.17%)	1 (2.17%)	3 (6.5%)	3 (6.5%)

* Patients for whom follow-up information was available

RCT: randomised controlled trial

4.3 Discussion

Published data suggest that RDN is safe in the short to medium term. Although RDN can cause visceral pain during the procedure, it is usually controlled with sedatives and narcotics, and the technique appears to be able to be applied without major complications. The reported rate of major complications that were related to the procedure or device was very low, most of which were resolved without major implications.

The reported frequency of adverse events varied widely (0% to 40.38%) in the included studies. In 2 of the RCTs (Ukena 2011; Pokushalov 2012), all non-RCTs (Mahfoud 2011b; Mahfoud 2012; Brandt 2012a) and many case series, safety was not considered the main endpoint, and complications and adverse events were incompletely reported (Voskuil 2011; Brinkmann 2012; Hering 2012; Ukena 2012; Zuern 2012; Prochnau 2012a; Fontenla 2013; Kaltehbach 2013). Often, the authors referred to the nonexistence of severe/major procedure-related complications or adverse events without defining a 'severe adverse event' or commenting on postprocedural adverse events, hampering interpretation of the evidence with regard to safety and making it impossible to perform a pooled analysis of the data.

One of the main complications of RDN in certain studies is the unwanted effects on postprocedure BP, which can result in hypotensive or hypertensive episodes that require hospitalisation. These or other indirect complications, such as the appearance of respiratory and cardiocirculatory depression that was related to the control of analgesia and sedation in Scheurig-Muenkler (Scheurig-Muenkler 2012), could have been underestimated in the included studies, which should be confirmed in adequately designed trials. Based on the available evidence, it is impossible to draw any conclusions with respect to the frequency of follow-up complications **(C0001)**.

The follow-up length was inadequate to analyse long-term complications. Concerns and doubts with regard to the aggravation of renal disease with RDN remain unresolved (Mahfoud 2011b; Mahfoud 2012). The Symplicity HTN-2 study and several other trials that analysed renal function (Symplicity HTN-2 2010; Esler 2012; Pokushalov 2012; Mahfoud 2011b; Mahfoud 2012; Prochnau 2012a; Fontenla 2013; Kaltenbach 2013; Ormiston 2013) reported no changes in eGFR, cystatin C or other parameters that are used to measure renal failure function in the 3-12 months of follow-up. However, in the Symplicity HTN-1 trial, with an extended follow-up of 24 months, eGFR remained stable in the first several years but fell dramatically in 10 patients who were followed for 2 years. Whether these disparities are attributed to differences in the study population or BP or the detrimental effect of renal denervation requires clarification, for which longer-term assessments are needed **(C0001)**.

There is uncertainty regarding the harmful effects of RDN on the anatomy of the renal arteries. Mild, hemodynamically irrelevant wall irregularities, corresponding to small local spasms or circumscribed wall oedema, were seen consistently after RDN, but they did not limit blood flow. Several of the studies (Esler 2012; Pokushalov 2012; Mahfoud 2011b; Mahfoud 2012; Symplicity HTN-1 2011; Prochnau 2012a; Fontenla 2013; Kaltenbach 2013) performed magnetic resonance angiography, computed tomographic scan and/or renal ultrasonography during the follow-up period and ruled out the appearance of renal artery aneurysms, stenosis, thrombosis and any other relevant vascular abnormalities in the short to medium term (6-12 months), but the evolution of the renal arteries over the long term is unknown **(C0001)**.

Information is limited regarding the use of RDN in patients with impaired renal function. Most patients who were treated in the initial RCTs and other included studies had an eGFR ≤45 ml/min/1.73 m^2 and preserved renal function. Hering et al. suggested that renal function remains unaltered in patients with moderate to severe renal disease (stage 3-4), but their study was limited by the design (case series) and the small sample size (Hering 2012). Scheurig-Muenkler et al. also noted that 2 patients with end-stage renal disease and 1 patient with chronic renal failure did not exhibit any exacerbation in renal function (Scheurig-Muenkler 2013), whereas Prochnau et al. reported that renal function remained unchanged in 4 patients with chronic renal insufficiency (Prochnau 2012a). Whether these patients are candidates for RDN should be determined in future studies **(C0005)**.

Current RDN experiences are based primarily on the Symplicity® catheter (Medtronic, Ardian Inc.). The other RDN systems and new generations of RDN systems have been assessed only in preliminary trials that have included few patients. Because these systems do not use exactly the same ablation mechanisms and because the diameter of the catheter can differ, they might have disparate risk profiles. These systems require further evaluation to establish their safety.

In summary, the evidence on the safety of RDN systems is compromised by the following methodological limitations, preventing firm conclusions from being drawn regarding this procedure:

- Most studies had small sample sizes and large overlaps of patients.
- Safety was not the primary endpoint in the majority of studies.
- In many studies, RDN was conducted in highly select patients by a small group of trained health professionals, which does not exclude the possibility of serious adverse effects if the technique is to be performed routinely in clinical practice.
- Possibility of bias due to lack of blinding.
- Large heterogeneity in individual responses to RDN.
- Short follow-up, which means that there is a lack of knowledge about the long-term potential of nerve fibre regeneration and the occurrence of long-term adverse effects. Potential conflicts of interest in most included studies due to their being financed by the manufacturer of the device in question and/or participation in research studies by the company's investigators (see evidence tables in Appendix 1).

5 CLINICAL EFFECTIVENESS

5.1 Methods

Domain framing

No deviation was required from the general scope of the project, per the final project plan.

The research questions for assessing the clinical efficacy of renal denervation systems are listed in the table below.

Endpoints for determining clinical effectiveness were derived from the 3 main categories of endpoints – 'mortality', 'morbidity' and 'quality of life' – as defined in the EUnetHTA guideline on clinical endpoints [see European Network for Health Technology Assessment (EUnetHTA). Endpoints used for relative effectiveness assessment of pharmaceuticals: clinical endpoints: EUnetHTA; 2013a.].

Research questions and evidence found for each question

Element ID	Research question	Outcomes (PICO/scope)	Assessed by (references and study design)
D0001	What is the effect of renal denervation on overall mortality?	Overall mortality	Davis 2013 (SR)
D0002	What is the effect of renal denervation on cardiovascular mortality?	Cardiovascular mortality	No SR or RCT or non-RCT found
D0005	How does renal denervation affect symptoms and findings?	Cardiovascular morbidity	Cardiovascular morbidity in terms of coronary heart disease, stroke, peripheral arterial obstructive disease, heart failure: Andersson 2013 (SR) Left ventricular hypertrophy: Andersson 2013 (SR) Mahfoud 2013b (non-RCT) Pokushalow 2012 (RCT)
D0006	How does renal denervation affect progression of treatment-resistant arterial hypertension?	Blood pressure	Davis 2013 (SR) Ahmed 2012 (RCT)
D0011	What is the effect of renal denervation on patients' body functions (e.g. kidney function)?	Kidney function	Gosain 2013 (SR)
D0016	How does the use of renal denervation affect activities of daily living?	Exercise	Exercise capacity reported as maximum work load and peak oxygen uptake (VO_2peak) Ukena (RCT) 2011
D0012	What is the effect of renal denervation on generic health-related quality of life?	Quality of life	No SR or RCT or non-RCT found
D0013	What is the effect of renal denervation on disease-specific quality of life?	Quality of life	No SR or RCT or non-RCT found
D0017	Were patients satisfied overall with renal denervation?	Quality of life	No SR or RCT or non-RCT found
D0018*	Would the patient be willing to undergo renal denervation?	Quality of life	No SR or RCT or non-RCT found
D0023*	How does renal denervation modify the need for other technologies and use of resources?	Activities of daily living (Decrease in number of medications)	Gosain 2013 (SR)

* These assessment elements were added since they were included in the first pilot (EndoBarrier™).

In terms of mortality, we considered overall mortality and cardiovascular mortality.

With regard to morbidity, we defined morbidity as cardiovascular morbidity (stroke, myocardial infarction and heart failure), changes in BP, left ventricular hypertrophy and change in ejection fraction (volume). For function, renal function (body function) and BP during exercise (activities of daily life) were assessed. Health-related quality of life and patient satisfaction were also examined, as was change in management (decrease in number of medications).

Sources

To answer the research questions in this domain, we used the results from a basic systematic literature search of the following sources (see Appendix 1: Documentation of search strategy):

- Biomedical databases (Medline via Ovid, Embase)
- Cochrane database, DARE and HTA databases via the Cochrane Library and CRD
- The ISI database
- Manual searches, including articles provided by the manufacturers
- WHO search portal ICTRP for identifying registered clinical trials

The relevant literature was selected by 2 people independently (see Appendix 1 for study selection). In terms of study design, SRs/HTAs, RCTs and, if data from RCTs were lacking or insufficient, prospective, controlled studies were selected to answer questions related to this domain. In cases in which more than 1 SR was available, the high-quality SR that assessed 1 or more of the predefined outcomes most recently was included.

Analysis

The sources were sufficient to answer the questions [i.e. it was sufficient (or feasible) to simply retrieve information from 1 of the sources, and it was not necessary to perform additional analyses, such as an indirect comparison].

To assess the quality of the SRs, the English version of the NOKC checklist for systematic reviews, adapted from the Cochrane EPOC group appraisal list for systematic reviews (Grimshaw 2003), was used (NOKC SR checklist 2013). The quality of the single studies was determined using the Cochrane risk of bias checklist for RCTs (Higgins 2011). The characteristics of the SRs and single trials with quality assessments and ongoing studies that were identified from the trial registry searches are presented in Appendix 1.

Quality of evidence was assessed using the GRADE instrument (GRADE 2004) and classified as high (i.e. “We are very confident that the true effect lies close to that of the estimate of the effect”), moderate (i.e. “We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different”), low (i.e. “Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect”) or very low (i.e. “We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect”). When appropriate, meta-analyses were performed using RevMan (version 5.2, available for download from http://ims.cochrane.org/revman). All reporting was done per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement 2012).

Synthesis

Research questions were answered in plain text format with reference to the GRADE evidence tables in Appendix 1.

5.2 Main results

Included studies

In evaluating clinical effectiveness, we included 3 SRs (Davis 2013; Gosain 2013; Andersson 2013) and 4 controlled studies – 3 RCTs and 1 non-RCT (Pokushalov 2012; Ukena 2011; Mahfoud 2013b; Ahmed 2012). The SRs and CTs were identified through literature searches (see flow charts in Appendix 1). All SRs were published within the last year, but additional results have since been published for some outcomes. Details of the included publications are shown in the 'Evidence tables for the 'safety' domain' below.

In general, the SRs had slightly different inclusion criteria, but all searched for controlled trials. Irrespective of how the individual studies were identified, all studies included patients with resistant hypertension, and RDN was compared with no (or sham) treatment and pharmacological treatment for hypertension. One study assessed the impact of renal artery denervation, added to PVI, in patients with a history of atrial fibrillation and drug-resistant hypertension (Pokushalov 2012).

Controlled studies implemented a follow-up period of 3 to 12 months. We rated the SRs as high-quality. Individual studies were assessed by the authors using the Cochrane risk of bias checklist for RCTs (Higgins 2011) or the Newcastle-Ottawa scale (Pokushalov 2012) in the SR by Davis et al. (Davis 2013). All scored well with regard to bias within their study type.

Mortality (D0001, D0002)

The SR by Davis et al. was the most recent SR with high quality that assessed overall mortality (Davis 2013). Davis et al. reported that no deaths occurred during the stipulated follow-up periods. In terms of cardiovascular mortality, none of the identified publications in this rapid assessment addressed this outcome.

Morbidity (D0005, D0006)

Cardiovascular morbidity

The SR by Andersson et al. examined cardiovascular morbidity in terms of coronary heart disease, stroke, peripheral arterial obstructive disease and heart failure but failed to identify any studies reporting on these outcomes (Andersson 2013). Among the RCT and non-RCTs (prospective controlled trials), none assessed these outcomes. The SR by Andersson et al. included 1 non-RCT that reported left ventricular hypertrophy in 64 patients 6 months following renal denervation using the Symplicity® system (Brandt 2012b). The mean difference in left ventricular mass was 23.8 g/m^2. This result significantly favoured renal denervation, but the quality of the evidence was very low. Moreover, 1 non-RCT of 46 patients assessed left ventricular hypertrophy 6 months after renal denervation using Symplicity® (Mahfoud 2013b) but measured left ventricular mass differently; the mean difference was 3.6 $g/m^{1.7}$ and not significant. The quality of this evidence was very low.

Finally, 1 RCT with 27 patients (13 in the intervention group and 14 in the control group) assessed left ventricular hypertrophy after 6 months but used the Navistar® ThermoCool® system (Pokushalov 2012). Left ventricular mass index (formula was not indicated) was 15.4 g/m lower in patients who had undergone renal denervation. The mean difference was significant, but the quality of this evidence was very low **(D0005).**

Blood pressure

The SR by Davis et al. was the most recent high-quality SR that examined changes in BP (Davis 2013). This group stated that once full articles were retrieved, studies were excluded if there was an overlap in patients with another study in the same analysis (in which case the study with the largest sample size was selected). Thus, overlaps between patient groups were avoided in the meta-analyses.

Three controlled studies assessed changes in SBP and DBP at 6 months (2 RCTs and 1 non-RCT). They included a total of 158 patients and used different types of catheters (1 RCT used the Navistar® ThermoCool® and 1 RCT and 1 non-RCT used the Symplicity® system) (Pokushalov 2012; Symplicity HTN-2 Investigators, Esler 2010; Krum 2009). Renal denervation effected a significant decrease in SBP, with a mean difference of 29.8 mm Hg (95% CI, 20.6–37.2 mm Hg), and a significant decrease in DBP, with a mean difference of 11.0 mm Hg (95% CI, 5.7–16.4 mm Hg); the quality of this evidence was low.

When we re-analysed the data and grouped studies by catheter type, pooling the 2 studies that included 131 patients (75 in the intervention group and 56 in the control group) and used the Symplicity® system resulted in mean differences in SBP of 33.6 mm Hg (95% CI, 25.9–41.3 mm Hg) and DBP of 13.8 mm Hg (95% CI, 7.3–20.3 mm Hg), both of which were statistically significant. Here, the quality of the evidence was moderate. The study that used the Navistar® ThermoCool® system included 27 patients and reported mean differences in SBP of 23 mm Hg (95% CI, 16.8–29.2 mm Hg) and DBP of 7.0 mm Hg (95% CI, 2.5–11.5 mm Hg), which were also significant; however, the quality of the evidence was very low **(D0006)**.

Function, quality of life, patient satisfaction and activities of daily living (D0011, D0016, D0012, D0013, D0017, D0018)

Kidney function

The SR by Gosain et al. (Gosain 2013) identified 1 RCT of 100 patients that measured changes in renal function in terms of change in eGFR after 6 months of follow-up using the Symplicity® system (Symplicity HTN-2 Investigators, Esler 2010). The mean difference between the intervention group and the control group was 0.7 ml/min/1.73m^2 and not significant. The quality of this evidence was low. The same RCT examined changes in renal function, based on serum creatinine levels after 6 months of follow-up using the Symplicity® system (Symplicity HTN-2 Investigators, Esler 2010). The mean difference was 1.3 µmol/L and not significant. The quality of this evidence was also low **(D0011)**.

Exercise

One RCT of 46 patients assessed changes in maximum work rate after 3 months of follow-up after renal denervation using the Symplicity® system (Ukena 2011). The mean difference between the intervention group and the control group was 3.0 Watts on the reclining ergometer and not statistically significant. The quality of this evidence was very low. The same RCT measured changes in peak oxygen uptake (VO_2 peak) 3 months after renal denervation using the Symplicity® system (Ukena 2011). The mean difference was 1.0 ml/min/kg and not significant. The quality of this evidence was very low, as well **(D0016)**.

Quality of life (QoL) and patient satisfaction

There was no documentation on issues that were related to QoL or patient satisfaction **(D0012, D0013, D0017, D0018)**.

Change in management in terms of decrease in number of medications (D0023)

The SR by Gosain et al. was the most recent high-quality SR to examine changes in management, expressed as a decrease in the number of medications (Gosain 2013).

Gosain and colleagues narratively summarised the changes in the number of medications in their included studies (Gosain 2013). They reported that the average number of antihypertensive medications that was used in most studies was 5 and noted a change in the number of antihypertensive medications after renal denervation in 9 studies. In 3 studies, with a total of 236 patients, 10% to 20% (52 patients) required fewer medicines, whereas 10% to 25% (25 patients) needed more medications. One study reported a decline in antihypertensive medications in 4 of 5 patients. Further, 3 studies of 129 patients observed a decrease in medications in 15% to 25% of renal denervation -treated patients. Finally, the remaining studies, totalling 60 patients, reported no change in the number of medications.

5.3 Discussion

No conclusion could be drawn from the available evidence regarding overall mortality. In addition, none of the ongoing studies in this rapid assessment listed mortality as its main research question. Because none of these studies addressed cardiovascular mortality, no conclusion could be drawn for this outcome, either.

There was no evidence available on cardiovascular morbidity, except for left ventricular hypertrophy. Although 2 of 3 studies reported less left ventricular hypertrophy in patients who underwent renal denervation using the Symplicity® and Navistar® ThermoCool® systems compared with patients who did not, the study samples were small, and it was not possible to pool the studies, because left ventricular mass was measured disparately. The poor quality of the evidence did not allow any definitive conclusions to be drawn.

All 3 controlled studies in the SR included for this outcome in this rapid assessment demonstrated a statistically significant decrease in SBP and DBP after 3 (171 patients) and 6 months (158 patients) of follow-up after renal denervation, thus favouring this procedure. The quality of the evidence, however, varied when assessed using GRADE, ranging from very low (1 study of 27 patients who used the Navistar® ThermoCool® system) to moderate (2 studies of 144 patients after 3 months of follow-up and 131 patients after 6 months of follow-up using the Symplicity® system). Thus, we conclude that renal denervation using the Symplicity® system decreases BP, whereas the effects of the Navistar® ThermoCool® system on BP are unknown.

BP is generally accepted as a surrogate endpoint for fatal and nonfatal cardiovascular diseases. However, when considering guidelines for pharmaceutical development, the current draft for a new guideline on medical products in the treatment of hypertension states that “positive effects on mortality and cardiovascular morbidity can only be evaluated properly in large-scale and long-term controlled clinical trials” (EMA 2013). Similar caution is likely to be reasonable in the development of devices and procedures, as associations might not be monocausal.

According to 1 RCT of 100 patients in the SR for this outcome, there was no change in kidney function, based on eGFR and creatinine levels, following renal denervation at the 6-month follow-up, but no definitive conclusion can be drawn, because the quality of the evidence was low.

In 1 RCT of 48 patients, there was no change in the activities of daily living in terms of exercise, based on maximum work rates and peak oxygen uptake, following renal denervation at the 3-month follow-up, but due to the low quality of the evidence, no definitive conclusion could be drawn.

Although data from 9 studies, totalling 430 patients, have suggested that the number of antihypertensive medications decreases following renal denervation, no conclusions can be made from this result.

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CONTENT OF APPENDIX

APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

METHODS

Project approach and methodology

For this pilot rapid assessment, Avalia-t were responsible for assessing the 'Safety' domain, CR.DK for the 'Health problem and current use of the technology' and 'Description and technical characteristics' domains. NOKC had the responsibility of assessing the 'Clinical effectiveness' domain, compiling all domains into a final report and write a final summary of the review.

The pilot rapid assessment was based primarily on a basic systematic literature search in the following sources:

- Biomedical databases (Medline via Ovid, Embase)
- Cochrane database, DARE and HTA databases via the Cochrane Library and CRD
- The ISI database
- The WHO search portal International Clinical Trials Registry Platform (ICTRP) to identify registered clinical trials.
- Hand searches including articles from the manufacturers

Relevant articles for the 4 domains were selected by the agency who answered research questions of the domain they were responsible for. References were included or excluded according to the PICO-scheme described in the project scope.
In terms of study design, SRs/HTAs, RCTs and, if data from RCTs were lacking or insufficient, prospective, controlled studies were selected for answering questions related to the domain 'Clinical effectiveness', while for questions in the 'Safety' domain any prospective study was included. For the two other domains 'Health problem and current use of the technology' and 'Description and technical characteristics', no restrictions in terms of study design were applied.
In cases where questions within the domains 'Health problem and current use of technology' and 'Description and technical characteristics of technology' and 'Safety' could not be answered using the information retrieved from the basic systematic literature search described above, additional searches within specific information sources (e.g. databases for clinical guidelines, registries etc.) and, if needed, hand searching were performed.

For assessing the quality of SRs, the English version of the NOKC checklist for systematic reviews adapted from the Cochrane EPOC group appraisal list for systematic reviews (Grimshaw 2003) was used (NOKC SR checklist 2013). The most recently published high quality SRs which assessed one or more of the predefined outcomes were included. Quality of studies was assessed using the Cochrane risk of bias checklist for RCTs (Higgins 2011).

From the selected studies (including ongoing studies identified from ICTRP), study characteristics and results concerning safety and clinical effectiveness were extracted into evidence tables covering the selected assessment elements for the rapid assessment. When applicable, evidence on clinical effectiveness and safety was assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (GRADE 2004). Reporting of clinical effectiveness and safety data was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement 2012).

Assessment elements selected and the translated research questions that were addressed in the assessment (see domain reports) are primarily based on assessment elements contained in the document 'Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals'. Additionally, assessment elements from other EUnetHTA Core Model Applications (for medi-

cal and surgical interventions, for diagnostic technologies or for screening) have been screened and included/merged with the existing questions if deemed relevant.

Documentation of the basic search strategies

Databases: Embase (Ovid), Ovid MEDLINE. Cochrane Library; Cochrane Reviews, DARE, CENTRAL, Technology Assessments. Centre for Reviews and Dissemination; DARE, HTA. ISI Web of Knowledge, WHO ICTRP (International Clinical Trials Registry Platform)

Search date: 2013.06.26

Results:		
	Systematic reviews/ HTA:	26
	RCT (CCT):	288
	All other study designs (Ovid, ISI)	4807

Databases: Embase 1980 to 2013 Week 25, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Search date: 2013.06.26

#	Searches	Results
1	Kidney/	454231
2	Kidney nerve/ use emez	1714
3	(kidney or renal).ti,ab,kw.	1338605
4	or/1-3	1495229
5	Denervation/	24253
6	Sympathectomy/	14911
7	Sympathetic innervation/ use emez	2587
8	Catheter Ablation/	40219
9	(denervation* or sympathectomy or sympathectomies or sympathetic or innervation* or (catheter adj2 ablat*)).ti,ab,kw.	253808
10	or/5-9	294316
11	Kidney Denervation/ use emez	1055
12	Kidney Innervation/ use emez	331
13	or/11-12	1328
14	(4 and 10) or 13	19220
15	exp Hypertension/	648646
16	exp Blood pressure/	602978
17	(hypertension or hypertensive or blood pressure).ti,ab,kw.	1001917
18	or/15-17	1438668
19	14 and 18	11515
20	Animals/	7088545
21	Humans/	27527866
22	20 not (20 and 21)	5180435
23	19 not 22	7699
24	23 use prmz	1927
25	23 use emez	5772
26	remove duplicates from 24	1855
27	remove duplicates from 25	5681
28	limit 26 to "reviews (maximizes specificity)" [SR M]	9
29	limit 26 to "therapy (maximizes specificity)" [RCT M]	81
30	limit 27 to "reviews (maximizes specificity)" [E]	12
31	limit 27 to "therapy (maximizes specificity)" [E]	135
32	28 or 29 or 30 or 31	237
33	26 or 27	7536
34	33 not 32 [no study design filter]	7299

Database: Cochrane Library

Search date: 26/06/13

Description:		
	Cochrane rev.	0
	Other reviews	1
	HTA	5
	Clinical trials	143

Search Name: 2013.06.27 Renal denervation

Date Run: 27/06/13 15:07:10.4

	Searches	Results

#1	(kidney or renal):ti,ab,kw	28031
#2	MeSH descriptor: [Catheter Ablation] explode all trees	992
#3	(denervation* or sympathectomy or sympathectomies or sympathetic or innervation* or catheter near/2 ablat*)):ti,ab,kw	4714
#4	#2 or #3	4714
#5	#1 and #4	225
#6	MeSH descriptor: [Blood Pressure] explode all trees	21962
#7	(hypertension or hypertensive or (blood next pressure)):ti,ab,kw	52626
#8	#6 or #7	52887
#9	#5 and #8	146

Database: CRD DARE and HTA
Search date: 2013.06.26
Results: SR 2, HTA 6

	Searches	Results
1	MeSH DESCRIPTOR Kidney IN DARE,HTA	71
2	((kidney or renal)) IN DARE, HTA	1729
3	#1 OR #2	1729
4	MeSH DESCRIPTOR Denervation IN DARE,HTA	17
5	MeSH DESCRIPTOR Sympathectomy IN DARE,HTA	16
6	MeSH DESCRIPTOR Catheter Ablation EXPLODE ALL TREES IN DARE,HTA	223
7	((denervation* or sympathectomy or sympathectomies or sympathetic or innervation* or catheter near2 ablation) IN DARE, HTA	340
8	#4 OR #5 OR #6 OR #7	340
9	MeSH DESCRIPTOR Hypertension EXPLODE ALL TREES IN DARE,HTA	450
10	MeSH DESCRIPTOR Blood Pressure EXPLODE ALL TREES IN DARE,HTA	388
11	((hypertension or hypertensive or "blood pressure")) IN DARE,HTA	234
12	#9 OR #10 OR #11	1636
13	#3 AND #8 AND #12	8
14	(#13) IN DARE	2
15	(#13) IN HTA	6

ISI Web of Knowledge
Date: 2013.06.26
Search (systematic reviews, HTA):
Topic=(kidney or renal) AND Topic=(denervation or sympathectomy or sympathetic innervation or catheter ablation) AND Topic=(hypertension or hypertensive or blood pressure) AND Topic=(systematic* or health technology assessment*)

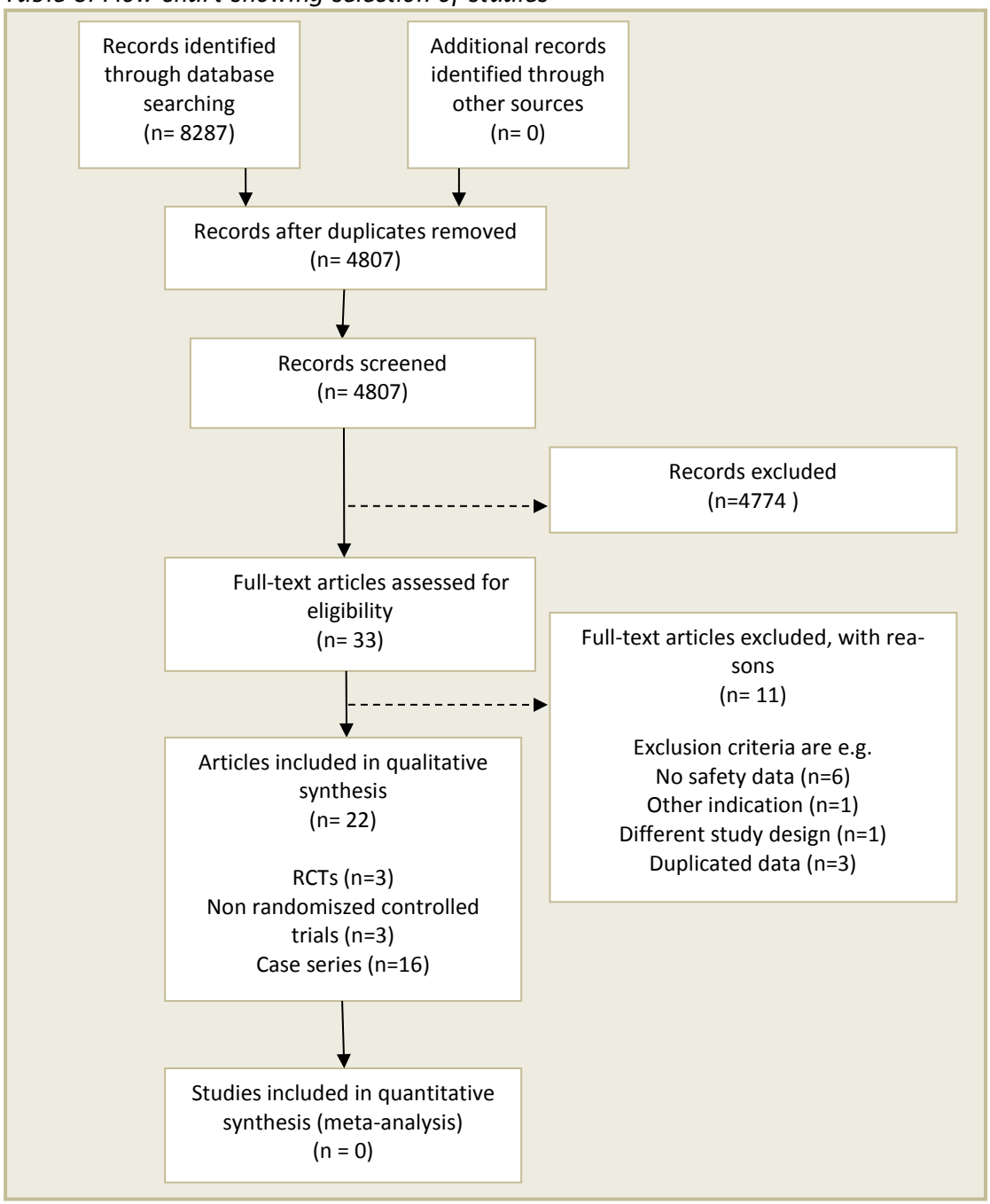
Search (single studies)
Result: 51
Topic=(kidney or renal) AND Topic=(denervation or sympathectomy or sympathetic innervation or catheter ablation) AND Topic=(hypertension or hypertensive or blood pressure) AND Document Types=(Article) AND Topic=(randomi* controlled or controlled clinical or prospective study or prospective trial) NOT Document Types=(Review)

Search (no study filter)
Result: 987
Topic=(kidney or renal) AND Topic=(denervation or sympathectomy or sympathetic innervation or catheter ablation) AND Topic=(hypertension or hypertensive or blood pressure) NOT Topic=(review or randomi* controlled or controlled clinical or prospective study or prospective trial)

Flow charts of study selection

Study selection for the 'safety domain'

Table 8: Flow chart showing selection of studies



Study selection for the 'clinical effectiveness' domain

Table 9: Flow chart showing selection of SRs

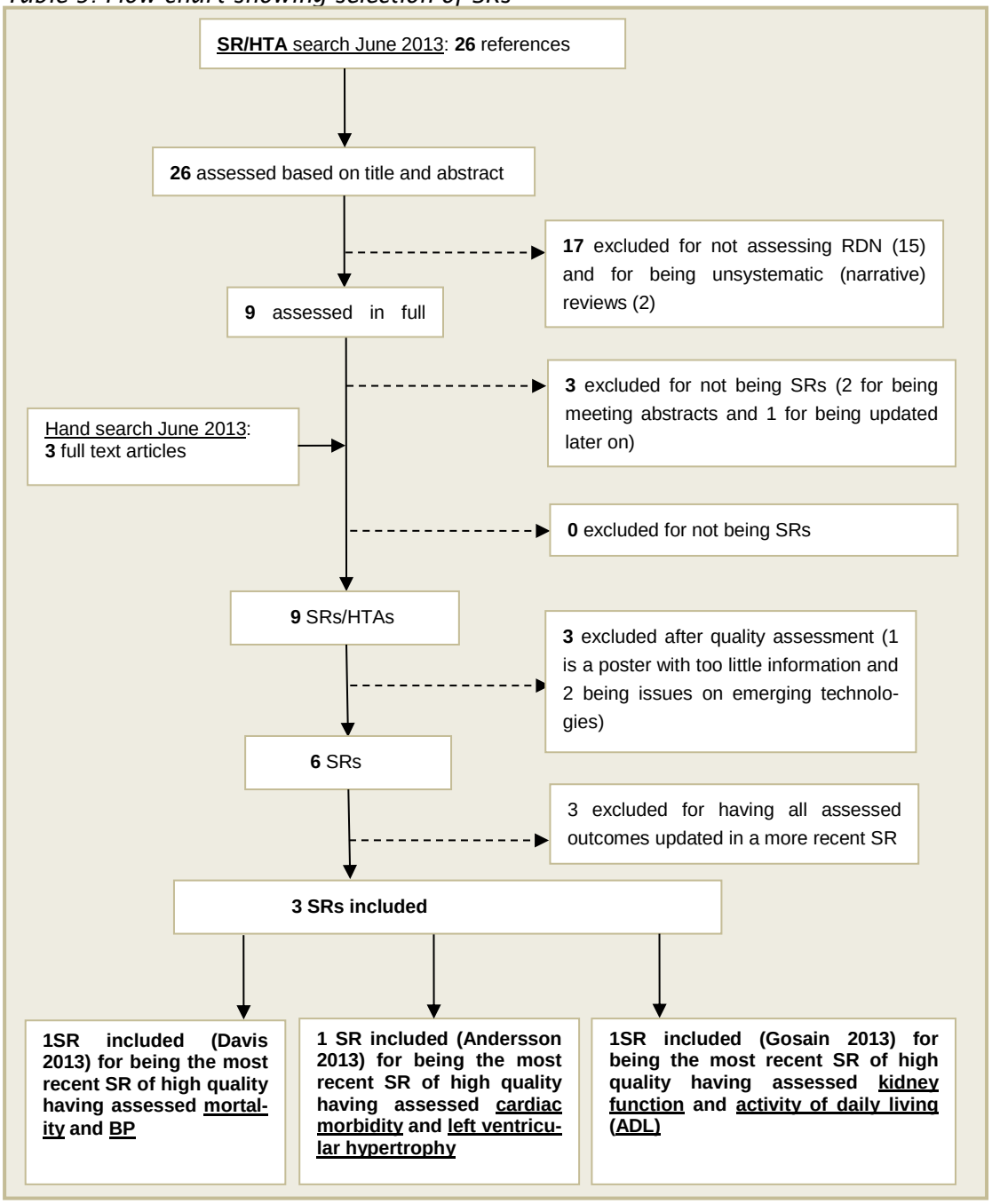
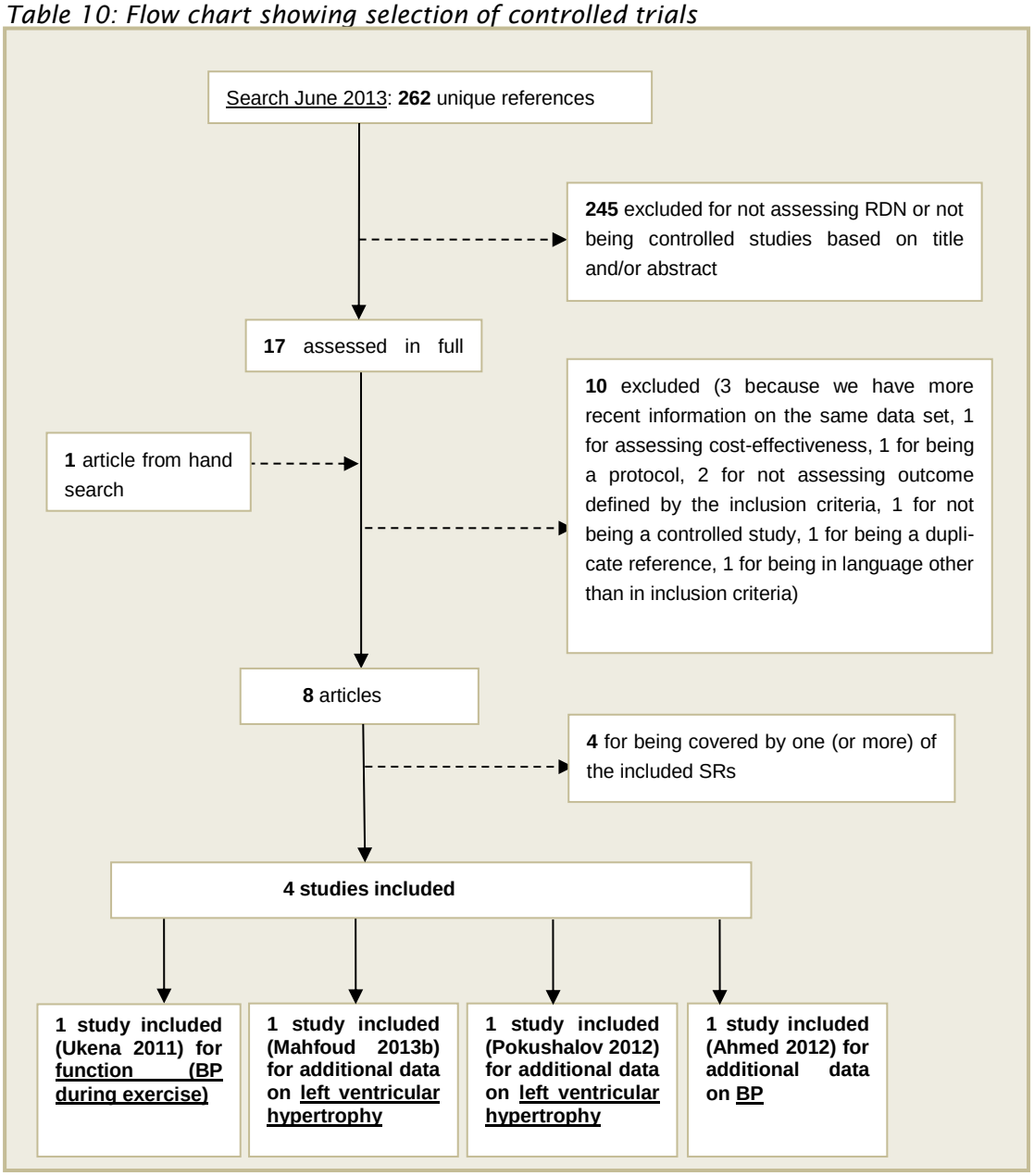


Table 10: Flow chart showing selection of controlled trials



DESCRIPTION OF THE EVIDENCE USED

Evidence tables of individual studies included

Evidence tables for the 'safety' domain

Table 11: Evidence table for RCTs

Author, year, reference number	**Symplicity HTN-2 Investigators (2010)** Lancet. 2010;376:1903–9.	**Ukena et al. (2011)** J Am Coll Cardiol. 2011;58(11):1176-82.	**Pokushalov et al. (2012)** J Am Coll Cardiol 2012;60:1163-70.
Country	Europe, Australia, New Zealand	Germany, Australia	Russia, Netherlands, USA
Declaration of funding source and competing interests	Funded by Ardian Inc.	Funded by Ardian Inc., Ministry of Science and Economy of the Federal State of the Saarland, Deutsche Hochdruckliga, Deutsche Forschungsgemeinschaft (KFO 196). An author is an employee of Medtronic/Ardian Inc.	Two authors have served as consultants with Medtronic and Biosense Webster. One author has received research grants from Medtronic and Biosense-Webster. One author is an employee of Medtronic/Ardian Inc.
Study design	RCT	RCT	RCT
Study objective	Show that catheter-based RDN can safely reduce BP in patients with treatment resistant hypertension	Investigate the effects of RDN on the cardiopulmonary response during cardiopulmonary exercise testing in patients with resistant hypertension	Assess the impact of RDN added to pulmonary vein isolation in patients with a history of AF and drug resistant hypertension
Intervention	RDN and antihypertension medication	RDN and antihypertension medication	RDN and Pulmonary Vein Isolation
Comparator	Only antihypertension medication	Only antihypertension medication	Only Pulmonary Vein Isolation
Type of catheter	Symplicity® (Ardian, Medtronic)	Symplicity® (Ardian, Medtronic)	ThermoCool® catheter (Biosense Webster)
Inclusion/ exclusion criteria	Patients aged 18–85 years with a systolic BP of 160 mm Hg or more (≥150 mm Hg in patients with type 2 diabetes), despite compliance with ≥ 3 antihypertensive drugs. Exclusion of estimated eGFR < than 45 ml/min per 1.73 m^2, type 1 diabetes, contraindications to MRI,substantial stenotic valvular heart disease, pregnancy, history of myocardial infarction, unstable angina, or CVA in the previous 6 months	Patients ≥18 years old with an office BP of ≥ 160 mm Hg (≥ 150 mm Hg for type 2 diabetic patients), despite being treated with ≥ 3 antihypertensive drugs (including a diuretic), with no changes in medication for a minimum of 2 weeks prior to enrolment	Patients with symptomatic drug-refractory AF (failure of ≥ 2 class I or III antiarrhythmic drugs) referred for catheter ablation (paroxysmal AF with ≥1 monthly episodes or persistant AF) that present an office-based systolic BP of ≥160 mm Hg, despite treatment with ≥ antihypertensive drugs (including 1 diuretic) and a eGFR ≥ 45 ml/min/1.73 m^2
Number of patients	Intervention= 52* Control= 54* *3 did not attend 6-month follow-up	Intervention= 37 Control= 9 28 patients included in Symplicity HTN2 investigators (Lancet 2010)	Intervention: 13 Control: 14
Age (mean)	Total: N/A Intervention: 58 Control: 58	Total: 60.2± 9.1 Intervention: 59.1± 9.4 Control: 64.9± 6.4	Total: N/A Intervention: 59.0±11.5 Control: 58.1±13.0
Sex (M/F)	Total:N/A Intervention: 34M, 18F Control: 27M, 27FF	Total: 32M, 14F Intervention: 25M, 12F Control:7M, 2F	Total: N/A Intervention: 11 M, 2F Control: 10 M, 4F
eGFR (ml/min per 1.73 m^2)	Total: N/A Intervention: 77 (19) Control: 86 (20)	Total: 69 ±23 Intervention: 70±24 Control: 64,5±16	Total: N/A Intervention: 78±6.1 Control: 80.2±4.6
Follow up	6 months	3 months	1 year

AF: atrial fibrillation; CVA: cardiovascular attack; eGFR: estimated glomerular filtration rate; F: female; M: male; MRI: magnetic resonance imaging; N/A: not available; RCT: randomised controlled trial; RDN: renal denervation; mm Hg: Millimeter mercury; min: minute; ml: milliliter

Table 12: Evidence table for non RCTs

Author, year, reference number	**Mahfoud et al. (2011b)** Circulation. 2011;123(18):1940-6.	**Brandt et al. (2012a)** J Am Coll Cardiol. 2012;60(19):1956-65.	**Mahfoud et al. (2012)** Hypertension. 2012;60:419-424.
Country	Germany, Australia	Germany, Austria	Germany, Australia
Declaration of funding source and competing interests	Funded by Ardian Inc., Ministry of Science and Economy of the Federal State of the Saarland, Deutsche Hochdruckliga, Deutsche Forschungsgemeinschaft (KFO 196). An author is an employee of Medtronic/Ardian Inc. An author is supported by an NHMRC Senior Research Fellowship.	Funded by Ardian Inc. An author is a consultant from Medtronic and other author have received grant support from Medtronic.	Funded by Ardian Inc., Ministry of Science and Economy of the Saarland, Deutsche Hochdruckliga, Deutsche Forschungsgemeinschaft (KFO 196) and National Health and Medical Research Council. An author is an employee of Medtronic/Ardian Inc.
Study design	Open, non randomised, controlled trial with matched patients	Open, non randomised, controlled trial	Open, non randomised, controlled trial
Study objective	Evaluate the relation between sympathetic activity and glucose metabolism and the role of therapeutic RDN	Evaluate the effectof RDN on central hemodynamic in patients with resistant hypertension	Assess the changes that occur in RRI, UAE, and renal function after interventional RDN in patients with resistant hypertension
Intervention	RDN and antihypertension medication	RDN and antihypertension medication	RDN and antihypertension medication
Comparator	Only antihypertension medication	Only antihypertension medication	Only antihypertension medication
Type of catheter	Symplicity® (Ardian, Medtronic)	Symplicity® (Ardian, Medtronic)	Symplicity® (Ardian, Medtronic)
Inclusion/Exclusion criteria	Patients with an office BP of ≥ 160 mm Hg (≥150 mm Hg for patients with type 2 DM) despite being treated with at least 3 antihypertensive drugs and a GFR ≥ 45 ml/min per 1.73 m^2, Exclusion of pregnant women, patients with inadequate renal artery anatomy for intervention, a history of prior renal artery interventions, type 1 diabetes mellitus, myocardial infarction, unstable angina pectoris, CVA within the last 6 months, or hemodynamically significant valvular disease.	Patients ≥18 years old with an office BP of ≥ 160 mm Hg (≥ 150 mm Hg for type 2 diabetic patients), despite being treated with ≥ 3 antihypertensive drugs (including a diuretic), with no changes in medication for a minimum of 3 months prior to enrolment	Patients > 18 years with an office BP of ≥ 160 mm Hg (≥150 mm Hg for patients with type 2 DM) despite being treated with at least 3 antihypertensive drugs and an eGFR ≥ 45 ml/min per 1.73 m^2, Exclusion of pregnant women, patients with inadequate renal artery anatomy for intervention, a history of prior renal artery interventions, type 1 diabetes mellitus, myocardial infarction, unstable angina pectoris, CVA within the last 6 months, or hemodynamically significant valvular disease.
Number of patients	Intervention= 37 Control= 13 26 patients included in Symplicity HTN 2 trial	Intervention= 110 Control = 10	Intervention= 88 Control= 12 19 patients included in Symplicity HTN1 or HTN 2 trial
Age (mean)	Total: 59.7±1.4 Intervention:58.7±1.6 Control: 62.5±2.9	Total:N/A Intervention: 63.1 ± 10.2 Control: 63.0 ± 15.3	Total: 61.7 ± 1.0 Intervention: 61.6 ± 1.1 Control: 61.9±3.6
Sex (M/F)	Total: 37M, 13F Intervention: 29M, 8F Control:8M, 5F	Total:85M, 35F Intervention: 77M, 33F Control:8M, 2F	Total:61M, 39F Intervention: 54M, 34F Control:7M, 5F
eGFR (ml/min per 1.73 m^2)	Total: 76.6±3.1 Intervention: 75.1±3.3 Control: 81.0±7.6	Total: N/A Intervention: N/A Control: N/A	Total: 86.1±3.3 Intervention: 84.6±3.6 Control: 97.9_7.4
Follow up time	3 months	6 months	6 months

CVA: cardiovascular attack; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; F: female; M: male; N/A: not available; RCT: randomised controlled trial; RDN: renal denervation; RRI: renal resistance index; UAE: urinary albumin excretion; mm Hg: Millimeter mercury; min: minute; ml: millilitre

Table 13: Evidence tables for observational studies

Author, year, reference number	**Symplicity HTN-1 Investigators (2011)** Hypertension 2011;57:911-7.	**Voskuil et al. (2011)** Neth Heart J (2011) 19:319–323.	**Brinkmann et al. (2012)** Hypertension. 2012;60:1485-1490.	**Hering et al. (2012)** J Am Soc Nephrol. 2012;23(7):1250-7.
Country	Europe, Australia, USA	Netherlands	Germany, Netherlands	Germany, Australia
Declaration of funding source and competing interests	Funded by Ardian Inc. Three authors are employees of Medtronic/Ardian Inc.	Not declared	Funded by Deutsche Forschungsgemeinschaft (JO 284/6-1) and German Space Agency. Absence of conflict of interest.	Funded in part by grants from the National Health and Research Council of Australia and the Victoria government's Operational Infrastructure Support Program. Various authors have been investigators in studies supported by Medtronic and/or have received honoraria from Medtronic and pharmaceutical companies. The Neurovascular Hypertension & Kidney Disease laboratory currently receives research funding from Medtronic Inc. and pharmaceutical companies. Two authors serving on scientific advisory boards of Medtronic and pharmaceutical companies. An author is an employee of Medtronic/Ardian Inc.
Study design	Case series	Case series	Case series	Case series
Study objective	Establish long-term outcomes of RDN	Report the results of the first Dutch experience with RDN	Test the hypothesis that MSNA reduction is a typical response to RDN	Assess short-term renal safety and efficacy in patients with concomitant moderate to severe CKD.
Intervention	RDN and antihypertension medication	RDN and antihypertension medication	RDN and antihypertension medication	RDN and antihypertension medication
Comparator	None	None	None	None
Type of catheter	Symplicity® (Ardian, Medtronic)	Not specified	Symplicity® (Ardian, Medtronic)	Symplicity® (Ardian, Medtronic)
Inclusion/exclusion criteria	Patients with an office systolic BP ≥160 mm Hg) despite taking ≥ 3 antihypertensive drug classes, 1 of which was a diuretic, at target or maximal tolerated dose. Patients were excluded if they had an eGFR of < 45 ml/min per 1.73 m^2, type 1 DM or a known secondary cause of hypertension other than sleep apnea or CKD, or significant renovascular abnormalities	Patients with office systolic BP ≥ 160 mmHg, despite being treated with at least three antihypertensive drugs, or confirmed intolerance to medication. Exclusion criteria: inadequate renal artery anatomy, pregnancy, age < 18 years, known secondary cause of hypertension, an eGFR <45 ml/min/1.73 m^2, type 1 diabetes, haemodynamically significant valvular disease, implantable cardioverter defibrillators, or treatment with clonidine, moxonidinerilmenidine or warfarin.	Patients with an uncontrolled essential hypertension despite treatment with ≥3 antihypertensive medications at full doses, including a diuretic. Exclusion of patients with secondary hypertension	Patients with resistant hypertension and concomitant moderate to severe CKD (stage 3-4)
Number of patients	153	11	12	15
Age (mean)	57±11	68±12	45-74	61 ± 9
Sex (M/F)	61%M, 39%F	1M, 10F	11M, 1F	9M, 6F
eGFR (ml/min per 1.73 m^2)	83±20	74±14	N/A	31.2±8.9
Follow up	2 years	1 month	6 months	12 months

CKD: chronic renal disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; F: female; M: male; N/A: not available; RDN: renal denervation; MSNA: muscle sympathetic renal activity; mm Hg: Millimeter mercury; min: minute; ml: millilitre

Author, year, reference number	**Mabin et al. (2012)** Eurointervention. 2012;8:57–61.	**Esler et al. (2012)*** Circulation. 2012;126:2976-82	**Prochnau et al. (2012a)** Int J Cardiol. 2012;157:447–8.	**Simonetti et al. (2012)** Radiol Med 2012;117:426–44.
Country	South Africa	Europe, Australia, New Zealand	Germany	Italy
Declaration of funding source and competing interests	Funded by ReCor Medical. One author is member of the ReCor Medical advisory board. Two authors are consultants to ReCor Medical. An author is an employee of ReCor Medical.	Funded by Ardian Inc.	Funding source: not declared. Absence of conflict of interest.	Funding source: not declared. Absence of conflict of interest.
Study design	Case series	Case series	Case series	Case series
Study objective	Evaluate the technical feasibility as well as the safety and efficacy of a novel modality for RDN	Report the 6 months outcomes from cross over patients from the Symplicity HTN-2 trial	Evaluate the efficacy (measured in the 24-h ambulatory BP monitoring) and safety	Investigate the efficacy and safety of the Ardian Symplicity catheter system
Intervention	RDN and antihypertension medication	RDN and antihypertension medication	RDN and antihypertension medication	RDN and antihypertension medication
Comparator	None	Only antihypertension medication	None	None
Type of catheter	PARADISE™ (ReCor Medical)	Symplicity® (Ardian, Medtronic)	(Marinr®; Medtronic)	Symplicity® (Ardian, Medtronic)
Inclusion/exclusion criteria	Patients with resistant hypertension as defined by the ESH and the ESC, i.e., with a minimum BP of 140/90 mmHg (office), 135/85 mmHg (home) and 130/80 mmHg (ambulatory) despite being treated with at least three antihypertensive drugs including a diuretic. Exclusion of patients under the age of 18 years, vascular abnormalities, pregnancy, allergic to contrast media, or with any known cause of secondary hypertension	Patients aged 18–85 years with a systolic BP of 160 mm Hg or more (≥150 mm Hg in patients with type 2 diabetes), despite compliance with ≥ 3 antihypertensive drugs Exclusion of estimated eGFR < than 45 ml/min per 1.73 m^2, type 1 diabetes, contraindications to MRI,substantial stenotic valvular heart disease, pregnancy and a history of myocardial infarction, unstable angina, or CVA in the previous 6 months.	Patients with drug-resistant hypertension despite treatment with at least four antihypertensive drugs (mean 6). Exclusion of secondary hypertension.	Essential arterial hypertension not responding to pharmacological treatment with ≥ 3 antihypertensive drugs, including a diuretic; SBP levels ≥160 mmHg; normal renal function or with low or moderate CRF; age >18 years and <75 years; absence of renal pathology or systemic disease with possible renal involvement; renal artery length ≥2 cm and minimum ostial diameter ≥4 mm; no evidence of accessory renal arteries; pathological microalbuminuria (>300 mg/24 h); or altered fundus oculi examination (varying degrees of hypertensive retinopathy) and left ventricular hypertrophy at echocardiography. Exclusion of patients with secondary causes of hypertension
Number of patients	11	35* * 6-month outcomes of crossover control patients from Symplicity HTN-2 trial who were treated with RD	30	5
Age (mean)	55 ± 14	62±14.3	62.4±12.8	50, 6
Sex (M/F)	36% M, 64% F	9 M, 3 F	20 M, 10 F	3 M, 2 F
eGFR (ml/min per 1.73 m^2)	-	88.8±20.7	N/A	N/A
Follow up	3 months (8 patients)	3 months	12 months	60 days

BP: blood pressure; CRF: chronic renal failure; CVA: cardiovascular disease; eGFR: estimated glomerular filtration rate; F: female; M: male; N/A: not available; RDN: renal denervation; mm Hg: Millimeter mercury; mm:millimeter; cm: centimeter; mg: milligram

Author, year, reference number	**Ukena et al. (2012)** Int J Cardiol (2012).	**Vase et al. (2012)** Dan Med J. 2012;59:A4439.	**Zuern et al. (2012)** Front Physiol. 2012;3:134.	**Scheurig-Muenkler et al. (2013)** Rofo. 2013;185:550–7.
Country	Germany	Denmark	Germany	Germany
Declaration of funding source and competing interests	Funded by Ardian (all authors have received per-patient payment for study involvement as part of the Symplicity HTN-1 or HTN-2 study), Ministry of Science and Economy	Funding source: not relevant. Absence of conflict of interest.	Funded in part by the program "Angewandte klinische Forschung" (AKF) of the University of Tübingen. Absence of any potential conflict of interest.	Not declared

	of the Federal State of the Saarland, Deutsche Hochdruckliga, Deutsche Forschungsgemeinschaft (KFO 196) and Deutsche Gesellschaft für Kardiologie (DGK). Differents authors have received speakers' honoraria from Ardian/Medtronic.			
Study design	Case series	Case series	Case series	Case series
Study objective	Investigate the effects of RDN on elevated HR and conduction times	Report the first Danish experiences and results with RDN	Test the hypothesis that RDN leads to a significant reduction of abnormal BP variability and instability	Analyse the data in respect of procedural details, complications, and radiation exposure
Intervention	RDN and antihypertension medication	RDN and antihypertension medication	RDN and antihypertension medication	RDN and antihypertension medication
Comparator	None	None	None	None
Type of catheter	Symplicity® (Ardian, Medtronic)	Symplicity® (Ardian, Medtronic)	Symplicity® (Ardian, Medtronic)	Symplicity® (Ardian, Medtronic)
Inclusion/exclusion criteria	Patients ≥18 years with resistant hypertension defined as office systolic BP of ≥160 mm Hg (≥150 mm Hg for type 2 diabetics), despite being treated with ≥ 3 antihypertensive drugs (including a diuretic), with no changes in medication for a minimum of 2 weeks prior to enrolment; not pregnant and with an eGFFR of ≥45 ml/min/1.73 m^2. Exclusion of patients with inadequate renal artery anatomy, type 1 DM, myocardial infarction, unstable angina pectoris, CVA within the last 6 months, or hemodynamically significant valvular disease.	Patients with systolic daytime 24-hour ambulatory BP ≥ 135 mmHg despite being treated with ≥ 3 antihypertensive drugs including a diuretic. Exclusion of patients with confirmed intolerance to medication in case of pregnancy; age < 18 years; secondary cause of hypertension; eGFR rate < 45 ml/min; LVEF < 50%, recent myocardial infarction or percutaneous coronary intervention, significant proximal coronary artery stenosis or haemodynamically significant valvular heart disease.	Patients were > 18 years, had an office systolic BP of ≥ 160mmHg (≥150mmHg for patients with type2 DM) despite being treated with at least three antihypertensive drugs (including one diuretic), with no changes in medication for a minimum of 2 weeks before enrolment. Patients were included if they were not pregnant and had an eGFR ≥ 45ml/min per 1.73m^2.	Patients with refractory hypertension Exclusion of patients with planted pacemakers or cardioverter defibrillators and a vessel diameter below 4mm, assessed in pre-interventional
Number of patients	136* *18 were part of Simplicity HTN2 Study	9	11	53
Age	62.2±0.8	56 ± 10	68.9	59
Sex	79M, 57F	3M, 6F	8M, 3F	35 M, 18 F
eGFR (ml/min per 1.73 m^2)	83±3.9	-	75.0 (18.4)	76.4 (Range: 71.5–81.4)
Follow up	6 months	1 month	24 months	None

BP: blood pressure; CVA: cardiovascular attack; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; F: female; HR: heart rate; M: male; N/A: not available; RDN: renal denervation; mm Hg: Millimeter mercury; min: minute; ml: milliliter; mm: millimeter; LVEF: left ventricular ejection fraction

Author, year, reference number	**Fontenla et al. (2013)** Rev Esp Cardiol. 2013;66(5):364–70.	**Kaltenbach et al. (2013)** Catheter Cardiovasc Interv. 2013;81(2):335-9.	**Ormiston et al. (2013)** EuroIntervention 2013;9:70-4.	**Worthley et al. (2013)** Eur Heart J. 2013;34(28):2132-40.
Country	Spain	Germany	New Zealand	Australia, Greece
Declaration of funding source and competing interests	Catheters funded by Fondation pour la prevention des maladies cardiovasculaires (Geneva, Switzerland). No conflict of interest.	Not declared	Funded by Covidien (Campbell, CA, USA). The first author is a minor shareholder in Covidien.	Funded by St. Jude Medical Inc. Some authors received research grants and honoraria from St Jude Medical, Medtronic, Inc., Astra Zeneca, Eli Lilly, Sanofi Aventis and Boston Scientific. One author is a board member from St Jude.
Study design	Case series	Case series	Case series	Case series

Study objective	Describe the results of establishing a multidisciplinary unit for the implementation of renal denervation in the management of resistant hypertension	Examine the effects of renal sympathetic denervation (feasibility, safety and effectiveness)	To provide hypothesis-generating safety and feasibility data concerning the OneShot™ renal denervation device	Evaluate the safety and efficacy of a multielectrode RF ablation catheter
Intervention	RDN and antihypertension medication	RDN and antihypertension medication	RDN and antihypertension medication	RDN and antihypertension medication
Comparator	None	None	None	None
Type of catheter	Symplicity® (Ardian, Medtronic)	Symplicity® (Ardian, Medtronic)	OneShot™ (Covidien)	EnligHTN™ Ablation Catheter (St. Jude Medical)
Inclusion/ exclusion criteria	Patients with a mean office systolic BP > 140mmHg or diastolic BP > 40 mmHg despite being treated with at least three antihypertensive drugs and complying with the following criteria: eGFR ≥ 45ml/min per 1.73m^2, no history of coronary or artery disease in the previous six months, coronary artery stenosis or contraindications for femoral artery catheterisation.	Patients with longstanding mild hypertension despite treatment with ≥ 3 antihypertensive drugs. Exclusion of patients with definite or presumed secondary causes of hypertension such as renal artery stenosis, hyperaldosteronism, or pheochromocytoma	Patients ≥ 18 years with consistent office-measured systolic BP ≥ 160 mmHg (or greater than 150 mmHg for patients with type 2 diabetes) despite treatment with ≥ 2 antihypertensive medications; renal artery diameters between 4 and 7 mm and a segment of artery at least 20 mm in length devoid of stenosis. Exclusion of patients with an eGFR rate < 45 ml/min/1.73 m^2.	Patient ≥18 and ≤80 years old with office systolic BP that remains ≥160 mmHg (≥150 mmHg for patient with type 2 diabetes) despite the stable use of ≥3 antihypertensive medications concurrently at maximally tolerated doses, of which one is a diuretic or patient that was on diuretic previously but documented to be diuretic intolerant, for a minimum of 14 days prior to enrolment and with an expectation to maintain for a minimum of 180 days Exclusion of patients with renal artery stenosis, multiple main renal arteries in either kidney, main renal arteries are ,4 mm in diameter or ,20 mm in length, an eGFR of < 45 ml/min per 1.73m^2, type 1 DM, identified secondary cause of hypertension or is in chronic atrial fibrillation/atrial flutter
Number of patients	11	20	9	46
Age	49 ± 13	6 1± 10.8	59.5±15.6	59.9+10.2
Sex	4M, 7F	11M, 9F	5M, 9F	31M, 15F
eGFR (ml/min per 1.73 m^2)	-	77.4± 24.8	-	-
Follow up	6 months (mean:72 days)	6 months	12 months	6 months

BP: blood pressure; eGFR: estimated glomerular filtration rate; DM: diabetes mellitus F: female; M: male; N/A: not available; RDN: renal denervation; mm Hg: Millimeter mercury; min: minute; ml: milliliter

Evidence tables and quality assessment for the 'clinical effectiveness' domain

Quality assessment of SRs (3 in total) was done using the English version of the NOKC check-list for systematic reviews (NOKC SR checklist 2013) adapted from the Cochrane EPOC group appraisal list for systematic reviews (Grimshaw 2003).

Table 14: Checklist for SR quality assessment

Reference	Yes (Y)	Unclear (U)	No (N)
1. Is the specific purpose (question to be answered) stated?			
Comment:			
2. Are the comparison groups clearly stated?			
Comment:			
3. Are the sources and search methods used to find evidence (primary studies) on the questions to be answered stated?			
Comment:			
4. Is the search strategy for evidence reasonably comprehensive?			
Comment:			
5. Are explicit criteria used for deciding which studies to include in the review?			
Comment:			
6. Is bias in the selection of articles likely to be avoided?			
Comment:			
7. Are the reasons for excluding studies from the review reported?			
Comment:			
8. Are the criteria used for assessing the quality of the studies reported?			
Comment:			
9. Is the quality of all the studies to be reviewed assessed using appropriate criteria?			
Comment:			
10. Are the methods used to combine the findings of the relevant studies reported?			
Comment:			
11. Are the methods used to combine the findings of the relevant studies appropriate to the questions to be answered by the review?			
Comment: (1) SBU checklist for appraisal of studies (2) No combined results performed thus not applicable			
Overall quality:			
Assessed by/date:			

Table 15: Evidence tables for SRs

Article	Full reference	Andersson B, Herlitz H, Manhem K, Zachrisson K, Völz S, Daxberg EL, et al. Renal sympathetic denervation in patients with therapy resistant hypertension: The Regional Health Technology Assessment Centre (HTA-centrum), Region Vastra Gotaland; 2013.
Project details	Reviewed by	KBF and TR
	Date of review	10 September 2013
	Project name	WP5 Strand B 2nd pilot: Renal denervation systems for treatment-resistant hypertension
	Project ID	WP5-SB-12

Study type	Type of publication	Health Technology Assessment
	Country (area) Year	Sweden (Västra Götaland) 2013
	Last updated search	August 2012
Research question/main objective	Is RDN an effective and safe technique to lower the BP in patients with treatment-resistant hypertension, and does it result in reduced mortality and less target organ damage?	
Included for	Clinical effectiveness	
Criteria for study design	*What study design(s) are included by the review:* RCTs SRs Studies with some kind of control group Case series: ≥ 10 patients (for outcome: complications) No case reports or review articles	
Population	*Patient characteristics:* Patients with treatment-resistant hypertension (medical treatment with at least three antihypertensive drugs) with BP ≥140/90 mm Hg	
	Disease/condition: Treatment-resistant hypertension (medical treatment with at least three antihypertensive drugs) with BP ≥140/90 mm Hg	
Intervention	Catheter-based renal denervation	
Comparison	Conventional pharmacological treatment	
Outcomes	*Outcomes assessed:* Mortality Cardiovascular morbidity Kidney involvement BP Complications Left ventricular hypertrophy/Systolic and diastolic cardiac function (not in our inclusion criteria) Glucose metabolism (not in our inclusion criteria)	
Sources of information	Systematic searches in PubMed, EMBASE, the Cochrane Library, and a number of HTA-databases.	
	Other sources of information: Reference lists of relevant articles were also scanned for additional references.	
Studies included for the different outcomes	*Total:* 15 studies included *For the outcomes:* Mortality: none Cardiovascular morbidity: none Kidney involvement: one non-randomised controlled study (Mahfoud 2012) BP: two RCTs (Esler 2010; Ukena 2011) and three non-randomised controlled studies (Brandt 2012b; Mahfoud 2012; Mahfoud 2011b) Complications (reported only for the intervention groups): four controlled studies (Esler 2010; Symplicity HTN-1 Investigators 2011; Mahfoud 2012; Mahfoud 2011b) and five case series (Krum 2009; Mabin 2012; Prouchnau 2012; Voskuil 2011; Zuern 2012) Left ventricular hypertrophy/Systolic and diastolic cardiac function: one non-randomised controlled study (Brandt 2012b)	
Main Conclusion	This catheter-based method, used for patients with therapy-resistant hypertension, significantly reduces BP. Even though follow-up data for more than two years are lacking, present data suggest that the method may be safely used as a treatment alternative in this category of patients. The present data suggests that the method may be a valuable treatment alternative in therapy resistant hypertension.	

Quality assessment (based on NOKC checklist for systematic reviews)

1	2	3	4	5	6	7	8	9	10	11	Quality
Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	HIGH

Comments:

Article	Full reference	Davis MI, Filion KB, Zhang D, Eisenberg MJ, Afilalo J, Schiffrin EL, Joyal D. Effectiveness of renal denervation therapy for resistant hypertension: a systematic review and meta-analysis. J Am Coll Cardiol. 2013 Jul 16;62(3):231-41.
Project details	Reviewed by	KBF and TR
	Date of review	10 September 2013
	Project name	WP5 Strand B 2nd pilot: Renal denervation systems for treatment-resistant hypertension
	Project ID	WP5-SB-12

Study type	Type of publication	Systematic review
	Country (area) Year	Canada 2013
	Last updated search	December 2012
Research question/main objective	This study sought to determine the current effectiveness and safety of sympathetic renal denervation (RDN) for resistant hypertension.	
Included for	Clinical effectiveness	
Criteria for study design	*What study design(s) are included by the review:* All study designs (controlled and before-after studies in a single group of patients) with at least 10 participants with at least 3 months follow-up	
Population	*Patient characteristics:* Patients with resistant hypertension	
	Disease/condition: Resistant hypertension	
Intervention	Renal denervation therapy (using contemporary percutaneous catheters and radiofrequency probes)	
Comparison	Standard medical therapy	
Outcomes	*Outcomes assessed:* BP Complications (procedural complications and adverse outcomes including death from any cause)	
Sources of information	*Databases:* PubMed, Embase, Cochrane Library	
	Other sources of information: Hand searched references of retrieved articles and use PubMed's related articles feature	
Studies included for the different outcomes	Totally 12 studies included (Originally 18 studies met all inclusion criteria, but studies were excluded if there was overlap in patients with another study within the same analysis). 2 RCTs (Esler 2010; Pokushalov 2012) 1 observational study with a control group (Krum 2009) 9 observational studies without a control group (Ahmed 2012; Hering 2012; Kaltenbach 2013; Mabin 2012; Prochnau 2012a; Symplicity HTN-1 Investigators 2011; Ukena 2012; Witkowski 2011; Zuern 2012) Mortality: no deaths reported during the stipulated study periods BP: all 12 studies (meta-analyses performed, separately for controlled and uncontrolled studies, and for different catheter type) Procedure safety	
Main Conclusion	RDN resulted in a substantial reduction in mean BP at 6 months in patients with resistant hypertension. The decrease in BP was similar irrespective of study design and type of catheter employed. Large RCTs with long-term follow-up are needed to confirm the sustained efficacy and safety of RDN.	

Quality assessment (based on NOKC checklist for systematic reviews)											
1	2	3	4	5	6	7	8	9	10	11	Quality
Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	HIGH
Comments:											

Article	Full reference	Gosain P, Garimella PS, Hart PD, Agarwal R. Renal Sympathetic Denervation for Treatment of Resistant Hypertension: A Systematic Review. J Clin Hypertens 2013;15(1):75-84.
Project details	Reviewed by	KBF and TR
	Date of review	10 September 2013
	Project name	WP5 Strand B 2nd pilot: Renal denervation systems for treatment-resistant hypertension
	Project ID	WP5-SB-12
Study type	Type of publication	Systematic review
	Country (area) Year	USA 2013
	Last updated search	June 2012
Research question/main objective	Systematically evaluate the existing literature on the safety and efficacy of renal sympathetic denervation in persons with resistant hypertension	
Included for	Clinical effectiveness	

Criteria for study design	*What study design(s) are included by the review:* RCTs Observational studies Case series Conference presentations Studies with <5 patients were excluded.
Population	*Patient characteristics:* Not clearly pre-defined in any inclusion criteria Resistant hypertension is defined as the failure to achieve a goal BP in persons adhering to full doses of a 3-drug antihypertensive regimen that includes a diuretic
	Disease/condition: -Resistant hypertension
Intervention	Not clearly pre-defined in any inclusion criteria Catheterbased endovascular renal artery sympathetic denervation
Comparison	Not clearly pre-defined in any inclusion criteria
Outcomes	*Outcomes assessed:* BP Complications (adverse events) Kidney function Decrease in number of medications (may affect activities of daily living, question D0016)
Sources of information	*Databases:* Medline; Cochrane Library
	Other sources of information: The American College of Cardiology, the American Society of Nephrology, and Google Scholar databases were also searched for conference proceedings and presentations.
Studies included for the different outcomes	*Total:* 19 studies included 2 RCTs (Ukena 2011; Esler 2010) 4 case-control studies (Mahfoud 2011b, Mahfoud 2012; Brandt 2012b; Krum 2012) 13 case series (Bauer 2012; Hering 2012; Himmel 2012; Mabin 2012; Mylotte 2012; Prochnau 2012a; Prochnau 2012b; Vase 2012; Verloop 2012; Simonetti 2011; Voskuil 2011; Witkowsky 2011) BP (change in BP, home-based BP measurement and ABPM, maintainance of BP reduction at 12 months) (2 RCTs (Ukena 2011; Esler 2010) and 4 case-control studies (Mahfoud 2012; Brandt 2012b; Mahfoud 2011b; Krum 2009) and in 8 case series (Hering 2012; Himmel 2012;Mabin 2012;Mylotte 2012; Verloop 2012; Symplicity HTN-1 2011; Voskuil 2011; Witkowsky 2011) Decrease in number of medications reported as narrative summary, reference to 11 studies. Change in renal function: 2 RCTs (Ukena 2011; Esler 2010) and 4 case-control studies (Mahfoud 2012; Brandt 2012b; Mahfoud 2011b; Krum 2009) and in 8 case series (Hering 2012; Prochnau 2012a; Prochnau 2012b; Vase 2012; Symplicity HTN-1 2011; Simonetti 2011; Voskuil 2011; Witkowsky 2011) Adverse events: -periprocedural adverse events (for pseudoaneurysm: Ukena 2011; Mahfoud 2011b; Brandt 2012b; Symplicity HTN-1 Investigators 2011 and for renal artery dissection: Brandt 2012b; Symplicity HTN-1 Investigators 2011) -back and/or flank pain (Mahfoud 2011b; Mabin 2012, Symplicity HTN-1 Investigators 2011) -intraprocedural bradycardia requiring atropine (Ukena 2011) -no changes in renal artery anatomy or development of clinical significant stenosis on follow-up CT-angiography and MR imaging studies (? Studies)
Main Conclusion	Our review suggests that renal sympathetic denervation has a role in the management of carefully selected patients with resistant hypertension. Currently ongoing and future research will provide further evidence about the efficacy and safety and should clarify unanswered questions about patient selection and the intervention itself.

Quality assessment (based on NOKC checklist for systematic reviews)

1	2	3	4	5	6	7	8	9	10	11	**Quality**
Y	U	Y	Y	Y	Y	Y	N	U	U	U	HIGH

Comments:

Table 16: Evidence tables for controlled trials

Article	Ahmed H, Neuzil P, Schejbalova M, Bejr M, Kralovec S, Reddy VY. Renal sympathetic denervation for the management of chronic hypertension (Relief): 40 patient analysis. Circulation 2012;Conference(var.pagings) Volume 126(21) Supplement, 20 November 2012. Abstracts From the American Heart Association 2012 Scientific Sessions and Resuscitation Science Symposium	
Project details	Reviewed by	TR and KBF
	Date of review	19 September 2013
	Project name	WP5 Strand B 2nd pilot: Renal denervation systems for treatment-

		resistant hypertension
	Project ID	WP5-SB-12
Study type	Prospective, randomised, single-blinded controlled trial	
Study objective	Considered whether renal sympathetic denervation (RSDN) could be achieved using an off-the-shelf saline-irrigated radiofrequency ablation (RFA) catheter typically employed for cardiac tissue ablation.	
Included for domain(s)	Clinical effectiveness	
Study inclusion/ exclusion criteria	Patients with hypertension refractory to ≥3 anti-hypertensive drugs, including one diuretic	
No. participants	Total: 40 Intervention: 19 Control: 21	
Population	**Baseline characteristics**	**Intervention** / **Control**
	Age (years, mean+/-SD)	Not reported / Not reported
	Sex	Not reported / Not reported
	Resting BP (mm Hg, mean+/-SD)	Not reported / Not reported
	eGFR (ml/min/1,73 m^2 , mean+/-SD)	Not reported / Not reported
	No. hypertensive drugs (mean+/-SD)	Not reported / Not reported
Intervention	Bilateral RSDN with a saline-irrigated RFA catheter	
Comparison	Sham procedure (manipulation of catheter within the renal arteries without the delivery of any energy)	
Co-intervention description	Not reported	
Follow-up	3 months (Measurements at baseline and at 3 mo.)	
Outcomes	Ambulatory BP recordings (24-hour)	

Article	Mahfoud et al.: Renal denervation reduces left ventricular mass in patients with resistant hypertension - results from a multicenter CMR-study. Journal of Cardiovascular Magnetic Resonance 2013b 15(Suppl 1):E108. (doi:10.1186/1532-429X-15-S1-E108)	
Project details	Reviewed by	TR and KBF
	Date of review	20 September 2013
	Project name	WP5 Strand B 2nd pilot: Renal denervation systems for treatment-resistant hypertension
	Project ID	WP5-SB-12
Study type	Controlled trial (non-randomised)	
Study objective	To investigate the effect of RD on left ventricular mass, assessed by cardiac magnetic resonance (CMR), in patients with resistant hypertension compared to a control group of medical treated patients.	
Included for domain(s)	Clinical effectiveness	
Study inclusion/ exclusion criteria	Patients with resistant hypertension (defined as office systolic BP >160 mmHg and >150 mmHg for patients with type 2 diabetes)	
No. participants	Total: 46 Intervention:37 Control: 9	

Population	**Baseline characteristics** / **Intervention** / **Control** Age (years, mean+/-SD) / 63 ± 11 / 70 ± 8 Sex / Not reported / Not reported Resting BP (mm Hg, mean+/-SD) / Not reported / Not reported eGFR (ml/min/1,73 m^2 , mean+/-SD) / Not reported / Not reported No. hypertensive drugs (mean+/-SD) / Not reported / Not reported Reported as poorly controlled BP and heavily medicated
Intervention	Catheter-based renal denervation (RD)
Comparison	Medical treated patients.
Co-intervention description	None
Follow-up	6 months
Outcomes	• left ventricular mass, assessed by cardiac magnetic resonance (CMR) • Ejection fraction • End systolic volume / end diastolic volume

Pokushalov was included in the SR by Davis 2013. It was described and assessed for risk of bias therein.

Article	Ukena C, Mahfoud F, Kindermann I, Barth C, Lenski M, Kindermann M, et al. Cardiorespiratory response to exercise after renal sympathetic denervation in patients with resistant hypertension. J Am Coll Cardiol 2011;58(11):1176-82.	
Project details	Reviewed by	TR and KBF
	Date of review	19 September 2013
	Project name	WP5 Strand B 2nd pilot: Renal denervation systems for treatment-resistant hypertension
	Project ID	WP5-SB-12
Study type	RCT. Multicentre, single country (Germany)	
Study objective	To investigate the effects of interventional renal sympathetic denervation (RD) on cardiorespiratory response to exercise.	
Included for domain(s)	Clinical effectiveness	
Study inclusion/ exclusion criteria	Resistant hypertension BP≥160 mm Hg (≥150 for type 2 diabetics) despite use of ≥3 antihypertensive drugs (including a diuretic). Exclusion criteria include: estimated glomerular filtration rate (eGFR; based on the Modification of Diet in Renal Disease criteria12) of less than 45 mL/min per 1.73 m^2, type 1 diabetes, contraindications to MRI, substantial stenotic valvular heart disease, pregnancy or planned pregnancy during the study, and a history of myocardial infarction, unstable angina, or cerebrovascular accident in the previous 6 months.	
No. participants	Total: 46 Intervention: 37 Control: 9	
Population	**Baseline characteristics** / **Intervention** / **Control** Age (years, mean+/-SD) / 59,1+/-9,4 / 64,9+/-6,4 Sex / Male 25 (68 %) / Male 7 (79 %) Resting BP (mm Hg, mean+/-SD) / SBP 172+/-24 DBP 94+/-19 / SBP 166+/-23 DBP 90+/-7 eGFR (ml/min/1,73 m^2 , mean+/-SD) / 70+/-24 / 64,5+/-16 No. hypertensive drugs (mean+/-SD) / 5,9+/-1,4 / 5,0+/-1,2	
Intervention	The femoral artery was accessed with the standard endovascular technique and the Symplicity catheter was advanced into the renal artery and connected to a radiofrequency generator. Four-to-six discrete, low-power radio frequency treatments were applied along the length of both main renal arteries.	
Comparison	Standard pharmaceutical treatment	
Co-intervention description	Changes to baseline doses of all anti-hypertensive drugs were not allowed, unless judged medically necessary because of changes in BP in association with signs or symptoms.	
Follow-up	3 months (Measurements at baseline and at 3 mo.)	

Outcomes	• Cardiopulmonary exercise testing: breath-by-breath gas exchange analyses. Exercise on reclining ergometer, work rate increased continuously by 15 W/min. ECG continuously, BP measured every 2 min. manually by experienced physician. • Maximum achieved work rate • Peak oxygen consumption • Oxygen uptake at the anaerobic threshold (AT) • VE/VCO_2 • Heart rate recovery: reduction in heart rate from peak exercise to the heart rate 1 min after the cessation of exercise

Risk of bias tables

Risk of bias tables for the 'safety' domain

Quality of bias was assessed using the Cochrane risk of bias checklist for RCTs (Higgins 2011), selecting the specific criteria relevant for each design.

Table 17: Risk of bias tables of included RCTs (3 in total)

Entry (Symplicity HTN-2 2010)	Judgment	Support for judgment
Random sequence generation (selection bias)	Low risk of bias	Patients randomly assigned to intervention or control group using a sealed envelope (1:1)
Allocation concealment (selection bias)	Low risk of bias	Patients randomly assigned using a sealed envelope
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Not reported. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is unclear if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	Three losses in each group.
Selective reporting (reporting bias)	Unclear risk of bias	Not all of the pre-specified safety outcomes have been reported in a pre-specified way.
Other biases	Unclear risk of bias	Funded by Ardian Inc.

Entry (Ukena 2011)	Judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk of bias	Random assignment of patients to control and RD group in a 1 to 3 ratio (9 control, 37 RD). However, this study included 28 patients included in the Simplicity HTN-2 trial but extended with an extra 18 patients with the same inclusion and exclusion criteria. The HTN-2 trial used 1:2 ratio and how this was converted to a 1:3 ratio is not described
Allocation concealment (selection bias)	High risk of bias	Not reported. Unclear if allocation was properly concealed as this study included patients from one study extended by additional patients.
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants knew treatment allocation. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is unclear if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	Complete outcome data acquired
Selective reporting (reporting bias)	High risk of bias	Safety outcomes are reported incompletely. Authors only report that RDN was performed without serious adverse events in all patients. Definitions of what is considered a serious adverse event are not provided and post-procedural adverse events are not reported.
Other biases	Unclear risk of	All authors have worked at centers receiving per-patient

	bias	payment for study involvement as part of the Simplicity HTN-1 and HTN-2 study.

Entry (Pokushalov 2012)	Judgment	Support for judgment
Random sequence generation (selection bias)	Low risk of bias	Patients randomly assigned to intervention or control group using a coded envelope system (14:13)
Allocation concealment (selection bias)	Low risk of bias	Patients randomly assigned to intervention or control group using a coded envelope system
Blinding of participants and personnel (performance bias)	Low risk of bias	Described as a prospective doble-blind randomised study.
Blinding of outcome assessment (detection bias)	Low risk of bias	Described as a prospective doble-blind randomised study.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data.
Selective reporting (reporting bias)	High risk of bias	Safety outcomes are not pre-specified and adverse events are reported incompletely. Authors only report that no procedure related complications or stenosis ocurred.
Other biases	Unclear risk of bias	Two authors have served as consultants with Medtronic and Biosense Webster. One author has received research grnas from Medtronic and Biosense Webster and another works for Ardian Inc.

Table 18: Risk of bias tables of included non-RCTs (3 in total)

Entry (Mahfoud et al 2012)	Judgment	Support for judgment
Random sequence generation (selection bias)		N/A
Allocation concealment (selection bias)	Unclear risk of bias	It is unclear how patients were allocated. It indicates that 88 patients were prospectively assigned to intervention group following protocols of ongoing trials and 12 to the control group. It states that patients were matched in terms of baseline characteristics. 19 patients were included in HTN-1 or HTN-2 trial.
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants knew treatment allocation. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments..
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data
Selective reporting (reporting bias)	High risk of bias	Safety outcomes are not pre-specified. Authors report that the procedure was performed without any complication in 97% of the patients and that no significant post-procedural artery stenosis or aneurysms were detected, Other post-procedural complications are not accounted for.
Other biases	Unclear risk of bias	Funded by Ardian Inc. An author is an employee of Ardian Inc. And another is supported by a Senior Research Fellowship.

Entry (Mahfoud et al 2011b)	Judgment	Support for judgment
Random sequence generation (selection bias)		N/A
Allocation concealment (selection bias)	Unclear risk of bias	Includes 37 intervention and 13 controls, uncertainty as to how patients were allocated (17 interventions and 9 controls included in the HTN-2 trial). Patients were matched in terms of baseline characteristics
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants knew treatment allocation. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data
Selective reporting (reporting bias)	High risk of bias	Safety outcomes are not pre-specified and adverse events are incompletely documented. Authors only report that

		one treated patient developed a pseudoaneurysm and state that no other complications were observed. Authors do not document on post-procedural complications in neither group,
Other biases	Unclear risk of bias	Funded by Ardian Inc. An author is an employee of Ardian Inc. And another is supported by a Senior Research Fellowship.

Entry (Brandt et al 2012a)	Judgment	Support for judgment
Random sequence generation (selection bias)	N/A	
Allocation concealment (selection bias)	Unclear risk of bias	Includes 46 interventions and 18 controls. Uncertainty as to how patients were allocated. It establishes that patient demographic and clinical characteristics did not differ between the RD and control groups
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants knew treatment allocation. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Low risk of bias	Analysers masked to treatment assignment and sequence of images. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data
Selective reporting (reporting bias)	High risk of bias	Safety outcomes are not pre-specified and and adverse events incompletely documented.
Other biases	Unclear risk of bias	Funded by Ardian Inc. An author is a conslultan of Ardian Inc. and another has received a grant support.

Table 19: Risk of bias tables of observational studies (16 in total)

Entry (Symplicity HTN-1)	Judgment	Support for judgment
Selection bias	Unclear risk of bias	Does not report if it includes all patients that comply with preselection criteria (consecutive patients).
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not blinded to treatment. It states that clinicians were encouraged not to change medication unless absolutely necessary and this was more strictly applied in the first year. It is uncertain if this could affect prescription and alter long term safety results.
Incomplete outcome data addressed (attrition bias)	Unclear risk of bias	81/92 patients have 6 months follow up data. It documents that the first 20 patients were assessed via angiography and the following patients by RMN, CT or duplex scan.
Selective reporting (reporting bias)	Low risk of bias	Safety outcomes are not pre-specified. Results given on periprocedural safety, renal vascular safety, renal function, postural hypotension and edema and pain.
Other biases	Unclear risk of bias	Funded by Ardian Inc. Three authors are employees of Ardian Inc.

Entry (Voskuil et al 2011)	Judgment	Support for judgment
Selection bias)	Unclear risk of bias	Does not report if it includes all patients that comply with preselection criteria (consecutive patients)
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Unclear risk of bias	81/92 patients have 6 months follow up data. It documents that intravascular ultrasound was carried out in 3 patients.
Selective reporting (reporting bias)	High risk of bias	Safety outcomes are not pre-specified and complications incompletely documented. Authors report that no patients showed endovascular damage at final angiography and that in the small subgroup IVUS was performed (n=3) no

		dissections or other intravascular complications were reported,
Other biases	Unclear risk of bias	Conflict of interests not declared.

Entry (Brinkmann et al 2012)	Judgment	Support for judgment
Selection bias	Unclear risk of bias	Authors state that they included non pre-selected patients but give no further information.
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data
Selective reporting (reporting bias)	High risk of bias	Safety outcomes are not pre-specified and adverse events are incompletely documented. Authors only report that they encountered no procedure related serious adverse events.
Other biases	Low risk of bias	Absence of conflict of interest.

Entry (Hering et al 2012)	Judgment	Support for judgment
Selection bias	Unclear risk of bias	Does not report if it includes all patients that comply with preselection criteria (consecutive patients)
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	Follow up data for all patients (n=11) at 3 months and 8 patients at 6 months.
Selective reporting (reporting bias)	Unclear risk of bias	Safety outcomes are not pre-specified. Authors declare that there were no peri or post procedural complications and no compromise of treated arteries.
Other biases	Unclear risk of bias	Several investigators have received honoraria from Medtronic. Two authors serving on scientific advisory board and one author employed by Ardian Inc.

Entry (Mabin et al 2012)	Judgment	Support for judgment
Selection bias	Low risk of bias	Consecutive patients included.
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	Follow-up measurements were available for all patients at two weeks and one month, and 8/11 patients at two and three months.
Selective reporting (reporting bias)	High risk of bias	Safety outcomes are not pre-specified and adverse events inadequately recorded. Authors document that they were no serious complications at the puncture site and yet they report one renal artery dissection. They state that there were no device related serious complications with the exception of the worsening of a headache condition.
Other biases	Unclear risk of bias	Funded by ReCor Medical. One author is a member of the advisory board, two are consultants and one is an employee of ReCor Medical.

Entry (Esler et al 2012)	Judgment	Support for judgment
Selection bias	High risk of bias	Uncertainty regarding patient selection. Study provides results for 46 control patients from the HTN-2 trial that

		decided to cross over to RDN (9 excluded).
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	Follow up data for 35/37 included patients.
Selective reporting (reporting bias)	High risk of bias	Safety outcomes are not pre-specified and complications inadequately reported. Authors only make reference to complications that require hospitalization.
Other biases	Unclear risk of bias	Funded by Ardian Inc.

Entry (Prochnau et al 2012a)	**Judgment**	**Support for judgment**
Selection bias	Unclear risk of bias	Does not report if it includes all patients that comply with preselection criteria (consecutive patients)
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No losses reported
Selective reporting (reporting bias)	High risk of bias	Safety outcomes are not pre-specified and adverse events inadequately documented. Authors only report that there were no renal artery stenosis or .other abnormalities in all patients
Other biases	Low risk of bias	Absence of conflict of interest

Entry (Simonetti et al 2012)	**Judgment**	**Support for judgment**
Selection bias	Unclear risk of bias	Does not report if it includes all patients that comply with preselection criteria (consecutive patients)
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data
Selective reporting (reporting bias)	Unclear risk of bias	Safety outcomes are not pre-specified. Authors document that no complications occurred either intra- or periprocedurally or at the 30- and 60-day follow-up
Other biases	Unclear risk of bias	Absence of conflict of interest
Entry (Ukena et al 2012)	**Judgment**	**Support for judgment**
Selection bias	Unclear risk of bias	Does not report if it includes all patients that comply with preselection criteria (consecutive patients)
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Low risk of bias	Analysers blinded to treatment.
Incomplete outcome data addressed (attrition bias)	Unclear risk of bias	127/136 patients presented at 3-month follow-up and 88 patients at 6-month follow-up (6 M).
Selective reporting (reporting bias)	High risk of bias	Safety outcomes are not pre-specified. Authors document that no serious complications occurred.
Other biases	Unclear risk of bias	Funded by Ardian. All authors have received payment for study involvement.

Entry (Vase et al 2012)	Judgment	Support for judgment
Selection bias	Unclear risk of bias	Does not report if it includes all patients that comply with preselection criteria (consecutive patients)
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data.
Selective reporting (reporting bias)	Unclear risk of bias	Safety outcomes are not pre-specified. Authors document that no complications occurred during or after the procedure.
Other biases	Low risk of bias	Absence of conflict of interest

Entry (Zuern et al 2012)	Judgment	Support for judgment
Selection bias	Low risk of bias	Consecutive patients included
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data.
Selective reporting (reporting bias)	Unclear risk of bias	Safety outcomes are not pre-specified. Authors document that procedure was performed without periprocedural complications.
Other biases	Low risk of bias	Absence of conflict of interest.

Entry (Scheurig-Muenker et al 2012)	Judgment	Support for judgment
Selection bias	Low risk of bias	Consecutive patients included
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data.
Selective reporting (reporting bias)	Low risk of bias	Safety outcomes are not pre-specified but complications adequately described.
Other biases	Unclear risk of bias	Conflict of interests not declared.
Entry (Fontela et al 2013)	**Judgment**	**Support for judgment**
Selection bias	Unclear risk of bias	Does not report if it includes all patients that comply with preselection criteria (consecutive patients)
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data.
Selective reporting (reporting bias)	Unclear risk of bias	Safety outcomes are not pre-specified. Authors document that procedure was performed without incidents.
Other biases	Low risk of bias	Absence of conflict of interest.

Entry (Kaltenbach et al 2013)	Judgment	Support for judgment
Selection bias	Unclear risk of bias	Does not report if it includes all patients that comply with preselection criteria (consecutive patients)

Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data.
Selective reporting (reporting bias)	Unclear risk of bias	Study only contemplates procedural safety defined as freedom from renal abnormalities. Authors make reference to no serious adverse events related to the procedure or device.
Other biases	Unclear risk of bias	Not declared.

Entry (Ormiston et al 2013)	Judgment	Support for judgment
Selection bias	Unclear risk of bias	Does not report if it includes all patients that comply with preselection criteria (consecutive patients)
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data.
Selective reporting (reporting bias)	Low risk of bias	Safety endpoints clearly pre-specified
Other biases	Hig risk of bias	Funded by Covidien. Some authors received grants and one author is a board member of St Jude.

Entry (Worthley et al 2013)	Judgment	Support for judgment
Selection bias	Unclear risk of bias	Does not report if it includes all patients that comply with preselection criteria (consecutive patients)
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Participants were not blinded to treatment. Unclear as to how this could influence compliance with pharmacological medication and thus have an effect on safety aspects (for example, hypotensive and hypertensive crisis).
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Analysers were not masked to treatment assignment. It is uncertain if this can influence antihypertension treatment adjustments or safety assessments.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	No incomplete data.
Selective reporting (reporting bias)	Low risk of bias	Study provides a complete list of serious and non serious adverse events
Other biases	Unclear risk of bias	Not declared

Risk of bias tables for the 'clinical effectiveness' domain

Quality of the controlled trials (4 in total) was assessed using the Cochrane risk of bias checklist for RCTs (Higgins 2011).

Table 20: Risk of bias tables of included controlled trials (3 in total)

Entry (Ahmed 2012)	Judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk of bias	Not reported, other than "prospective, randomised, single-blinded trial"
Allocation concealment (selection bias)	Unclear risk of bias	Not reported, other than "prospective, randomised, single-blinded trial"
Blinding of participants and personnel (performance bias)	Low risk of bias	Participants blinded (reported as single-blinded trial)
Blinding of outcome assessment (detection bias)	Low risk of bias	Ambulatory BP recordings (24-hour) unlikely to be affected
Incomplete outcome data addressed (attrition bias)	Low risk of bias	Complete outcome data acquired

Selective reporting (reporting bias)	Low risk of bias	None detected
Other biases	Unclear risk of bias	Author Disclosures: H. Ahmed: None. P. Neuzil: None. M. Schejbalova: None. M. Bejr: None. S. Kralovec: None. V.Y. Reddy: Consultant/Advisory Board; Modest; Medtronic, Philips, Cardioinsight. Research Grant; Significant; Biosense-Webster, Medtronic, St Jude Medical, Boston-Scientific, Cardiofocus, Voyage Medical, Philips, ACT, Endosense, Vytronus. Consultant/Advisory Board; Significant; Biosense-Webster, St Jude Medical, Boston Scientific, Cardiofocus, Voyage Medical, ACT, Endosense, Vytronus

Entry (Mahfoud 2013b)	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	High risk of bias	Randomisation not described or not performed. "CMR was performed in 37 patients at baseline and 6 months after RD in a multicenter setting with 9 subjects serving as controls."
Allocation concealment (selection bias)	Unclear risk of bias	It is described as a mulitcenter study, but allocation is not described.
Blinding of participants and personnel (performance bias)	Low risk of bias	Lack of blinding unlikely to affect the outcomes LV mass and ejection fraction
Blinding of outcome assessment (detection bias)	Low risk of bias	"Clinical data and CMR results were analyzed blinded at both times."
Incomplete outcome data addressed (attrition bias)	High risk of bias	Patient flow not reported, neither how many that are included in the analyses and results
Selective reporting (reporting bias)	Unclear risk of bias	Seems like not all data are presented. Data reported as before-after within each group and not across groups.
Other biases	Unclear risk of bias	Funding by Medtronic.

Pokushalov was included in the SR by Davis 2013. It was described and assessed for risk of bias therein.

Entry (Ukena 2011)	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk of bias	Random assignment of patients to control and RD group in a 1 to 3 ratio (9 control, 37 RD). However, this study included 28 patients included in the Simplicity HTN-2 trial but extended with an extra 18 patients with the same inclusion and exclusion criteria. The HTN-2 trial used 1:2 ratio and how this was converted to a 1:3 ratio is not described
Allocation concealment (selection bias)	High risk of bias	Not reported. Hence, unclear if allocation was properly concealed as this study included patients from one study extended by additional patients.
Blinding of participants and personnel (performance bias)	Low risk of bias	Participants knew treatment allocation. Unclear if that would influence their exercise effort. "The physician supervising the exercise testing was blinded to the randomization"
Blinding of outcome assessment (detection bias)	Low risk of bias	"experienced physician used manual sphygmomanometer". Other assessments based on automated equipment.
Incomplete outcome data addressed (attrition bias)	Low risk of bias	Complete outcome data acquired
Selective reporting (reporting bias)	Low risk of bias	None detected
Other biases	Unclear risk of bias	All authors have worked at centers receiving per-patient payment for study involvement as part of the Simplicity HTN-1 and HTN-2 study.

GRADE profiles for the different outcomes

The classification and definitions of the quality of the evidence include: high (i.e. "We are very confident that the true effect lies close to that of the estimate of effect"), moderate (i.e. "We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different"), low (i.e. "Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect") and very low (i.e. "We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect").

GRADE profiles for 'safety' domain

Table 21: GRADE profiles for 'safety'

N° of studies / patients	Design	Risk of bias	Inconsistency	Indirectness	Other consider-ations	Effect size (%)	Quality of evidence	Importance
Outcome: total adverse events (in % of patients)								
3/228	RCTs	no serious risk of bias	no serious inconsistency	serious[1,2]	none	0-40.38 vs.0-9.26	⊕⊕OO LOW	CRITICAL
3/260	Open, non randomised, controlled	no serious risk of bias	no serious inconsistency	no serious indirectness	none	0-23.9 vs. 0	⊕⊕OO LOW	CRITICAL
18/599	Observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	none	0-100	⊕OOO VERY LOW	CRITICAL
Outcome: major adverse events (in % of patients)								
4/274	RCTs	no serious risk of bias	no serious inconsistency	serious[1,2]	none	0-15.38 vs. 0-9.26	⊕⊕OO LOW	CRITICAL
3/260	Open, non randomised, controlled	no serious risk of bias	no serious inconsistency	no serious indirectness	none	0 vs. 0	⊕⊕OO LOW	CRITICAL
18/599	Observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	none	0-33.33	⊕OOO VERY LOW	CRITICAL

[1]Tested pulmonary vein isolation +/- renal denervation. Participants had atrial fibrillation in addition to treatment resistant hypertension.
[2] Combination of different catheter types. Uncertain transferability.

GRADE profiles for 'clinical effectiveness' domain

Table 22a: GRADE profiles for 'clinical effectiveness'– mortality and cardiovascular morbidity

Quality assessment							N° of patients		Effect		Quality	Importance
N° of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consid-erations	Renal denervation	Control	Relative (95% CI)	Absolute		
Overall mortality												
Assessed narratively as No change (Davis 2013)												CRITICAL
Cardiovascular mortality												
This was not assessed in any of the included SRs and controlled trials												CRITICAL
Stroke, heart failure, heart disease												
No evidence available												CRITICAL
LV mass (hypertrophy) - Symplicity° - LV mass post treatment at 6 months (measured with: LV mass/body surface area (g/m2); Better indicated by lower values)												
1	non-RCT	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	very serious[1,3]	none	46	18	-	MD 23.8 lower (40.16 to 7.44 lower)	⊕OOO VERY LOW	IMPORTANT
LV hypertrophy - Symplicity° - LV mass post treatment at 6 months (measured with: LV mass indexed to height 1.7 (g/m1.7); better indicated by lower values)												

1	non-RCT	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	very serious[1,3]	none	37	9	-	MD 3.6 higher (3.57 lower to 10.77 higher)	⊕OOO VERY LOW	IMPORTANT
LV hypertrophy – Navistar ThermoCool®- LV mass change at 6 months (measured with: LVMI (g/m); better indicated by lower values)												
1	RCT	no serious risk of bias	no serious inconsistency	serious[4]	very serious[1,3]	none	13	14	-	MD 15.4 lower (20.05 to 10.75 lower)	⊕OOO VERY LOW	IMPORTANT

[1]Few participants (GRADE give suggested recommendation for imprecision: total population size is less than 400 (a threshold rule-of-thumb value; using the usual Iǂ and I², and an effect size of 0.2 standard deviation (SD), representing a small effect)
[2] Controlled but not randomised trial.
[3] Only one study, unknown reproducibility
[4]Tested pulmonary vein isolation +/- renal denervation. Participants had atrial fibrillation in addition to treatment-resistant hypertension.
LV: left ventricular

Table 22b: GRADE profiles for 'clinical effectiveness' – BP

Quality assessment							**N° of patients**		**Effect**		**Quality**	**Importance**
N° of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consider-ations**	**Renal denervation**	**Control**	**Relative (95% CI)**	**Absolute**		
Change in systolic BP at 6 months (follow-up 6 months; measured with: Office based (mm Hg); Better indicated by lower values)												
3	RCTs	no serious risk of bias[1]	no serious inconsistency	serious[2,3]	serious[4]	none	88	70	-	MD 29.80 lower (37.2 to 20.6 lower)	⊕⊕OO LOW	CRITICAL
Symplicity® - Change in SBP at 6 months (measured with: Office-based (mm Hg); Better indicated by lower values)												
2	RCTs	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[4]	none	75	56	-	MD 33.6 lower (41.33 to 25.88 lower)	⊕⊕⊕O MODERATE	CRITICAL
Navistar - Change in SBP at 6 months (measured with: Office based (mm Hg); Better indicated by lower values)												
1	RCT	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4,5]	none	13	14	-	MD 23 lower (29.2 to 16.8 lower)	⊕OOO VERY LOW	CRITICAL
Change in DBP at 6 months (follow-up 6 months; measured with: Office based (mm Hg); Better indicated by lower values)												
3	RCTs	no serious risk of bias[1]	no serious inconsistency	serious[2,3]	serious[4]	none	88	70	-	MD 11.04 lower (16.41 to 5.68 lower)	⊕⊕OO LOW	CRITICAL
Symplicity® - Change in DBP at 6 months (measured with: Office-based (mm Hg); Better indicated by lower values)												
2	RCTs	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[4]	none	75	56	-	MD 13.76 lower (20.25 to 7.27 lower)	⊕⊕⊕O MODERATE	CRITICAL
Navistar - Change in DBP at 6 months (measured with: Office based (mm Hg); Better indicated by lower values)												
1	RCT	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4,5]	none	13	14	-	MD 7 lower (11.53 to 2.47 lower)	⊕OOO VERY LOW	CRITICAL

[1] Mix of randomised and non-randomised CT (Combined as in the SR).
[2] Tested pulmonary vein isolation +/- renal denervation. Participants had atrial fibrillation in addition to treatment-resistant hypertension.
[3] Combination of different catheter types. Uncertain transferability.
[4] Few participants (GRADE give suggested recommendation for imprecision : total population size is less than 400 (a threshold rule-of-thumb value; using the usual Îǂ and Î², and an effect size of 0.2 SD, representing a small effect).
[5] Only one study, unknown reproducibility
Mm Hg: millimeter mercury; MD: Mean difference

Table 22c: GRADE profiles for 'clinical effectiveness' – body function

Quality assessment							**N° of patients**		**Effect**		**Quality**	**Importance**
N° of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consider-ations**	**Renal dener-vation**	**Control**	**Relative (95% CI)**	**Absolute**		
Change in eGFR at 6 months - RCT (measured with: lab analysis; Better indicated by lower values)												
1	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	49	51	-	MD 0.7 lower (5.21 lower to 3.81 higher)	⊕⊕OO LOW	IMPORTANT
Change in creatinine at 6 months - RCT (measured with: lab analysis; Better indicated by lower values)												
1	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	49	51	-	MD 1.3 higher (4.38 lower to 6.98 higher)	⊕⊕OO LOW	IMPORTANT

[1] Few participants (GRADE give suggested recommendation for imprecision : total population size is less than 400 (a threshold rule-of-thumb value; using the usual Iǂ and I², and an effect size of 0.2 SD, representing a small effect).
[2] Only one study, unknown reproducibility
MD: Mean difference; eGFR: estimated glomerular filtration rate

Table 22d: GRADE profiles for 'clinical effectiveness' – activities of daily living

Quality assessment							N° of patients		Effect		Quality	Importance
N° of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Activity of daily living: exercise	Control	Relative (95% CI)	Absolute		
Change in max work rate at 3 months (follow-up 3 months; measured with: Watts on reclining ergometer; Better indicated by lower values)												
1	RCT	serious risk of bias[1]	no serious inconsistency	no serious indirectness[2]	very serious[3,4]	none	37	9	-	MD 3 higher (7.66 lower to 13.66 higher)	⊕OOO VERY LOW	IMPORTANT
Change in peak oxygen uptake at 3 months (follow-up 3 months; measured with: VO_2 peak ml/min/kg; Better indicated by higher values)												
1	RCT	serious risk of bias[1]	no serious inconsistency	no serious indirectness[2]	very serious[3,4]	none	37	9	-	MD 1.00 lower (2.46 lower to 0.46 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Unclear how randomization and allocation was performed.
[2] Unclear how well this test represent the patients' ability to manage activity of daily living.
[3] Only one study, unknown reproducibility
[4] Few participants (GRADE give suggested recommendation for imprecision : total population size is less than 400 (a threshold rule-of-thumb value; using the usual Î± and Î², and an effect size of 0.2 SD, representing a small effect).
MD: Mean difference; VO_2 peak: peak oxygen uptake

Table 22e: GRADE profiles for 'clinical effectiveness' - health related quality of life and patient satisfaction

Quality assessment							N° of patients		Effect		Quality	Importance
N° of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Renal denervation	Control	Relative (95% CI)	Absolute		
Quality of Life: generic (Better indicated by lower values)												
No evidence available												IMPORTANT
Quality of Life: disease specific (Better indicated by higher values)												
No evidence available												IMPORTANT
Patient satisfaction (Better indicated by higher values)												
No evidence available												IMPORTANT
Patient willingness to undergo renal denervation												
No evidence available												IMPORTANT
Change in need for medication (Better indicated by lower values)												
Assessed narratively as No change (Gosain 2013)												IMPORTANT

List of ongoing and planned studies

We performed searches in the WHO ITRP (International Clinical Trials Registry Platform) on 2.10.2013 with the following search combinations: Hypertension (in title) AND Denervation or catheter ablation (in intervention) which resulted in 65 records for 64 trials and Renal or kidney (in title) AND Hypertension (condition) AND Denervation or catheter ablation (Intervention) which resulted in 64 records for 63 trials. Out of these, 26 controlled studies were identified by 1 person and are listed in the table below.

Input from dedicated reviewers identified additionally 4 ongoing trials on renal denervation. They are added at the end of the table.

Table 23: Ongoing and planned studies

ID	Study name	Health condition (selected inclusion criteria) Target sample size	Intervention	Control	Primary outcomes
NCT01911078	Renal Sympathetic Denervation for Treatment of Metabolic Syndrome Associated Hypertension (Metabolic Syndrome Study)	Metabolic Syndrome Uncontrolled Hypertension N=60	Device: EnligHTN™ Renal Denervation System. Procedure: Renal Denervation	NR Study described as: Allocation: Randomised, Endpoint Classification: Efficacy Study, Intervention Model: Parallel Assignment, Masking: Open Label, Primary Purpose: Treatment	Insulin resistance BP 3 and 12 months
NCT01918111	Effects of ReEnal Denervation for Resistant Hypertension on Exercise Diastolic Function and Regression of Atherosclerosis and the Evaluation of NEW Methods Predicting A successfuL Renal Sympathetic Denervation (RENEWAL-EXERCISE, -REGRESS, and -PREDICT Trial From RENEWAL RDN Registry)	Systolic BP>140 mmHg (>130 mmHg for diabetes) or diastolic BP>90mmHg (>80 mmHg for diabetes) despite adequate administration of ≥3 different classes of anti-hypertensives N=52	Procedure: Renal denervation	Drug: adenosine infusion treatment Study described as: Allocation: Randomised, Intervention Model: Crossover Assignment, Masking: Open Label, Primary Purpose: Treatment	Change in coronary atheroma (24 months)
NCT01903187	Multi-center, Randomiszed, Single-blind, Sham Controlled Clinical Investigation of Renal Denervation for Uncontrolled Hypertension	Office Systolic BP = 160 mmHg (office Systolic BP = 150mmHg for DM2) N=590	Device: EnligHTN™ Renal Denervation	Other: Sham	Reduction of Office Systolic BP (6 months) Proportion of subjects who experience any Major Adverse Event
NCT01897545	Combined Treatment of Arterial Hypertension and Atrial Fibrillation	Arterial Hypertension Atrial Fibrillation N=60	Procedure: PVI + renal denervation	Procedure: Circumferential PVI	Freedom of AF or other atrial arrhythmias (1 year) Systolic BP lowering (1year)
NCT01874470 Allegro-HTN	Renal Denervation by Allegro System in Patients With Resistant Hypertension	Resistant hypertension N=160	Procedure: Renal denervation	Other: standard medication	Change in office-based systolic BP (SBP) (6 months)
NCT01865240	Renal Denervation for Resistant Hypertension	systolic BP =140mmHg or 130mmHg for patients with diabetes Concurrent treatment with 3 anti-hypertensive drugs N=100	Procedure: Renal Denervation	NR Study described as: Allocation: Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Open Label,	BP control (6 months)

ID	Study name	Health condition (selected inclusion criteria) Target sample size	Intervention	Control	Primary outcomes
				Primary Purpose: Treatment	
NCT01850901	Renal Sympathetic Denervation as a New Treatment for Therapy Resistant Hypertension	Mean day-time SBP = 135 mmHg (ABPM), while using 3 or more antihypertensives N=300	Procedure: Renal sympathetic denervation	NR Study described as: Allocation: Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Open Label, Primary Purpose: Treatment	Change in BP (measured by ABPM) (6 months)
NCT01713270	Renal Sympathetic Denervation in Patients With Drug-resistant Hypertension and Symptomatic Atrial Fibrillation	N=100	Procedure: Direct-Current Cardioversion Procedure: renal sympathetic denervation	NR Study described as: Allocation: Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Single Blind (Outcomes Assessor), Primary Purpose: Treatment	Change in atrial fibrillation burden (12 months)
NCT01673516	Effect of Renal Sympathetic Denervation on Resistant Hypertension and Cardiovascular Hemodynamic in Comparison to Intensive Medical Therapy Utilizing Impedance Cardiography	Average SBP >140mmHg, measured per guidelines ≥3 antihypertensives N=60	Device: The HOTMAN® System Procedure: The Symplicity® Renal Denervation System	NR Study described as: Allocation: Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Open Label, Primary Purpose: Treatment	Absolute change in office systolic BP (SBP) (6 months)
NCT01656096	Renal Sympathetic Denervation in Mild Refractory Hypertension	Refractory hypertension: 3 or more antihypertensive agents of different classes (including a diuretic) N=70	Device: Renal sympathetic denervation (Symplicity® ablation catheter, Medtronic Inc. Minneapolis, Minnesota, USA)	Other: Sham procedure	Change in systolic BP (ABPM mean value) (6 months)
NCT01635998	Adjunctive Renal Sympathetic Denervation to Modify Hypertension as Upstream Therapy in the Treatment of Atrial Fibrillation	History of AF planned catheter ablation procedure Hypertension (SBP =160 mm Hg and/or DBP =100 mmHg) and receiving treatment with at least one antihypertensive medication N=300	Procedure: Renal sympathetic denervation	NR Study described as: Allocation: Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Double Blind (Subject, Outcomes Assessor), Primary Purpose: Treatment	Anti-arrhythmic drug (AAD)-free single-procedure freedom from atrial fibrillation recurrence (12 months)
NCT01644604	Renal Denervation by MDT-2211 System in Patients With Uncontrolled Hypertension	≥3 anti-hypertensives of which one must be a diuretic Office systolic BP (SBP) of = 160 mmHg N=100	Device: MDT-2211 Renal Denervation System	NR Study described as: Allocation: Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Open Label, Primary Purpose: Treatment	Change in Office Systolic BP (6 months)
NCT01628172	Renal Sympathetic Denervation for the Management of Chronic Hypertension	Uncontrolled hypertension (SBP = 140 mmHg during 24H ABPM) >= 3 anti-hypertensive drugs (including at least one diuretic) N=100	Device: Biosense Webster Celcius Thermacool® catheter	NR Study described as: Allocation: Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment,	Change in 24h ABPM (6 months)

ID	Study name	Health condition (selected inclusion criteria) Target sample size	Intervention	Control	Primary outcomes
				Masking: Single Blind (Subject), Primary Purpose: Treatment	
NTR3444	Comparison of renal sympathetic denervation with spironolactone in patients with still a high BP despite the use of 3 different antihypertensive agents.	Hypertension, Renal sympathetic denervation, Spironolactone N=120	The intervention consists of endovascular renal sympathetic denervation	Addition of spironolactone to existing antihypertensive treatment.	Difference in 24h ABPM - between spironolactone and renal denervation (6 months)
NCT01570777	Renal Denervation in Hypertension	Office BP =140 and/or 90 mmHg ≥ 3 anti-hypertensives including a diuretic N=120	Procedure: renal denervation and optimised medication regimen	Procedure: optimised medication regimen	Cost-effectiveness evaluation (1 year) Mean diurnal systolic BP assessed by ABPM (6 months)
NCT01522430	Study of Catheter Based Renal Denervation Therapy in Hypertension	> 3 antihypertensives including a thiazide or a loop diuretic and at least one attempt to treat with spironolactone Daytime ABPM 135 mmHg and/or 85 mmHg, respectively, is acceptable for inclusion in the study if the patient takes four or more antihypertensive medications N=120	Procedure: Renal angiography followed by renal sympathetic denervation	Procedure: Renal angiography alone	Ambulatory systolic and diastolic BP (6 months) Glomerular filtration rate (6 months)
NCT01505010	Renal Denervation for Management of Drug-Resistant Hypertension	Under maximal therapy, the 24-h ambulatory BP should be 130 mm Hg systolic or 80 mm Hg diastolic or higher. N=84	Procedure: Renal denervation	NR Study described as: Allocation: Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Single Blind (Outcomes Assessor), Primary Purpose: Treatment	Decrease in systolic BP on daytime ambulatory measurement (36 months)
NCT01418261	Renal Denervation in Patients With Uncontrolled Hypertension (SYMPLICITY HTN-3)	≥3 anti-hypertensives one must be a diuretic Office systolic BP (SBP) of 160 mmHg N=530	Device: Renal denervation (Symplicity® Catheter System)	NR Study described as: Allocation: Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Single Blind (Subject), Primary Purpose: Treatment	Change in Office Systolic BP (6 months) Incidence of Major Adverse Events through 1 month post-randomisation (Renal artery stenosis measured at 6 months)
NCT01390831	Renal Denervation in Patients With Uncontrolled Hypertension in Chinese	Systolic BP of 160 mmHg or more and/or a diastolic BP of 90 mmHg or more Receiving and adhering to at least ≥ 3 appropriate antihypertensives N=100	Device: THERMOCOOL® Catheter	NR Study described as: Allocation: Non-Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Single Blind (Outcomes Assessor), Primary Purpose: Treatment	BP Reduction (1year)
NCT01366625	Renal Denervation in Patients With Resistant Hypertension and Obstructive Sleep	Systolic BP ≥140 mmHg (office); ≥3 antihypertensives (including diuretic)	Device: Renal denervation with a catheter-based procedure (Sym-	NR Study described as: Allocation: Randomised, Endpoint Classi-	BP Reduction (3 months)

ID	Study name	Health condition (selected inclusion criteria) Target sample size	Intervention	Control	Primary outcomes
	Apnea	N=100	plicity® Catheter System)	fication: Efficacy Study, Intervention Model: Parallel Assignment, Masking: Open Label, Primary Purpose: Treatment	
NCT01117025	Combined Treatment of Resistant Hypertension and Atrial Fibrillation	N=26	Procedure: Circumferential PV isolation Procedure: Circumferential PVI+renal denervation	Allocation: Randomized, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Double Blind (Subject, Outcomes Assessor), Primary Purpose: Treatment	Pokushalov, INCLUDED
NCT00888433	Renal Denervation in Patients With Uncontrolled Hypertension (Symplicity HTN-2)	N=106	Device: Renal Denervation (Symplicity® Catheter System)	Allocation: Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Open Label, Primary Purpose: Treatment	Published HTN-2 INCLUDED
NTR4109	Ablation of Sympathetic Atrial Fibrillation	Atrial Fibrillation, High BP N=243 Recruitment pending	Procedure: Renal artery denervation Renal artery denervation and pulmonary vein isolation	Pulmonary vein isolation	Time to first detection of atrial fibrillation >30 seconds, with the monitoring period starting 3 months after the intervention
NCT01785732	Renal Sympathetic Denervation and Insulin Sensitivity (RENSYMPIS Study)	Resistant Hypertension (systolic BP >160mmHg and 3 or more antihypertensive agents in use N=60	Procedure: Renal Denervation	NR Study described as: Allocation: Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Open Label, Primary Purpose: Treatment	Office BP (2 years)
NCT01848275	Full Length Versus Proximal Renal Arteries Ablation	Office systolic BP of 160 mm Hg or more, ≥3 antihypertensives N=40	Device: Thermocool® catheter	NR Study described as: Allocation: Randomised, Endpoint Classification: Safety/Efficacy Study, Intervention Model: Parallel Assignment, Masking: Open Label, Primary Purpose: Treatment	BP (1 year)
NCT01888315	Influence of Catheter-based Renal Denervation in Diseases With Increased Sympathetic Activity	Patient scheduled for renal sympathetic denervation using market-released device. N=1000	Renal denervation with EnligHTN™ St. Jude Medical Renal denervation with Paradise™ ReCor Medical Renal denervation with Symplicity® Flex Medtronic/Ardian Renal denervation with Vessix V2™ Boston Scientific	Described as non-randomised	Safety and efficacy of renal denervation (6 months)
NCT01560312	Renal Denervation in Refractory Hypertension PRAGUE-15	Hypertension, Resistant to Conventional Therapy	Device: Renal denervation (Symplicity®	Study described as: Allocation: Randomised, Endpoint Classi-	BP difference (6 months, 5 years)

ID	Study name	Health condition (selected inclusion criteria) Target sample size	Intervention	Control	Primary outcomes
		N=150	Catheter System™)	fication: Efficacy Study, Intervention Model: Single Group Assignment, Masking: Open Label, Primary Purpose: Treatment	
NCT01459900	Renal Sympathectomy in Treatment-resistant Essential Hypertension, a Sham Controlled Randomized Trial ReSET	Hypertension (Systolic daytime ambulatory BP at least 145 mmHg and compliance to a minimum of 3 antihypertensive drugs, including a diuretic, or in case of diuretic intolerance at least 3 nondiuretic antihypertensive drugs.) N=70	Procedure: Renal angiography Procedure: Renal artery ablation	Study described as: Allocation: Randomised, Endpoint Classification: Efficacy Study, Intervention Model: Parallel Assignment, Masking: Double Blind (Subject, Caregiver), Primary Purpose: Treatment	Daytime systolic BP assessed by 24 hours ambulatory BP measurement (3 months)
EudraCT 2012-001066-14	Sympathetic renal denervation versus increment of pharmacological treatment in resistant arterial hypertension DENERVHTA	Subjects with diagnosed resistant arterial hypertension (office BP ≥ 140 and/or 90 mmHg despite ≥3 antihypertensive drugs given at the maximum tolerated therapeutic dosage, one diuretic), for at least the last 3 months. N=50	Percutaneous catheter-based renal sympathetic denervation	Addition of spironolactone to the baseline pharmacological treatment	Change in ambulatory 24h-systolic BP (SBP) from baseline (Visit 0) to Final Examination (6 months).
EudraCt 2011-004995-13	Endovascular renal sympathetic denervation versus spironolactone for treatment-resistant hypertension: a randomized, multicentric study	Treatment-resistant hypertension N=130	Endovascular renal sympathetic denervation	Spironolactone (up to 50 mg)	Difference in 24-hour ambulatory BP decrease between the RFSD and spironolactone group (6 months)

ABPM-ambulatory blood pressure monitoring; BP: blood pressure; mmHg: millimetre mercury; DM: diabetes mellitus; PVI: pulmonary vein isolation; AF: atrial fibrillation; SBP: systolic blood pressure; NR: not reported; ABPM: ambulatory blood pressure monitoring; DBP: diastolic blood pressure; AAD: anti-arrythmic drug

Applicability table

Table 24: Summary table characterising the applicability of the body of evidence

Domain	Description of applicability of evidence
Population	The major studies included patients older than 18 years, with office based SBP of ≥160 mm Hg despite use of at least 3 antihypertensive drugs at adequate dose (including one diuretic). They excluded patients with secondary causes of hypertension, type 1 diabetes, renovascular abnormalities, reduced kidney function (eGFR <45 ml/min/1.73 m^2 by modification of diet in renal disease criteria). These criteria seem to be in accordance with the intended patient population of treatment-resistant hypertensions. The need for normal renal nerve anatomy/access is necessary based on how the procedure is performed.
Intervention	Renal denervation was performed in addition to continuation of full pharmaceutical treatment. The procedure requires delivery of radiofrequency along the renal arteries to result in denervation. There is no immediate way to determine if the ablation has been successful. Currently the Symplicity® catheter has been used in most of the controlled studies, but other catheters are currently being explored. There may or may not be differences in efficacy and safety depending on the catheter used and mode of ablation. The surgeon's technical expertise could influence the risk for local side effects. If being introduced as a new treatment method in European hospitals, the procedure will (as all new interventions) be accompanied by a learning curve.
Comparators	The comparator in the controlled studies was either no intervention or sham treatment. Both intervention and control group continued with standard pharmacological treatment. As the inclusion criteria was treatment-resistant hypertension despite at least 3 different drugs, one could argue that addition of further classes of antihypertensive drugs, change in dosing or other interventions might have been a valid alternative. However, Gosain and colleagues reported that the average number of antihypertensive medications was 5 in most studies so it may be difficult to find a suitable pharmacological comparator (Gosain 2013).
Outcomes	Short-term outcomes and surrogate outcomes have been used in the studies while important clinical endpoints (overall mortality, cardiovascular mortality and major events like stroke, myocardial infarction and heart failure) have not been analysed. Neither have the studies focused on how this intervention may affect outcomes such as patient satisfaction, quality of life and activities of daily living. The full clinical benefit is therefore unknown.
Setting	Participants in the studies were recruited from secondary or tertiary care in Europe, Australia and USA. This probably reflects the setting in which this intervention may typically be used. Study duration was 3 to 12 months in the controlled trials. However, some extensions or uncontrolled trials used other durations. As hypertension usually requires continued follow-up over an extensive time-frame this is also relevant for renal denervations to be able to detect changes over time.

APPENDIX 2: RESULT CARDS

Health Problem and Current Use of the Technology

A0001: For which indication or for what purposes is renal denervation used, and are there any contra-indications?

Methods

☒ See general description of methods (Appendix 1)

Source of information:

- Basic search ☒
- Domain search ☐
- Other: additional search for guidelines in pubmed, searching reference lists

Critical appraisal criteria not applicable

Method of synthesis: narrative

Result

An expert consensus document with the contribution from 11 European countries published in 2013 from the European Society of Cardiology on catheter-based renal denervation forms the basis for the following criteria that patients should comply with before renal denervation is considered (Mahfoud 2013a):

- Office-based systolic BP ≥ 160 mm Hg (≥150 mm Hg diabetes type 2) despite use of ≥3 antihypertensive drugs in adequate dosage and combination (incl. diuretic)
- Treatment resistance to lifestyle modification
- Exclusion of secondary hypertension
- Exclusion of pseudo-resistance using ambulatory BP monitoring (average BP >130 mm Hg or mean daytime BP >135 mm Hg)
- Preserved renal function (glomerular filtration rate ≥45 ml/min/1.73 m^2)
- Eligible renal arteries: no polar or accessory arteries, no renal artery stenosis, no prior revascularization

A position paper from the European Society of Hypertension published in 2012 (Schmieder 2012) describe criteria which are generally in accordance with the above. Patients are eligible if they have:

- "…(severe) treatment-resistant hypertension defined by office SBP at least 160 systolic (>150 mm Hg in type 2 diabetes) despite treatment with at least three antihypertensive drugs of different types in adequate doses, including one diuretic, which is equivalent to stage 2 or 3 hypertension".
- Pseudoresistance have to be excluded
- Non-adherence to drug therapy must be refuted

- "Persisting high office BP in spite of drug treatment should be confirmed with home and most importantly with 24-h ambulatory BP monitoring, since up to one-third of treatment-'resistant' hypertensive patients have normal BP outside the office (false resistant hypertension due to persisting white-coat effect during treatment)"
- Identification of contributing lifestyle factors must be made along with screening for secondary causes of hypertension in order to attempt to control BP by removal.

The following contraindications are described in the above papers:

- Previous renal artery intervention (balloon angioplasty or stenting)
- Evidence of renal artery atherosclerosis (defined as a renal artery stenosis > 50 %)
- Presence of multiple main renal arteries in either kidneys or main renal arteries of < 4 mm in diameter or <20 mm in length
- Patients should be in stable clinical conditions (RDN is not an emergency treatment), thus ruling out patients with recent myocardial infarction, unstable angina pectoris, or a cerebrovascular accident within the past 3–6 months.

Discussion

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References

Mahfoud F. Expert consensus document from the European Society of Cardiology on catheter-based renal denervation. Eur Heart J. 2013a;34(28):2149-57.

Schmieder RE, Redon J, Grassi G, Kjeldsen SE, Mancia G, Narkiewicz K et al. ESH Position Paper: Renal denervation – an interventional therapy of resistant hypertension. J Hypertens. 2012;30(5):837-41.

Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

A0002: What is the precise definition of treatment-resistant arterial hypertension and which diagnosis is given according to ICD-10?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic search ☒
- Domain search ☐
- Other: additional search for guidelines and searching WHO in relation to ICD-10, and PubMed.

Critical appraisal criteria not applicable

Method of synthesis: narrative

Result

Guidelines from the ESH and the ESC (Mancia 2013) present the following definitions and classification of office BP levels (mm Hg)*:

Classification of office BP levels (mm Hg)

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120 – 129	and/or	80 – 84
High normal	130 – 139	and/or	85 – 89
Grade 1 hypertension	140 – 159	and/or	90 – 99
Grade 1 hypertension	160 – 179	and/or	100 – 109
Grade 1 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

* The blood pressure (BP) category is defined by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension should be graded 1, 2, or 3 according to systolic BP values in the ranges indicated.

The condition r*esistant hypertension* appears when appropriate treatment including lifestyle measures and three antihypertensive drugs (one of them being a diuretic) fails to lower Systolic BP and Diastolic BP values to 140 and 90 mm Hg respectively. All drug agents should be prescribed at optimal dose amounts (Calhoun 2008).

There is no designation for ‘‘resistant hypertension’’ in the ICD-10 despite the increasing recognition of resistant hypertension as a major clinical entity (Giles, 2012). Resistant hypertension has been designated as 997.91 in the ICD-9 codes. Giles et al. notes the unfortunate development in the fact that resistant hypertension no longer can be classified as it should be in relation to its complexity. Giles continues by recommending that resistant hypertension must be dealt with by adding complexity of illness codes. For now “resistant hypertension” can be classified in the category “I99: Other and unspecified disorders of circulatory system” using the ICD-10 Version: 2010 (WHO 2010).

Discussion

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References

Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008;117(25):e510-26.

Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.

Giles TD, Sander GE. The new International Classification of Diseases (ICD-10): the hypertension community needs a greater input. J Clin Hypertens (Greenwich). 2012;14(1):1-2.

WHO: International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2010. Available at: http://apps.who.int/classifications/icd10/browse/2010/en#/I99

Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

A0003: What are the known risk factors for treatment-resistant arterial hypertension?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic search ☒
- Domain search ☐
- Other: additional search for guidelines

Critical appraisal criteria not applicable

Method of synthesis: narrative

Result

Resistant hypertension can be real or only apparent. Apparent or pseudo-resistant hypertension is e.g. caused by non-adherence to medicine. The ESH and the ESC have divided risk factors for real or true resistant hypertension into five categories (Mancia 2013):

- Lifestyle factors: obesity or large weight gains, excessive alcohol consumption, high sodium intake
- Chronic intake of vasopressor or sodium-retaining substances
- Obstructive sleep apnoea
- Undetected secondary forms of hypertension
- Advanced and irreversible organ damage, particularly when it involves renal function or leads to a marked increase in arteriolar wall–lumen ratio or reduction of large artery distensibility.

The American Heart Association (AHA) identifies older age and obesity as the strongest risk factors for resistant hypertension (Calhoun 2008). Comparing a group of >75 year old patients to ≤60 old patients revealed significantly more patients in the older age group not having their BP controlled after treatment. Using diastolic BP as reference patients being obese didn't experience treatment success as often as non-obese patients. AHA has tabulated the following characteristics associated with resistant hypertension:

- Older age
- High baseline BP
- Obesity
- Excessive dietary salt ingestion
- Chronic kidney disease
- Diabetes
- Left ventricular hypertrophy
- Black race
- Female sex
- Residence in South Eastern United States

Discussion

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References

Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008;117(25):e510-26.

Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

A0004: What is the natural course of treatment-resistant arterial hypertension?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic search ☒
- Domain search ☐
- Other: additional search for guidelines

Critical appraisal criteria not applicable

Method of synthesis: narrative

Result

The natural course for particularly resistant hypertension has been inadequately appraised. Hypertension will if untreated increase the risk of e.g. cardiovascular disease, stroke and renal failure. The risk increases with higher BP, duration of hypertension and other risk factors. The natural course or prognosis is probably impaired as the patient typically has endured a longlasting and poorly controlled hypertension.
The patients frequently have to face associated cardiovascular risk factors such as diabetes, obstructive sleep apnea and left ventricular hypertrophy (Calhoun 2013).

Discussion

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References

Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008;117(25):e510-26.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

A0005: What is the burden of treatment-resistant arterial hypertension for the patient?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic search ☒
- Domain search ☐
- Other: additional search for guidelines

Critical appraisal criteria not applicable

Method of synthesis: narrative

Result

Hypertension itself usually is not noticed by the patient (Calhoun 2008) and the patient normally present with no symptoms. Some patients might experience fatigue or headache. Others might experience nosebleed. The higher the BP is the higher the likelihood that the patient exhibit symptoms of hypertension. Result cart A0001 – "For which indication or for what purposes is renal denervation used" describes criteria for considering renal denervation. Result card A0004: "What is the natural course of treatment-resistant arterial hypertension?" describe some of the possible long term consequences for the patient when the condition cannot be treated.

Discussion

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References

Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008;117(25):e510-26.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

A0006: What is the burden of treatment-resistant arterial hypertension for society in terms of prevalence, incidence and costs?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic search ☒
- Domain search ☐
- Other: additional search for guidelines and in pubmed

Critical appraisal criteria not applicable

Method of synthesis: narrative

Result

Overall the exact prevalence of resistant hypertension is unknown (Calhoun, 2008), but it is assumed to be a commen clinical condition. In an older and more obese population the prevalence is expected to increase (Jentzer 2013). Jentzer et al. reports in an American population that approximately 5-10 % of patients with inadequately-controlled Hypertension have resistant Hypertension, defined as BP above goal despite use of ≥3 antihypertensive drugs in adequate dosage and combination (incl. diuretic) (Jentzer 2013). The ESH and the ESC report that depending on the population examined and the level of medical screening, the prevalence of resistant hypertension has been reported to range from 5–30 % of the overall hypertensive population, but probably less than 10 % (Mancia 2013). The prevalence of hypertension (all cases) is estimated to be approximately 30–45 % of the general population. The prevalence increases with older age. One should be aware about differences in BP across countries (Mancia 2013). The Regional HTA Centre in Vastra Gotaland, Sweden reports that the prevalence of resistant hypertension may be 2 – 6 % in an adult general population based on literature and figures of prevalence (Andersson 2013).

No literature has been found on the specific costs of resistant hypertension.

Discussion

Above data/ statistics are subject to uncertainty and should only cautiously be used in further analysis.

References

Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008;117(25):e510-26.

Jentzer J, Batal O, Rao S, Rahman A. Resistant Hypertension: A Comprehensive Overview. J Hypertens 2013, 2:1

Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.

Andersson B, Herlitz H, Manhem K, Zachrisson K, VöLz S, Daxberg EL, et al. Renal sympathetic denervation in patients with therapy resistant hypertension.: The Regional Health Technology Assessment Centre (HTA-centrum), Region Vastra Gotaland; 2013.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

A0007: What is the target population in this assessment?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic search ☒
- Domain search ☐
- Other: additional search for guidelines

Critical appraisal criteria not applicable

Method of synthesis: narrative

Result

As refered in result card A0001regarding which indication or for what purposes renal denervation is used the target population is patients suffering from resistant hypertension, a condition which links to sympathetic nervous system overactivity involving the kidneys (Schmieder 2012). Patients found eligible for the intervention can be treated with catheter-based renal denervation. The goal of the treatment is prevention of hypertensive end-organ damage and reduction of cardiovascular morbidity and mortality (Mahfoud 2011a)

The European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) emphasise the importance of investigating/ try to understand what makes renal denervation effective or ineffective (patient characteristics or failure to achieve renal sympathectomy) (Mancia 2013).

Discussion

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References

Schmieder RE, Redon J, Grassi G, Kjeldsen SE, Mancia G, Narkiewicz K et al. ESH Position Paper: Renal denervation – an interventional therapy of resistant hypertension. J Hypertens. 2012;30(5):837-41.

Mahfoud F, Himmel F, Ukena C, Schunkert H, Böhm M, Weil J. Treatment strategies for resistant arterial hypertension. Dtsch Arztebl Int. 2011a;108(43):725-31.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

A0011: What is the expected annual utilization of renal denervation?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic search ☒
- Domain search ☐
- Other: additional search for guidelines, PubMed and Google searches

Critical appraisal criteria not applicable

Method of synthesis: narrative

Result

Two factors make it quite difficult to come up with a reasonable estimate on the expected annual utilization of the procedure: 1) the uncertain figures of prevalence and 2) the potential number of candidates based on indications/contraindications for the surgical procedure. As indicated earlier in result card A0006 the figures of resistant hypertension in a general adult population is uncertain, so is the number of candidates extracted from the "resistant hypertension" group as surgical candidates based on the criteria described in result card A0001. Figures indicate potentially many candidates for renal denervation. More research, experience and time will add data to the expected annual utilization of renal denervation.

Discussion

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References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

A0020: What is the marketing authorisation status of renal denervation systems?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: see 'Description and technical characteristics of technology' (B0003).

- Basic search ☒
- Domain search ☐
- Other:

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

Questions regarding marketing authorisation status of renal denervation systems will be answered in the next section 'Description and technical characteristics of technology' (B0003).

Discussion

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References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

A0021: What is the reimbursement status of renal denervation systems?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: see 'Description and technical characteristics of technology' (B0003)

- Basic search ☐
- Domain search ☐
- Other: Google search for each specific RDN system

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

Questions regarding reimbursement status of renal denervation systems are answered in the next section 'Description and technical characteristics of technology' (B0003).

Discussion

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References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

A0024: How is treatment-resistant arterial hypertension currently diagnosed according to published guidelines and in practice?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic search ☒
- Domain search ☐
- Other: additional search for guidelines and PubMed searches

Critical appraisal criteria not applicable

Method of synthesis: narrative

Result

The American Heart Association appropriately points out that: *"The evaluation of patients with resistant hypertension should be directed toward confirming true treatment resistance; identification of causes contributing to treatment resistance, including secondary causes of hypertension; and documentation of target-organ damage."* (Galhoun 2008).

Further, AHA emphasised that most cases of resistant hypertension doesn't origen in solitary factors/ causes but is multifactorial in etiology caused by variably factors such as obesity, excessive dietary sodium intake, obstructive sleep apnea, and chronic kidney disease being particularly common factors (Calhoun 2008; Mahfoud 2013a).

The diagnostic strategy to identify resistant hypertension requires detailed information on the patient's history, a careful and detailed physical examination, laboratory tests (to reveal associated risk factors – organ damage, alterations of glucose metabolism, renal dysfunction) (Mancia 2013). Additionally any secondary causes of hypertension should be identified: e.g. primary aldosteronism and renal artery stenoses of an atherosclerotic nature.

Discussion

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References

Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008 Jun 24;117(25):e510-26.

Mahfoud F. Expert consensus document from the European Society of Cardiology on catheter-based renal denervation. Eur Heart J. 2013a;34(28):2149-57.

Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.

Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

Description and Technical Characteristics of Technology

B0001: What is renal denervation and what are the treatment alternatives?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other: additional search in Google

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

Most of the renal nerve ablation systems or renal denervation system use use low-level radio frequency energy to modulate the output of nerves that lie within the renal artery wall and lead into and out of the kidneys," in order to reduce blood flow and thereby reducing hypertension by de-activating hyperactive nerves, and without affecting other abdominal, pelvic, or lower extremity nerves (CADTH 2013). There are however also systems that use ultrasound for ablation.

The mechanism by which renal sympathetic denervation improves management of BP is complex and involves the following factors (Wojakowski 2012):

- Decreasing efferent sympathetic signaling to kidneys
- Reducing norepinephrine spillover
- Natriuresis
- Increasing renal blood flow
- Lowering plasma rennin activity
- Decreasing renal afferent signalling and central sympathetic activation

The system's energy, either through radiofrequency or ultrasound, increases the local temperature in the limited area of the vascular wall, and leads to ablation of afferent and efferent sympathetic nerves (Wojakowski 2012).

Currently there are a number of renal denervation (RDN) systems using different treatment strategies available (Table DTC1):

DTC1. Different systems for RDN, their manufacturer and regulatory stage

Device	ufacturer	narked	review
Radiofrequency			
Symplicity®	Medtronic	Y	2014 or 15
MarinR®	Medtronic	N	N
EnligHTN™	St. Jude Medical	Y	N
Vessix V2™	Boston Scientific	Y	N
OneShot™	Covidien	Y	N
Iberis™	Terumo	Y	N
ThermoCool®	Biosense Webster	N	N
Ultrasound			
PARADISE™	ReCor Medical	Y	N

Y=Yes, N=No

Most of these systems use radiofrequency energy to target renal sympathetic nerves except for the ultrasound-based Recor's Paradise system (Mahfoud 2013).

The catheter is introduced through the femoral artery and threaded up, under fluoroscopic control, into the renal artely lumen. Once in place, a series of 4 to 6 radio frequency treatments are applied within each renal artery to ablate the sympathetic nerves coursing along the outside of the artery (CADTH 2013). The procedure takes about 40-60 minutes (Mahfoud 2013a). The technology behind delivery of radiofrequency ablation is however evolving with the introduction of devices that improve time efficiency (Mahfeld 2012).

Ultrasound is being investigated as an alternative to radiofrequency energy to provide more targeted nerve ablation without the need for direct vessel contact. Currently, only the PARADISE device of these ultrasound devices is CE-marked. In development for RDN is non-invasive ultrasound. . A transducer positioned outside the body delivers targeted ultrasound energy that 'surrounds' the artery and treats the nerves located in the vicinity of the vessel. The idea behind creating a focused energy field around the outside of the artery, is that it might result in a more complete and effective ablation that does not impact the walls of the artery (KONA Medical 2013).

Catheters designed to inject therapeutic agents directly and non-systemically through the renal artery wall, such as the Cricket and Bullfrog Micro-Infusion Catheters (Mercator MedSystems) are also in development for RDN. The Mercator micro-infusion catheters are CE-marked in Europe and approved by the FDA.

Current practice and other developments for treatment of resistant hypertension

The Task Force for the management of arterial hypertension of the ESH and the ESC (Mancia 2013) describe in their guideline that most patients with resistant hypertension require the administration of more than three drugs. In current practice this combination of drugs exist of a thiazide diuretic, a long-acting calcium channel blocker, an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, and a beta-blocker in patients younger than 60 years of age (CADTH 2013).

Another alternative to drug treatment is carotid baroreceptor stimulation, which includes chronic field electrical stimulation of carotid sinus nerves via implanted devices. However, both renal denervation and carotid baroreceptor stimulation are recommended to be restricted to resistant hypertensive patients at particularly high risk, after fully documenting the inefficacy of additional antihypertensive drugs to achieve BP control (Mancia 2013).

Discussion

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References

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Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.

Wojakowski W, Tendera M, Jadczyk T, Januszewicz A, Witkowski A. Catheter-based renal denervation. E-journal of the ESC Council for Cardiology Practice. 2012; 10 (22). http://www.escardio.org/communities/councils/ccp/e-journal/volume10/Pages/catheter-based-renal-denervation-tendera-m-wojakowksy-w.aspx#.Up2lJ9IyLDs (Visited 26.11.13)

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

B0002: What is the approved indication and claimed benefit of renal denervation and the treatment alternatives?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other: additional Google search

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

The European Society of Cardiology's consensus document states that according to the available evidence, patients are eligible for renal denervation if they have (severe) treatment-resistant hypertension defined by office SBP ≥160 mm Hg (≥150 mmHg in type 2 diabetes) despite treatment with at least three antihypertensive drugs of different types in adequate doses, including one diuretic (Mahfoud 2013a). In certain centres, uncontrolled BP values 140/90 mm Hg are taken as reference (Mahfoud 2013a). Box DTC1 below describes in more detail which criteria patients should comply with before renal denervation is considered.

Box DTC1 Criteria patients should comply with before renal denervation is considered

– Office-based systolic BP ≥ 160 mmHg (≥150 mm Hg diabetes type 2)
– ≥3 antihypertensive drugs in adequate dosage and combination (incl. diuretic)
– Lifestyle modification
– Exclusion of secondary hypertension
– Exclusion of pseudo-resistance using ABPM (average BP 130 mm Hg or mean day-time BP 135 mm Hg)
– Preserved renal function (GFR ≥45 ml/min/1.73m2)
– Eligible renal arteries: no polar or accessory arteries, no renal artery stenosis, no prior revascularization

The claimed benefit is that renal denervation results in systolic and diastolic BP reductions. The risk of cardiovascular death is cut in half with every 20 mm Hg decrease in systolic BP. RDN trials to date have shown an average reduction of about 25 mm Hg (Fornell 2013).

Discussion

Mahfoud et al. point out that BP rarely changes immediately after the procedure. It often takes several weeks to months before a notable BP reduction occurs, suggesting that a slowly progressive resetting of sympathetic neural regulation occurs (Mahfoud 2013a). Furthermore, it is stated that renal denervation as currently deployed is designed to improve BP control in patients whose BP is resistant to control with conventional drug therapy. In this regard, renal denervation is unlikely to significantly reduce pill burden in most patients and is not a cure for hypertension. It is an add-on therapy, thus leading to additional health care resources in terms of the cost of the system, the training of specialist staff, and the use of hospital radiology services during the procedure (CADTH 2013).

References

CADTH. Catheter-based renal denervation fortreatment-resistant hypertension. Issues in emerging Health Technologies CADTH issue 121, March 2013.

Fornell D. The development of Renal denervation therapy. Diagnostic and Interventional Cardiology Magazine, July 30, 2013. http://www.dicardiology.com/article/development-renal-denervation-therapy. Visited 29-09-2013.

Mahfoud F. Expert consensus document from the European Society of Cardiology on catheter-based renal denervation. Eur Heart J. 2013a;34(28):2149-57.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

B0003: What is the phase of development and implementation of renal denervation systems and the treatment alternatives?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☒

- Domain search ☐
- Other: Google search for each specific RDN system

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

As the original Symplicity® catheter required multiple ablations, each time requiring the catheter to be rotated to create a continuous lesion, now the technology is being adapted to simplify this procedure. St Jude, Covidien and Boston Scientific for example developed new catheter designs to simplify and shorten the procedure, and also Medtronic itself is developing a follow-up on the original Symplicity® system.

Of all the renal denervation systems, the Symplicity®, One shot™ , EnligHTN™, Vessix V2™-, and Iberis™ system are CE-marked in Europe. None of the systems are FDA approved, yet all are in pursuit (Medlatest 2013). Of the ultrasound devices currently under development only the PARADISE™ system (ReCor Medical) received the CE mark.

Medtronic's Symplicity® Renal Denervation Device has a several year lead on the other CE-marked systems, and was accepted for parallel review in the US in March 2013. This program allows the Centers for Medicare and Medicaid Services (CMS) to begin consideration for national coverage determination, while the FDA completes its review of safety and efficacy. The parallel review will be based primarily on results from Symplicity HTN-3 trial. This trial was expected to conclude in the summer of 2013, and FDA and CMS reviews will likely take place in 2014 or 2015 (Gaffney 2013).

The Symplicity® renal denervation system is available in more than 70 countries worldwide; it is only available for investigational use in the U.S. and Japan (Medtronic 2013). Health Canada issued a Class IV Licence to Medtronic Inc. for the Symplicity® Renal Denervation System in March 2012.

The Vessix V2™ system additionally received regulatory approval from the Therapeutic Goods Authority of Australia and is available for sale in Australia, New Zealand, the Middle East, and select markets in Asia.

Table 5 shows that in 13 countries in Europe, RDN is reimbursed and in most cases regardless of the type of device. Reimbursement is in the majority of countries decided upon through formal processes, i.e. described in national policy. In one country, Medtronic's Symplicity® received conditional coverage. In 5 countries a decision on reimbursement is in process, 2 countries do not reimburse RDN, and in 3 countries the reimbursement status is unknown.

Table 5: Reimbursement status of renal denervation in Europe

Country	Reimbursement Yes/No	Technology-specific vs. non-technology-specific reimbursement
Austria	Yes (temporary, formal)	All devices
Belgium	- (formal: submissions to the authorities)	All devices
Croatia	No	-
Denmark	Yes (formal)	All devices
England	- (Commissioning through evaluation; reimbursement planned to start in 2014)	All devices
Estland	- (application under process)	Unknown

Finland	Yes (as part of hospital fees)	All devices
France	- (formal: process waits for STIC results)	All devices
Germany	Yes (formal)	All devices
Hungary	Unknown	Unknown
Greece	Unknown	Unknown
Italy	Yes (formal)	All devices
Ireland	Yes (decision at local hospital level)	All devices
Lithuania	Yes (formal)	All devices
Malta	No	-
Netherlands	Yes (Conditional Coverage)	Currently only Medtronic Symplicity® Flex For other technologies, discussion is on-going
Norway	Yes	All devices
Poland	- (formal: submissions to the authorities)	All devices
Portugal	Yes (formal)	All devices
Serbia	Unknown	Unknown
Slovakia	Yes (formal)	EnligtHTN™ and Symplicity® reimbursed from 01.01.2014
Spain	Yes (formal)	All devices
Sweden	Yes (formal)	All devices
Switzerland	Yes (formal)	All devices

Source: Information on reimbursement status was kindly provided by the EUCOMED Hypertension Working Group and Medtronic. The information has been cross-checked and updated from WP5 Strand B members. Answers were received from Croatia, England, Finland, Germany, Hungary, Ireland, Italy, Lithuania, Malta, Poland and Slovakia.

STIC: Support Programme for Innovative and Costly Techniques

Pharmacological Therapy

Several new pharmacological therapies for hypertension are being investigated in phase 2 and 3 clinical trials including drugs with new pharmacological targets (such as dual vasopeptidase inhibitors, a dual-acting angiotensin receptorneprilysin inhibitor, endothelin antagonists, nitric oxide donors, and angiotensin vaccines) and novel, fixed-dose combination drug products (CADTH 2013).

Discussion

Although BP has been the primary outcome variable in the studies, there are several reports that suggest beneficial effects also in patients with diabetes mellitus, metabolic syndrome, cardiac arrhythmias, sleep apnea and heart failure. In the U.S. it is foreseen that once RDN systems gain FDA market approval, physicians will begin using them off-label for conditions other than hypertension (Fornell 2013). In Europe indication widening may also become an issue that, as here the devices are only CE-marked, and not fixed to a certain indication.

References

CADTH. Catheter-based renal denervation fortreatment-resistant hypertension. Issues in emerging Health Technologies CADTH issue 121, March 2013.

Fornell D. The development of Renal denervation therapy. Diagnostic and Interventional Cardiology Magazine, July 30, 2013. http://www.dicardiology.com/article/development-renal-denervation-therapy. Visited 29-09-2013.

Medlatest. Renal Denervation: Just How Big Is The Bandwagon? June 18, 2013. http://www.medlatest.com/2012/06/18/renal-denervation-just-how-big-is-the-bandwagon/ accessed 12.09.13.)

Medtronic. 25 may 2013. http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&id=1823583 visited 12.09.13).

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒ however the information needs to be updated regularly
Partly ☐
Not ☐

B0004: Who performs or administers renal denervation and the treatment alternatives?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

RDN can be performed in a catheterization laboratory, for cardiovascular interventions (Andersson 2013; CADTH 2013). The procedure can be performed by interventional cardiologists, or – radiologist, and angiologists. The European Society of Cardiology recommends that the procedure is performed by staff that has been trained in performing this intervention, and who are qualified to manage potential complications, such as acute dissection of renal arteries by stent implantation. The procedure is performed under analgesic or conscious sedation (CADTH 2013). During the procedure, vital signs need to be

monitored. The presence of an anaesthesiologist is not generally necessary, however in some countries required (Mahfoud 2013a).

Discussion

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References

Andersson B, Herlitz H, Manhem K, Zachrisson K, VöLz S, Daxberg EL, et al. Renal sympathetic denervation in patients with therapy resistant hypertension.: The Regional Health Technology Assessment Centre (HTA-centrum), Region Vastra Gotaland; 2013

CADTH. Catheter-based renal denervation for treatment-resistant hypertension. Issues in emerging Health Technologies CADTH issue 121, March 2013.

Mahfoud F. Expert consensus document from the European Society of Cardiology on catheter-based renal denervation. Eur Heart J. 2013a;34(28):2149-57.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

B0005: In what context and level of care are renal denervation systems and the treatment alternatives used?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☒

- Domain search ☐
- Other:

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

Andersson et al. recommend that in the selection of patients, primary care physicians and specialist in internal medicine, nephrology, interventional cardiology or radiology should be involved (Andersson 2013). Appropriate expertise can be assumed in centres with >25 renal interventions per year.

The long term follow-up of RDN treated patients is similar to usual care of hypertensive patients. It can be done by specialists in cardiology, internal medicine or nephrology, as well as primary care physicians (Andersson 2013).

Discussion

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References

Andersson B, Herlitz H, Manhem K, Zachrisson K, VöLz S, Daxberg EL, et al. Renal sympathetic denervation in patients with therapy resistant hypertension.: The Regional Health Technology Assessment Centre (HTA-centrum), Region Vastra Gotaland; 2013

Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

B0008: What kind of special premises are needed to use renal denervation systems and treatment alternatives?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

See B0005

Discussion

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References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

B0009: What materials are needed to use renal denervation systems and the treatment alternatives?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

There will be a slight increase in the demand for functional and morphological diagnostic protocol prior to RDN (Andersson 2013). In the CADTH assessment it is concluded that RDN is associated with additional health care resources in terms of the cost of the system, the training of specialist staff, and the use of hospital radiology services during the procedure, as RDN is currently used as an adjunct to available therapies for hypertension (CADTH 2013).

Discussion

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References

Andersson B, Herlitz H, Manhem K, Zachrisson K, Völz S, Daxberg EL, et al. Renal sympathetic denervation in patients with therapy resistant hypertension: The Regional Health Technology Assessment Centre (HTA-centrum), Region Vastra Gotaland; 2013

CADTH. Catheter-based renal denervation for treatment-resistant hypertension. Issues in emerging Health Technologies CADTH issue 121, March 2013.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

B0010: What kind of data and records are needed to monitor the renal denervation systems and the treatment alternatives?

Methods

See B0011

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

See B0011

Discussion

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References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

B0011: What kind of registry is needed to monitor the use renal denervation systems and treatment alternatives?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other: Google search: renal denervation and registry

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

The Joint UK Societies consensus statement on RDN for resistant hypertension (Caulfield 2012) states that any institution carrying out the procedure should have the commitment and capability to include data in a National Registry. This will allow for analysis of the procedural success acutely and at long-term follow-up (Mahfoud 2013a).

Discussion

In the case of indication-widening registries would have to be set up for each indication.

References

Caulfield M, De Belder M, Cleveland T, Collier D, Deanfield J, Gray H, Knight C, Lobo M, Matson M, Moss J, Simpson I, Tomson C, Williams B. The Joint UK Societies' Consensus Statement on Renal Denervation for Resistant Hypertension. January 2012. http://www.bhsoc.org/docs/The-Joint-UK-Societies'-Consensus-on-Renal-Denervation-for-resistant-hypertension.pdf

Mahfoud F. Luscher TF, Andersson B, Baumgartner I, Cifkova R, DiMario C et al. Expert consensus document from the European Society of Cardiology on catheter-based renal denervation. Eur Heart J. 2013a;34(28):2149-57.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

Safety

C0001: What are the adverse events and serious adverse events in patients treated with renal denervation?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☐
- Domain search ☒
- Other:

Critical appraisal criteria: Cochrane risk of bias tool.

Method of synthesis: GRADE

Result

The evidence for the safety domain comes from three RCT articles, three non-RCT articles and 16 case series studies reporting on 904 patients. For 91 patients information could be partly duplicated. Twenty-six patients of the Mahfoud study (Mahfoud 2011b), 28 patients of the Ukena study from 2011 (Ukena 2011) and 18 of the Ukena study from 2012 (Ukena 2012) were part of the Symplicity HTN-2 trial (Symplicity HTN-2 2010; Esler 2012) and 19 patients of the Mahfoud study (Mahfoud 2012) were included in the Symplicity HTN-1 or Symplicity HTN-2 trials.

In two of the three RCTarticles, all of the non-RCT studies and 11 of the 16 cases series, the RDN procedure involved radiofrequency ablation (RF) applied with the Symplicity® catheter (Medtronic, Ardian Inc). A total of 784 patients underwent RDN using this system. One RCT including 13 patients carried out the intervention using a Navistar® ThermoCool® Irrigated Tip Catheter (Biosense Webster) (Pokushalov 2012). One case series with 30 patients used the Marinr® RF ablation catheter (typically used for cardiac ablation) (Prochnau 2012a), one with 46 patients used the EnligHTN® multi-electrode renal denervation system (EnligHTN1 trial) (Worthley 2013) and one with 9 patients used the OneShot™ (Covidien) RDN system (RHAS trial) (Ormiston 2013). One case series with 11 patients carried out RDN with the Paradise™ technology (ReCor Medical), which uses a catheter that emits ultrasound energy (Mabin 2012) and one with 11 patients did not specify the type of system used (Voskuil 2011).

Overall, out of the 22 studies, thirteen reported procedure-related complications (Symplicity HTN-2 2010, Mahfoud 2011b; Mahfoud 2012; Symplicity HTN-1 2011; Esler 2012; Mabin 2012; Ukena 2012; Vase 2012; Fontenla 2013; Kaltenbach 2013; Ormiston 2013; Scheurig-Muenkler 2013; Worthley 2013). The pooling of these studies to estimate frequencies of complications was not possible due to the high risk of selective outcome reporting.

Reported adverse events related to the procedure or device
Even though not quantified in the majority of studies as an adverse event, it is documented that RDN frequently causes 'diffuse visceral abdominal pain' during the procedure that can be adequately controlled with narcotics or anaesthesics (Mahfoud 2011b; Symplicity HTN-1 2011; Hering 2012; Mabin 2012; Prochnau 2012a; Simonetti 2012; Vase, 2012; Fontenla 2013; Worthley 2013). The most commonly reported procedure or device related complica-

tions were of a mild to moderate nature: hypotensive episodes (1.92%-55.5%) (Symplicity HTN-2 2010; Esler 2012; Vase 2012; Worthley 2013), femoral artery pseudoaneurysms/hematomas at the access site (1.5 % - 44.4 %) (Symplicity HTN-2 2010; Mahfoud 2011b; Mahfoud 2012; Symplicity HTN-1 2011; Ukena 2012, Fontenla 2013; Ormiston 2013; Worthley 2013), bradychardias (4.35 % -18 %) (Symplicity HTN-2 2010; Symplicity HTN-1 2011; Fontenla 2013; Worthley 2013), , renal artery spasms series (5 % - 26 %) (Vase 2012; Kaltenbach 2013; Worthley 2013), transient vagal reactions (3.9 % -11.1 %) (Symplicity HTN-1 2011, Ukena 2012; Ormiston 2013; Worthley 2013;) and vomiting (2.17 % - 11.1 %) (Ormiston 2013; Worthley 2013). Other minor periprocedural events notified in isolated studies were: haematuria (4.35 %) (Worthley 2013), dizziness (3.92 %) (Symplicity HTN-1 2011), urine infections (Symplicity HTN-2 2010), paraesthesias (1.92 %) (Symplicity HTN-2 2010), and contrast medium allergic reactions (1.14 %) (Mahfoud 2012). Several studies denoted the appearance of minor focal renal artery irregularities not flow limiting attributed to minor spasm and/or edema but these were not counted as complications (Symplicity HTN-1 2011; Mabin 2012; Prochnau 2012a; Simonetti 2012; Scheurig-Muenkler 2013).

Major complications related to the procedure or the device were reported in four studies. Three studies accounted for renal artery dissection on placement of catheter (0.65 % - 9.9%) (Symplicity HTN-1 2011; Esler 2012; Mabin 2012), one study reports a psoas hematoma secondary to placement of catheter (9.09%) (Fontenla 2013) and one study describes one case of respiratory and cardiocirculatory depression due to analgosedation (1,89 %) and one case of severe artery spasm that resulted in residual stenosis of no hemodynamic relevance (1,89 %) (Scheurig-Muenkler 2013).. No intervention-related mortality has been reported.

The frequency of complications related to the procedure notified in the included studies are outlined in the table below.

Frequency of main procedure or device related complications reported in the included studies

Author, date	Study type	N	Minor adverse events, n (%)							Major adverse events, n (%)					Total adverse events n, (%)
			Hypo-tensive events	Femoral artery pseudo-aneurysm/ Hematoma	BC	Renal artery spasms	TVR	Other	Total	Renal artery dissection	Psoas hematoma	Respiratory and CP depression	Severe artery spams	Total	
Symplicity HTN-2 2010	RCT	52	1 (1.92%)	1 (1.92%)	7 (13.46%)	0	0	3 (5.77%)	12 (23.08%)	0	0	0	0	0	12 (23.08%)
Ukena 2011	RCT	37	0	0	0	0	0	0	0	0	0	0	0	0	0
Pokushalov 2012	RCT	13	0	0	0	0	0	0	0	0	0	0	0	0	0
Mahfoud 2011	Non RCT	37	0	1 (2.70%)	0	0	0	0	1 (2.70%)	0	0	0	0	0	1 (2.70%)
Brandt 2012	Non RCT	110	0	0	0	0	0	0	0	0	0	0	0	0	0
Mahfoud 2012	Non RCT	88	0	2 (2.27%)	0	0	0	1 (1.14%)	3 (3.41%)	0	0	0	0	0	3 (3.41%)
HTN1 2011	Case series	153	0	3 (1.96%)	15 (9.80%)	0	6 (3.92%)	0	24 (15.69%)	1 (0.65%)	0	0	0	1 (0.65%)	25 (16.34%)
Voskuil 2011	Case series	11	0	0	0	0	0	0	0	0	0	0	0	0	0
Brinkmann 2012	Case series	12	0	0	0	0	0	0	0	0	0	0	0	0	0
Esler 2012*	Case series	35	1 (2.86%)	0	0	0	0	0	1 (2.86%)	1 (2.86%)	0	0	0	1 (2.86%)	2 (5.71%)
Hering 2012	Case series	15	0	0	0	0	0	0	0	0	0	0	0	0	0
Mabin 2012	Case series	11	0	0	0	0	0	1 (9.09%)	1 (9.09%)	1 (9.09%)	0	0	0	1 (9.09%)	2 (18.2%)
Prochnau 2012	Case series	30	0	0	0	0	0	0	0	0	0	0	0	0	0
Simonetti 2012	Case series	5	0	0	0	0	0	0	0	0	0	0	0	0	0
Ukena 2012	Case series	136	0	2 (1.47%)	0	0	8 (5.88%)	0	10 (7.35%)	0	0	0	0	0	10 (7.35%)
Vase 2012	Case series	9	5 (55.56%)	0	0	1 (11.11%)	0	0	6 (66.67%)	0	0	0	0	0	6 (66.67%)
Zuern 2012	Case series	11	0	0	0	0	0	0	0	0	0	0	0	0	0
Fontenla 2013	Case series	11	0	1 (9.09%)	2 (18.18%)	0	0	1 (9.09%)	4 (36.36%)	0	1 (9.09%)	0	0	1 (9.09%)	5 (45.45%)
Kaltehbach 2013	Case series	20	0	0	0	1 (5%)	0	0	1 (5%)	0	0	0	0	0	1 (5%)
Ormiston 2013**	Case series	9	0	4 (44.44%)	0	0	1 (11.11%)	4 (44.44%)	9 (100%)	0	0	0	0	0	9 (100%)
Scheurig-Muenkler 2013	Case series	53	0	0	0	0	0	2 (3.77%)	2 (3.77%)	0	0	1 (1.89%)	1 (1.89%)	2 (3.77%)	4 (7.55%)
Worthley 2013	Case series	46	3 (6.52%)	8 (17.39%)	2 (4.35%)	12 (26.09%)	3 (6.52%)	4 (8.70%)	32 (69.57%)	0	0	0	0	0	32 (69.57%)

* Only crossover group patients included. **Article refers to adverse events and specifies that they were mostly periprocedural.
BC: bradychardia; CP: cardiopulmonary; RCT: randomized controlled trial; TVR: transient vagal reactions

Follow up adverse events

Nine studies (Symplicity HTN-1 2011; Symplicity HTN-2 2010; Mahfoud 2011b; Mahfoud 2012; Brinkmann 2012; Esler 2012; Mabin 2012; Kaltenbach 2013; Worthley 2013) documented complications during the follow up period (maximum of 2 years).

The most common minor complication was the lowering of blood levels below target BP or the development of hypotensive symptoms (18.2%-35.1%) (Mahfoud 2011b, Mahfoud 2012, Mabin 2012). Other minor complications include edemas (1.92 % - 5 %) (Symplicity HTN-1 2011; Symplicity HTN-2 2010; Kaltenbach 2013) and flank pain (2.6 %) (Symplicity HTN-1 2011)

Six studies reported major adverse events during follow (n=315 patients) (Symplicity HTN-2 2010; Esler 2012; Brinkmann 2012, Kaltehbach 2013, Worthey 2013). The documented frequency of complications were: hypertensive emergencies and crisis (5%- 33.3 %) (Symplicity HTN-2 2010; Esler 2012; Brinkmann 2012; Kaltenbach 2013); hypotensive events requiring hospitalization (2% - 2.86 %) (Symplicity HTN-2 2010; Esler 2012; Worthley 2013), angina

(2.04 %) (Symplicity HTN-2 2010), transient ischaemic attacks (2.04 %) (Symplicity HTN-2 2010), progression of existing stenosis (0.65%-2.17%) (Symplicity HTN-2 2010; Symplicity HTN-1 2011; Worthley 2013), and hypertensive renal disease progression: (2.17 %) (Worthley 2013). None of the studies reported aortic stenosis, thrombosis or important abnormalities.

The frequency of follow up complications notified in the included studies are outlined in the table below.

Frequency of main procedure or device related complications reported in the included studies

Author, date	Study type	N*	Follow up (months)	Minor complications, n (%)			Major complications, n (%)								Total
				Hypotensive events	Other	Total	Nausea and/or oedemas	Hypertensive episodes (hospital admission)	Hypotensive episodes (hospital admission)	Angina	Transient ischaemic attack	Progress of existing stenosis	Progress of renal disease	Total	n (%)
Symplicity HTN-2 2010	RCT	I:49 C:51	6	0 0	00	0 0	1 (2.0%) 0	4 (8.2%) 2 (3.92%)	1 (2.0%) 0 (0%)	1 (2.0%) 1 (1.96%)	1 (2.0%) 2 (3.92%)	1 (2.0%) 0 (0%)	0 (0%) 0 (0%)	9 (18.3%) 5 ((9.8%	9 (18.3%) 5 (9.8%
Ukena 2011	RCT	I:37 C:9	3	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Pokushalov 2012	RCT	I:13 C:14	12	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mahfoud 2011	Non RCT	I: 37 C:13	3	13 (35.1%) 0	0 0	13 (35.1%) 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	13 (35.1%) 0
Brandt 2012	Non RCT	I:110 C: 10	6	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mahfoud 2012	Non RCT	I:88 C:12	6	18 (20.4%) 0	0 0	18 (20.4%) 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	18 (20.4%) 0
HTN1 2011	Case series	153	24	0	4 (2.61%)	4 (2.61%)	0	0	0	0	0	1 (0.65%)	0	1 (0.65%)	5 (3.3%)
Voskuil 2011	Case series	11	1	0	0	0	0	0	0	0	0	0	0	0	0
Brinkmann 2012	Case series	12	6	0	0	0	0	4 (33.3%)	0	0	0	0	0	4 (33.3%)	4 (33.3%)
Esler 2012	Case series	35	12	0	0	0	0	2 (5.7%)	1 (2.86)	0	0	0	0	3 (8.57%)	3 (8.57%)
Hering 2012	Case series	15	12	0	0	0	0	0	0	0	0	0	0	0	0
Mabin 2012	Case series	11	3	2 (18.2%)	0	2 (18.2%)	0	0	0	0	0	0	0	0	2 (18%)
Prochnau 2012	Case series	30	12	0	0	0	0	0	0	0	0	0	0	0	0
Simonetti 2012	Case series	5	2	0	0	0	0	0	0	0	0	0	0	0	0
Ukena 2012	Case series	136	6	0	0	0	0	0	0	0	0	0	0	0	0
Vase 2012	Case series	9	1	0	0	0	0	0	0	0	0	0	0	0	0
Zuern 2012	Case series	11	24	0	0	0	0	0	0	0	0	0	0	0	0
Fontela 2013	Case series	11	6	0	0	0	0	0	0	0	0	0	0	0	0
Kaltehbach 2013	Case series	20	6	0	2 (10%)	2 (10%)	0	1 (5%)	0	0	0	0	0	1 (5%)	3 (15%)
Ormiston 2013	Case series	9	12	0	0	0	0	0	0	0	0	0	0	0	0
Worthley 2012	Case series	46	6	0	0	0	0	0	1 (2.17%)	0	0	1 (2.17%)	1 (2.17%)	3 (6.5%)	3 (6.5%)

*Patients for whom follow up information was available
RCT: randomized controlled trial

The quality of the evidence was low or very low. The table below shows the Grade profile for total adverse events and major adverse events.

Evidence profile for total and major adverse events

Evidence profile: safety of the RDN (all patients)								
N° of studies / patients	Design	Risk of bias	Inconsistency	Indirectness	Other considerations	Effect size (%)	Quality of evidence	Importance
Outcome: total adverse events (in % of patients)								
3/228	RCTs	no serious risk of bias	no serious inconsistency	serious[1,2]	none	0–40.38 vs.0–9.26	⊕⊕OO LOW	CRITICAL
3/260	Open, non randomised, controlled	no serious risk of bias	no serious inconsistency	no serious indirectness	none	0–23.9 vs. 0	⊕⊕OO LOW	CRITICAL
18/599	Observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	none	0–100	⊕OOO VERY LOW	CRITICAL
Outcome: major adverse events (in % of patients)								
4/274	RCTs	no serious risk of bias	no serious inconsistency	serious[1,2]	none	0–15.38 vs. 0–9.26	⊕⊕OO LOW	CRITICAL
3/260	Open, non randomised, controlled	no serious risk of bias	no serious inconsistency	no serious indirectness	none	0 vs. 0	⊕⊕OO LOW	CRITICAL
18/599	Observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	none	0–33.33	⊕OOO VERY LOW	CRITICAL

[1]Tested pulmonary vein isolation +/– renal denervation. Participants had atrial fibrillation in addition to treatment resistant hypertension.
[2] Combination of different catheter types. Uncertain transferability.

Discussion

The reporting frequency of adverse events was very heterogeneous (0 % - 40.38 %) in the included studies and this raises important uncertainties regarding the overall rate of complications. In two of the RCT studies (Ukena 2011; Pokushalov 2012), all of the non RCT studies (Mahfoud 2011b; Mahfoud 2012; Brandt 2012a) and many of the case series safety was not considered the main endpoint and complications and adverse events were reported incompletely (Voskuil 2011; Brinkmann 2012; Hering 2012; Ukena 2012; Zuern 2012; Prochnau 2012a; Fontenla 2013; Kaltehbach 2013). Often authors only make reference to the non existence of major/severe complications or adverse events related to the procedure without defining what was meant with severe adverse event, or commenting on post-procedure adverse events, which hampers the interpretation of evidence related to safety, making it impossible to perform pooled analysis of data.. One of the main complications of RDN are the

unwanted effects with respect to BP regulation post procedure, which can derive in hypotension or hypertension episodes that can require hospitalization. It cannot be dismissed that these or other indirect complications, such as the appearance of respiratory and cardiocirculatory depression related to the control of analgesia and sedation mentioned in the study of Scheurig-Muenkler (Scheurig-Muenkler 2012) are underestimated in the included studies.

The follow-up time was inadequate to analyze long term complications. Renal function concerns and doubts as to the aggravation of renal disease are still to be resolved (Mahfoud 2011b; Mahfoud 2012). The Symplicity HTN-2 investigations and several other trials that analyzed renal function (Symplicity HTN-2 2010; Esler 2012; Pokushalov 2012; Mahfoud 2011b; Mahfoud 2012; Prochnau 2012a; Fontenla 2013; Kaltenbach 2013; Ormiston 2013) observed no changes in estimated glomerular filtration rate (eGFR), cystatin C or other parameters used to detect renal failure function in the 3-12 months' follow-up period. However, in the Symplicity HTN-1 trial with extended follow-up of 24 months, estimated GFR remained stable within the first years, but in 10 patients followed 2 years a dramatic decrease in the eGFR rate was observed. Whether these differences might be attributed to different study population, differences in BP levels or the detrimental effect of renal denervation requires clarification. For this purpose, longer term assessments are needed.

There is uncertainty regarding the detrimental effect on the anatomy of the renal arteries with this invasive procedure. Mild, hemodynamically irrelevant wall irregularities corresponding to small local spasms or circumscribed wall edema were consistently seen after ablation, but these were not flow limiting. Several of the included studies (Esler 2012; Pokushalov 2012; Mahfoud 2011b; Mahfoud 2012; Symplicity HTN-1 2011; Prochnau 2012a; Fontenla 2013; Kaltenbach 2013) carried out a magnetic resonance angiography, computed tomographic scan and or renal ultrasound during the follow up period and ruled out the appearance of renal artery aneurisms, stenosis, thrombosis or any other relevant vascular abnormalities in the short to medium term (6-12 months) but the evolution of the renal arteries in the long term is unknown.

Current RDN experiences are mainly based on the Symplicity® catheter (Medtronic, Ardian, Inc). The other RDN systems and new generations of RDN systems have only been assessed in preliminary trials that include very few patients. Since these systems do not use exactly the same ablation mechanisms and the diameter of the catheter can be different, it cannot be dismissed that they could present a different risk profile. These systems require further assessment to establish their safety.

In summary, evidence about safety is compromised by the following methodological limitations that impede drawing up definitive conclusions about this procedure:

- The majority of studies present a small sample size and many an overlap of patients.
- Safety is not the primary end point in the vast majority of studies and complications are incompletely recorded
- In many of the studies, the RD intervention was conducted in highly selected patients by a small group of trained health professionals, which does not exclude the possibility of serious adverse effects if the technique is performed routinely in clinical practice.
- Possibility of bias due to lack of blinding.
- Large heterogeneity in individual responses to renal sympathetic ablation.
- Short follow-up, which means that there is a lack of knowledge about long-term potential of nerve fiber regeneration and the occurrence of adverse effects.
- Potential conflicts of interest in most of the included studies because of their financing from the manufacturer of the device and / or participation in research studies of company's invetigators (see evidence tables in Annex 1).

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

C0002: Are there any dose relationship of the harms (e.g. intensity, length of treatment)?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☐
- Domain search ☒
- Other:

Critical appraisal criteria: Cochrane risk of bias tool.

Method of synthesis: GRADE

Result

This question can not be answered with the available evidence.

Discussion

-

References

-

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

C0004: What are the potential short- and long term harms, their frequency, and differences according to settings?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☐
- Domain search ☒
- Other:

Critical appraisal criteria: Cochrane risk of bias tool.

Method of synthesis: GRADE

Result

There is no evidence to establish if the safety profile of the technology varies between different RDN systems or organizational settings.

Discussion

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References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

C0005: Are there any susceptible patient groups more likely to be harmed?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☐
- Domain search ☒
- Other:

Critical appraisal criteria: Cochrane risk of bias tool.

Method of synthesis: GRADE

Result

Patients with chronic renal disease could be more susceptible to RDN harm. All initial RCTs and other included studies restrict inclusion criteria to patients that have an estimated GFR (eGFR) ≤45 ml/min per 1.73 m^2. Only one of the included studies (Hering 2012) evaluates patients with moderate to severe renal disease (stage 3-4). This study finds no significant alteration in renal function as assessed by estimation of GFR according to serumcreatinine or cystatin C levels and according to plasma creatinine, cystatin C, or urea. Scheurig-Muenkler et al. reports that two patients with end stage renal disease and one patient with chronic renal failure that received RDN in their study did not exhibit any worsening in renal function (Scheurig-Muenkler 2013). In the series presented by Prochnau et al. serum creatinine and proteinura, used as markers of renal function, remains unchanged in four patients with chronic renal insufficiency (Prochnau 2012a).

Discussion

Renal function concerns and doubts as to the aggravation of renal disease are still to be resolved (Mahfoud 2011b; Mahfoud 2012). Information is limited regarding the use of renal denervation in patients with impaired renal function and long term assessments are needed. The main limitation observed in great majority of initial randomised clinical trials and other included studies is that patients have an estimated GFR (eGFR) ≤45 ml/min per 1.73 m^2) and present preserved renal function. The study of Hering et al. suggests that the renal function remains unaltered in patients with moderate to severe renal disease (stage 3-4) but this study is limited by the design (case series) and small number of patients. It should be clarified in further studies whether these patients are candidates for RDN.

References

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Scheurig-Muenkler C, Weiss W, Foert E, Toelle M, van der Giet M, Kroncke TJ, et al. Renal denervation for refractory hypertension - technical aspects, complications and radiation exposure. Rofo. 2013;185(6):550-7.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

C0007: Can adverse events be caused by the behaviour of patients, professionals or manufacturers?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☐
- Domain search ☒
- Other:

Critical appraisal criteria: Cochrane risk of bias tool.

Method of synthesis: GRADE

Result

This question can not be answered with the available evidence. However, based on the technical requirements it is reasonable to assume that procedure-related complications might depend on professional experience.

Discussion

In many of the studies, the RDN intervention was conducted in highly selected patients by a small group of trained health professionals, which does not exclude the possibility of major adverse effects if the technique is to be performed routinely in clinical practice.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐

Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

C0008: What is the safety of renal denervation in relation to standard of care (which includes additional pharmacological treatment, device based therapy of hypertension and sham treatment)?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: Cochrane risk of bias tool.

Method of synthesis: GRADE

Result

The Symplicity HTN-2 RCT (Symplicity HTN-2 2010) reported that 40.3% of the patients (n= 21) treated with RF ablation suffered minor and major complications with respect to 9.26 % of the patients (n=5) that received only pharmacological medications. The majority of adverse events in the RDN group were related to the procedure or device. During the 6 months follow up period major complications appeared in 16.3 % (n=8) and 9.8 % (n=5) of the patients, respectively (Table below). One RDN patient and 2 control patients suffered a transient ischemic attack and one patient from each group an angina. Additional serious events requiring hospitalization among patients who underwent RDN, included one case nausea and oedema (n=1), one hypotensive episode (n=1) three hypertensive emergencies unrelated to non persistence with drugs and one hypertensive crisis after stopping clonidine. Two control groups presented hypertensive emergencies. Renal function, as assessed by serum creatinine, eGFR, and cystatin C concentrations were unchanged from baseline in both groups at 6 months.

In the extension of the Symplicity HTN2-trial (Ukena 2011) authors declare that RD was performed without any major adverse events in all patients (37 interventions and 9 controls) but do not provide results on overall complications. The publication of Mahfoud from 2011 (Mahfoud 2011b) reports that one patient from the RDN treated group (n=37) developed a pseudoaneurysm of the femoral artery site (2.7%) and after 3 months, 13 patients experienced hypotension associated with symptoms (35%). Two patients that received only pharmacological medication (n=13) presented signs or symptoms consistent with hypertension (15.4%). In the 2012 publication (Mahfoud 2012) it is stated that the RDN procedure was performed

without any complication in 97% of the patients (n=110). Two patients developed a pseudo-aneurysm of the femoral artery site (2.27%) and one experienced a contrast medium allergic reaction (1.14%). During the 6 months follow up period antihypertensive drug regimens had to be reduced in 18 treated patients (18%) and increased in 7 due to development of symptoms. The mean cystatin C glomerular filtration rate and urinary albumin excretion remained unchanged after RDN in all of the studies. No abnormalities of the renal arteries (significant artery stenosis or aneurysms) were observed during the study period.

In the RCT that assessed the impact of renal artery denervation (Navistar® ThermoCool® catheter) added to PVI in respect to carrying out only PVI, no acute adverse events or renal artery stenosis were reported in either group at 6 months; the manuscript does not comment on other post-procedural adverse events (Pokushalov 2012).

Reported follow up complications in included trials

Author, date	Study type	N*	Follow up (months)	Minor complications, n (%)			Major complications, n (%)								Total
				Hypotensive events	Other	Total	Nausea and/or oedemas	Hypertensive episodes (hospital admission)	Hypotensive episodes (hospital admission)	Angina	Transient ischaemic attack	Progress of existing stenosis	Progress of renal disease	Total	n. (%)
Symplicity HTN-2 2010	RCT	I:49 C:51	6	0 0	00	0 0	1 (2.0%) 0	4 (8.2%) 2 (3.92%)	1 (2.0%) 0 (0%)	1 (2.0%) 1 (1.96%)	1 (2.0%) 2 (3.92%)	1 (2.0%) 0 (0%)	0 (0%) 0 (0%)	9 (18.3%) 5 ((9.8%)	9 (18.3%) 5 (9.8%)
Ukena 2011	RCT	I:37 C:9	3	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Pokushalov 2012	RCT	I:13 C:14	12	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mahfoud 2011	Non RCT	I: 37 C:13	3	13 (35.1%) 0	0 0	13 (35.1%) 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	13 (35.1%) 0
Brandt 2012	Non RCT	I:110 C: 10	6	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mahfoud 2012	Non RCT	I:88 C:12	6	18 (20.4%) 0	0 0	18 (20.4%) 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	18 (20.4%) 0

*Patients for whom follow up information was available
RCT: randomized controlled trial

The overall quality of the evidence is low (Table below). The incompletely recording of adverse events in included studies makes impossible pooling data to estimate frequencies of adverse events.

Evidence profiles for total and major adverse events

Evidence profile: safety of the RDN (all patients)								
N° of studies / patients	Design	Risk of bias	Inconsistency	Indirectness	Other considerations	Effect size (%)	Quality of evidence	Importance
Outcome: total adverse events (in % of patients)								
3/228	RCTs	no serious risk of bias	no serious inconsistency	serious[1,2]	none	0-40.38 vs.0-9.26	⊕⊕OO LOW	CRITICAL
3/260	Open, non randomised, controlled	no serious risk of bias	no serious inconsistency	no serious indirectness	none	0-23.9 vs. 0	⊕⊕OO LOW	CRITICAL
Outcome: major adverse events (in % of patients)								
4/274	RCTs	no serious risk of bias	no serious inconsistency	serious[1,2]	none	0-15.38 vs. 0-9.26	⊕⊕OO LOW	CRITICAL
3/260	Open, non randomised, controlled	no serious risk of bias	no serious inconsistency	no serious indirectness	none	0 vs. 0	⊕⊕OO LOW	CRITICAL

[1]Tested pulmonary vein isolation +/- renal denervation. Participants had atrial fibrillation in addition to treatment resistant hypertension.
[2] Combination of different catheter types. Uncertain transferability.

Discussion

As it may be anticipated, RDN patients present procedure related complications that are not seen in pharmacological treated patients but the majority are mild-moderate in nature and can be successfully controlled.

Since safety was not the main endpoint in four of the five included trials (Ukena 2011; Pokushalov 2012; Mahfoud 2011b; 2012; Brandt 2012a), post-procedural complications are incompletely reported. Results suggest that RDN treated patients could have more problems with the regulation of their BP, which could result in more hospital admissions due to hypo-

tensive and hypertensive emergencies. However, this is to be confirmed in trials adequately designed. With the available evidence it is impossible to make any conclusion with respect to the frequency of follow up complications.

The follow up time was inadequate to analyze long term complications. Renal function concerns and doubts as to the aggravation of renal disease are still to be resolved (Mahfoud 2011b; Mahfoud 2012). The included trials did not observe changes in estimated glomerular filtration rate (eGFR), cystatin C or other parameters used to detect renal failure function in the 3-12 months' follow-up period. However, in the Symplicity HTN-1 trial with extended follow-up of 24 months, estimated GFR remained stable within the first years, but in 10 patients followed 2 years a dramatic decrease in the eGFR rate was observed. Whether these differences might be attributed to different study population, differences in BP levels or the detrimental effect of renal denervation requires clarification. For this purpose, longer term assessments are needed.

There is uncertainty regarding the detrimental effect on the anatomy of the renal arteries with this invasive procedure. Mild, hemodynamically irrelevant wall irregularities corresponding to small local spasms or circumscribed wall oedema were consistently seen after RDN, but did not limit blood flow. Several of the included trials (Symplicity HTN-2 2010; Pokushalov 2012; Mahfoud 2011b; Mahfoud 2012) carried out a magnetic resonance angiography, computed tomographic scan and/or renal ultrasound during the follow-up period and ruled out the appearance of renal artery aneurisms, stenosis, thrombosis or any other relevant vascular abnormalities in the short to medium term (6-12 months), but the evolution of the renal arteries in the long term is unknown.

References

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Esler MD, Krum H, Schlaich M, Schmieder RE, Bohm M, Sobotka PA. Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. Circulation. 2012;126(25):2976-82.

Mahfoud F, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC, et al. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. Circulation. 2011b;123(18):1940-6.

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Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, et al. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. J Am Coll Cardiol. 2012;60(13):1163-70.

Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

Clinical Effectiveness

D0001: What is the effect of renal denervation on overall mortality?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: Davis 2013 (SR)

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: NOKC check-list for systematic reviews

Method of synthesis: narrative (GRADE not applicable)

Result

According to Davis and colleagues, no deaths were reported during the stipulated follow-up periods (Davis 2013).

Discussion

No conclusion can be drawn from the evidence available. None of the ongoing studies identified in this rapid assessment listed mortality as their main research questions.

References

Davis MI, Filion KB, Zhang D, Eisenberg MJ, Afilalo J, Schiffrin EL, Joyal D. Effectiveness of renal denervation therapy for resistant hypertension: a systematic review and meta-analysis. J Am Coll Cardiol 2013;62(3):231-241.

Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

D0002: What is the effect of renal denervation on cardiovascular mortality?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: No SR or RCT or non-RCT (i.e. prospective controlled trial) found

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

None of the identified publications in this rapid assessment have addressed cardiovascular mortality.

Since no mortality was reported in the identified publications, one can extrapolate that there has been no cardiovascular mortality either.

Discussion

Since none of the identified studies in this rapid assessment have addressed cardiovascular mortality, no conclusion can be drawn. None of the ongoing studies identified in this rapid assessment are assessing this research question as their main focus.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

D0005: How does renal denervation affect symptoms and findings?

- Cardiovascular morbidity: (stroke, myocardial infarction, heart failure)
- Left ventricular hypertrophy

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: for cardiovascular morbidity in terms of stroke, myocardial infarction, heart failure: Andersson 2013 (SR), and for left ventricular hypertrophy: Andersson 2013 (SR), Mahfoud 2013b (non-RCT, i.e. prospective controlled trial) and Pokushalov 2012 (RCT)

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: NOKC check-list for systematic reviews and Cochrane risk of bias checklist for RCTs

Method of synthesis: GRADE for the outcome left ventricular hypertrophy (GRADE was not applicable for cardiovascular morbidity)

Result

Cardiovascular morbidity

The SR by Andersson et al. was the only SR having assessed cardiovascular morbidity in terms of stroke, myocardial infarction and/or heart failure (Andersson 2013), but found no studies. Among the RCT and non-RCTs (prospective controlled trials) we identified none that had assessed this outcome.

Change in left ventricular mass (for left ventricular hypertrophy)

The SR by Andersson et al. included one non-RCT which assessed left ventricular hypertrophy in 64 patients (46 in the intervention group and 18 in the control group) 6 months following renal denervation using the Symplicity® system (Brandt 2012b). The mean difference in left ventricular mass (grams) per body surface (square meters) was 23.8 g/m^2. This result was significant in favor of renal denervation, but the quality of this evidence was very low (Table EFF1).

One non-RCT (prospective controlled trial) with 46 patients (37 in the intervention group and 9 in the control group) assessed left ventricular hypertrophy also 6 months after renal denervation using Symplicity® (Mahfoud 2013b), but measured left ventricular mass (grams) indexed to height 1.7 meter. The mean difference between the two groups was 3.6 $g/m^{1.7}$ and not significant. The quality of this evidence was very low (Table EFF1).

One RCT with 27 patients (13 in the intervention group and 14 in the control group) also assessed left ventricular hypertrophy after 6 months, but used the Navistar® ThermoCool® system (Pokushalov 2012). The left ventricular mass index measured in g/m (calculation formula was not indicated) was 15.4 g/m lower in the patients who had undergone renal denervation. The mean difference which was significant, but the quality this evidence was very low (Table EFF 1).

Table EFF1: Difference in left ventricular mass

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Renal denervation	Control	Relative (95% CI)	Absolute		
LV hypertrophy - Symplicity - LV mass post treatment at 6 months (measured with: LV mass/body surface area (g/m2); better indicated by lower values)												
1	non-RCT	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	very serious[1,3]	none	46	18	-	MD 23.8 lower (40.16 to 7.44 lower)	⊕OOO VERY LOW	IMPORTANT
LV hypertrophy - Symplicity - LV mass post treatment at 6 months (measured with: LV mass indexed to height 1.7 (g/m1.7); better indicated by lower values)												
1	non-RCT	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	very serious[1,3]	none	37	9	-	MD 3.6 higher (3.57 lower to 10.77 higher)	⊕OOO VERY LOW	IMPORTANT
LV hypertrophy – Navistar ThermoCool- LV mass change at 6 months (measured with: LVMI (g/m); better indicated by lower values)												
1	RCT	no serious risk of bias	no serious inconsistency	serious[4]	very serious[1,3]	none	13	14	-	MD 15.4 lower (20.05 to 10.75 lower)	⊕OOO VERY LOW	IMPORTANT

[1] Few participants (GRADE give suggested recommendation for imprecision : total population size is less than 400 (a threshold rule-of-thumb value; using the usual Î± and Î², and an effect size of 0.2 SD, representing a small effect)
[2] Controlled but not randomized trial.
[3] Only one study, unknown reproducibility
[4] Tested pulmonary vein isolation +/- renal denervation. Participants had atrial fibrillation in addition to treatment-resistant hypertension.

Discussion

Although two out of three studies showed less left ventricular hypertrophy in patients having undergone renal denervation using Symplicity® and Navistar® ThermoCool® systems compared with patients who had not, study sizes were small, left ventricular mass was measured differently and different study designs were used. The poor quality of the evidence does not allow for drawing any definite conclusions.

None of the ongoing studies identified in this rapid assessment are assessing this research question as their primary objective.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒

Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

D0006: How does renal denervation affect progression of treatment-resistant arterial hypertension?

- BP

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: Davis 2013 (SR) for both three and six months' follow-up and Ahmed 2012b (RCT) for three months follow-up

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: for the SR, we used the NOKC check-list for systematic reviews and Cochrane risk of bias (RoB) checklist for RCTs and non-RCTs; for the study by Ahmed et al., results were reported narratively, as we lacked information on the type of catheter used and variability of data (SE, SD or CI), and the type of test used to generate p-values.

Method for synthesis: RevMan and GRADE. Davis et al. performed meta-analyses of controlled studies (two RCTs and one non-RCT, i.e. (prospective controlled trial), and studies having used different types of catheters (one RCT used the Navistar ThermoCool®, while one RCT and one non-RCT used the Symplicity® system). We therefore chose to re-perform the meta-analyses so that we also could show the separate estimates for each of the catheter types.

Davis et al. stated that once full articles were retrieved, studies were further excluded if there was an overlap in patients with another study within the same analysis (in which case the largest sample size of the two studies was selected). In this way, overlaps of patients were avoided in the meta-analyses.

Result

Change in BP after 3 months

Change in systolic BP (3 months)

Three controlled studies having assessed change in systolic BP at three months (two RCTs and one non-RCT) using different types of catheters (one RCT used the Navistar® Thermo-

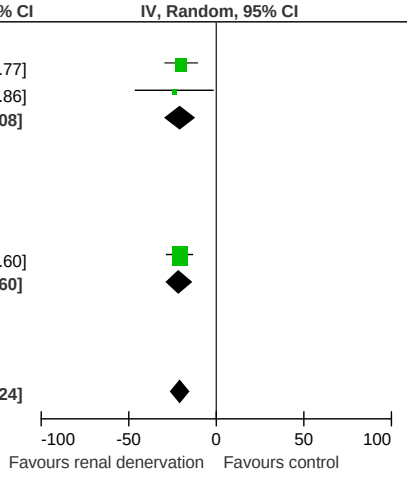
Cool®, while one RCT and one non-RCT used the Symplicity® system) were pooled (Pokushalov 2012; Symplicity HTN-2 Investigators, Esler 2010; Krum 2009). They included 171 patients in total (101 in the intervention group and 70 in the control group). The total estimate showed a significant decrease in systolic BP (Figure EFF1) with a mean difference of 20.8 mm Hg with a 95 % CI (15.2 – 26.4 mm Hg), thus in favor of renal denervation. The quality of the evidence was low (Table EFF3).

We re-analyzed the data, and grouped studies according to catheter type. Pooling the two studies including totally 144 patients (88 in the intervention group and 56 in the control group) that used the Symplicity® system (Figure EFF1) resulted in a decrease of 20.6 mm Hg systolic BP with 95 % CI (12.1 – 20.1 mm Hg), which was significant. Here, the quality of the evidence was moderate (Table EFF3).

As shown in Figure EFF1, the study that used the Navistar® ThermoCool® system included 27 patients (13 in the intervention group and 14 in the control group) showed a mean difference of 21 mm Hg with 95 % CI (13.6 – 28.4 mm Hg), a decrease which also was significant. However in this case, the quality of the evidence was very low (Table EFF3).

Figure EFF1: Forest plots of change in systolic BP after 3 months

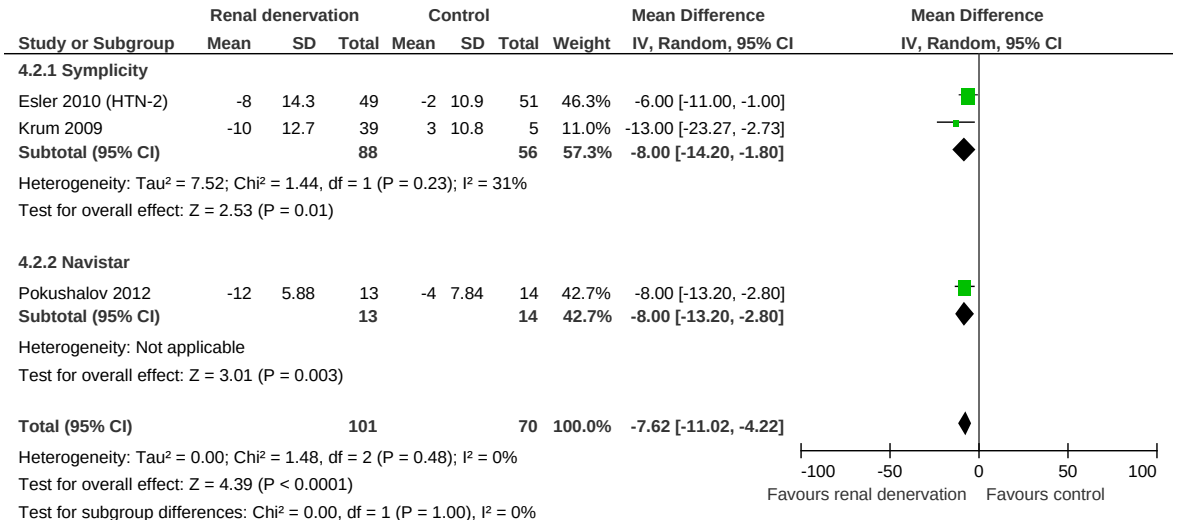
	Renal denervation			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
4.1.1 Symplicity									
Esler 2010 (HTN-2)	-24	25	49	-4	21.9	51	36.6%	-20.00 [-29.23, -10.77]	
Krum 2009	-21	22	39	3	24	5	6.4%	-24.00 [-46.14, -1.86]	
Subtotal (95% CI)			**88**			**56**	**43.0%**	**-20.59 [-29.11, -12.08]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%									
Test for overall effect: Z = 4.74 (P < 0.00001)									
4.1.2 Navistar									
Pokushalov 2012	-27	9.8	13	-6	9.8	14	57.0%	-21.00 [-28.40, -13.60]	
Subtotal (95% CI)			**13**			**14**	**57.0%**	**-21.00 [-28.40, -13.60]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 5.56 (P < 0.00001)									
Total (95% CI)			**101**			**70**	**100.0%**	**-20.82 [-26.41, -15.24]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 2 (P = 0.95); I² = 0%									
Test for overall effect: Z = 7.31 (P < 0.00001)									
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%									



Change in diastolic BP (3 months)

As for systolic BP, the three controlled studies having assessed change in diastolic BP at three months (two RCTs and one non-RCT) using different types of catheters (one RCT used the Navistar® ThermoCool®, while one RCT and one non-RCT used the Symplicity® system) were pooled (Pokushalov 2012; Symplicity HTN-2 Investigators, Esler 2010; Krum 2009). Likewise, they included 171 patients in total (101 in the intervention group and 70 in the control group). The total estimate showed a significant decrease in diastolic BP (Figure EFF2) with a mean difference of 7.6 mm Hg with 95 % CI (4.2 – 11.0 mm Hg). The quality of the evidence was low (Table EFF3).

Figure EFF2. Forest plots of change in diastolic BP after 3 months



We re-analysed the data, and grouped studies according to catheter type, as for systolic BP at three months. Pooling the two studies including totally 144 patients (88 in the intervention group and 56 in the control group) that used the Symplicity® system (Figure EFF2) resulted in a mean difference of 8.0 mm Hg with 95 % CI (1.8 – 14.2 mm Hg), a decrease in diastolic BP which also was significant. The quality of the evidence was moderate (Table EFF3).

As shown in Figure EFF2, and as for systolic BP, the study that used the Navistar® ThermoCool® system included 27 patients (13 in the intervention group and 14 in the control group) showed a mean difference of 8.0 mm Hg with 95 % CI (2.8 – 13.2 mm Hg), a decrease which was significant too. The quality of the evidence was very low (Table EFF3).

Davis et al. showed separately mean differences in systolic BP at three months after renal denervation in which they included patients from the intervention group of RCTs, non-RCTs and observational studies for the different types of renal denervation systems. As shown in Table EFF2, 6 studies using the Symplicity® system were pooled, which resulted in a significant decrease in systolic BP. However, except for one trial, the studies lacked control group. Four other studies were presented which also assessed systolic BP at three months using Celcius® ThermoCool®, Navistar® ThermoCool®, MarinR® and PARADISE™ systems respectively (Ahmed 2012a; Pokushalov 2012; Prochnau 2012a; Mabin 2012). Each study indicated decreases in systolic BP, which also were significant. As these trials are mostly without a control group, and we have results from controlled trials on this outcome, we have not performed GRADE evaluations for

Table EFF2. Difference in systolic BP (3 months)

Catheter type	Studies included	Number of patients (pre- and post treatment)	Estimate (mean difference in mm Hg)
Symplicity®	6	379 – 341	-21,18 (-25,77 to -16,59)
Celcius® ThermoCool®	1	10 – 10	-22 (-28 ,80 to -15,20)
Navistar® ThermoCool®	1	13 – 13	-27,00 (-32,33 to -21,67)
Marinr®	1	30 – 30	-25,50 (-32,65 to -18,35)
PARADISE™	1	10 – 8	-36,00 (-49,86 to -22,14)

The RCT by Ahmed and colleagues (Ahmed 2012b) included 40 patients with drug-resistant hypertension (19 in the intervention group and 21 in the control group). They reported having used an off-the shelf saline-irrigated radiofrequency ablation catheter typically employed for cardiac tissue ablation, but do not mention from whom this catheter was purchased (Ahmed 2012b). After three months, systolic BP was decreased by 11 mm Hg (p-value 0.006) while diastolic BP was decreased by 7 mm Hg, however lack of key information to date, as mentioned in the method section above, prevents us for assessing the quality of the evidence thus drawing any conclusions.

Change in BP after 6 months

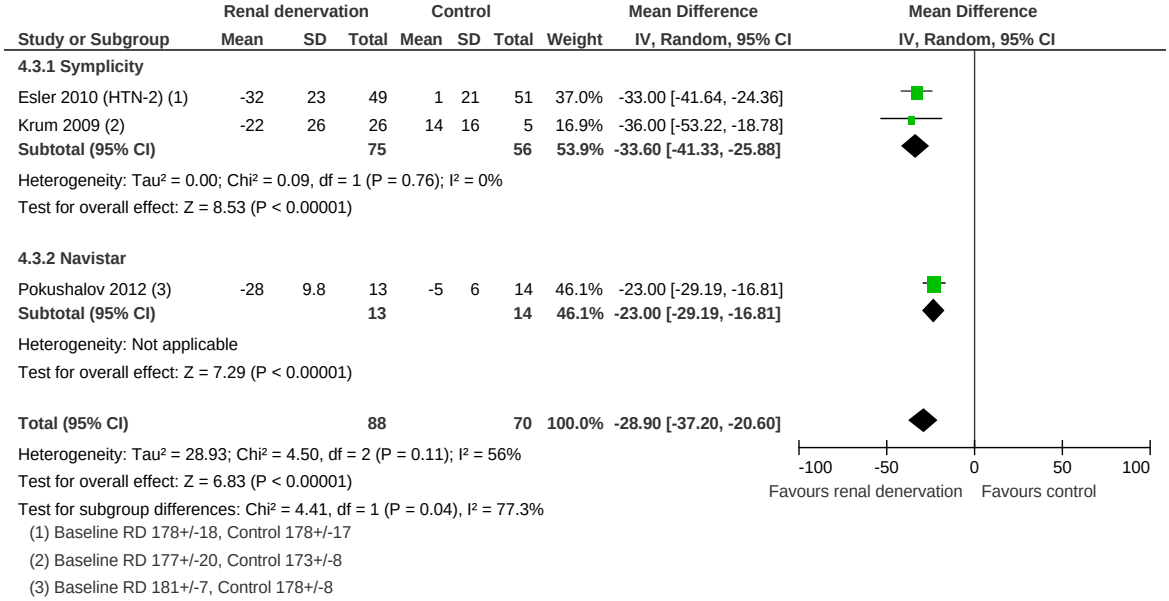
Change in systolic BP (6 months)

As for systolic BP measured at three months, three controlled studies had assessed change in systolic BP at six months (two RCTs and one non-RCT) using different types of catheters (one RCT used the Navistar® ThermoCool®, while one RCT and one non-RCT used the Symplicity® system) were pooled (Pokushalov 2012; Symplicity HTN-2 Investigators, Esler 2010; Krum 2009). They included 158 patients (88 in the intervention group and 70 in the control group). The overall estimate for renal denervation showed a significant decrease in systolic BP (Figure EFF3) with a mean difference of 29.8 mm Hg with a 95% CI (20.6 – 37.2 mm Hg). The quality of the evidence was low (Table EFF3).

We re-analyzed the data, and grouped studies according to catheter type. Pooling the two studies including totally 131 patients (75 in the intervention group and 56 in the control group) that used the Symplicity® system (Figure EFF3) resulted in a mean difference of 33.6 mm Hg with 95 % CI (25.9 – 41.3 mm Hg), which was significant. The quality of the evidence was moderate (Table EFF3).

As shown in Figure EFF3, the study that used the Navistar® ThermoCool® system included 27 patients (13 in the intervention group and 14 in the control group) showed a mean difference of 23 mm Hg with 95 % CI (16.8 – 29.2 mm Hg), which also was significant. The quality of the evidence was very low (Table EFF3).

Figure EFF3. Forest plots of change in systolic BP after 6 months



Change in diastolic BP (6 months)

As for systolic BP, the three controlled studies having assessed change in diastolic BP at six months (two RCTs and one non-RCT) using different types of catheters (one RCT used the Navistar® ThermoCool®, while one RCT and one non-RCT used the Symplicity® system) were pooled (Pokushalov 2012; Symplicity HTN-2 Investigators, Esler 2010; Krum 2009). Likewise, they included 158 patients (88 in the intervention group and 70 in the control group). The total estimate showed a significant decrease in diastolic BP (Figure EFF4) with a mean difference of 11.0 mm Hg with 95 % CI (5.7 – 16.4 mm Hg). The quality of this evidence was low (Table EFF3).

We re-analyzed the data, and grouped studies according to catheter type, as for systolic BP at three months. Pooling the two studies including 131 patients (75 in the intervention group

and 56 in the control group) that used the Symplicity® system (Figure EFF4) resulted in a mean difference of 13.8 mm Hg with 95 % CI (7.3 – 20.3 mm Hg), which also was significant. The quality of this evidence was moderate (Table EFF3).

As shown in Figure EFF4, as for systolic BP, the study that used the Navistar® ThermoCool® system included 27 patients (13 in the intervention group and 14 in the control group) and showed a mean difference of 7.0 mm Hg with 95 % CI (2.5 – 11.5 mm Hg), which was significant too. The quality of the evidence was very low (Table EFF3).

Figure EFF4. Forest plots of change in systolic BP after 6 months

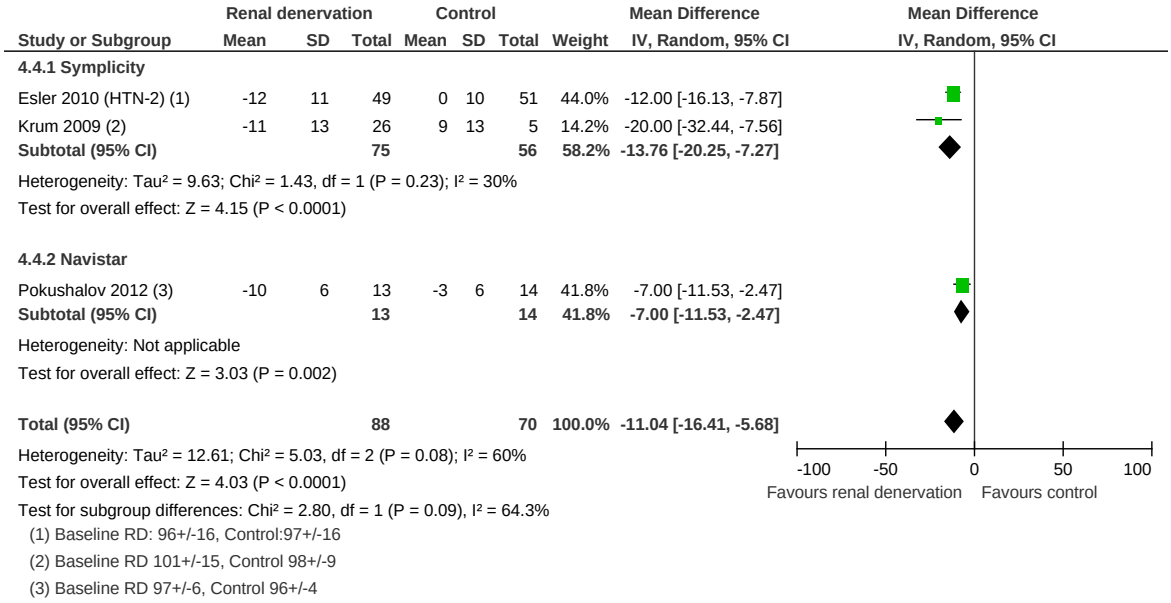


Table EFF3. GRADE profiles for BP

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Renal denervation	Control	Relative (95% CI)	Absolute		
Change in systolic BP at 3 months (measured with: Office-based (mm Hg); better indicated by lower values)												
3	2 RCTs 1 non-RCT	no serious risk of bias[1]	no serious inconsistency	serious[2,3]	serious[4]	none	101	70	-	MD 20.82 lower (26.41 to 15.24 lower)	⊕⊕OO LOW	CRITICAL
Change in systolic BP at 3 months - Symplicity (measured with: Office-based (mm Hg); better indicated by lower values)												
2	1 RCTs 1 non-RCT	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[4]	none	88	56	-	MD 20.59 lower (29.11 to 12.08 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in systolic BP at 3 months - Navistar (measured with: Office based (mm Hg); better indicated by lower values)												
1	RCT	no serious risk of bias	no serious inconsistency	serious[2,5]	very serious[4]	none	13	14	-	MD 21 lower (28.4 to 13.6 lower)	⊕OOO VERY LOW	CRITICAL
Change in diastolic BP at 3 months (measured with: Office based (mm Hg); better indicated by lower values)												
3	2 RCTs 1 non-RCT	no serious risk of bias[1]	no serious inconsistency	serious[2,3]	serious[4]	none	101	70	-	MD 7.62 lower (11.02 to 4.22 lower)	⊕⊕OO LOW	CRITICAL
Change in diastolic BP at 3 months - Symplicity (measured with: Office based (mm Hg); better indicated by lower values)												
2	1 RCTs 1 non-RCT	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[4]	none	88	56	-	MD 8 lower (14.2 to 1.8 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in diastolic BP at 3 months - Navistar (measured with: Office based (mm Hg); better indicated by lower values)												
1	RCT	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4,5]	none	13	14	-	MD 8 lower (13.2 to 2.8 lower)	⊕OOO VERY LOW	CRITICAL
Change in systolic BP at 6 months (measured with: Office based (mm Hg); better indicated by lower values)												
3	2 RCTs 1 non-RCT	no serious risk of bias[1]	no serious inconsistency	serious[2,3]	serious[4]	none	88	70	-	MD 29.80 lower (37.2 to 20.6 lower)	⊕⊕OO LOW	CRITICAL
Change in systolic BP at 6 months - Symplicity (measured with: Office based (mm Hg); better indicated by lower values)												
2	1 RCTs 1 non-RCT	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[4]	none	75	56	-	MD 33.6 lower (41.33 to 25.88 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in systolic BP at 6 months - Navistar (follow-up 6 months; measured with: Office based (mm Hg); better indicated by lower values)												
1	RCT	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4,5]	none	13	14	-	MD 23 lower (29.2 to 16.8	⊕OOO VERY LOW	CRITICAL

										lower)		
Change in diastolic BP at 6 months (follow-up 6 months; measured with: Office based (mm Hg); better indicated by lower values)												
3	2 RCTs 1 non-RCT	no serious risk of bias[1]	no serious inconsistency	serious[2,3]	serious[4]	none	88	70	-	MD 11.04 lower (16.41 to 5.68 lower)	⊕⊕OO LOW	CRITICAL
Change in diastolic BP at 6 months - Symplicity (measured with: Office based; better indicated by lower values)												
2	1 RCTs 1 non-RCT	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[4]	none	75	56	-	MD 13.76 lower (20.25 to 7.27 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in diastolic BP at 6 months - Navistar (measured with: Office based (mm Hg); better indicated by lower values)												
1	RCT	no serious risk of bias	no serious inconsistency	serious[2]	very seri-ous[4,5]	none	13	14	-	MD 7 lower (11.53 to 2.47 lower)	⊕OOO VERY LOW	CRITICAL

[1] Mix of randomised and non-randomised CT (combined as in the SR).
[2] Tested pulmonary vein isolation +/- renal denervation. Participants had atrial fibrillation in addition to treatment-resistant hypertension.
[3] Combination of different catheter types. Uncertain transferability.
[4] Few participants (GRADE give suggested recommendation for imprecision: total population size is less than 400 (a threshold rule-of-thumb value; using the usual Î± and Î², and an effect size of 0.2 SD, representing a small effect).
[5] Only one study, unknown reproducibility.

Discussion

All three controlled studies identified by the SR included in this rapid assessment showed a statistically significant decrease in systolic and diastolic BP both after three (171 patients) and six months (158 patients) of follow-up, thus favored renal denervation. The quality of the evidence was however variable when assessed using GRADE, ranging from very low (one study including 27 patients that used the Navistar® ThermoCool® system) to moderate (two studies including 144 patients after three months' follow-up and 131 patients at six months' follow-up using the Symplicity® system). We therefore conclude that renal denervation using the Symplicity® system seems to decrease BP, while there is uncertainty about effect on BP using the Navistar® ThermoCool® system.

In this rapid assessment we identified 26 ongoing studies in the ICTRP database, most focus on BP control (see Appendix 1).

Supplementary documentation received from the other manufacturers (Boston Scientific, St Jude and Covidien, Medtronic) indicate that these companies plan their first, or additional RCT in the next year or two.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

D0011: What is the effect of renal denervation on patients' body functions?

- Kidney function

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: Gosain 2013 (SR)

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: NOKC check-list for systematic reviews

Method of synthesis: GRADE

Result

Change in eGFR (estimated Glomerular Filtration Rate)

The SR by Gosain et al. (Gosain 2013) identified one RCT including 100 patients (49 in the intervention group and 51 in the control group) which assessed change in renal function in

terms of change in eGFR (estimated Glomerular Filtration Rate) after six months of follow up using the Symplicity® system (Symplicity HTN-2 Investigators, Esler 2010). The mean difference between the two groups was 0.7 mL/min/1.73m^2 (baseline levels retrieved from Esler et al. were 77+/-17 mL/min/1.73m^2 in the renal denervation group and 86+/-20 mL/min/1.73m^2 in the control group) and not significant. The quality of this evidence was low (Table EFF4).

Change in serum creatinine levels

The same RCT with 100 patients (also with 49 in the intervention group and 51 in the control group) assessed change in renal function in terms of change in serum creatinine levels after six months of follow up using the Symplicity® system (Symplicity HTN-2 Investigators, Esler 2010). The mean difference between the two groups was 1.3 µmol/L (baseline levels retrieved from Esler et al. were 91+/-25 µmol/L in the renal denervation group and 78+/-18 µmol/L in the control group) and not significant. The quality of this evidence was low (Table EFF4).

Table EFF4. GRADE profiles for kidney function

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Renal denervation	Control	Relative (95% CI)	Absolute		
Change in eGFR at 6 months - RCT (measured with: lab analysis (estimated glomerular filtration rate in mL/min/1.73m^2); better indicated by lower values)												
1	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	49	51	-	MD 0.7 lower (5.21 lower to 3.81 higher)	⊕⊕OO LOW	IMPORTANT
Change in creatinine at 6 months - RCT (measured with: lab analysis (creatinine in µmol/L); better indicated by lower values)												
1	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	49	51	-	MD 1.3 higher (4.38 lower to 6.98 higher)	⊕⊕OO LOW	IMPORTANT

[1] Few participants (GRADE give suggested recommendation for imprecision : total population size is less than 400 (a threshold rule-of-thumb value; using the usual Î± and Î², and an effect size of 0.2 SD, representing a small effect).
[2] Only one study, unknown reproducibility

Discussion

According to one RCT with 100 patients identified by the included SR, there was no change in kidney function assessed by measuring eGFR and creatinine levels following renal denervation at six months' follow-up, however no definite conclusion can be drawn as the quality of the evidence is low.

References

Symplicity HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 2010;376(9756):1903-1909.

Gosain P, Garimella PS, Hart PD, Agarwal R. Renal Sympathetic Denervation for Treatment of Resistant Hypertension: A Systematic Review. J Clin Hypertens 2013;15(1):75-84.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

D0016: How does the use of renal denervation affect activities of daily living?

- Exercise

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: Ukena 2011 (RCT)

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: Cochrane risk of bias checklist for RCTs

Method of synthesis: GRADE

Result

Change in maximum work rate

One RCT including 46 patients (37 in the intervention group and 9 in the control group) assessed change in maximum work rate after three months' of follow-up after renal denervation using the Symplicity® system (Ukena 2011). The mean difference between the two groups was 3.0 Watts on reclining ergometer (baseline levels were 123+/-36 Watts in the renal denervation group and 130+/-26 Watts in the control group) and not significant. The quality of this evidence was very low (Table EFF5).

Change in peak oxygen uptake

The same RCT assessed change in peak oxygen uptake (VO_2 peak) three months' after renal denervation using the Symplicity® system (Ukena 2011). The mean difference between the two groups was 1.0 ml/min/kg (baseline levels were 19+/-4 ml/min/kg in the renal denervation group and 20+/-4 ml/min/kg in the control group) and not significant. The quality of this evidence was very low (Table EFF5).

Table EFF5. GRADE profiles for activities of daily living (exercise)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Activity of daily living: exercise	Control	Relative (95% CI)	Absolute		
Change in max work rate at 3 months (follow-up 3 months; measured with: Watts on reclining ergometer; Better indicated by lower values)												
1	RCT	serious risk of	no serious inconsistency	no serious indirectness[2]	very serious[3,4]	none	37	9	-	MD 3 higher (7.66 lower to 13.66	⊕OOO VERY	IMPORTANT

		bias[1]								higher)	LOW	
Change in peak oxygen uptake at 3 months (follow-up 3 months; measured with: VO2 peak ml/min/kg; Better indicated by higher values)												
1	RCT	serious risk of bias[1]	no serious inconsistency	no serious indirectness[2]	very seri-ous[3,4]	none	37	9	-	MD 1.00 lower (2.46 lower to 0.46 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Unclear how randomization and allocation was performed.
[2] Unclear how well this test represent the patients' ability to manage activity of daily living.
[3] Only one study, unknown reproducibility
[4] Few participants (GRADE give suggested recommendation for imprecision : total population size is less than 400 (a threshold rule-of-thumb value; using the usual Î± and Î², and an effect size of 0.2 SD, representing a small effect).

Discussion

According to one RCT (including 46 patients) identified in this rapid assessment, there was no change in activities of daily living in terms of exercise assessed with measurements of maximum work rates and peak oxygen uptake following renal denervation at three months' follow-up, however no definite conclusion could be drawn as the quality of the evidence was low.

References

Ukena C, Mahfoud F, Kindermann I, Barth C, Lenski M, Kindermann M, et al. Cardiorespiratory response to exercise after renal sympathetic denervation in patients with resistant hypertension. J Am Coll Cardiol 2011;58(11):1176-82.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

D0012: What is the effect of renal denervation on generic health-related quality of life?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: No SR or RCT or non-RCT (i.e. prospective controlled trial) found

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

None of the identified studies in this rapid assessment have addressed generic health-related quality of life.

Discussion

Since none of the identified studies in this rapid assessment have addressed generic health-related quality of life, no conclusion can be drawn. None of the ongoing studies identified in this rapid assessment are assessing this research question.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

D0013: What is the effect of renal denervation on disease-specific quality of life?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: No SR or RCT or non-RCT (i.e. prospective controlled trial) found

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

None of the identified studies in this rapid assessment have addressed disease-specific quality of life.

Discussion

Since none of the identified studies in this rapid assessment have addressed disease-specific quality of life, no conclusion can be drawn. None of the ongoing studies identified in this rapid assessment are assessing this research question.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

D0017: Were patients overall satisfied with renal denervation?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: No SR or RCT or non-RCT (i.e. prospective controlled trial) found

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

None of the identified studies in this rapid assessment have addressed patient satisfaction.

Discussion

Since none of the identified studies in this rapid assessment have addressed patient satisfaction, no conclusion can be drawn. None of the ongoing studies identified in this rapid assessment are assessing this research question.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

D0018: Would the patient be willing to undergo renal denervation?

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: No SR or RCT or non-RCT (i.e. prospective controlled trial) found

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: not applicable

Method of synthesis: not applicable

Result

None of the identified studies in this rapid assessment have addressed patients' willingness to undergo renal denervation.

Discussion

Since none of the identified studies in this rapid assessment have addressed patients' willingness to undergo renal denervation, no conclusion can be drawn. None of the ongoing studies identified in this rapid assessment are assessing this research question.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

D0023: How does renal denervation modify the need for other technologies and use of resources?

- Decrease in number of medications

Methods

☒ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information: Gosain 2013 (SR)

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria: NOKC check-list for systematic reviews

Method of synthesis: narrative (GRADE not applicable)

Result

Decrease in number of medications

Gosain and colleagues narratively summarised the change in number of medications in their included studies (Gosain 2013). They stated that average number of antihypertensive medications used in most studies were five, and reported change in number of antihypertensive medications after renal denervation in nine studies. Table EFF6 below, tabulates the information Gosain and colleagues present in text. It shows number of studies and number of patients included in these studies with the corresponding recorded changes in medications and number of patients related to the change in question.

Table EFF6. Change in number of antihypertensive medications

Studies (total number of patients)	Change	In how many/which patients?
3 (236)	10 - 20 % decrease	52 patients
	10 – 25 % increase	25 patients
1 (5)	Decrease (? %)	4 patients
3 (129)	15 - 25 % decrease	Not specified
2 (60)	No change	Not specified

In three studies with totally 236 patients, 52 patients noted the 10-20% reduction in the number of antihypertensive medications used, while 25 patients required 10 to 25 % (increase in the number of medications. One study with 5 patients reported reduction in antihypertensive medications in 4 patients. Further, three studies including 129 patients in total reported a decrease in medications of 15 to 25 % in renal denervation group. Finally, the remaining studies with a total of 60 patients reported no change in number of medications.

Discussion

Although data from nine studies including 430 patients in total may suggest a decrease in number of anti-hypertensive medications following renal denervation, no conclusion can be drawn.

References

Gosain P, Garimella PS, Hart PD, Agarwal R. Renal Sympathetic Denervation for Treatment of Resistant Hypertension: A Systematic Review. J Clin Hypertens 2013;15(1):75-84.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

Checklist for potential ethical, organisational, social and legal aspects

1. Ethical	
1.1. Does the introduction of renal denervation and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new ethical issues (equal access to the treatment, resource allocation/shortage etc.)?	Yes
1.2. Does comparing renal denervation to the defined, existing comparators point to any differences which may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of renal denervation and its potential use/nonuse instead of the defined, existing comparators require organisational changes in terms of training in procedure, need for facilities, equipment and resources?	Yes
2.2. Does comparing renal denervation to the defined, existing comparators point to any differences which may be organisationally relevant (e.g. shift from primary to secondary care, transportation, etc.)?	Yes
3. **Social**	
3.1. Does the introduction of renal denervation and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing renal denervation to the defined, existing comparators point to any differences which may be socially relevant?	No
4. **Legal**	
4.1. Does the introduction of renal denervation and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing renal denervation to the defined, existing comparators point to any differences which may be legally relevant?	No

