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Systematic review

Renal Artery Ablation in Patients with Treatment - Resistant Hypertension: a systematic review

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Systematic review

Renal Artery Ablation in Patients with Treatment - Resistant Hypertension

Foreword

This year Agenas has produced a systematic review of renal artery ablation in patients with treatment resistant hypertension, on behalf of the *Commissione Unica Dispositivi Medici (CUD)* of the Italian Ministry of Health.

The need to investigate renal artery ablation in patients with treatment resistant hypertension arose from the awareness that hypertension is a significant public health problem as it is universally considered the major cardiovascular risk factor due to the great prevalence in the general population and the impact on cardiovascular mortality and morbidity. Since resistant hypertension patients are exposed to a greater cardiovascular risk, it is crucial to identify that subgroup of patients as well as to choose specific treatments to adequately control blood pressure.

The systematic review and its content are as always the product of a long and laborious process of consultation with experts, (internal and external) reviewers, and other stakeholders.

This systematic review represents the first experience of performing a research activity of evidence synthesis by Agenas with the collaboration of the Italian Regions, within the Rete Italiana of Health Technology assessment (RIHTA) or Italian HTA network.

The approach followed to develop this document was structured in two different but complementary activities. The first activity, the systematic review, was aimed at identifying, appraising and synthesizing the available evidence of the effects of denervation of renal artery by catheter-based radioablation.

The second activity, the budget impact analysis, was developed to measure the potential economic impact of the use and diffusion of such medical device in one Italian Regional Health System.

To evaluate the efficacy, safety and economic evidence of denervation of renal artery by catheter-based radioablation, is important and necessary to ensure that patients are given the appropriate therapy to treat resistant hypertension as well as to provide the decision maker with important information to manage the acquisition and use of the technology.

Fulvio Moirano

Executive Director Agenas

Premessa

Quest'anno l'Agenas ha prodotto, su mandato del Ministero della Salute (Commissione Unica Dispositivi Medici - CUD), una revisione sistematica sulla procedura di denervazione renale mediante ablazione con radiofrequenza nei pazienti con ipertensione resistente alla terapia farmacologica.

La necessità di indagare la procedura di denervazione renale nei pazienti ipertesi resistenti, è nata dalla consapevolezza che l'ipertensione costituisce un problema rilevante di salute pubblica, essendo universalmente considerato il più importante fattore di rischio cardiovascolare, sia per la sua elevata prevalenza nella popolazione generale sia per il suo impatto sulla mortalità e morbilità cardiovascolare. Dal momento che i pazienti ipertesi resistenti sono esposti ad un maggiore rischio cardiovascolare, è di cruciale importanza identificare tale sottogruppo di pazienti così come scegliere i trattamenti appropriati per controllare adeguatamente la pressione arteriosa.

La revisione sistematica, come tutti i prodotti dell'Agenzia, è il frutto di un lungo e laborioso processo di consultazione con esperti, revisori e altri stakeholders.

Questa revisione sistematica rappresenta la prima esperienza, nella realizzazione di un'attività di analisi e sintesi dell'evidenza, svolta da Agenas in collaborazione con le Regioni Italiane, nell'ambito della Rete Italiana di Health Technology assessment (RIHTA) o Italian HTA network.

Ciò che ha caratterizzato la presente revisione sistematica è il suo sviluppo in due linee di attività distinte ma complementari.

La prima linea di attività è finalizzata ad identificare, valutare e sintetizzare l'evidenza attualmente disponibile sulla procedura di denervazione renale mediante ablazione con radiofrequenza. La seconda linea di attività, la budget impact analysis, è sviluppata per misurare il potenziale impatto economico dell'utilizzo e della diffusione della procedura nell'ambito di un Sistema Sanitario Regionale Italiano (Regione Veneto).

Valutare le prove di efficacia clinica e di sicurezza e le prove economiche della procedura di denervazione è particolarmente importante e necessario per fornire l'appropriata terapia ai pazienti ipertesi resistenti nonché per fornire ai decisori le informazioni utili in merito all'acquisizione e all'utilizzo della tecnologia.

Fulvio Moirano

Direttore Agenas

Executive Summary

Introduction

Hypertension is a significant public health problem as it is universally considered the major cardiovascular risk factor due to the great prevalence in the general population and the impact on cardiovascular mortality and morbidity. Systolic and diastolic blood pressure values are directly and continuously associated with an increased incidence of coronary and cerebrovascular events, peripheral vascular disease, and heart and renal failure. Essential hypertension is often associated with other cardiovascular risk factors, including the alteration of glucidic and lipid metabolism. The combination of risk factors causes an exponential increase of the risk of cardiovascular events. A subgroup of hypertensive patients does not achieve the target levels of systolic and diastolic blood pressure, in spite of a therapeutic plan including adherence to lifestyle measures and the prescription of at least three drugs (including a diuretic) in adequate doses. Such subgroup, called resistant hypertension patients, is exposed to a greater cardiovascular risk. It is very important to identify that subgroup of patients as well as to choose specific treatments to adequately control blood pressure.

Objectives

The aim of this systematic review is to identify and synthesize the available evidence about the effectiveness, safety and cost-effectiveness of denervation of renal artery by catheter-based radio-ablation in patients with resistant hypertension and to measure the potential economic impact of its use and diffusion in one Italian Regional Health System (Veneto Region).

Methods

We identified, assessed and synthesized all available effiectiveness, safety and economic evidence on denervation of renal artery by catheter-based radioablation plus anti-hypertensive standard medications for treatment-resistant hypertension compared with anti-hypertensive standard medications.

We ran searches on five electronic bibliographic databases (Medline, EMBASE, Cochrane Library, CINAHL and Web of Science) and included clinical efficacy and safety studies published since January 2005, comparing denervation of renal artery by catheter-based radioablation plus anti-hypertensive standard medications versus standard pharmacological therapy. A specific search was performed to identify economic evidence and applied to Medline, EMBASE and Cochrane Library from January 2005 to February 2012. Independently, two reviewers extracted, quality assessed and synthesized the data, both for clinical efficacy and safety evidence and for economic evidence.

We developed a model for a budget impact analysis (BIA) to estimate the potential economic impact of the use and diffusion of denervation of renal artery by catheter-based radioablation in Veneto Region. The model for a BIA was developed on the basis of a regional survey, collecting context data, a literature search and national and regional databases.

Results

We included two clinical efficacy and safety studies. Both included studies were comparative, although randomization was performed only in one of them. Population within the studies ranged from 50 to 106 patients, with blood pressure values higher than 140/90 mmHg (millimeters of mercury), in spite of receiving an average of five anti-hypertensive drugs.

Changes in blood pressure levels (primary outcome) were reported in both studies. Office-based blood pressure measurements were taken in both studies, while home-based and 24 hour ambulatory monitoring measurements only in one. Blood pressure changes were measured at a short follow up period (three and six months respectively). Safety outcomes were stated in one study; no safety outcome was explicitly defined in the other one.

The included studies were appraised using an adaptation of the Cochrane risk of bias tool and resulted to be at high risk of bias. Besides, all studies were sponsored by manufacturer, which was involved in the study design and analysis.

The efficacy and safety evidence shows percutaneous renal denervation to be effective in reducing systolic and diastolic blood pressure in patients suffering from refractory hypertension and to be safe. No serious complications were related to the device or procedure.

Nevertheless, follow up was too short to assess the stability or the improvement of the effect in a longer term, taking also into consideration that renal nerve fibers may regenerate. In addition, due to the lack of evidence concerning long term duration of the antihypertensive effect of renal denervation, no direct or indirect proof exists to support the beneficial effect of this technique on clinical hard end-points.

We did not find any cost-effectiveness, cost minimization or cost-utility analyses on denervation of renal artery by catheter-based radioablation in patients with resistant hypertension.

The regional survey, carried out in the Veneto Region, indicated that only one centre, out of the two surveyed, performed the catheter based denervation both in the setting of clinical practice (limited as to compassionate use) and research. The survey also provided the estimated number of patients potentially eligible to the procedure and the average resources consumption. This information, as well as data collection on unit costs and epidemiological

data, were used to populate the budget impact model. 216,136 uncontrolled hypertensive patients (systolic blood pressure>140 mmHg) were estimated in Veneto. Of these, 7.86% are at high risk, on multi-therapy with at least 3 antihypertensive drugs, resulting in 16,988 hypertensive subjects resistant to therapies (target population). We also considered a yearly increase equal to 0.25% for eligible patients, with a total of 42, 106, 170 patients at 1st, 2nd and 3rd year respectively, from the introduction of procedure, an estimate of procedure cost equal to €7,327 and a cost of current therapies equal to €581, yearly, per treated patient.

Although with some limitations, the model estimated that the introduction of the device in clinical practice would increase regional expenditure for resistant hypertension treatment by 3%, 7% and 12%, respectively at 1st, 2nd and 3rd year from denervation implementation. The Model is sensitive to procedure, current therapies costs and rates of eligible patients.

Conclusions

Clinical comparative studies included in this systematic review point out a significant reduction of blood pressure levels (both systolic and diastolic) in patients with treatment resistant essential hypertension. However since the available evidence is scarce, there is a need for more comparative clinical studies with longer follow-up. Long term efficacy and safety data are required to assess the actual effect of the renal artery ablation on the blood pressure and, accordingly, to evaluate how blood pressure reduction could affect the development of hypertension related diseases and mortality.

An economic evaluation for renal artery ablation should be performed alongside such evidence generation studies.

Sintesi

Introduzione

L'ipertensione costituisce un problema rilevante di salute pubblica. E' universalmente riconosciuto che l'ipertensione arteriosa rappresenta il più importante fattore di rischio cardiovascolare, sia per la sua elevata prevalenza nella popolazione generale, sia per il suo impatto sulla mortalità e sulla morbilità cardiovascolare. I valori della pressione arteriosa sistolica e diastolica sono associati in maniera diretta e continua ad un'aumentata incidenza di eventi coronarici e cerebrovascolari, di vasculopatia periferica, di scompenso cardiaco e di insufficienza renale. Inoltre, l'ipertensione arteriosa si associa, frequentemente, ad altri fattori di rischio, come - ad esempio - le alterazioni del metabolismo glicolipidico. La combinazione di più fattori di rischio aumenta in modo esponenziale il rischio di eventi cardiovascolari. All'interno della popolazione dei pazienti ipertesi, è individuato un sottogruppo di pazienti definiti "ipertesi resistenti" esposto a rischio cardiovascolare più elevato poiché, nonostante la prescrizione di uno schema terapeutico che comprenda le modifiche dello stile di vita e l'assunzione di almeno tre farmaci anti-ipertensivi (incluso un diuretico) a dosi piene, non riesce a ridurre la pressione sistolica e diastolica al di sotto del valore raccomandato. Per un efficace trattamento dei pazienti affetti da ipertensione resistente, è fondamentale sia definire accuratamente l'iter diagnostico sia identificare le appropriate opzioni terapeutiche.

Obiettivi

Scopo principale della presente revisione sistematica è quello di identificare ed analizzare le prove di efficacia clinica, sicurezza e costo-efficacia della denervazione mediante ablazione con radiofrequenza delle arterie renali. Ulteriore obiettivo è quello di misurare il potenziale impatto economico dell'utilizzo e della diffusione di tale procedura nell'ambito del Sistema Sanitario Regionale (SSR) della Regione Veneto.

Metodi

Abbiamo identificato, valutato e sintetizzato l'evidenza attualmente disponibile concernente la procedura di denervazione renale mediante ablazione con radiofrequenza, con il mantenimento della terapia farmacologia anti-ipertensiva standard, rispetto alla sola terapia farmacologica anti-ipertensiva standard, nei pazienti ipertesi resistenti.

Abbiamo condotto le ricerche bibliografiche in cinque banche dati elettroniche (Medline, EMBASE, Cochrane Library, CINAHL and Web of Science), includendo gli studi di efficacia clinica e di sicurezza, pubblicati a partire da gennaio 2005, in cui la procedura di denervazione renale con terapia farmacologica standard è stata confrontata alla sola terapia farmacologica standard. E' stata inoltre condotta una ricerca bibliografica specifica, nelle banche dati Medline, EMBASE e Cochrane Library, per individuare l'evidenza economica

pubblicata nel periodo compreso tra gennaio 2005 e febbraio 2012 (mese di effettuazione della ricerca). Sia per le dimensioni di efficacia clinica e di sicurezza sia per quella economica, due revisori, in maniera indipendente, hanno valutato la qualità degli studi inclusi e ne hanno estratto i dati riportati, analizzandoli e sintetizzandoli.

Per la stima del potenziale impatto economico dell'utilizzo e della diffusione della denervazione renale mediante ablazione con radiofrequenza, nella Regione Veneto, abbiamo sviluppato un modello di Budget Impact Analysis (BIA), elaborato sulla base dello svolgimento delle seguenti attività:

- conduzione di una survey regionale, per la raccolta dei dati regionali di contesto;
- ricerca della letteratura, per l'individuazione dei dati di efficacia, di sicurezza e di costo, nonché dei dati epidemiologici dell'ipertensione resistente a livello nazionale ed internazionale;
- consultazione di banche dati nazionali e regionali, per l'identificazione della popolazione target nazionale e regionale.

Risultati

Abbiamo incluso due studi di efficacia clinica e sicurezza. Entrambi gli studi inclusi sono comparativi, sebbene la randomizzazione sia stata eseguita solo in uno di essi. La popolazione degli studi varia da 50 a 106 pazienti, con valori di pressione arteriosa superiori a 140/90 mmHg (millimetri di mercurio), nonostante l'assunzione – in media – di cinque farmaci anti-ipertensivi.

Entrambi gli studi riportano i cambiamenti dei livelli pressori come esito clinico primario. In particolare, le misurazioni della pressione arteriosa, presso studio medico, sono riportate in entrambi gli studi, mentre le misurazioni a casa e ambulatoriali (con monitoraggio su 24 ore), in uno solo. Le variazioni dei valori della pressione arteriosa sono state misurate durante visite di follow up di breve periodo (tre e sei mesi rispettivamente). Gli esiti inerenti la sicurezza sono stati descritti solo in uno studio mentre l'altro mancava della definizione stessa di tali esiti.

La qualità metodologica degli studi inclusi è stata valutata utilizzando una versione adattata dello strumento *Cochrane Risk of Bias*. Entrambi gli studi sono stati giudicati ad alto rischio di bias. E' da rilevare che entrambi gli studi sono stati finanziati dall'azienda produttrice, che ha partecipato al disegno dello studio e all'analisi dei dati.

Le prove di efficacia clinica e di sicurezza mostrano l'efficacia della procedura di denervazione renale nel ridurre i livelli diastolici e sistolici della pressione arteriosa, nei pazienti con ipertensione resistente, nonché la sicurezza della stessa. Negli studi non sono registrate complicazioni gravi collegate al dispositivo o alla procedura.

Tuttavia, il periodo di follow-up estremamente breve, non permette di valutare la stabilità o il miglioramento degli effetti a più lungo termine, tenendo conto del fatto che le fibre nervose renali possono rigenerarsi. Inoltre, a causa della mancanza di prove a lungo termine sull'effetto anti-ipertensivo della denervazione renale, non esiste nessuna prova diretta o indiretta a sostegno dell'effetto benefico di questa tecnica sugli esiti clinici rilevanti.

In merito all'analisi delle evidenze economiche, non è stato individuato nessuno studio di costo efficacia, minimizzazione dei costi o di costo utilità sulla denervazione renale mediante ablazione con radiofrequenza, nei pazienti con ipertensione resistente.

In merito alla misurazione del potenziale impatto economico dell'utilizzo e della diffusione di tale procedura nell'ambito del Sistema Sanitario Regionale (SSR) della Regione Veneto, la survey regionale ha mostrato che soltanto uno dei due centri indagati ha eseguito la procedura di denervazione renale sia nell'ambito della pratica clinica - limitatamente all'uso compassionevole - sia nell'ambito della ricerca. La survey ha inoltre fornito la stima dei pazienti potenzialmente candidabili alla procedura, nonché il consumo medio di risorse alla stessa collegato. Tali informazioni, insieme ai dati raccolti sui costi unitari ed ai dati epidemiologici, sono stati utilizzati per popolare il modello della BIA. Si è stimato, nella regione Veneto, un numero pari a 216.136 di pazienti ipertesi non controllati (pressione arteriosa sistolica>140 mmHg). Il 7,86% dei pazienti ipertesi non controllati, pari a 16.988, è ad alto rischio, poiché "resistente" alla terapia anti-ipertensiva multi farmacologica comprendente almeno 3 farmaci (popolazione di riferimento). Si è ipotizzato, nell'arco temporale di tre anni a partire dall'introduzione della procedura di denervazione nella Regione, un incremento dello 0,25% dei pazienti potenzialmente eleggibili, per un totale di 42, 106, 170 soggetti rispettivamente al 1°, 2° e 3° anno. Il costo della procedura è stato stimato pari a € 7.327 ed il costo annuale delle terapie farmacologiche, attualmente utilizzate nella pratica clinica, pari a € 581 per paziente.

Sebbene presenti alcuni limiti, il modello ha stimato che l'introduzione della procedura nella pratica clinica, aumenterebbe la spesa regionale per il trattamento dell'ipertensione resistente mediante ablazione con radiofrequenza del 3%, 7% e 12% rispettivamente al 1°, 2° e 3° anno dall'implementazione. Il modello è risultato sensibile al costo della procedura e delle terapie attuali, nonché alla percentuale dei pazienti potenzialmente eleggibili.

Conclusioni

Gli studi clinici comparativi, inclusi in questa revisione sistematica, evidenziano una riduzione significativa dei livelli di pressione arteriosa (sia sistolica che diastolica) nei pazienti con ipertensione resistente alla terapia multi farmacologica. Tuttavia, poiché l'evidenza disponibile è scarsa, vi è la necessità di ulteriori studi clinici comparativi, con periodi di follow-up più lunghi. Infatti, dati di efficacia clinica e di sicurezza a lungo termine consentono di misurare l'effetto reale della procedura di denervazione renale sulla pressione arteriosa e,

di conseguenza, valutare come la riduzione della pressione arteriosa possa influenzare lo sviluppo delle patologie e della mortalità ad essa correlate.

Infine, analisi economiche della procedura di denervazione renale mediante ablazione con radiofrequenza dovrebbero essere eseguite congiuntamente a tali studi di generazione delle prove di efficacia e sicurezza.

1. Introduction

Burden of disease

Hypertension, or high blood pressure, is a condition where the force that blood is exerting on the walls of the arteries of the body is higher than desirable. Hypertension is universally considered the major cardiovascular risk factor due to the great prevalence in the general population and the impact on cardiovascular mortality and morbidity [Ezzati M, 2002]. A large number of observational studies have documented that systolic and diastolic blood pressure values are directly and continuously associated with an increased incidence of coronary and cerebrovascular events, peripheral vascular disease, and heart and renal failure. Essential hypertension is often associated with other cardiovascular risk factors, including the alteration of glucidic and lipid metabolism [Mancia G, 2005]. The combination of risk factors causes an exponential increase of the risk of cardiovascular events [Multiple Risk Factor Intervention Trial Research Group, 1986]. In 2007 hypertension was the highest ranked cause of death in the USA, being responsible for 17.4% of total mortality [Roger VL, 2011]. In addition the world prevalence of hypertension in adults aged 25 and over was around 40% in 2008 [http://www.who.org] and it is increasing as high blood pressure rises with age, obesity and sedentary lifestyles. According to one estimate in 2025 more than 1.5 billion of people will be hypertensive [Kearney PM, 2005].

In Italy the prevalence of hypertension in the adult population aged 35-74 decreased from 1998 to 2008, going from 59.0% to 53.7% in men and from 48.4% to 39.4% in women. Although blood pressure control has also improved throughout these years, only 51.4% of hypertensive men and 61.9% of hypertensive women take an antihypertensive pharmacological treatment and more than half of treated patients are characterized by uncontrolled blood pressure values [Palmieri L, 2010].

Diagnosis and treatment

Although blood pressure values are linked to cardiovascular risk by a continuous linear relationship, at least up to the lower limit of 115/75 mmHg, hypertension is classically defined as systolic blood pressure (SBP) values of 140 mmHg or greater and/or diastolic blood pressure (DBP) values of 90 mmHg or greater. According to the *European Society of Hypertension and the European Society of Cardiology (ESH/ESC) Guidelines*, a lower threshold for hypertension diagnosis (and need for drug treatment) should be considered, based on the level and profile of total cardiovascular risk [Mancia G, 2007]. Hypertension is classified in grades according to the degree of blood pressure values. These referral values should be applied to clinic (by a doctor or nurse) blood pressure measurements, as they are not valid for home blood pressure or ambulatory blood pressure monitoring [Mancia G, 2007]. The diagnosis of hypertension should be based on multiple blood pressure measurements, taken on separate occasions over a period of time (from weeks to months).

Lifestyle changes should be instituted in all patients with hypertension to lower blood pressure or cardiovascular risk. Pharmacological treatment should be immediately started in the presence of high cardiovascular risk or if lifestyle changes are not sufficient to reach the required blood pressure target. The benefits of reducing blood pressure on the risk of major cardiovascular events are well established. A meta-analysis of 147 randomized clinical trials, including about 958,000 patients, demonstrated that compared to placebo, antihypertensive pharmacological treatment causes a significant reduction of cardiovascular mortality and morbidity (around 30-40% reduction of cerebrovascular events or around 20% reduction of coronary events) and also of total mortality [Law MR, 2009]. The beneficial effect of treatment has been demonstrated in all age ranges, including the very elderly, and independently from gender, race and associated disease [Turnbull F, 2003] [Mancia G, 2007].

Although several drug classes[1] are available, hypertension is not controlled in more than half of patients under pharmacological treatment. The main reasons for such therapeutic failure can be summarized as follows:

- physician or patient therapeutic inertia;
- low patient compliance to lifestyle modifications and frequent autosuspension of the therapy [Corrao G, 2008];
- inadequate therapy (low drug dosing, non rational combinations);
- side effects of drugs that limit patient compliance;
- intrinsic difficulty to normalize systolic blood pressure, due to age- and hypertension-induced structural vascular changes, in particular reduced elasticity and compliance of large arteries [Chobanian AV, 2007].

Resistant hypertension

Hypertension is usually defined as resistant or refractory to treatment when a therapeutic plan including adherence to lifestyle measures and the prescription of at least three drugs (including a diuretic) in adequate doses has failed to lower systolic and diastolic blood pressure to reach the target level recommended for the patients' risk category [Calhoun DA, 2008]. As defined, resistant hypertension includes patients with uncontrolled blood pressure with 3 or more drugs as well as patients whose blood pressure is controlled with 4 or more drugs [Calhoun DA, 2008]. Thus, resistant hypertension does not coincide with uncontrolled hypertension which has a prevalence of around 50% of hypertensive population under

[1] Thiazide diuretics, calcium antagonists, ACE-inhibitors, angiotensin receptor antagonists and beta-blockers.

pharmacological treatment. According to a recent analysis of the *National Health and Nutrition Examination Survey (NHANES Study)*, in United States 12.8% of treated patients correspond to the definition of resistant hypertension [Persell SD, 2011]. Among the patients referred to a specialist hypertension unit, resistant hypertension is even more frequent, around 19.4% of treated hypertensive patients [Bruno RM, 2011]. It is very important to diagnose this clinical condition in order to identify a subgroup of patients exposed to a greater cardiovascular risk.

To correctly approach the diagnosis of resistant hypertension it is crucial to exclude first the presence of "pseudo-resistant hypertension"[2] which can be caused by a non accurate blood pressure measurement, "white coat" hypertension, low compliance to treatment, a therapeutic scheme characterized by non rational combinations of antihypertensive drugs or compounds given at low doses [Calhoun DA, 2008]. Moreover resistant hypertensive patients are characterized by a greater incidence of secondary causes of hypertension, including especially primary aldosteronism and sleep apnea syndrome [Douma S, 2008] [Pedrosa RP, 2011]. If these causes are identified it is possible to choose specific treatments and reach an adequate blood pressure control.

Recently the use of innovative treatments by specific devices such as renal denervation or carotid baroreceptor stimulation has been proposed for patients with resistant hypertension.

Description of technology

The kidney plays a vital role in the regulation of blood pressure (sodium filtration, blood volume, etc.) and renal sympathetic nerve hyperactivity has been demonstrated to be a major factor in the pathophysiology of hypertension [Mundy L, 2010]. Deactivation of the sympathetic nerve supply to the arteries of kidneys may lead to a sustainable reduction in blood pressure, affecting the mechanical, hormonal and electrical activities of the kidneys themselves [NHSC, 2011].

Renal denervation is achieved through ablation of sympathetic nerves using radio-frequency energy. The main purpose of renal artery radiofrequency ablation (RF) is the interruption of the sympathetic renal efferent and afferent fibers. The flow of RF energy through the renal artery wall raises the temperature of the tissue or cells that are in contact with or near the electrode to the point at which proteins of the nerve fibers cells becomes denatured. Systems usually work in the monopolar mode, meaning that one electrode is located on the tip of a catheter positioned against the renal artery wall through standard catheterization technique, while the other electrode is a ground pad placed on the patient thigh to collect all

[2] There is evidence that around 1/3 of patients classified as resistant by clinic blood pressure measurement show normal values by 24 hours ambulatory blood pressure measurement [de la Sierra A, 2011].

current flow back to the generator. Little power is needed to achieve the desired effect on renal nerves. Modern systems usually are provided with a temperature control system on the tip of the catheter. This allows the system to interrupt current delivery when temperature of the tissue overcomes a given threshold (usually 70°C).

Renal denervation is a new procedure performed by interventionalists in a standard catheterization laboratory, using standard renal artery catheterization techniques. The procedure is minimally-invasive and image-guided[3]: access is achieved via a peripheral access to the vascular system and the displacement of the catheter is visualized using X-ray fluoroscopy. A special ablation catheter, connected to a specific generator, is delivered through a guiding catheter, along the femoral artery and advanced into renal artery - under fluoroscopic control - to the desired point. The catheter is positioned in contact with the vessel wall and the generator is activated, thus delivering RF. Ablation is carried out in many places along the vessel wall since many points of the tissue are innervated. The procedure is usually performed with the patient under local anaesthesia with conscious sedation. Anticoagulation is generally used during the procedure [NICE, 2010]. After ablation, the device is withdrawn and the arterial access site may be closed as with standard interventional techniques.

The following systems were available with at least one clinical trial either completed or ongoing at the time of writing our research protocol [December 2011]:

- Medtronic Symplicity Renal Denervation System [http://www.medtronicrdn.com];
- Johnson & Johnson (J&J) Thermocool Irrigated tip Catheter to be used with Stockert 70 RF Generator and Cool Flow Pump [http://www.biosensewebster.com];
- St. Jude Medical EnligHTN Renal Denervation System http://www.sjm.com/corporate/media-room/media-kits/new-products/enlightn.aspx].

The systems are composed of two parts: a multi-use RF generator (the J&J device combines in the same machine both the RF generator and the irrigation pump) and an ablation catheter (single use).

The main differences are that Johnson & Johnson (J&J) Thermocool Irrigated tip Catheter is an irrigated system, while Medtronic isn't. Medtronic Symplicity Renal Denervation System provides a catheter with a 6FR shaft, while J&J provides 7FR catheter; in addition, the Medtronic catheter is equipped with a set of controls placed directly on the handle design. Moreover, Medtronic generator is provided with proprietary control algorithms, based on the combination of different ablation parameters (power, temperature, impedance, time), to

[3] The imaging test usually performed together with renal artery ablation is the arteriography.

manage the delivery of RF energy through the tip of the catheter, ensuring low power (8W maximum for two minutes).

Medtronic Symplicity RD system gained the CE mark in February 2008[4]. Thermocool irrigated tip catheter has been developed for electrophysiology; however it granted the CE mark for renal denervation in March 2012[5].

St. Jude EnligHTN system is a unique multi-electrode ablation technology for renal denervation, comprised of a guiding catheter, ablation catheter and ablation generator. The generator uses a proprietary, temperature-controlled algorithm to deliver effective therapy. EnligHTN system gained the CE mark in May 2012.

None of above mentioned RD systems is yet approved for use in the United States (Food and Drug Administration Approval).

We are aware that new modalities and systems for renal artery denervation are been made available since the research protocol was written to date. Those systems use other energy sources that are also being developed to address the interruption of the sympathetic renal efferent and afferent fibers, like ultrasound, cryo-ablation or nerves-toxic drugs direct injection into the renal artery wall. A description of these systems is at Appendix 1. The systems will not be considered further.

[4] Information provided by MedTronic.

[5] Information provided by Johnson & Johnson.

2. Rationale

To evaluate the efficacy and safety of *"denervation of renal artery by catheter-based radioablation"* is important and necessary to ensure that patients are given the appropriate therapy to treat resistant hypertension. It is also necessary to assess the economic sustainability of the potential use and diffusion of the technology. This will provide the decision makers with important information to manage the acquisition and use of the technology.

3. Objectives and research questions

The main objective of this review was:

- To systematically assess and synthesise the evidence of effectiveness, safety, cost-effectiveness on the denervation of renal artery by catheter-based radio-ablation in patients with resistant hypertension.

A secondary objective was:

- To analyze the utilisation and diffusion level of the technology within the Veneto Regional Healthcare System.

The research questions were:

- Is the denervation of renal artery by catheter-based radioablation effective and safe according to available evidence for the treatment of resistant hypertension?
- What is the potential economic impact of use and diffusion of denervation of renal artery by catheter-based radioablation for the treatment of resistant hypertension in Veneto Regional Healthcare System?

4. Methods

The objectives were achieved by performing two research activities:

- A systematic review to systematically assess and synthesise the effectiveness, safety and economic evidence on the renal artery ablation in patients with resistant hypertension;
- A model budget impact analysis to estimate the potential economic impact of the use and diffusion of denervation of renal artery by catheter-based radioablation in the Veneto Region (see Annex 1 - Case study).

Systematic review (primary objective)

We carried out searches of literature to identify and assess the available effectiveness, safety and economic evidence on denervation of renal artery by catheter-based radioablation plus anti-hypertensive standard medications for treatment-resistant hypertension compared with anti-hypertensive standard medications.

Efficacy and safety evidence

Evidence for the effectiveness and safety on the denervation of renal artery by catheter-based radioablation plus anti-hypertensive standard medications for treatment-resistant hypertension, was assessed by conducting a systematic review of published research evidence. The search aimed to identify all studies relating to catheter based renal denervation procedure in patients with resistant hypertension.

We searched the following main electronic databases: Medline, EMBASE, Cochrane Library, CINAHL and Web of Science (Science Edition). Searches were conducted from 21st to 27th February 2012 to identify all studies published from 2005 to present date, without language restriction. Time horizon has been chosen to identify unpublished pre-marketing studies since the first catheter to be marketed for renal artery denervation gained the CE mark in 2008.

Search strategies were constructed by appropriate combinations of the following keywords: refractory (hypertension or high blood pressure or HBP); resistant (hypertension or high blood pressure or HBP); drug resistant hypertension; treatment resistant hypertension; renal denervation; RDN; renal sympathetic denervation; RSD; nerves ablation; catheter ablation; sympathectomy; kidney; renal artery; Symplicity; ThermoCool. Search strategies are reported in details in Appendix 2.

Reference lists of all relevant papers identified were scanned for additional relevant studies.

We also considered information from "grey literature" (conference proceedings, websites, ongoing clinical studies, unpublished work and data from national and international registries).

Current research was identified through searching the US National Institutes of Health web site [http://clinicaltrials.gov/] on 17th and 25th April 2012. The search terms "renal denervation" and "hypertension" were combined.

The titles and abstracts of records identified from our literature search were screened for relevance by two reviewers (IA and ST) independently. The full text of any potentially relevant paper was retrieved and assessed for inclusion, according to the inclusion and exclusion criteria listed in the Box 1, independently and in duplicate by two reviewers (IA and ST). If it was unclear from an abstract whether a study was relevant or not, the full paper of the study was obtained for further information. Studies which met the inclusion criteria were included. Any discrepancies were resolved by discussion.

Box 1: Inclusion Criteria

We included all the studies meeting the following inclusion criteria:

Population: patients with hypertension resistant to standard treatment (including at least three anti-hypertensive drugs at the highest tolerated dose). Patients with any potential cause of pseudo-resistant hypertension will be excluded.

Intervention: denervation of renal artery by catheter-based radioablation plus anti-hypertensive standard medications.

Comparator: anti-hypertensive standard medications.

Outcome:

- Change in average measurements of systolic and/or diastolic blood pressure;

- All causes mortality;

- Cardiac mortality;

- Major cardiovascular events (myocardial infarction, heart failure, stroke, etc.).

Adverse events: acute procedural safety, chronic procedural safety (kidney failure, renal artery stenosis, etc).

Study design: Comparative studies: Randomized Clinical Trials (RCTs), Cohort Studies, Case-control Studies, Controlled Before-After Studies (CBAs).

Data extraction from included studies was performed by two reviewers independently using two standardized data extraction forms.

The first data extraction standard form aimed to collect background information and the characteristics of the study; it included details of the study design, randomization, allocation

concealment, blinding, intention to treat, sample size, baseline characteristics, blood pressure measurements, intervention, duration of follow-up, number of patients lost to follow-up, outcomes, statistical analyses and reporting. Whereas the second data extraction form was used to record data related to the efficacy and safety outcomes of the renal artery denervation by catheter-based radioablation. See Appendix 3 for the template of the forms.

We resolved factual differences between the two reviewers by re-checking the source. Any disagreements were resolved by discussion.

Quality of included studies was appraised by two reviewers (IA and ST) using an adaptation of *Cochrane risk of bias tool* [Higgins JPT et al, 2011], consistently with the design of the included studies.

Each study was scored as Low risk of Bias, High risk of Bias or Unclear risk of Bias.

We produced a Summary of Findings table specific to the risk-of-bias assessment for each included study.

Authors of trials and studies reporting incomplete information were contacted to provide the missing information, allowing us to perform a quantitative analysis (meta-analysis).

Data from all included studies were synthesised through a narrative review.

Economic evidence

Economic evidence on the denervation of renal artery by catheter-based radioablation was identified through a literature search. Electronic databases searched included: Medline, Embase, Cochrane Library, including the NHS Economic Evaluation Database (NHS EED) and HTA databases. The search terms, related to the target disease and intervention – reported in the previous subparagraph – were combined with the following keywords, to search economic evidence: cost analysis, CMA, cost effectiveness, CEA, cost utility, CUA, health care costs, economic evaluation, economic analysis, economic aspect, economic assessment.

We aimed to include all cost effectiveness, cost utility and cost minimization analyses of the denervation of renal artery by catheter-based radioablation in patients with hypertension resistant to standard treatment, published since 2005; no language restriction was applied. See Appendix 4 for detailed search strategy of economic literature.

Titles and abstracts, identified by the search strategy for the systematic review of the economic evidence, were screened for potential eligibility by two reviewers (MC and MRP) independently. The full papers of relevant papers were then retrieved and two reviewers (MC and MRP) formally assessed them, independently, with respect to their potential relevance according to the inclusion criteria. If it was unclear from an abstract whether a study was

relevant, the full paper of the study was obtained for further information. Resolution of the disagreements in the selection process was achieved through discussion.

Data extraction was planned to be performed, independently and in duplicate, by two reviewers (MC and MRP). We intended to extract economic data related to the costs of performing the denervation of renal artery by catheter-based radioablation using an ad hoc form. The form template is reported in Appendix 5.

5. Results

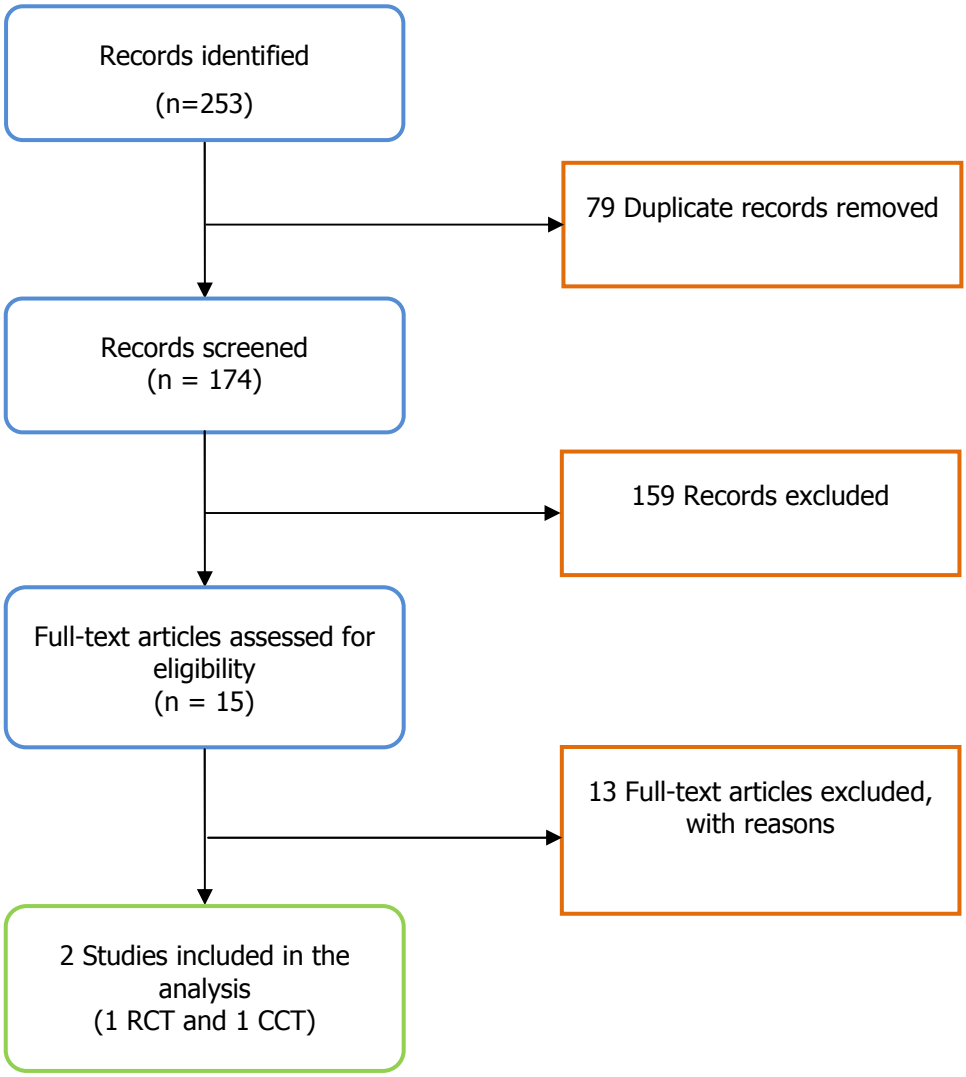
Efficacy and safety evidence

The literature search of efficacy and safety evidence yielded 253 records, excluding grey literature and current research [http://clinicaltrials.gov/].

Seventy-nine records out of 253 were duplicates. Based on the relevance of titles and abstracts, 15 articles underwent full-text screening. Thirteen articles were excluded, either because were non-comparative studies or because they were not relevant to our objectives; their bibliographic references were listed, alongside reasons for their exclusion, in Appendix 6.

Two articles met our eligibility criteria (Figure 1). The bibliographic references of the studies included in this systematic review were reported at Appendix 6.

Figure 1: Flow-chart of Efficacy and Safety evidence



There was a moderate agreement among investigators for title and abstract screening (kappa=0.415) [95% CI, 0.270 - 0.560] and perfect agreement for the full text screening (kappa=1) [McGinn T et al, 2004].

Our search of grey literature and current research identified 27 Clinical trials. 23 ongoing studies seemed to fulfil[6] our inclusion criteria, while 4 did not, as the study population did not meet the inclusion criteria. However, none of the 23 had been completed. Details of these 23 ongoing studies are provided in Appendix 7.

Description of Included Studies

Two clinical studies that compared renal artery ablation to anti-hypertensive standard medications, were included in this systematic review. Esler MD et al. is a randomised controller trial (RCT) and Mahfoud F et al. is a controlled clinical trial (CCT).

In a multicenter study, between June 2009 and Jan 2010, Esler MD et al. randomly allocated 106 patients with resistant hypertension to catheter-based renal denervation for reduction of blood pressure (52 patients) or usual care (54 patients). Mean age of participants was 58 years, participants were receiving at least 5 anti-hypertensive medications in more than 50% of the cases; their average values were 178 (SD 18) for systolic blood pressure (SBP) and 97 (SD 16) for diastolic blood pressure (DBP) and participants were similar in terms of other prognostic factors. Follow-up was 6 months. Three patients, in both groups (renal denervation group and usual care group), did not attend six-month follow up. The study was funded by Ardian[7] who manufactured the catheter based renal denervation system (Symplicity). The sponsor was involved in the study design and analysis.

In a controlled clinical trial Mahfoud F et al. allocated 37 patients to renal denervation (with the Symplicity Catheter System) and 13 patients to usual care to assess the effect of catheter-based renal sympathetic denervation on glucose metabolism and blood pressure control in patients with resistant hypertension. Participants in the renal denervation group were 58.7 (SD 1.6) of age, significantly lower than the age in the control group 62.5 (SD 2.9). Mean values of systolic and diastolic blood pressure, in all patients, were 178 (±3) and 97 (±2) respectively. Participants in the two groups were receiving on average 5.6 (±0.2) anti-hypertensive medications. Follow-up was 3 months period. Patients lost to follow up were not explicitly stated. The study was funded by Ardian and the sponsor was involved in the study design and analysis.

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[6] Such uncertainty is due to the lack of information about the characteristics of some of the studies and to the quality and clarity of information recorded in the clinical trials database.

[7] Ardian has been acquired by Medtronic.

In Esler MD et al. effectiveness was measured primarily by change in average office-based measurements of SBP from baseline to 6 months and, secondarily, by change in 24 hour (24-h) ambulatory and in home-based BP measurements. Whereas the primary outcome in Mahfoud was the change in systolic and diastolic office blood pressures at 1 and 3 months. Safety outcomes (e.g. acute procedural safety and chronic procedural safety) were stated in Esler while no safety outcome was explicitly defined in Mahfoud.

It is important to explicit that 26 out of 50 patients enrolled in Mahfoud, 17 belonging to the renal denervation group and 9 to the control group, were included in the randomized controlled Symplicity Hypertension-2 trial (NCT00888433) [Esler MD et al, 2010]. In all other patients the measurements were performed as an extension to the Simplicity protocol using the same inclusion and exclusion criteria.

The main general data of the studies are reported in the following table1.

Table 1: General data of the included studies

Study	Year	Objective	Study design	Participants		Outcomes		Follow up	Funding
				Intervention group	*Control group*	*Primary*	*Secondary*		
Esler MD et al.	2010	To assess effectiveness and safety of catheter-based renal denervation for reduction of blood pressure in patients with treatment-resistant hypertension	RCT	*Number:* 52 *Age:* 58 (SD 12) *Antihypertensive drugs:* 5.2 (1.5) *SBP/DBP:* 178(SD18)/97(SD16)	*Number:* 54 *Age:* 58 (SD 12) *Antihypertensive drugs:* 5.3 (1.8) *SBP/DBP:* 178(SD16)/98(SD17)	Between-group change in average office-based measurements of SBP from baseline to 6 months	(a) acute procedural safety (b) chronic procedural safety (c) a composite cardiovascular endpoint (d) additional measurements of BP reduction at 6 months consisting of occurrence of 10 mmHg or more systolic response (e) achievement of target SBP (f) change in 24-h ambulatory BP (g) change in home-based BP measurements	6 months	For profit agency
Mahfoud F et al.	2011	To investigate the effect of catheter-based renal sympathetic denervation on glucose metabolism and blood pressure control in patients with resistant hypertension	CCT	*Number:* 37 *Age:* 58.7 (±1.6) *Antihypertensive drugs:* 5.8 (±0.2) *SBP/DBP:* 177(±3)/96(±6)	*Number:* 13 *Age:* 62.5 (±2.9) *Antihypertensive drugs:* 5.0 (±0.4) *SBP/DBP:* 184(±6)/94(±4)	Change in systolic and diastolic office blood pressures (SEM) at 1 and 3 months	(a) Change in fasting glucose at 3 months (b) Change in fasting insulin (c) Change in C-peptide (d) Change in homeostasis model assessment–insulin resistance (HOMA-IR) at 1 and 3 months compared with baseline (e) mean 2-hour glucose levels during oral glucose tolerance test	3 months	For profit agency

Legend

RCT: Randomised Clinical Trial; CCT: Controlled Clinical Trial; SD: standard deviation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

The fulfilled data extraction forms are reported in Appendix 8.

Methodological Quality and Risk of Bias

The included studies were appraised using an adaptation of the *Cochrane risk of bias tool.*

A summary findings table about to the methodological quality and risk-of-bias assessment for each included study is reported in the Appendix 9.

The RCT [Esler MD et al, 2010] was unclear about the allocation concealment since it reported only that *"Patients were randomly assigned to intervention group with sealed envelopes at every clinical site"* without providing more details about the assignment. Although blinding participants and investigators was impractical, the study did not attempt to blind the outcome assessor or data analysis. Methodological quality was judged to be at high risk of bias while Reporting and Analysis at low risk.

The controlled clinical study [Mahfoud F et al, 2011] is not randomised and it is not immune from selection bias. Most of the risk of bias items in this study were unclear or not stated. This study was considered of high risk of bias.

Efficacy Results[8]

The two included studies were comparable in terms of age, values of systolic and diastolic blood pressure, the average number and types of anti-hypertensive drugs used, and were potentially eligible for inclusion in a quantitative analysis. However, available data of the studies did not allow us to perform a meta-analysis. We contacted authors of studies to gather the missing information, but only Mahfoud provided us with the requested data by the assigned deadline. Data sent by Esler, after the deadline, will be used in the update of this systematic review.

Analysis and synthesis of the included studies were carried out through narrative review.

Change in average measurements of systolic and/or diastolic blood pressure (BP)

Esler's primary and secondary outcomes were measured at 6 month follow-up. Blood pressure was measured through office-based, home-based and 24-h ambulatory monitoring measurements.

[8] Extraction forms containing the outcome data of the included studies are reported in Appendix 10.

Office-based measurements of blood pressure of 49 patients in the renal denervation group were reduced by 32/12 mmHg (SD 23/11) at 6 months, from 178/97 mmHg (SD 18/16) at baseline ($p<0.0001$ for both outcomes). Differently, in the control group (51 patients analysed), office-based measurements at 6 months changed by +1/0 mmHg (SD 21/10) from 178/97 mmHg (SD 17/16) at baseline.

Home-based measurements were similar to the office-based; blood pressure fell by 20/12 mmHg (SD 17/11) in 32 patients in renal denervation group, compared with a rise of 2/0 mmHg (SD13/7) in 40 controls.

Average blood pressure measurements from 24-h ambulatory BP monitoring changed in the same way of office-based and home-based measurements, although those measurements were available for 20 patients in the renal denervation group and 25 in the control group. 24-h ambulatory BP recordings showed a mean decrease of 11/7 mmHg (SD 15/11) in the interventional group whereas averages did not change for patients in the control group -3/-1 mmHg (SD 19/12).

In Mahfoud's study the change in systolic and diastolic office blood pressures (primary outcome) was assessed at 1 and 3 months compared with baseline. Blood pressure was measured only through office-based measurements. The measures of BP significantly decreased by 28/10 mmHg (SD 2/2) at 1 month and even more at 3 month -32/-12 (SD 4/2), in the denervation group compared to baseline. By contrast control patients had a slight, but not significant, change in BP of -8/-4 mmHg (SD 6/4) and -5/-3 mmHg (SD 5/3) at 1 and 3 months respectively.

All causes mortality

No mortality event was recorded in the included studies.

Cardiac mortality

No data related to cardiac events were reported in the included studies.

Major cardiovascular events

The composite cardiovascular endpoints considered in Esler MD et al. were: myocardial infarction, sudden cardiac death, new-onset heart failure, death from progressive heart failure, stroke, aortic or lower limb revascularization procedure, lower limb amputation, death from aortic or peripheral arterial disease, dialysis, death because of renal failure, hospital admission for hypertensive emergency unrelated to non-adherence or non-persistence with drugs, and hospital admission for atrial fibrillation. No significant events occurred except for five hospital admissions for hypertensive emergency (three patients in the experimental and two in the control) that were unrelated to non-adherence or non-

persistence with drugs only five hospital admissions occurred in the two groups without any significant difference.

No cardiovascular event occurred in Mahfoud's study (personal communication).

Safety Results

Adverse Events: Acute procedural safety

In Esler's study patients that underwent denervation were reported to have the following minor periprocedural adverse events, requiring treatment and possibly related to the procedure: transient intraprocedural bradycardia requiring atropine in 7 patients out of 52 treated, post procedural drop in blood pressure resulting in a reduction in antihypertensive drugs in 1 patient, extended hospital admission for assessment of paraesthesias in 1 treated patient, and back pain in 1 patient treated with analgesics that resolved after 1 month. Because of post procedural drop in blood pressure in 1 treated patient antihypertensive drugs had to be reduced. Urinary tract infection was reported only for 1 treated patient. None of these events occurred in the control group.

Although no safety outcome was explicitly defined in Mahfoud F et al., 1 patient out of 37, in the denervation group, was reported to develop a pseudoaneurysm at the femoral access site that was treated without further sequelae. No other complications were observed either in the denervation and in the control group.

"Chronic procedural safety (kidney failure, renal artery stenosis, etc)"

Esler MD et al. reported that a reduction of more than 25% of the glomerular filtration rate occurred in 2 patients in the experimental and in 3 in the control group. No events of reduction greater than 50% of the eGFR was observed in any of the groups.

Serious events, requiring hospital admissions, were reported in 5 treated patients and in 3 control patients. Specifically, patients in the renal denervation group experienced, respectively, nausea and oedema, hypertension crisis after abrupt stopping of clonidine, transient ischaemic attack, hypotensive episode and angina requiring the implantation of a coronary stent. 2 controls had transient ischaemic attacks and 1 received a coronary stent for angina.

Effect of denervation on drug therapy

In Esler study, 10 patients (20%) who underwent renal denervation had a reduction of drug usage compared to 3 patients (6%) in the control group (p=0.04).

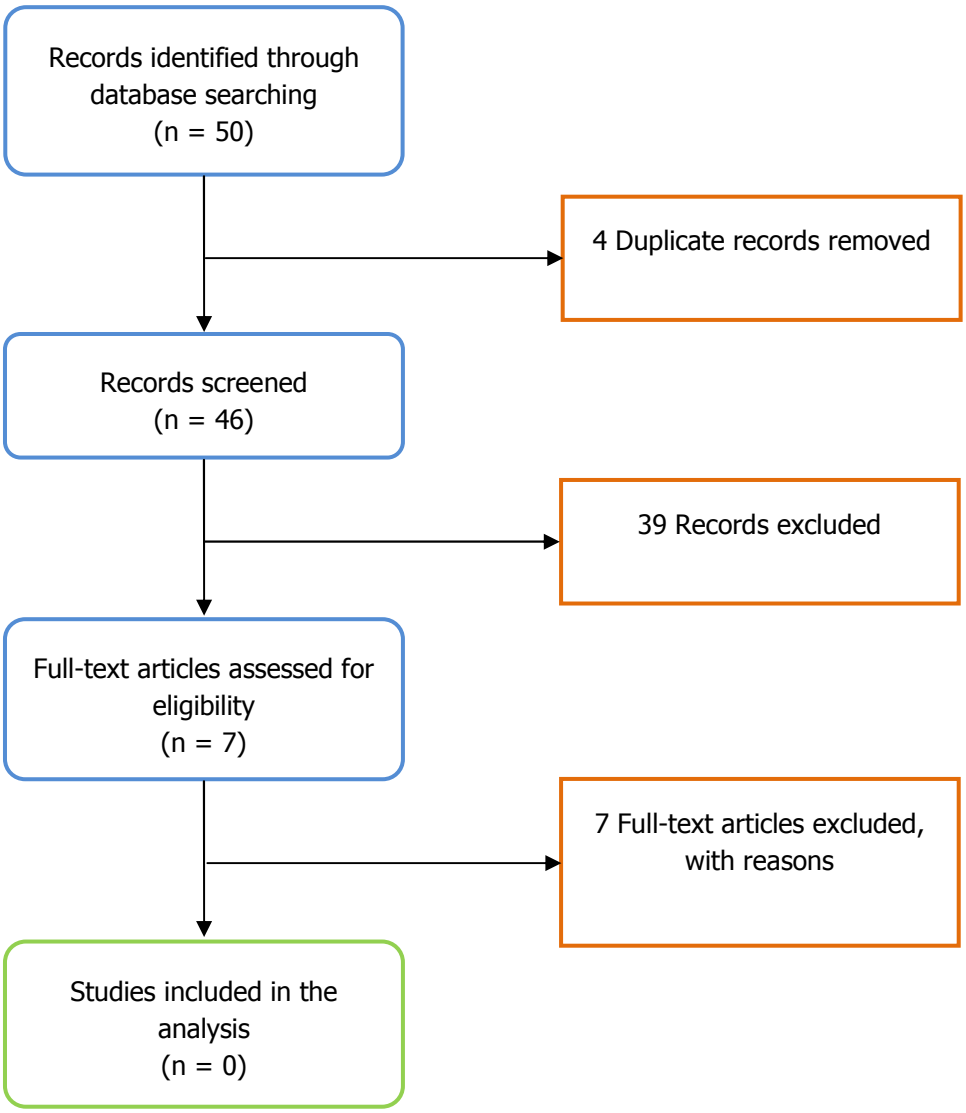
Mahfoud reported that, after the 3 month follow up visit, in 13 (35.1%) treated patients, antihypertensive medication had to be reduced owing to hypotension associated with symptoms. In 2 (15.4%) control patients and 1 (2.8%) treatment patient, antihypertensive medication had to be further increased after the development of symptoms or signs considered to be consequences of the hypertension.

None of the preplanned subgroup or sensitivity analyses were performed due to lack of data. In conclusion the clinical evidence shows that percutaneous renal denervation appears to significantly reduce both systolic and diastolic blood pressure in patients suffering from refractory hypertension.

Economic evidence

Literature search identified 50 references. Four out of fifty were duplicates, so they were removed. After initial screening of titles and abstracts, 7 references were retrieved for full text assessment. No study was included since none of them fulfilled our inclusion criteria. The total number of published papers included at each stage of the selection process is shown in the flow chart in Figure 2.

Figure 2: Flow chart of Economic studies



References of the studies retrieved for full text analysis but subsequently excluded, along with the reasons of exclusion, are reported in Appendix 11.

6. Discussion

Two comparative experimental trials, comparing renal artery ablation to anti-hypertensive standard medications in patients with treatment-resistant hypertension, were identified and included in this systematic review.

The efficacy and safety evidence shows that percutaneous renal denervation appears to be safe and effective in reducing systolic and diastolic blood pressure in patients suffering from refractory hypertension. In both studies, the group of patients treated with the renal artery ablation experimented a significantly greater decrease in blood pressure levels. Moreover, the measurements at different moments of follow-up (6 months in one study and 3 months in the other one) show that the decrease in blood pressure, in patients who had renal denervation, is maintained, if not improved, over time. However the follow up is very short to assess the stability or the improvement of the effect in a longer term, taking also into consideration that renal nerve fibers may regenerate.

The main outcome variable - BP reduction - would have been better explored by a 24-h BP monitoring, which was performed only in a subgroup of the Symplicity HTN-2 study [Esler MD et al, 2010]. Interestingly, 24-h BP monitoring data showed a relevantly smaller BP reduction in comparison to that highlighted by office BP. Moreover, if we consider the very high values of standard deviations of blood pressure reduction, it is conceivable that the technique is highly effective in some patients while it is devoid of efficacy in others. Thus, considering the invasive nature and the cost of the procedure it should be important to identify responders and non responder patients. Furthermore, and in agreement with the previous issue, the possible inclusion of white-coat hypertensive patients, as well as patients with secondary hypertension, make the results of the study of difficult interpretation.

Due to the limited time of follow-up observed, no cardiovascular event was recorded. In addition, considering the lack of evidence concerning long-term duration of the antihypertensive effect of renal denervation, no direct or indirect proof exists supporting the beneficial effect of this technique on clinical hard end-points.

No serious complications were related to the device or procedure although the incidence of acute adverse events was reported only in one study [Esler MD et al, 2010]. Periprocedural events occurred only in patients that underwent renal denervation and were resolved without significant clinical consequences.

The two included studies had several limitations and were classified as a high level of risk of bias. Some data in both studies were incompletely reported and this prevented the possibility of performing a meta-analysis. All the studies included were funded by manufacturer and the sponsor was involved in the study design and analysis.

As regards the economic evidence, no cost-effectiveness or cost minimization or cost-utility study on the renal denervation in patients with resistant hypertension has been identified in this systematic review.

We are aware that this review has certain limitations. The evidence is poor and many studies are ongoing, so the results of this systematic review are approximate; caution is therefore necessary in their interpretation. More accurate and complete information about the effectiveness, safety and economic implications or effects of the renal denervation radio ablation requires waiting for the results of further and more studies with a longer follow up. In addition, synthesis of the included studies has been performed in narrative way; although 2 studies were included in the review of clinical effectiveness and safety, incomplete data did not let us able to perform a meta analysis.

There is a need for more comparative clinical studies with longer follow-up. Long term efficacy and safety data are required to assess the actual effect of the renal artery ablation on the blood pressure and, accordingly, evaluate how the BP reduction could affect the development of hypertension related disease and mortality.

An economic evaluation for renal artery ablation should be performed. The analysis should be based upon evidence of the intervention effectiveness and relevant economic data, particularly with regards to the saved costs due to the avoided hypertension related diseases.

7. Conclusions

Renal denervation is undoubtedly an area of high interest and fast development. During the last 6 months, 9 systems have been made available or are under investigation, compared to only 3 in December 2011. The high interest in this field is also shown by the many ongoing clinical trials aimed at assessing the effectiveness and safety of the different renal denervation systems in the treatment of patients with resistant hypertension.

By contrast the evidence is scarce. We included two clinical comparative studies in this systematic review. The results of the included studies are in favour of renal denervation, showing a significant reduction of blood pressure levels (either systolic and diastolic) in patients with treatment resistant essential hypertension. However both of them are subjected to risk of bias due to unclear allocation concealment and unmasked data analysis for the RCT. The CCT, lacking of randomisation, is not immune from selection, performance and detection biases making the study susceptible to a high risk of bias.

The scarce evidence available to date and the short follow up point to the need for performing clinical studies to assess the actual effectiveness and safety of the procedure in the long term.

8. Funding

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Agenas takes sole responsibility for the final form and content of this systematic review. The views expressed herein do not necessarily represent the views of the Italian Ministry of Health or any regional government.

9. Competing interests declaration

The authors declare that they will not receive either benefits or harms from the publication of this systematic review. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

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Annex 1 - Case Study

Renal artery ablation in patients with treatment resistant hypertension – a model for a budget impact analysis in the Veneto Region

Introduction

The systematic review on artery ablation in patients with treatment resistant hypertension, identified great interest on the Renal Denervation system, even if the available published evidence on effectiveness, safety and cost effectiveness of this medical device is still very poor or is lacking.

The second objective in this project was to assess the potential economic impact of use and diffusion of denervation of renal artery by catheter-based radioablation for the treatment of resistant hypertension in one Italian Regional Healthcare System: that of the Veneto Region.

In 2008 Veneto Region started to promote the HTA, developing a regional program (PRIHTA – Programma per la Ricerca, l'innovazione e l'HTA, Veneto Region decree, number 2187/2008). The regional Committee of Medical Devices Evaluation has been established as the body in charge of express recommendations on medical devices (CTRDM - Commissione Tecnica per il Repertorio Unico Regionale dei Dispositivi Medici; Veneto Region decree, number 4534/2007). Its recommendations, although not mandatory, should be taken in consideration by public healthcare structures when building their local list of medical devices and during acquisition procedures.

After establishing a ceiling in the medical devices regional expenditure since January 2013 (President of the Italian Republic, national decree n.98/2011), CTRDM's recommendations became executive after the final decision of the healthcare regional secretary (Veneto Region decree, number 2346/2011).

As regards the medical device for Renal denervation, in the meeting of the 19/12/2011 the CTRDM decided for a controlled introduction of the RD procedure in the clinical practice on the basis of current, available clinical evidences, identifying two regional centres allowed to perform the procedure.

The analysis of the controlled introduction and use of renal denervation in the clinical practice, based on the available evidence, could be useful to assess the economic impact of it.

It is important to highlight that catheter based renal artery ablation is still not implemented in Veneto Region; therefore no data source is available on the procedure in that regional context. In particular, the data related to the number of patients eligible for the procedure to

be fitted in the economic impact model, was estimated from the number of patients who will be enrolled in the regional Centres of Veneto participating in the *Italian prospective registry project on renal denervation in patients with arterial hypertension resistant to therapy*. This analysis should be considered as a model for a BIA, specifically to be linked to any future new evidence generated. The effect of a possible growth of the number of enrolled patients will be explored through sensitivity analysis.

Methods

We performed a regional survey and a budget impact analysis to estimate the potential economical impact resulting from the use and diffusion of denervation of renal artery by catheter-based radioablation in the treatment of resistant hypertension patients in the North-Eastern Italian Region of Veneto. The model estimated potential cost of the new technology in comparison with the current clinical practice – pharmacological antihypertensive treatment defined as "current therapy" - in patients affected by resistant hypertension.

To estimate the potential extra cost deriving from the introduction of the technology, the model considered the number of resistant patients and the rates of patients progressively eligible for the new procedure over a tree-year horizon, the cost of the renal denervation procedure and the cost of the current treatment. The perspective used was that of the Regional healthcare system.

The model was mainly developed on three sources of data:

- a regional survey collecting information on the use of the catheter-based radioablation device and data of the healthcare resource consumption in performing the procedure;
- a literature search to estimate target population and cost of treatments;
- other sources, like epidemiological national databases and regional prescriptions databases, to put the analysis in its proper context.

The regional context was investigated through a structured, ad-hoc questionnaire. The drafted questionnaire aimed at retrieving information on resource consumption and costs. We retrieved resource consumption estimates for the use of the device in clinical practice or in clinical trials, including eventual activities volume. Pre-operative exams, procedure duration, operating room time occupation, personnel working time, length of hospital stay, one-year follow-up tests, overhead costs were also requested to estimate the costs.

The questionnaire was submitted to selected healthcare organisations of Veneto Region. The selection of centres to be involved in the survey was based on a recent decision of CTRDM. The CTRDM decided for a controlled, first-year introduction of the catheter-based radioablation device in the clinical practice. Two regional centres were identified, as they are

the biggest clinical research centres in the regional context: the University Hospital of Padua (General Medicine Department IV) and the University Hospital of Verona (Cardiology Department). They were allowed to select target patients on the basis of an approved clinical protocol.

The questionnaire was sent by mail to the 2 centres on 5th of April and one reminder was sent by mail on 19th of April. The deadline was 20th of April. The questionnaire is reported in Appendix 12.

Literature search was used to estimate the target population (patients with Treatment - Resistant Hypertension). The main hypothesis is that denervation procedure is performed on patients affected by resistant hypertension (diastolic blood pressure >140 mm/Hg) on multi-therapy treatment with three or more antihypertensive drugs, including a diuretic, according to international guidelines [Mancia G, 2007; Mancia G, 2010]. The target model population includes an estimate of subjects actually hypertensive and resistant to therapies (according to the clinical indication of the medical device). This excludes patients affected by secondary hypertension, considering the issues of hypertension sub-diagnosis, blood pressure control achievement and adherence to treatments. The target patient is also likely to be affected by comorbidities, like cardiovascular disease and diabetes, according to the clinical profile provided by radioablation clinical trials.

The estimation of the number of target patients is based on literature data, searched from the main literature databases (Pubmed, Embase, Cochrane Library). Articles in English and Italian languages, published in the last 10-year, were retrieved, using the following keywords: "Hypertension, detection AND control", "antihypertensive therapy", "blood pressure control", "drug therapy", "secondary hypertension AND epidemiology".

For 2010, number of inhabitants of the Veneto Region was retrieved from ISTAT (Istituto nazionale di statistica) [http://www.istat.it] database and rates of hypertensive subjects from the Italian Society Of Hypertension (Società Italiana dell'ipertensione arteriosa – SIIA) database [http://siia.it/i-numeri-in-italia-2/].

The estimation of the number of eligible patients to potentially undergo the renal artery ablation procedure, was based on the results of regional survey. Rates of patients to be admitted to the "current treatment" were derived as difference to 100%.

Cost items and data on the resources consumption to perform the renal artery ablation, were collected from the regional survey. Unit costs were retrieved from the accounting centre of the university hospitals participating to the regional survey and tests were valued by the regional ambulatory tariffs (Veneto Region decree, number 859/2011).

Estimation of costs of hypertensive drug therapy (current therapy) was based on literature data: studies including monitoring costs and hypertension complications managing costs

were preferred. The following databases were searches: Pubmed, Embase, Cochrane Library, using the keywords: "economic burden AND hypertension AND Italy ", "hypertension AND cost", "antihypertensive AND cost" a 5-year limit was considered, in English and Italian languages.

Costs were actualized by consumer prices index [http://www.istat.com].

Finally, remunerability of DRG tariff of denervation procedure was evaluated in the Hospital perspective by comparing current, regional reimbursement tariff (Veneto Region decree, number 1805/2011) and hospital expenditure over three years.

Sensitivity analyses were performed on major variables: number of target patients, rates of procedure eligible patients, cost of antihypertensive therapy and cost of procedure to test the model robustness.

Results

Data from the regional survey indicated that only one centre, out of the two surveyed, performed the catheter based denervation both in the setting of clinical practice and research.

In the setting of clinical practice, the procedure was performed only on 3 target patients as test phase; the catheters for the renal denervation were provided free of charge. The procedure required 40 minutes in the haemodinamic operating theatre, with one cardiologist and one radiologist and one technician performing it. Two nurses were involved in two-hour monitoring. Usual neuroleptoanalgesia were also performed. The procedure was followed up by a couple of days of admission in the cardiology ward. Three specialists visits, renal functional tests and 24 hour blood pressure monitoring are required during one-year follow-up.

The regional survey didn't provide any information on the procedure codes[9] identifying the renal denervation, since it was performed on three patients for compassionate use.

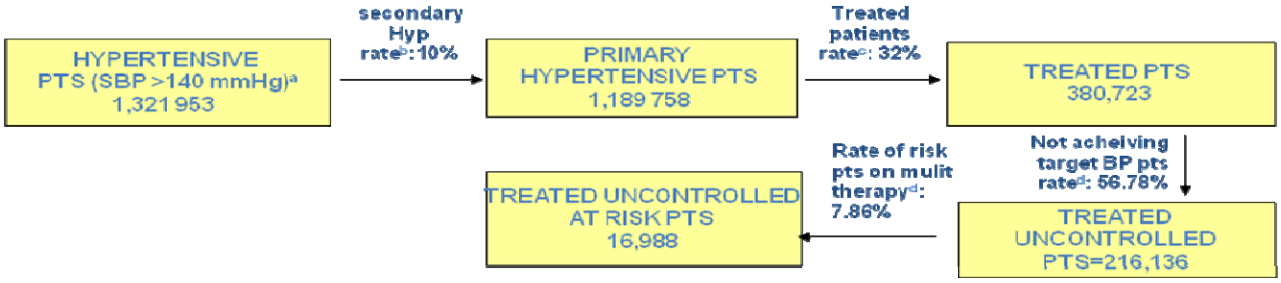
To estimate the target population of the Veneto region in the context of our analysis, national and international epidemiological evidence and national information sources were used to quantify patients affected by hypertension resistant to drug therapies. The focus was put on the most up to date evidence, clearly related to the Italian context.

According to the data of the Italian Society Of Hypertension (Società Italiana dell'ipertensione arteriosa – SIIA) [http://siia.it/i-numeri-in-italia-2/], in 2010, 56% (male) and 43% (female) Italian people are affected by hypertension (SBP>140 mmHg). In the

[9] See the Appendix 13 (Fulfilled questionnaires).

same year (2010) the inhabitants of Veneto region, aged 35-75 years old[10], were 2,672,314 [http://www.istat.it]. We assumed that 1,321,953 subjects are affected by hypertension in Veneto Region. Excluding 10% of patients affected by secondary hypertension [Onusko A, 2003] and not belonging to the target population, the final hypertensive population is equal to 1,189,758. Furthermore, under treatment is a crucial issue in the management of hypertension that should be considered: only 32% of patients is actually treated with antihypertensives [Wolf-Maier K, 2004] and only 43.23% of them achieves target blood pressure (SBP<140 mmHg) [Filippi A et al, 2009]. Hence there are 216,136 patients uncontrolled hypertensive subjects in the regional context. Of these, 7.86% is on multi-therapy (diuretics, β-blockers, ACE inhibitors, calcium antagonists, other antihypertensives and their associations) with at least 3 antihypertensive drugs [Filippi A et al, 2009] resulting in 16,988 hypertensive subjects resistant to therapies (target population). A scheme of the target population estimate is pictured in Figure 1.

Figure 1: Scheme of the target population estimate



[a] SIIA, 2010; ISTAT, 2010; [b]Onusko, 2003; [c] Wolf-Maier K, 2004; [d]Filippi, 2009

Legend

Hyp=hypertension; pts=patients.

The economic data inputs of the Model for catheter based renal artery denervation, are reported in Table 1. The detailed resource consumption and unit costs as well as items of costs are described for each phase of the procedure (pre-intervention, intervention and follow-up).

Cost items and data of resources consumption were retrieved from the regional survey and unit costs were obtained from ambulatory, regional tariff list, the accounting office of one regional, university hospital, national drugs databases. The regional survey did not provide information on the material used during arteriography, whose cost was approximated to the regional ambulatory tariff (€220.8 code 85.45).

[10] This range was selected from the observational studies on renal denervation [Krum H, 2009].

Table 1: Resource consumption and unit costs: model data input

pre-intervention phase			
cost items	**resource consumption**	**unit cost**	**comment**
specialsit visit	1 visit	€14.25	ambulatory tariff*, code 8901
creatinine	1 test	€ 2	ambulatory tariff*, code 90164
cistatine C	1 test	€ 19	ambulatory tariff*, code 9013a
urine test	1 test	€2.55	ambulatory tariff*, code 90443
haemoglobine	1 test	€11.7	ambulatory tariff*, code 90281
intervention phase			
cost items	**resource consumption**	**unit cost**	**comment**
arteriography	1	€220.8	ambulatory tariff*, code 8845
haemodinamic operatign room	40 minutes	€559.1/hour	full cost**, including depreciation charge
cardiologist	40 minutes	€61.05, cost per hour	full cost**
radiologist	40 minutes	€62.06 cost per hour	full cost**
nurse	2x120 minutes	€26.32 cost per hour	full cost**
Healthcare technician	40 minutes	€ 26.10 cost per hour	full cost**
analgesia	droperidolo, morphine sulphate***	€4.3	full cost**
cardiology ward	2 days	95.48 per day of admission	full cost**
renal denervation catheter	1	€5,000	NHS price
follow-up phase			
cost items	**resource consumption**	**unit cost**	**comment**
potassium	1 test	1.4	ambulatory tariff*, code 903704
sodium	1 test	1.4	ambulatory tariff*, code 904004
renal arterial ultrasound	1 test	68.4	ambulatory tariff*, code 887451
24-hours blood pressure measure	1 test	45.6	ambulatory tariff*, code 89611
specialist visits	3 visits	14.25	ambulatory tariff*, code 8901
overhead costs	15%		year 2010**

* ambulatory tariff, source: Veneto Region decree, number 859/2011
** full costs, source: university hospital account office
*** droperidol dosage 0.625-1.25mg ; morphine sulphate dosage 6-12mg; NHS prices source: www.giofil.it

The total cost of renal denervation, including pre-intervention, intervention and follow-up phases, was estimated to be €7,327. The composition of this estimation is: 84% (€6,189) was represented by the cost of procedure; 13% were overheads costs, remaining costs for pre-intervention and follow-up costs were marginal. In particular 81% of procedure cost was covered by the device, 6% by admission, a further 6% by operating room costs, 4% by arteriography and 3% by healthcare personnel. The estimate does not include the cost of antihypertensive drugs at follow-up because the clinical evidences does not report a statistically significant difference between case and control arms after procedures [Esler MD et al, 2010]. Similarly, the cost of management of adverse events was not estimated [Esler MD et al, 2010].

In absence of evidence of the use of renal denervation in the clinical practice, the number of eligible patients was supposed to be equal to the number of patients consecutively enrolled in the clinical register at regional centres. This project is the Italian prospective registry on renal denervation in patients with arterial hypertension resistant to therapy (approximately 40 patients per year in Veneto region). Therefore, the BIA considered increasing 0.250% rates of eligible patients, with a total, of 42, 106, 170 patients at first, second and third years, respectively, from the introduction of procedure.

For current therapy, the literature search on costs of antihypertensive drugs produced about 2,000 articles. No specific article on the cost of antihypertensive multi-therapies in the target population was available. Nevertheless, one article [Scholtze J, 2010] was relevant because it included complete information on costs of drugs, monitoring, cardiovascular complications

and adherence to treatments. Scholtze estimated that the cost of treatment, for an hypertensive patient, is €581 per year (values 2008, discounted at 2010) - with a level of adherence to treatments of 30%. This value, representing the cost for the whole management of the hypertensive patient (including: medications, visits and complications), is likely to be underestimated considering that in Veneto Region the expenditure on antihypertensive drugs alone is about €600 per treated patient [Andretta M, 2010].

As reported in table 2, the introduction of renal denervation would increase costs from €9,862,154 (eligible patients equal to 0%) up to €11,008,195 at 3rd year (1% of eligible patients).

Table 2: Budget Impact Analysis for the Veneto Region: base case results

	"current therapy" cost €581				renal denervation procedure €7,327						
	%	Number of patients	Cost/patient (€)		%	Number of patients	Cost/patient (€)	Total costs (€)	Difference (€)	Difference (%)
Year 0	**1**	**16,988**	**9,862 154**	**Year 0**	**0**	**0**	**0**	**9,862 154**	**-**	**-**
	99.9	16,967	9,849 826		0.125	21	155,583	10,005 409	143,255	1
Year 1	**99.8**	**16,945**	**9,837 499**	**Year 1**	**0.250**	**42**	**311,166**	**10,148 664**	**286,510**	**3**
	99.6	16,925	9,825 171		0.375	64	466,748	10,291 919	429,765	4
	99.5	16,903	9,812 843		0.5	85	622,331	10,435 174	573,020	6
Year 2	**99.4**	**16,882**	**9,800 515**	**Year 2**	**0.625**	**106**	**777,914**	**10,578 429**	**716,275**	**7**
	99.3	16,861	9,788 187		0.750	127	933,497	10,721 685	859,530	9
	99.1	16,840	9,775 860		0.875	149	1,089 079	10,864 940	1,002 785	10
Year 3	**99.0**	**16,818**	**9,763 533**	**Year 3**	**1.00**	**170**	**1,244 662**	**11,008 195**	**11,460 401**	**12**
Total	**-**	**16,988**	**29,586 462**			**319**	**2,333 742**	**31, 735 288**	**2,148 876**	**7**

The introduction of the device in clinical practice would increase regional expenditure for resistant hypertension treatment by 3%, 7% and 12%, respectively at 1st, 2nd and 3rd year from denervation implementation.

A number of parameters were tested in the sensitivity analysis.

The model is sensitive to the cost of current therapies, which is likely to be higher in the clinical practice than what here assumed, mostly due to cost of comorbidities management: variations of +50% in the cost of management of resistant hypertension produce a lower relative increase in the regional expenditure for resistant hypertension management due to new treatment (at 3rd year, +12% in the base case vs +7% in this sensitivity). Conversely, a reduction of the cost of current treatment could cause a broader relative incremental regional expenditure (from +12% in the base case to +24% at 3rd year).

The model is less sensitive to variations in the procedure cost, which could be underestimated only as to materials costs (±20%): higher procedure cost causes a relative increase regional by +14% at 3rd year.

Similar variations of the incremental expenditures derive from changes in the rates of denervation eligible patients: if this rate was 50% higher (input data is likely underestimated if considering that was derived from data registers) the relative increase of regional expenditure would be+18% at 3rd year since introduction; if 50% lower, it would be kept down (+6%).

Furthermore, clinical trials report the occurrence of further instrumental test at 6 months of follow-up for some patients underwent the renal denervation [Esler MD et al, 2010]: the inclusion of renal RM and CT angiography in, respectively, 10% of patients does not influence the final result of the model.

Finally, the rate of hypertensive patients on multi-therapy with at least 3 antihypertensive drugs was tested to adapt it to the regional context. Data provided by regional databases of prescription in patients in charge of regional Local Health Units indicated that 98,927 subjects, over a total of 1,075,765 hypertensive patients receiving antihypertensive drug prescriptions, equal to 9.2%, received antihypertensive multi-therapies (≥3 drugs) for at least one month during 2010. The model was not sensitive to changes in this parameter.

From the regional survey it emerged the lack of regional codes identifying the procedure. Literature reported the scenario of the Lombardia Region, the only region which provided official information on procedure codes, was applied [Filippi A, 2012]. On the basis of ICD9CM list (version 2007) and the DRG Grouper 24, renal denervation is identified by the diagnosis codes 401.9 (essential hypertension) procedures codes 8845 (arteriography) and 0525 (periarterial sympatectomy). This results in the DRG code 120 (Other interventions on the cardiovascular district), with regional tariff for reimbursement of €6,901 (Veneto Region decree, number 1805/2011).

Considering reimbursement by the DRG code 120 and in the hypothesis of two regional patient selecting centres, as recently decided by the CTRDM, the implantation of renal denervation would cause the Hospital a loss of about €5,641 at 1st year up to €22,565 at 3rd year due to the difference between the cost of the procedure and the DRG tariff reimbursement.

Discussion

This Budget impact analysis considered the CTRDM decision for a controlled introduction of renal denervation procedure, in order to define the regional context of use. The survey, sent to the selected centres, identified the use in the framework of clinical trials and in a sort of phase test in the framework of the compassionate use. The survey was used as source for resource consumption data collection and to estimate the most likely rate of patients potentially eligible to the procedure.

According to the indication of the labelling of the catheter and the inclusion criteria of the clinical trials, all patients affected by resistant hypertension are potentially eligible to the procedure, estimated to be in about 17,000 in the Veneto region (2010 estimates). Clearly, a key point of the BIA was to estimate the starting number of patients more likely and performing the procedure and to estimate the speedy of change of this rate over the 3-year time horizon.

The Ispor Task Force for BIA states that: "*The ideal way to obtain this estimate would be from the epidemiological data in the decision-maker's own population before and after the introduction of the new technology. As these data are not usually readily available even for the current technologies, various alternative methods can be used to provide default estimates for a budget impact model*" [Mauskopf J, 2007]. In absence of regional databases, due to unavailability of the procedure in the clinical practice, and of producers' market share, we decided for the most conservative hypothesis, i.e. considering patients eligible in clinical registers as the best proxy for the model (estimation were retrieved from the survey and from national register protocol) and considering a slow increasing of this rate due to the fact that clinical studies on the procedure are still ongoing. This approach was also supported by the Ispor Task Force which states that "*The purpose of a BIA is not to produce exact estimates of the budget consequences of an intervention, but to provide a valid computing framework (a "model"), at a particular point in time….that allows users to understand the relation between the characteristics of their setting and…..reflects local intended restrictions on use (and reimbursement)* [Mauskopf J, 2007]. Furthermore, it was found that the model is less sensitive to changes in the rate of patients eligible to procedure than it is to the cost of "current treatment". Apart from these considerations, the results as to the impact of the "denervation eligible patients" variable should be surely better investigated by the implementation of procedure registers in which patients are selected by uniform, homogeneous and clinical trials-related inclusion criteria.

Finally, epidemiological estimates of the number of patients affected by hypertension in this model are comparable with data provided by regional databases (respectively, about 1,322,000 vs 1,100,000). In the same way, the rate of risk patient affected by resistant hypertension, treated with more than 3 antihypertensive drugs was comparable with the

same group of patients provided by the regional prescriptions database (respectively, 7.86% vs 9.20%).

The use of prescription regional database in the model population was excluded as source both for epidemiological data and for antihypertensive costs data. The adoption of regional prescription databases seemed to be inappropriate for several reasons: regional databases are not homogeneous, they do not link a primary diagnosis of hypertension to prescription and would not allow to build the analysis on a homogeneous definition of adherence to treatment. In addition furthermore, associations/combinations of antihypertensive is extremely wide and variable among regional contexts and literature data collection appears to be the most reliable methodological option aiming at the reproducibility of the model in different regional contexts.

As to the costs of "current treatment", literature retrieval of suitable articles was difficult because most of studies estimated costs on an incidence-base more than a prevalence-based approach, or were assessed in foreign country or were old or provided only partial information (absence of the adherence rate to treatment or estimation of monitoring blood pressure costs). We selected the study of Scholtze because it provided a prevalence-based cost of illness estimation in the Italian context. Positive aspects were reporting a rate of adherence to drug therapies and a complete estimation of direct costs of hypertension treatments (drugs, monitoring, comorbidities). The negatives were that the whole study is based on old estimation of the costs actualised to 2008. Furthermore, this estimation of costs are underestimated as the regional expenditure is about €600 per patient only for antihypertensive drugs [Dati Sfera, 2009].

Sensitivity analysis demonstrated that increasing the cost of current treatment would decrease the impact of the new technology on the regional expenditure. This highlights the need to implement regional databases estimating the actual, updated cost of hypertension management in the naturalistic context, including cardiovascular and diabetes management costs reporting details on when they occur to get more reliable estimations of the impact of the new technology on regional expenditure.

The need to estimate the real cost of renal denervation procedure is also to be underlined. The regional survey was used also in this case as a source of resource consumption. Nevertheless, in absence on specific and detailed information on materials used during an arteriography, the regional ambulatory tariff was used as a proxy. As recognised in the scientific community, tariff is underestimated proxy for costing: therefore, the remaining items are all to be added to the cost of arteriography. The sensitivity analysis on this parameter demonstrated the robustness of the model.

Increasing availability of medical technologies requires that decision makers consider the governance of their diffusion by developing pattern of controlled introduction of the technology in the clinical practice; patterns able to blend clinical outcomes assessment and knowledge of varied implications of the innovative technologies introduction, including economic implications, which will increasingly influence the decisional process in the future [Baker L, 2003; Bodenheimer T, 2005; Schreyögg J, 2009]. The controlled introduction of renal denervation procedure in the clinical practice of the Veneto region, with all the limits declared in this report, would cause a modest increasing of the regional expenditure (in the range of 3%-12%). As the regional expenditure for medical devices in 2010 was about 391 million Euros, the new technology would impact only in the marginal range of 0.04%-0.29% (Veneto Region decree, number 2346/2011).

Nevertheless, in the hospital perspective the procedure implementation would cause an increasing loss of economic resources due to the lack of DRG tariff remunerability (€6,901 vs €7,167 if including pre-intervention and intervention phase). This result is sensitive to the variation in the number of treated patient and to the cost of procedure: a reduction of 20% in the cost of procedure annulated the loss of income and made the tariff remunerative. This again underlines the need to exactly estimate the cost of procedure in the clinical practice.

Finally, literature evidence shows the statistical correlation between increasing blood pressure levels and cardiovascular events occurrence [Prospective Study Collaboration, 2002]. However it is not currently possible to implement a complete economic evaluation, identifying the benefit of renal denervation in terms of avoiding cardiovascular events and therefore savings of consequent hospitalizations in comparison with the increment of regional expenditure due to the introduction of the new technology: further clinical evidence is required.

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http://www.serveneto.it/public/File/documents/articoli_di_bollettino/ies201004/PrestazioniFarmTerritoriali.pdf (Dati Sfera, 2009) [last access: May 231, 2012]

Legal sources

President of the Italian Republic, national decree n.98/2011: www.lavoro.gov.it [last access: May 2, 2012]

Veneto Region decree, number 4534/2007: www.regione.veneto.it [last access: May 2, 2012]

Veneto Region decree, number 2187/2008: www.regione.veneto.it [last access: May 2, 2012]

Veneto Region decree, number 859/2011: www.regione.veneto.it [last access: May 2, 2012]

Veneto Region decree, number 1805/2011: www.regione.veneto.it [last access: May 2, 2012]

Veneto Region decree, number 2346/2011: www.regione.veneto.it [last access: May 2, 2012]

Appendix 1

Renal artery denervation systems

Trade name	Manufacturer	Technical characteristics	CE Mark	FDA Approval
Externally applied focused ultrasound	Kona Medical	Externally focused ultrasound based approach. The systems delivers energy from outside the patient to the renal nerves.	Still in the preclinical studies on animal	No
The TIVUS system	CardioSonic Ltd	The system uses high intensity non focused ultrasound waves to generate the heat needed to achieve renal artery denervation.	Preclinical studies	Not specified
Paradise	ReCor Medical Inc.	The system uses ultrasound waves to generate the heat needed to destroy the cell and interrupt the electrical continuity of the biological system. The ultrasound probe is embedded in a angioplasty catheter displaced to the point of ablation.	Yes (2011)	No
Bullfrog microinfusion catheter	Mercator MedSystems, Inc.	The system performs renal denervation through delivering nerves-toxic drugs direct injection into the renal artery wall.	Not specified	Yes
The Oneshot renal denervation system	Maya medical (acquired by Covidien in 2012)	New angioplasty balloon with embedded electrodes. RF energy is delivered through all electrodes at the same time.	Yes (2012)	No
V^2 radiofrequency balloon	Vessix Vascular, Inc.	New angioplasty balloon with embedded electrodes. RF energy is delivered through all electrodes at the same time.	Yes (2012)	Not specified

http://bmctoday.net/evtoday/2012/02/article.asp?f=renal-artery-denervation-a-brave-new-frontier
http://konamedical.com/technology/
http://www.masshightech.com/stories/2012/05/07/daily28-Covidien-to-pay-up-to-230M-for-Maya-Medical.html
http://www.vessixvascular.com/news.html

Appendix 2

Search Strategy - Efficacy and Safety

- **MEDLINE** (Pubmed)

DATE: 23 February 2012
LIMITS: Humans, Publication Date from 2005/01/01 to 2012/02/23

Key words and search strategy

#1 "hypertension"[Mesh]
#2 hypertension[Text Word]
#3 "high blood pressure"[Text Word]
#4 HBP[Text Word]
#5 (#1 OR #2 OR #3 OR #4)
#6 refractory[Text Word]
#7 resistant[Text Word]
#8 (#6 OR #7)
#9 (#5 AND #8)
#10 "nerve ablation"[Text Word]
#11 "denervation"[Mesh]
#12 "sympathectomy"[Mesh]
#13 RSD[Text Word]
#14 "sympathetic denervation"[Text Word]
#15 catheter denervation
#16 "catheter ablation"[Mesh]
#17 "catheter ablation"[Text Word]
#18 Symplicity[Text Word]
#19 Thermocool[Text Word]
#20 (#10 OR #11 OR #13 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 renal[Text Word] OR kidney[Text Word]
#22 (#20 AND #21)
#23 (#9 AND #22)
#24 (#9 AND #22 Limits: Humans, Publication Date from 2005/01/01 to 2012/02/23)

Results: 37

- **EMBASE** (Embase.com)

DATE: 23 February 2012
LIMITS: Humans, Publication Date from 2005 to 2012

Key words and search strategy

#1. 'hypertension'/exp OR hypertension
#2. 'high blood pressure'/exp OR 'high blood pressure'
#3. hbp
#4. 'hypertension'/exp OR hypertension OR 'high blood pressure'/exp OR 'high blood pressure' OR hbp
#5. refractory
#6. resistant

#7. refractory OR resistant
#8. 'hypertension'/exp OR hypertension OR 'high blood pressure'/exp OR 'high blood pressure' OR hbp AND (refractory OR resistant)
#9. 'nerve ablation'
#10. 'denervation'/exp
#11. 'sympathectomy'/exp
#12. rsd
#13. 'sympathetic denervation'
#14. 'catheter'/exp OR catheter AND ('denervation'/exp OR denervation)
#15. 'catheter ablation'/exp OR 'catheter ablation'
#16. Simplicity
#17. thermocool
#18. 'nerve ablation' OR 'denervation'/exp OR 'sympathectomy'/exp OR rsd OR 'sympathetic denervation' OR ('catheter'/exp OR catheter AND ('denervation'/exp OR denervation)) OR 'catheter ablation'/exp OR 'catheter ablation' OR symplicity OR thermocool
#19. renal OR 'kidney'/exp OR kidney
#20. 'nerve ablation' OR 'denervation'/exp OR 'sympathectomy'/exp OR rsd OR 'sympathetic denervation' OR ('catheter'/exp OR catheter AND ('denervation'/exp OR denervation)) OR 'catheter ablation'/exp OR 'catheter ablation' OR symplicity OR thermocool AND (renal OR 'kidney'/exp OR kidney)
#21. 'hypertension'/exp OR hypertension OR 'high blood pressure'/exp OR 'high blood pressure' OR hbp AND (refractory OR resistant) AND ('nerve ablation' OR 'denervation'/exp OR 'sympathectomy'/exp OR rsd OR sympathetic denervation' OR ('catheter'/exp OR catheter AND ('denervation'/exp OR denervation)) OR 'catheter ablation'/exp OR 'catheter ablation' OR symplicity OR thermocool) AND (renal OR 'kidney'/exp OR kidney)
#22. 'hypertension'/exp OR hypertension OR 'high blood pressure'/exp OR 'high blood pressure' OR hbp AND (refractory OR resistant) AND ('nerve ablation' OR 'denervation'/exp OR 'sympathectomy'/exp OR rsd OR sympathetic denervation' OR ('catheter'/exp OR catheter AND ('denervation'/exp OR denervation)) OR 'catheter ablation'/exp OR 'catheter ablation' OR symplicity OR thermocool) AND (renal OR 'kidney'/exp OR kidney) AND [humans]/lim AND [2005-2012]/py

Results: 117

- **Cochrane Library** (Bibliosan.it)

DATE: 21 February 2012
LIMITS: Publication Date from 2005 to 2012

Key words and search strategy

#1 MeSH descriptor Hypertension explode all trees
#2 "high blood pressure"
#3 (HBP)
#4 (hypertension)
#5 (#1 OR #2 OR #3 OR #4)
#6 (Refractory)
#7 (Resistant)
#8 (#6 OR #7)
#9 (#5 AND #8)
#10 "nerve ablation"
#11 MeSH descriptor Denervation explode all trees

#12 MeSH descriptor Sympathectomy explode all trees
#13 (RSD)
#14 "sympathetic denervation"
#15 (catheter denervation)
#16 MeSH descriptor Catheter Ablation explode all trees
#17 "Catheter Ablation"
#18 (symplicity)
#19 (thermocool)
#20 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (renal) or (kidney)
#22 (#20 AND #21)
#23 (#9 AND #22)
#24 (#23), from 2005 to 2012

Results: 5

- **Web of Science**

DATE: 27 February 2012
LIMITS: Publication Date from 2005 to 2012

Key words and search strategy

#1 (hypertension OR "high blood pressure" OR "HBP" OR "Hypertension")
#2 (refracto*) OR (resistan*)
#3 (#2 AND #1)
#4 ("nerve ablation" OR "Denervation" OR "Sympathectomy") OR ("RSD" OR "sympathetic denervation" OR "catheter denervation") OR ("Catheter Ablation" OR symplicity OR thermocool)
#5 (renal OR kidney)
#6 (#5 AND #4)
#7 (#6 AND #3)

Results: 89

- **CIHNAL** (EBSCOhost)

DATE: 27 February 2012
LIMITS: Publication Date from 2005 to 2012

Key words and search strategy

S1 "Hypertension" OR "high blood pressure" OR HBP OR hypertension
S2 Resistant OR Refractory
S3 (S1 AND S2)
S4 "nerve ablation" OR "Denervation" OR "Sympathectomy" OR RSD OR "sympathetic denervation" OR catheter denervation OR "Catheter Ablation OR Catheter Ablation OR simplicity OR thermocool
S5 renal OR kidney
S6 (S4 AND S5)
S7 (S3 AND S6)

Results: 5

Appendix 3

Data Extraction Form – Study Description

Background information

Screener Initials	
Study ID (first Author)	
Published (Y/N)	
Year	
Period study conducted	
Country(ies) of study	
Objective(s)	

Type of the study *(mark one of the following)*

□ Randomised Controlled Trial (RCT)
□ Clinical Controlled Trial (CCT)
□ Cohort study
□ Case-control study
□ Cross-sectional study
□ Controlled before-after study

Characteristics of the study – RCT/CCT

Trial registration number:

1. Type of trial	☐ Two arms ☐ Multiple arms ☐ Superiority ☐ Non-inferiority ☐ Equivalence ☐ Early stopped trial	
2. Participants *(a) Number of participants* *(b) Age*[11] *(c) Antihypertensive drugs*[1] *(d) Systolic/diastolic BP at Baseline*[12]	Intervention group	Comparison group
3. Comparison	Intervention: ☐ Denervation Type of system: ☐ Symplicity (Medtronic) ☐ Thermocool (J&J) ☐ St Jude ☐ Other, _____	Comparator: ☐ _____ ☐ _____

4. Primary outcome: _____ Outcome measure: _____

5. Secondary outcome: (a) _____ Outcome measure: _____

(b) _____ _____

(c) _____ _____

(d) _____ _____

[11] Please record data as reported in the study (e.g. Mean, mean and [Range], mean ± Standard deviation (SD), etc.).

[12] Mean ± Standard deviation (SD), if reported.

6. Follow up (in months)		
7. Funding	☐ For profit agency ☐ Private not for profit ☐ Governmental ☐ Not funded ☐ Not reported	Sponsor involved in study design or conduct ☐ yes ☐ no
8. Authors' Conclusions:		

Reporting

Flow-chart	☐ Yes	☐ No
Sample size	☐ Yes	☐ No
Post-randomisation exclusion	☐ Yes	☐ No
Lost-to-follow up	☐ Yes	☐ No

Methodological Quality

Allocation concealment	☐ Central randomisation (computer, fax, internet) ☐ Sequentially numbered, opaque, sealed envelopes ☐ Coded medication containers ☐ Any other method which appeared random (e.g. coin tossing, etc.) ☐ Unconcealed randomisation ☐ Not reported ☐ Not randomized ☐ Unclear		
Blinding of patients	☐ Yes	☐ No	☐ Unclear

Blinding of investigators	☐ Yes	☐ No	☐ Unclear
Blinding of data collectors	☐ Yes	☐ No	☐ Unclear
Blinding of outcome adjudicators	☐ Yes	☐ No	☐ Unclear
Blinding of data analysts	☐ Yes	☐ No	☐ Unclear
Intention to treat (ITT) statements			
Intention to treat reporting	☐ ITT ☐ Unclear	☐ mITT[13]	
ITT reporting	☐ No description reported ☐ Correctly described as ITT	☐ Different ITT description reported:_____	
"no ITT"	☐ Possible description of how analysis are performed_____		

Analysis

Post-randomisation exclusions (PRE)	☐ Yes	☐ No	☐ Unclear
Reasons for PRE	☐ Yes If yes, specify _____	☐ No	☐ Unclear

Lost-to-follow up (LTFU)

Lost-to-follow up reporting	☐ LTFU occurred	☐ LTFU NOT occurred	☐ No explicit statement

Notes

Reviewer Conclusions:

[13] mITT refers to trials reporting the use of a "modified intention-to-treat" approach.

Data Extraction Form – Efficacy and Safety Outcomes

OUTCOMES

1. All causes mortality

Study ID	Definition[14]	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	

2. Change in average measurements of systolic and/or diastolic blood pressure

2.a Change in Systolic blood pressure (SBP)

Study ID	Intervention Group		Control Group		Comments
	Mean ± SD mm Hg (*p value*)	N. events/N. patients	Mean ± SD mm Hg (*p value*)	N. events/N. patients	Follow up

2.b Change in Diastolic blood pressure (DBP)

Study ID	Intervention Group		Control Group		Comments
	Mean ± SD mm Hg (*p value*)	N. events/N. patients	Mean ± SD mm Hg (*p value*)	N. events/N. patients	Follow up

[14] In the "Definition" field is reported the specification of the kind of the events (e.g cause of mortality, cardiovascular events, adverse events, etc.).

3. Cardiac mortality

Study ID	Definition	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	

4. Major cardiovascular events (myocardial infarction, heart failure, stroke…)

Study ID	Definition	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	

SAFETY

5.1. Adverse Events: Acute procedural safety

Study ID	Definition	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	

5.2. Adverse Events: "Chronic procedural safety (kidney failure, renal artery stenosis, etc)"

Study ID	Definition	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	

Appendix 4

Search Strategy – Economic literature

- **MEDLINE** (Pubmed)

DATE: 27 February 2012
LIMITS: Humans, Publication Date from 2005/01/01 to 2012/02/27

Key words and search strategy

#1 "nerve ablation"[Text Word]
#2 "denervation"[Mesh]
#3 "sympathectomy"[Mesh]
#4 RSD[Text Word]
#5 "sympathetic denervation"[Text Word]
#6 catheter denervation
#7 "catheter ablation"[Mesh]
#8 "catheter ablation"[Text Word]
#9 Symplicity[Text Word]
#10 Thermocool[Text Word]
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 renal[Text Word] OR kidney[Text Word]
#13 (#11 AND #12)
#14 (cost[Text Word]) AND analysis[Text Word]
#15 ("cost minimization"[Text Word]) OR CMA[Text Word]
#16 ("cost effectiveness"[Text Word]) OR CEA[Text Word]
#17 ("cost utility"[Text Word]) OR CUA[Text Word]
#18 (economic) AND (evaluation OR analysis OR aspects OR assessment OR comparison)
#19 ("health care") AND cost*
#20 (#14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (#13 AND #20)
#22 (#13 AND #20 Limits: Humans, Publication Date from 2005/01/01 to 2012/02/27)

Results: 7

- **EMBASE** (Embase.com)

DATE: 28 February 2012
LIMITS: Humans, Publication Date from 2005 to 2012

Key words and search strategy

#1. 'nerve ablation'

#2. 'denervation'/exp

#3. 'sympathectomy'/exp

#4. rsd

#5. 'sympathetic denervation'

#6. 'catheter'/exp AND 'denervation'/exp

#7. 'catheter ablation'/exp OR 'catheter ablation'

#8. Simplicity

#9. thermocool

#10. 'nerve ablation' OR 'denervation'/exp OR 'sympathectomy'/exp OR rsd OR 'sympathetic denervation' OR ('catheter'/exp AND 'denervation'/exp) OR 'catheter ablation'/exp OR 'catheter ablation' OR symplicity OR thermocool

#11. renal OR 'kidney'/exp OR kidney

#12. ('nerve ablation' OR 'denervation'/exp OR 'sympathectomy'/exp OR rsd OR 'sympathetic denervation' OR ('catheter'/exp AND 'denervation'/exp) OR 'catheter ablation'/exp OR 'catheter ablation' OR symplicity OR thermocool) AND (renal OR 'kidney'/exp OR kidney)

#13. 'cost'/exp OR cost AND ('analysis'/exp OR analysis)

#14. 'cost minimization'/exp OR 'cost minimization' OR cma

#15. 'cost effectiveness'/exp OR 'cost effectiveness' OR 'cea'/exp OR cea

#16. 'cost utility'/exp OR 'cost utility' OR cua

#17. economic

#18. 'evaluation'/exp OR 'analysis'/exp OR aspects OR assessment OR 'comparison'/exp

#19. economic AND ('evaluation'/exp OR 'analysis'/exp OR aspects OR assessment OR 'comparison'/exp)

#20. 'health care'/exp AND cost*

#21. 'cost'/exp OR cost AND ('analysis'/exp OR analysis) OR 'cost minimization'/exp OR 'cost minimization' OR cma OR 'cost effectiveness'/exp OR 'cost effectiveness' OR 'cea'/exp OR cea OR 'cost utility'/exp OR 'cost utility' OR cua OR (economic AND ('evaluation'/exp OR 'analysis'/exp OR aspects OR assessment OR 'comparison'/exp)) OR ('health care'/exp AND cost*)

#22. (('nerve ablation' OR 'denervation'/exp OR 'sympathectomy'/exp OR rsd OR 'sympathetic denervation' OR ('catheter'/exp AND 'denervation'/exp) OR 'catheter ablation'/exp OR 'catheter ablation' OR symplicity OR thermocool) AND (renal OR 'kidney'/exp OR kidney)) AND ('cost'/exp OR cost AND ('analysis'/exp OR analysis) OR 'cost minimization'/exp OR 'cost minimization' OR cma OR 'cost effectiveness'/exp OR 'cost effectiveness' OR 'cea'/exp OR cea OR 'cost utility'/exp OR 'cost utility' OR cua OR (economic AND ('evaluation'/exp OR 'analysis'/exp OR aspects OR assessment OR 'comparison'/exp)) OR ('health care'/exp AND cost*))

#23. (('nerve ablation' OR 'denervation'/exp OR 'sympathectomy'/exp OR rsd OR 'sympathetic denervation' OR ('catheter'/exp AND 'denervation'/exp) OR 'catheter ablation'/exp OR 'catheter ablation' OR symplicity OR thermocool AND (renal OR 'kidney'/exp OR kidney)) AND ('cost'/exp OR cost AND ('analysis'/exp OR analysis) OR 'cost minimization'/exp OR 'cost minimization' OR cma OR 'cost effectiveness'/exp OR 'cost effectiveness' OR 'cea'/exp OR cea OR 'cost utility'/exp OR 'cost utility' OR cua OR (economic AND ('evaluation'/exp OR 'analysis'/exp OR aspects OR assessment OR 'comparison'/exp)) OR ('health care'/exp AND cost*)) AND [humans]/lim AND [2005-2012]/py

Results: 29

- **Cochrane Library** (Bibliosan.it)

DATE: 28 February 2012
LIMITS: Publication Date from 2005 to 2012

Key words and search strategy

#1	"nerve ablation"
#2	MeSH descriptor Denervation explode all trees
#3	MeSH descriptor Sympathectomy explode all trees
#4	(RSD)
#5	"sympathetic denervation"
#6	(catheter) and (denervation)
#7	MeSH descriptor Catheter Ablation explode all trees
#8	"catheter ablation"
#9	(symplicity)
#10	(thermocool)
#11	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12	(renal) OR (kidney)
#13	(#11 AND #12)
#14	(cost) AND (analysis)
#15	"cost minimization" OR (CMA)
#16	"cost effectiveness" OR (CEA)
#17	"cost utility" OR (CUA)
#18	(economic) AND (evaluation OR analysis OR aspects OR assessment OR comparison)
#19	"health care" AND (cost*)
#20	(#14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21	(#13 AND #20)
#22	(#21), from 2005 to 2012

Results: 14

Appendix 5

Data Extraction Form

General information	
Reviewer name:	Date of extraction:
Author/Year:	
Title:	
Journal:	
Source of funding:	
Study Characteristics	
Objective of study:	
Study population:	
Intervention:	
Comparator:	

Economic Study Type		*Perspective*	
Cost-effectiveness Analysis	☐		
Cost-utility Analysis	☐	NHS	☐
Cost-benefit Analysis	☐	Societal	☐
Cost-Consequence Analysis	☐	Hospital	☐
Cost-Study	☐	Not Stated	☐
Other (specify)	☐	Other (please specify)	☐
Not reported	☐		

Modelling

Was a model used?

Yes ☐

No ☐ If yes, state purpose and type:	
Source of Data	
Source of effectiveness data Single study ☐ Synthesis of Previous Publication ☐	*Source of Cost Data* Actual source (survey,direct contact, etc.) ☐ Literature source ☐

Source of effectiveness data

Effectiveness data from a single study

Study design

☐ RCT

☐ Non-RCT with concurrent controls

☐ Cohort study

☐ Historical control

☐ Before and after study

☐ Case series

☐ Other (specify)

☐ Not reported

Study population

Number of patients in intervention group ☐

Number subject in control group ☐

Number excluded from study ☐

Methods of sample selection:

Follow-up

Duration of follow-up ☐

Loss to follow-up ☐

Number of centres:

Any blinding for assessment of outcomes:

Analysis of clinical studies:

□ Treatment completers

□ Intention to treat

Effectiveness results:

<table>
<tr><td colspan="3">Effectiveness data from a synthesis of previous publications (model)</td></tr>
<tr><td>Study inclusion criteria:</td><td rowspan="4">Study designs included:

☐ RCT

☐ Non-RCT with concurrent controls

☐ Cohort study

☐ Historical control

☐ Before and after study

☐ Case series

☐ Other (specify)

☐ Not reported</td><td rowspan="2">Number of primary studies included:</td></tr>
<tr><td>Study exclusion criteria reported:</td></tr>
<tr><td>Sources searched reported:</td><td rowspan="3">Method of combination of primary study:

☐ Meta-analysis

☐ Narrative methods

☐ Other (specify)</td></tr>
<tr><td>Criteria used to judge validity:

☐ Concealment of randomisation

☐ Blind assessment

☐ Low dropout rates

☐ Other (specify)

☐ Not reported</td></tr>
<tr><td colspan="3">Results of the review (Effectiveness results):</td></tr>
<tr><td colspan="3">Economic evaluation</td></tr>
<tr><td colspan="3">Measures of Benefits used in the Economic Analysis yes ☐ no ☐

If yes, specify:

Side effect considered yes ☐ no ☐</td></tr>
</table>

Direct costs: Health service

Estimation based on:

☐ A guess

☐ Actual data

☐ Derived using Modelling

☐ Other

☐ Not reported

Direct costs: Patients

Estimation based on:

☐ A guess

☐ Actual data

☐ Derived using Modelling

☐ Other

☐ Not reported

Source of Direct costs Data:	**Discounting Undertaken?**
Price Year	Yes ☐ No ☐
Currency:	**Discount rate**
Conversion rates used:	

Indirect Costs

Estimation based on:

☐ A guess

☐ Actual data

☐ Derived using Modelling

☐ Other

☐ Not reported

Source of indirect Cost Data:	**Discounting Undertaken?**
Price Year	Yes No ☐ **Discount rate**
Currency:	**Conversion rates used:**

Statistical/sensitivity analyses

Statistical tests carried out?	Types of tests used in analysis of costs:
Yes ☐ No ☐	

Type of sensitivity analysis

☐ One-way analysis

☐ Two-way analysis

☐ Multi-way analysis

☐ Threshold analysis

☐ Analysis of Extremes

☐ Probabilistic analysis

☐ Other

☐ Not reported

☐ Not carried out

Areas of uncertainty tested:

Results of study
Clinical Outcome/benefit: Duration of Benefits: **Costs results:** **Cost of adverse events considered Yes □ No □ Not relevant □**
How were the estimates of costs and benefits combined? □ Cost/Life saved □ Cost/life Gained □ Cost/QALY □ Not benefit □ Incremental net benefit □ Other □ Not Combined
Results of Synthesis of costs and benefits:
Author's conclusion:
Reviewer's conclusion:
Overall assessment of study quality:

Adapted from Bamford J, *et al*. Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen. *Health Technol Assess* 2007;11(32).

Appendix 6

Excluded and included studies

List of excluded studies with reasons for exclusion

Not found studies:

Krum, H., M. Schlaich, et al. (2009). "Symplicity I: Does catheter-based renal sympathetic denervation maintain blood pressure reduction in patients with resistant hypertension over the subsequent 12 months? Complete 12-month efficacy and safety results." American Journal of Cardiology 104(6A): XX-XX.

Non comparative studies:

Bilge, M., H. Tolunay, et al. (2012). "Percutaneous renal denervation in patients with resistant hypertension first experiences in Turkey." Anadolu Kardiyoloji Dergisi 12(1): 79-80.

Esler, M., M. Schlaich, et al. (2009). "Catheter-Based Renal Denervation reduces total body and renal noradrenaline spillover and blood pressure in resistant hypertension." Journal of Hypertension 27: S167-S167.

Katholi, R. E. and K. J. Rocha-Singh (2011). "Catheter-based renal sympathetic denervation reduces systolic blood pressure by 32 mm Hg in people with treatment-resistant hypertension." Evidence-Based Medicine 16(4): 109-110.

Krum, H., M. Schlaich, et al. (2009) Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 1275-1281

Krum, H., P. Sobotka, et al. (2011). "Device-Based Antihypertensive Therapy Therapeutic Modulation of the Autonomic Nervous System." Circulation 123(2): 209-215.

Schlaich, M. P., H. Krum, et al. (2009). "Effects of Renal Sympathetic Denervation on noradrenaline spillover and systemic blood pressure in patients with resistant hypertension." Journal of Hypertension 27: S154-S154.

Schlaich, M. P., N. Straznicky, et al. (2011). "Renal denervation: a potential new treatment modality for polycystic ovary syndrome?" Journal of Hypertension 29(5): 991-996.

Walton, A., M. Esler, et al. (2011). "Renal denervation for refractory hypertension." Heart Lung and Circulation 20: S19.

Secondary publication:

Alvarez Pellicer, J. (2010). "Catheter-based renal sympathetic denervation for resistant hypertension: A multicentre safety and proof-of-principle cohort study." Revista Clinica Espanola 210(5): 243.

Ukena, C., F. Mahfoud, et al. (2011). "Cardiorespiratory response to exercise after renal sympathetic denervation in patients with resistant hypertension." European Heart Journal 32: 960.

Extension study with outcome not of interest:

Ukena, C., F. Mahfoud, et al. (2011). "Cardiorespiratory response to exercise after renal sympathetic denervation in patients with resistant hypertension." Journal of the American College of Cardiology 58(11): 1176-1182.

Correspondence:

Witkowski, A., A. Prejbisz, et al. (2011). "Response to renal denervation for sleep apnea and resistant hypertension: Alternative or complementary to effective continuous positive airway pressure treatment?" Hypertension 58(6): e192.

List of included studies

Esler, M. D., H. Krum, et al. (2010). "Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial." Lancet 376(9756): 1903-1909.

Mahfoud, F., M. Schlaich, et al. (2011). "Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: A pilot study." Circulation 123(18): 1940-1946.

Appendix 7

Ongoing Clinical Trials (clinical trial.gov)

Official title (trial number)	System	Purpose	Primary outcomes [Time frame]	Type	Phase	Arms		Enrolment	Date (Start – Completion)	Country	Sponsor
						Intervention	*Comparator*				
Active, Not Recruiting											
RD in Patients With Uncontrolled Hypertension (NCT00888433)	Symplicity® Catheter System™	An international, multi-center, prospective, randomized, controlled study of the safety and effectiveness of RD in patients with uncontrolled hypertension	• BP Reduction [6 months]	Interventional	NR	RD + maintenance of anti-hypertensive medications	Maintenance of anti-hypertensive medications	106	June 2009 – July 2013	Australia, Austria, Belgium, France, Germany, Latvia, Poland, Spain, Switzerland, UK	Medtronic Vascular
RD in Patients With Refractory Hypertension (NCT00483808)	Ardian Symplicity™ Catheter	To investigate the clinical utility of RD in the treatment of refractory hypertension	• To provide confirmation that RD is safe and feasible [1 year]	Interventional	1	RD using the Symplicity Catheter	NR	73	June 2007 – April 2013	Australia, Poland	Ardian Inc
RD in Patients With Refractory Hypertension (NCT00753285)	Ardian Catheter	The purpose of this study is to investigate the clinical utility of RD for the treatment of refractory hypertension	• Safety - complications associated with delivery and/or use of the Ardian Catheter, adverse renal events, electrolyte disturbances, hemodynamic events [3 years]	Interventional	1	NR	NR	20	September 2008 – December 2011	USA	Ardian Inc
RD in Patients With Refractory Hypertension (NCT00664638)	Symplicity® Catheter System™	To investigate the clinical utility of RD in the treatment of refractory hypertension	To provide confirmation that RD is safe and feasible [1 year]	Interventional	1	Denervation	NR	45	April 2008 – April 2013	Germany	Ardian Inc

RD in End Stage Renal Disease Patients With Refractory Hypertension (NCT00753116)	Ardian Catheter	The purpose of this study is to investigate the clinical utility of RD in the treatment of ESRD patients with refractory hypertension	• Safety - complications associated with delivery and/or use of the Ardian Catheter, adverse renal events, electrolyte disturbances, hemodynamic events [1 years]	Interventional	1	NR	NR	20	September 2008 – December 2009	USA	Ardian Inc
Ablation-induced RSD Trial (NCT01438229)	St. Jude Medical renal artery ablation system	This is a prospective, multicenter, feasibility study on the safety and efficacy of RD in patients with RH	• All adverse events [6 months] • Office BP [6 months]	Interventional	NR	Renal artery ablation	NR	47	October 2011 – March 2013	Australia, Greece	St. Jude Medical
Recruiting											
Effects of RD on BP and Clinical Course of Obstructive Sleep Apnea in Patients With RH (NCT01366625)	Symplicity® Catheter System™	The purpose of this study is to investigate the clinical utility of RD for the treatment of RH coexisting with obstructive sleep apnea	• BP Reduction [3 months]	Interventional	2	RD + maintenance of anti-hypertensive medications + continuous positive airway pressure therapy	Maintenance of anti-hypertensive medications + continuous positive airway pressure therapy	60	July 2011 – December 2013	Poland	Institute of Cardiology , Warsaw
RD - Hope for Patients With Refractory Hypertension? (NCT01560312)	Symplicity® Catheter System™	Open, multi-center, randomised study is enrolling patients in 3 sites in Czech Republic. Patients with refractory hypertension will be randomized in 1:1 manner either to RD + optimal medical antihypertensive treatment or to antihypertensive treatment alone	• BP difference [6 months, 5 years]	Interventional	3	RD + conventional antihypertensive medical treatment	Conventional antihypertensive medical treatment	150	October 2011 - NR	Czech Republic	Charles University

Study of Efficacy and Safety of Radiofrequency Sympathetic RD for Treatment of Drug RH (NCT01499810)	NR	Single-center, single group study of the efficacy and safety of transcatheter RD for treatment of patients with essential hypertension uncontrolled despite combined pharmacotherapy including 3 or more hypotensive drugs one of which is a diuretic. Bilateral transcatheter RD will be performed on the top of existed pharmacotherapy	• Change in office BP [12 months] • Number of Serious Adverse Events [12 months]	Interven tional	2 3	NR	NR	30	March 2010 – August 2012	Russian Federation	Russian Academy of Medical Sciences
The Evaluation of RD on Several Biological Variables in Patients With Uncontrolled Hypertension. An Observational Feasibility Study (NCT01427049)	Symplicity® Catheter System™	This current study is an observational exploratory study. The main objective of this study is to learn more on the effects of RD. We wish to do that by quantifying the effects of RD on various biological variables. Those variables are studied in four sets of investigations: a radiological set, a laboratorial set, a set of BP measurements and a set of investigations in the vascular laboratory.	• Change in BP related endpoints [0, 6, 12 months]	Observat ional	NR	Groups/Cohorts: intervention assigned - percutaneous selective renal sympathetic denervation		30	August 2011 – August 2013	Netherland s	UMC Utrecht

NR (NCT01418261)	Symplicity® Catheter System™	The Symplicity HTN-3 study is a, multi-center, prospective, single-blind, randomized, controlled study of the safety and effectiveness of RD in subjects with uncontrolled hypertension	• Change in Office SBP [6 months] • Incidence of Major Adverse Events [6 months]	Interventional	3	RD + maintenance on baseline anti-hypertensive medications	Maintenance on baseline anti-hypertensive medications	530	September 2009 – NR	USA	Medtronic Vascular
Denervation of renal sympathetic activity and hypertension study (NCT01522430)	Simplicity (TM) catheter (Ardian/Medtronic)	The DEPART study end points are to provide conclusive evidence, using a randomized, double blinded, sham procedure controlled study design, that radiofrequency RD: reduces daytime ambulatory BP, improves nocturnal dipping in BP at the ambulatory BP recording.	• Glomerular filtration rate [6 months] • Ambulatory systolic and diastolic BP [6 months]	Interventional	3	Renal angiography followed by renal sympathetic denervation	Renal angiography alone	120	January 2012 – December 2016	Belgium	Erasme University Hospital
Treatment of RH Using a Radiofrequency Percutaneous Transluminal Angioplasty Catheter (NCT01541865)	V2 Renal Denervation System	The Study objective is to assess the performance of the Vessix V2 RD System for the treatment of medication RH using an innovative percutaneous RF balloon catheter RD device	• Acute safety of the procedure [24 hours]	Interventional	NR	NR		64	February 2012 – August 2014	Austria	Vessix Vascular, Inc

Influences of Catheter-based RD on Central Sympathetic Nervous System Regulation in Refractory Hypertension (NCT01355055)	NR	Primary hypothesis: Catheter-based RD reduces central sympathetic activation in patients with refractory hypertension. Secondary hypotheses: magnitude of the individual depressor response after catheter-based RD depends on the extent of sympathoinhibition	NR	Observational	NR	NR		26	March 2011 – NR	Germany	Hannover Medical School
RD by ultraSound Transcatheter Emission (NCT01529372)	ReCor Medical PARADISE	The REALISE trial is a single-arm, open-label, prospective, first-in-man study to be conducted on twenty (20) eligible patients with a twelve month follow-up period	• % of successful interventions [24 hours] • % of patients with device - or procedure-related adverse events [12 months]	Interventional	NR	Percutaneous RD	NR	20	January 2012 – July 2013	France	ReCor Medical, Inc.
Global ProSpective RegistrY for SyMPathetic RD In Selected IndiCatIons Through 3-5 Years Registry (NCT01534299)	Medtronic Symplicity™ RD System	The purpose of the registry is to document the long-term safety and effectiveness of RD in a real world patient population with hypertension and gathering data for other diseases characterized by elevated sympathetic drive, such as diabetes mellitus type 2, heart failure, renal insufficiency, etc.	• BP measurements [6 months]	Interventional	4	All patients treated with RD procedure will be enrolled as part of this single arm registry		5000	February 2012 – July 2011	Germany	Medtronic Vascular

Renal Sympathectomy in Treatment Resistant Essential Hypertension, a Sham Controlled Randomized Trial (NCT01459900)	Ardian Medtronic Simplicity catheter	The purpose of this double blind, randomized and sham controlled study is to determine whether RD in terms of catheter based ablation in the renal arteries is effective in lowering BP in patients with treatment RH	• Daytime SBP assessed by 24 hours ambulatory BP measurement [3 months]	Interven tional	NR	Renal artery ablation	Sham (Renal Angiography)	70	September 2011 – May 2013	Denmark	Skejby Hospital
Renal Sympathetic Modification in Patients With Essential Hypertension (NCT01417221)	THERMOCO OL®	The purpose of this study is to observe the incident of composite cardiovascular events after renal sympathetic modification using THERMOCOOL® catheter in patients with essential hypertension, and evaluate safety and efficacy of the intervention	• Composite cardiovascular events [3 years]	Interven tional	1 2	Renal sympathetic modification	Absolute medicine therapy	800	August 2011 – August 2016	China	The Second Affiliated Hospital of Chongqing Medical University
Understanding the Mechanisms of Progressive Decrease in BP After Renal Nerve Ablation (NCT01442883)	Simplicity Catheter system	The objective of the study is to understand the pathogenetic mechanisms of RD beyond the reduced activity of the sympathetic nervous system	• office BP • 24-h ABPM • Magnetic resonance imaging • Albuminuria • local renin angiotesin system (RAS) activity • systemic RAS activity • vascular structure and function of large and small arteries [All: 0, 6 months]	Observat ional	NR	Groups/Cohorts: treatment resistant hypertensives with Chronic Kidney Disease 3-5		100	November 2010 – December 2012	Germany	University of Erlangen-Nürnberg Medical School

Not Yet Recruiting											
RD in Patients With RH (NCT01570777)	Symplicity® Catheter System™	The DENER-HTN study is a, multi-center, prospective, open, randomized, controlled study of the effectiveness and costs of RD in addition to standardized medical treatment compared to medical treatment alone in subjects with RH	• Mean diurnal SBP assessed by ABPM [6 months] • Cost-effectiveness evaluation [1 year]	Interventional	4	RD + optimized medication regimen	Optimized medication regimen	120	April 2012 – July 2014	France	Assistance Publique - Hôpitaux de Paris
Investigator-Steered Project on Intravascular RD for Management of Drug-Resistant Hypertension (NCT01505010)	Symplicity® Catheter System™	INSPiRED is a multicenter parallel-group trial comparing usual medical treatment (control group) or usual medical treatment plus RD (intervention). In both groups adherence will be monitored both before randomization and during 36 months of follow-up	• Decrease in SBP on daytime ambulatory measurement [36 months]	Interventional	2	RD + standard antihypertensive drug treatment	Standard antihypertensive drug treatment	84	February 2012 – February 2015	Belgium, Switzerland	Katholieke Universitei t Leuven
RD in Patients With Uncontrolled Hypertension in Chinese (NCT01390831)	THERMOCOOL® Catheter	The purpose of this study is to determine whether RD is safe and effective in the treatment of Chinese patients with uncontrolled hypertension	• BP Reduction [1 year]	Interventional	1 2	Catheter-based RD + maintenance of anti-hypertensive medications	Maintenance of anti-hypertensive medications	100	November 2011 – June 2015	NR	The Second People's Hospital of Chengdu

Rapid RSD for RH Using the Maya Medical OneShot™ Ablation System	Maya Medical OneShot™ Ablation System	Maya Medical OneShot™ Ablation System use is to deliver low-level radio frequency (RF) energy through the wall of the renal artery to denervate the human kidney	• Acute Procedural Safety [1 Week]	Interventional	2	Rapid RD	NR	40	March 2012 – December 2013	Belgium, Netherlands	Maya Medical

Legend

ABPM: Ambulatory blood pressure measurements
BP: Blood pressure
RD: Renal Denervation
RH: Resistant Hypertension
RSD: Renal Sympathetic Denervation
SBP: Systolic blood pressure

Glossary

ACTIVE, NOT RECRUITING: study is ongoing (i.e., patients are being treated or examined), but enrollment has completed
NOT YET RECRUITING: participants are not yet being recruited or enrolled
RECRUITING: participants are currently being recruited and enrolled

Appendix 8

Data extraction forms fulfilled

Esler, M. D., H. Krum, et al. (2010). "Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial." Lancet 376(9756): 1903-1909.

Background information

Screener Initials	IA & ST
Study ID (first Author)	Esler MD
Published (Y/N)	Y
Year	2010
Period study conducted	between June 9, 2009, and Jan 15, 2010
Country(ies) of study	International, multicentre study: 24 centres in Europe, Australia and New Zealand.
Objective(s)	To assess effectiveness and safety of catheter-based renal denervation for reduction of blood pressure in patients with treatment-resistant hypertension.

Type of the study *(mark one of the following)*

x Randomised Controlled Trial (RCT)
□ Clinical Controlled Trial (CCT)
□ Cohort study
□ Case-control study
□ Cross-sectional study
□ Controlled before-after study

Characteristics of the study – RCT/CCT

Trial registration number: NCT00888433

1. Type of trial	X Two arms ☐ Multiple arms ☐ Superiority ☐ Non-inferiority ☐ Equivalence ☐ Early stopped trial	
2. Participants	Intervention group	Comparison group
(a) Number of participants	52	54
(b) Age[15] mean (SD)	58 (12)	58 (12)
(c) Antihypertensive drugs[1]	5.2 (1.5)	5.3 (1.8)
(d) Systolic/diastolic BP at Baseline[16]	178 (18) / 97 (16)	178 (16) / 98 (17)
3. Comparison	Intervention: X Denervation Type of system: X Symplicity (Medtronic) ☐ Thermocool (J&J) ☐ St Jude ☐ Other, _____	Comparator: ☐ antihypertensive drugs therapy ☐ _____

[15] Please record data as reported in the study (e.g. Mean, mean and [Range], mean ± Standard deviation (SD), etc.).

[16] Mean ± Standard deviation (SD), if reported.

4. Primary outcome: *between-group change in average office-based measurements of systolic blood pressure from baseline to 6 months after randomisation.*	Outcome measure: *Mean difference* in mmHg diastolic and systolic *(continuous outcome)*
5. Secondary outcome:	Outcome measure:
(a) acute procedural safety	proportion of patients having side effect (dichotomous outcome)
(b) chronic procedural safety	proportion of patients with reduction of eGFR >25% or new stenosis >60% confirmed by angiogram at 6 months (dichotomous outcome)
(c) a composite cardiovascular endpoint	proportion of patients myocardial infarction, sudden cardiac death, new-onset heart failure, death from progressive heart failure, stroke, aortic or lower limb revascularisation procedure, lower limb amputation, death from aortic or peripheral arterial disease, dialysis, death because of renal failure, hospital admission for hypertensive emergency unrelated to non-adherence or non-persistence with drugs, and hospital admission for atrial fibrillation (dichotomous outcome)
(d) additional measurements of blood-pressure reduction at 6 months after randomisation consisting of occurrence of 10 mm Hg or more systolic response	proportion of patients who had a reduction in systolic blood pressure of 10 mm Hg or more (dichotomous outcome)
(e) achievement of target systolic blood pressure	Dichotomous outcome (proportion of patients who had reductions in systolic blood pressure of 10 mm Hg or greater more common, as was achievement of a target of less than 140 mm Hg (all p<0.0001).
(f) change in 24-h ambulatory blood pressure	mean decrease in mm Hg (continuous outcome)
(g) change in home-based blood-pressure measurements	absolute difference in mmHg (continuous outcome)

6. Follow up (in months)	6 months	
7. Funding	X For profit agency	Sponsor involved in study design

	☐ Private not for profit ☐ Governmental ☐ Not funded ☐ Not reported	or conduct X Yes ☐ no
8. Authors' Conclusions: Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients.		

Reporting

Flow-chart	☒ Yes	☐ No
Sample size	☒ Yes	☐ No
Post-randomisation exclusion	☒ Yes	☐No
Lost-to-follow up	☒ Yes	☐ No

Methodological Quality

Allocation concealment	☐ Central randomisation (computer, fax, internet) ☐ Sequentially numbered, opaque, sealed envelopes ☐ Coded medication containers ☐ Any other method which appeared random (e.g. coin tossing, etc.) ☐ Unconcealed randomisation ☐ Not reported ☐ Not randomized **X** Unclear [17]		
Blinding of patients	☐ Yes	☒ No	☐ Unclear
Blinding of investigators	☐ Yes	☒ No	☐ Unclear

[17] "*Patients were randomly assigned to intervention group with sealed envelopes at every clinical site*". From the text it was unclear if the envelopments were opaque and numbered, conditions for the allocation concealment to be considered proper.

Blinding of data collectors	☐ Yes	☒ No	☐ Unclear
Blinding of outcome adjudicators	☐ Yes	☒ No	☐ Unclear
Blinding of data analysts	☐ Yes	☒No	☐ Unclear
Intention to treat (ITT) statements			
Intention to treat reporting	☐ ITT ☐ No ITT	☐ mITT[18]	☒ Unclear
ITT reporting	☒ No description reported ☐ Correctly described as ITT	☐ Different ITT description reported:_____	
"no ITT"	☒ Possible description of how analysis are performed: *Data for all patients at randomization minus those lost to follow-up*		

Analysis

Post-randomisation exclusions (PRE)	☒ Yes	☐ No	☐ Unclear
Reasons for PRE	☒ Yes If yes, specify: 3 withdrew consent, 3 missed visit *(see flow-chart for details)*	☐ No	☐ Unclear

Lost-to-follow up (LTFU)

Lost-to-follow up reporting	☒ LTFU occured	☐ LTFU NOT occured	☐ No explicit statement

Notes

Reviewers Conclusions: This a randomised study where the conclusions are clearly on favour to the renal

[18] mITT refers to trials reporting the use of a "modified intention-to-treat" approach.

denervation.
However, the study is subjected to a risk of bias due to:

- unclear allocation concealment and unmasked data analysis;
- data analyses were made by the sponsor.

In addition the sample size was small opening to a type I error.
The device seems to determine a large BP reduction with high standard deviation.

Mahfoud, F., M. Schlaich, et al. (2011). "Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: A pilot study." Circulation 123(18): 1940-1946.

Background information

Screener Initials	IA & ST
Study ID (first Author)	Mahfoud F
Published (Y/N)	Y
Year	2011
Period study conducted	March 2009 - May 2010
Country(ies) of study	
Objective(s)	To investigate the effect of catheter-based renal sympathetic denervation on glucose metabolism and blood pressure control in patients with resistant hypertension.

Type of the study *(mark one of the following)*

□ Randomised Controlled Trial (RCT)
X Clinical Controlled Trial (CCT)
□ Cohort study
□ Case-control study
□ Cross-sectional study
□ Controlled before-after study

Characteristics of the study – RCT/CCT

Trial registration number:

1. Type of trial	X Two arms ☐ Multiple arms X Superiority ☐ Non-inferiority ☐ Equivalence ☐ Early stopped trial	
2. Participants	Intervention group	Comparison group
(a) Number of participants	37	13
(b) Age[19]	58.7 ± 1.6	62.5 ± 2.9
	5.8 ± 0.2	5.0 ± 0.4
(c) Antihypertensive drugs[1]	177 (± 3) / 96 (± 6)	184 (± 6) / 94 (± 4)
(d) Systolic/diastolic BP at Baseline[20]		
3. Comparison	Intervention: X Denervation Type of system: X Symplicity (Medtronic) ☐ Thermocool (J&J) ☐ St Jude ☐ Other, _____	Comparator: X antihypertensive drugs ☐ _____

4. Primary outcome: Change in systolic and diastolic office blood pressures (SEM) at 1 and 3 months compared with baseline.	Outcome measure: mm Hg of blood pressure (continuous data)
5. Secondary outcome:	Outcome measure:
(a) Change in fasting glucose at 3 months	mg/dL of glucose (continuous data)
(b) Change in fasting insulin	mg/dL of glucose (continuous data)

[19] Please record data as reported in the study (e.g. Mean, mean and [Range], mean ± Standard deviation (SD), etc.).

[20] Mean ± Standard deviation (SD), if reported.

(c) Change in C-peptide	0.9 ng/mL of C-petide (continuous data)	
(d) Change in homeostasis model assessment–insulin resistance (HOMA-IR) at 1 and 3 months compared with baseline.	Change in score	
(e) mean 2-hour glucose levels during oral glucose tolerance test	mg/dL of glucose (continuous data)	
6. Follow up (in months)	3 months	
7. Funding	X For profit agency ☐ Private not for profit ☐ Governmental ☐ Not funded ☐ Not reported	Sponsor involved in study design or conduct X yes ☐ no
8. Authors' Conclusions: Renal denervation improves glucose metabolism and insulin sensitivity in addition to a significantly reducing blood pressure. However, this improvement appeared to be unrelated to changes in drug treatment. This novel procedure may therefore provide protection in patients with resistant hypertension and metabolic disorders at high cardiovascular risk.		

Reporting

Flow-chart	☐ Yes	☒ No
Sample size	☒ Yes	☐ No
Post-randomisation exclusion	☐ Yes	☒ No
Lost-to-follow up	☐ Yes	☒ No

Methodological Quality

Allocation concealment	☐ Central randomisation (computer, fax, internet) ☐ Sequentially numbered, opaque, sealed envelopes ☐ Coded medication containers ☐ Any other method which appeared random (e.g. coin tossing, etc.) ☐ Unconcealed randomisation

	☐ Not reported ☒ Not randomized ☐ Unclear		
Blinding of patients	☐ Yes	☒ No	☐ Unclear
Blinding of investigators	☐ Yes	☒ No	☐ Unclear
Blinding of data collectors	☐ Yes	☒ No	☐ Unclear
Blinding of outcome adjudicators	☐ Yes	☒ No	☐ Unclear
Blinding of data analysts	☐ Yes	☒ No	☐ Unclear
Intention to treat (ITT) statements			
Intention to treat reporting	☐ ITT ☒ No ITT	☐ mITT[21]	☐Unclear
ITT reporting	☒ No description reported ☐ Correctly described as ITT	☐ Different ITT description reported:_____	
"no ITT"	☒ Possible description of how analysis are performed: *All the enrolled patients completed the study*		

Analysis

Post-randomisation exclusions (PRE)	☐ Yes	☐ No	☒Unclear
Reasons for PRE	☐ Yes If yes, specify _____	☐ No	☒Unclear

[21] mITT refers to trials reporting the use of a "modified intention-to-treat" approach.

Lost-to-follow up (LTFU)

Lost-to-follow up reporting	☐ LTFU occurred ☐ LTFU NOT occurred ☒ No explicit statement

Notes

Reviewer Conclusions: The conclusions of the study are clearly in favour of the treatment under investigation. However, though it is not clearly reported the study is a controlled clinical trial. Consequently it is not immune from selection, performance and detection bias making the study susceptible to a high risk of bias.

Appendix 9

Methodological Quality and Risk-of-bias assessment

Criteria	Items	Esler MD et al, 2010	Mahfoud F et al, 2011
Methodological Quality	*Allocation concealment*	U	N
	Blinding of patients	N	N
	Blinding of investigators	N	N
	Blinding of data collectors	N	N
	Blinding of outcome adjudicators	N	N
	Blinding of data analysts	N	N
Analysis	*Post-randomisation exclusions (PRE)*	Y	U
	Reasons for PRE	Y	U
Reporting	*Flow-chart*	Y	N
	Sample size	Y	Y
	Post-randomisation exclusion	Y	N
	Lost-to-follow up	Y	NR
Intention to treat (ITT) statements	*Intention to treat reporting*	U	N
	ITT reporting	NR	NR
	"no ITT"	Data for all patients at randomization minus those lost to follow-up	All the enrolled patients completed the study
Risk of Bias		**High**	**High**

Legend
Y: Yes
N: No
NR: Not reported
U: Unclear

Appendix 10

Outcomes Data

Esler, M. D., H. Krum, et al. (2010). "Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial." Lancet 376(9756): 1903-1909.

OUTCOMES

1. All causes mortality

Study ID	Definition[22]	Intervention Group		Control Group		Comments
		N. events	N. patients[23]	N. events	N. patients[23]	
Esler	Deaths	0	49	0	51	6 months follow up

2. Change in average measurements of systolic and/or diastolic blood pressure (BP)

2.a.1 Change in Systolic blood pressure (SBP) - Office-based measurements

Study ID	Intervention Group		Control Group		Comments
	Mean ± SD mm Hg (p value)	N. events/N. patients	Mean ± SD mm Hg (p value)	N. events/N. patients	
Esler	- 32 ± 23 (p<0.0001)	49/49	+1 ± 21 (p=0.77)	51/51	6 month follow up

2.a.2 Change in Systolic blood pressure (SBP) - home-based measurements

Study ID	Intervention Group		Control Group		Comments
	Mean ± SD mm Hg (p value)	N. events/N. patients	Mean ± SD mm Hg (p value)	N. events/N. patients	
Esler	- 20 ± 17 (n.r.)	32/49	+ 2 ± 13 (n.r.)	40/51	6 month follow up

2.a.3 Change in Systolic blood pressure (SBP) - 24-h ambulatory monitoring

Study ID	Intervention Group		Control Group		Comments
	Mean ± SD mm Hg (p value)	N. events/N. patients	Mean ± SD mm Hg (p value)	N. events/N. patients	
Esler	- 11 ± 15 (p=0.006)	20/49	- 3 ± 19 (p=0.014)	25/51	6 month follow up

2.b.1 Change in Diastolic blood pressure (DBP) - Office-based measurements

Study ID	Intervention Group		Control Group		Comments
	Mean ± SD mm Hg (p value)	N. events/N. patients	Mean ± SD mm Hg (p value)	N. events/N. patients	
Esler	- 12 ± 11 (p<0.0001)	49/49	0 ± 10 (p=0.83)	51/51	6 month follow up

[22] In the "Definition" field is reported the specification of the kind of the events (e.g cause of mortality, cardiovascular events, adverse events, etc.).

[23] "Number patients" referred to patients analysed at 6 months (three patients were lost at follow-up in both groups).

2.b.2 Change in Diastolic blood pressure (DBP) - home-based measurements

Study ID	Intervention Group		Control Group		Comments
	Mean ± SD mm Hg (p value)	N. events/N. patients	Mean ± SD mm Hg (p value)	N. events/N. patients	
Esler	- 12 ± 11 (n.r.)	32/49	0 ± 7 (n.r.)	40/51	6 month follow up

2.b.3 Change in Diastolic blood pressure (DBP) - 24-h ambulatory monitoring

Study ID	Intervention Group		Control Group		Comments
	Mean ± SD mm Hg (p value)	N. events/N. patients	Mean ± SD mm Hg (p value)	N. events/N. patients	
Esler	- 7 ± 11 (p=0.51)	20/49	-1 ± 12 (p=0.75)	25/51	6 month follow up

3. Cardiac mortality

Study ID	Definition	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	
Esler	Deaths	0	49	0	51	6 month follow up

4. Major cardiovascular events (myocardial infarction, heart failure, stroke…)

Study ID	Definition	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	
Esler	hospital admissions for hypertensive emergency that were unrelated to non-adherence or non-persistence with drugs	3	49	2	51	6 month follow up

SAFETY

5.1. Adverse Events: Acute procedural safety

Study ID	Definition	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	
Esler	Minor Periprocedural events, specifically:	12	52	0	54	Requiring treatment and possibly related to the procedure
	*Femoral artery pseudoaneurysm**	*1*		*0*		**treated with manual compression*
	*Postprocedural drop in blood pressure***	*1*		*0*		***resulting in a reduction in antihypertensive drugs*
	Urinary tract infection	*1*		*0*		
	Extended hospital admission for assessment of paraesthesias	*1*		*0*		
	*Back pain****	*1*		*0*		****treated with analgesics and resolved after 1 month*
	*Transient intraprocedural bradycardia*****	*7*		*0*		*****requiring atropine; none had any sequelae*
	Serious adverse events, specifically:	5	52	3	54	Requiring hospital admission
	Nausea and oedema+	*1*		*0*		*+Related to underlying hypertension*
	Hypertension crisis++	*1*		*0*		*++After abrupt stopping of clonidine*

	Transient ischaemic attack	*1*		*2*		
	Hypotensive episode[+++]	*1*		*0*		*[+++]Resulting in a reduction of antihypertensive drugs*
	Coronary stent for angina	*1*		*1*		

5.2. Adverse Events: "Chronic procedural safety (kidney failure, renal artery stenosis, etc.)"

Study ID	Definition	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	
Esler	Renal function, specifically:	3	49	3	51	6 month follow up
	Decrease of more than 50% in eGFR	*0*		*0*		
	Decrease of more than 25% in eGFR	*2*		*3*		
	*A possible progression of an underlying atherosclerotic lesion (stenosis)**	*1*		*0*		**No intervention was needed; the stenosis was not at location where radiofrequency was delivered during the procedure*

Legend
n.r.: Not reported

Mahfoud, F., M. Schlaich, et al. (2011). "Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: A pilot study". Circulation 123(18): 1940-1946.

OUTCOMES

1. All causes mortality

Study ID	Definition[24]	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	
Mahfoud	Deaths	0	37	0	13	

2. Change in average measurements of systolic and/or diastolic blood pressure (BP)

2.a Change in Systolic blood pressure (SBP) – Office-based measurements

Study ID	Intervention Group		Control Group		Comments
	Mean ± SD mm Hg (p value)	N. events/N. patients	Mean ± SD mm Hg (p value)	N. events/N. patients	
Mahfoud	- 28 ± 2 mm Hg ($p < 0.001$)	37	- 8 ± 6 mm Hg ($p = 0.192$)	13	1 month after denervation
	- 32 ± 4 mm Hg; ($p < 0.001$)	37	- 5 ± 5 mm Hg; ($p = 0.494$)	13	3 months after denervation

2.b Change in Diastolic blood pressure (DBP) - Office-based measurements

Study ID	Intervention Group		Control Group		Comments
	Mean ± SD mm Hg (p value)	N. events/N. patients	Mean ± SD mm Hg (p value)	N. events/N. patients	
Mahfoud	- 10 ± 2 mm Hg; ($p < 0.001$)	37	- 4 ± 4 mm Hg; ($p = 0.154$)	13	1 month after denervation
	- 12 ± 2 mm Hg; ($p < 0.001$)	37	- 3 ± 3 mm Hg; ($p = 0.277$)	13	3 months after denervation

3. Cardiac mortality

Study ID	Definition	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	
Mahfoud	Cardiac deaths	0	37	0	13	

4. Major cardiovascular events (myocardial infarction, heart failure, stroke…)

Study ID	Definition	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	
Mahfoud	Cardiovascular events	0	37	0	13	

[24] In the "Definition" field is reported the specification of the kind of the events (e.g cause of mortality, cardiovascular events, adverse events, etc.).

SAFETY

5.1. Adverse Events: Acute procedural safety

Study ID	Definition	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	
Mahfoud	Pseudoaneurysm at the femoral access site	1	37	0	13	Treated without further sequelae

5.2. Adverse Events: "Chronic procedural safety (kidney failure, renal artery stenosis, etc)"

Study ID	Definition	Intervention Group		Control Group		Comments
		N. events	N. patients	N. events	N. patients	
Mahfoud	Other adverse events; specifically:	14	37	2	13	3 month follow up
	Post-procedural renovascular abnormalities	*0*	*37*	*0*	*13*	*Renal duplex ultrasound was performed*
	Hypotension associated with symptoms	*13*	*37*	*0*	*13*	*Antihypertensive medication had to be reduced*
	Symptoms or signs considered to be consequences of hypertension	*1*	*37*	*2*	*13*	*Antihypertensive medication had to be further increased*

Appendix 11

List of excluded studies with reasons for exclusion

Not found studies:

Hering D, Esler MD, Krum H et al. Recent advances in the treatment of hypertension. Exp. Rev. Cardiovasc. Ther. 2011; 9(6):729-44.

Not meet study design criterion:

Blankestijn PJ. How renal denervation may be effective for the treatment of resistant hypertension. Cardiovasc. Intervent. Radiol. 2011; 34:432-4.

Schlaich MP, Krum H, Esler MD. New therapeutic approaches to resistant hypertension. Curr. Hypertens. Rep. 2010; 12(4):296-302.

Not meet the population criterion:

Other disease than hypertension:

Kavoussi L, Nielsen M, Solomon S. Percutaneous, image guided urological procedures: Barbarians at the gate. J. Urol. 2005; 174(1):11.

Veale JL. Editorial Comment. J. Urol. 2007; 178(6):2513.

Not resistant hypertension:

Mensah GA, Bakris G. Treatment and Control of High Blood Pressure in Adults. Cardiol. Clin. 2010; 28(4):609-22.

Werko L. High blood pressure - Disease or risk factor? Scand. Cardiovasc. J. 2006; 40(3):131-3.

Appendix 12

Regional Survey: Questionnaire

Please fill this questionnaire and send it to teresa.gasparetto @.regione.veneto.it

1. Place of completion of questionnaire	
2. Date of completion of questionnaire	

1. Is the denervation of renal artery by catheter based radioablation used in your hospital?

– *Current clinical activity* - Clinical practice Yes go to question 2-7 No
– *Research activity* - Clinical trials Yes go to question 8-12 No

2. *Current clinical activity* – what kind of patients undergo catheter based radioablation? Please, report patients clinical characteristics

3. *Current clinical activity* - please describe follow-up activities after radioablation:

- How many specialist visits are performed at 1-year follow-up?

_____

- Are antihypertensive drugs required? If yes, which one do you prescribe? Please report name of drug, dosage and duration of therapy?

_____

- Which clinical exams do you prescribe at 1-year follow-up? (i.e. creatinine, renal functioning ect.)

_____

4. *Current clinical activity* - What is the purchasing price of the catheter ? Please, report price excluding VAT:

_____€

5 *Current clinical activity* - What type of acquisition procedure are used? Please, specify if the catheter is rented, acquired for free, acquisition by tender:

_____

6. *Current clinical activity* – What are the activity volumes of the radioablation in the last 12 months in your institution?

Total number per year_____

7. *Current clinical activity* – What is the total annual expenditure for the catheter based radioablation in the last 12 months in your institution?

Total expenditure per year_____

8. *Research activity* – what are the inclusion criteria of patients undergoing catheter based radioablation according to the approved clinical protocol?

9. *Research activity* – what are the exclusion criteria of patients undergoing catheter based radioablation according to the approved clinical protocol?

10. *Research activity* – study timelines

- What is the study start date?

_____

- How long is the enrolment period?

_____

- What is the follow-up of the study?

_____

11. *Research activity* – which outcomes do you collect in the clinical trials according to the approved protocol?

12. *Research activity* – in your institution, how many patients are estimated to be enrolled in the clinical trial according to the approved protocol?

13. *Centre characteristics* – what are the required characteristics of the centre implementing a catheter based radioablation? (please refer to type operating room, type of healthcare figures involved, structural needs etc)

14. *Procedure characteristics* – what is the average resource consumption for a catheter based radioablation procedure?

- operating room occupation _____ minutes

- healthcare personnel type (please differentiate among clinician, nurse, technician etc and specify number and average working time)
  _____
  _____
  _____
  _____
  _____

  materials required (please specify type and number of durables require during procedure):

  _____
  _____
  _____
  _____
  _____

  drugs used during procedure (please specify name of drug and dosage during procedure):

  _____
  _____
  _____
  _____
  _____

15. *Procedure codes* – Please report:

- what are the diagnosis codes related to the procedure? (please , specify the ICD9-CM version you refer to):
  _____

_____
_____
_____

- what are the procedure codes related to renal ablation? (please , specify the ICD9-CM version you refer to):
  _____
  _____
  _____
  _____
- what are the DRG codes relative to renal ablation? (please , specify the ICD9-CM version you refer to):
  _____
  _____
  _____
  _____

Appendix 13

Regional Survey: Fulfilled Questionnaires

RENAL ARTERY ABLATION SURVEY

Please fill this questionnaire and send it to teresa.gasparetto @.regione.veneto.it

1. Place of completion of questionnaire	Azienda Ospedaliera Integrata di Verona
2. Date of completion of questionnaire	April 11, 2012

1. Is the denervation of renal artery by catheter based radioablation used in your hospital?

– *Current clinical activity* - Clinical practice Yes go to question 2-7 X No

– *Research activity* - Clinical trials Yes go to question 8-12 X No

2. *Current clinical activity* – what kind of patients undergo catheter based radioablation? Please, report patients clinical characteristics

3. *Current clinical activity* - please describe follow-up activities after radioablation:

- How many specialist visits are performed at 1-year follow-up?

_____

- Are antihypertensive drugs required? If yes, which one do you prescribe? Please report name of drug, dosage and duration of therapy?

_____

- Which clinical exams do you prescribe at 1-year follow-up? (i.e. creatinine, renal functioning ect.)

_____

4. *Current clinical activity* - What is the purchasing price of the catheter ? Please, report price excluding VAT:

_____€

5 *Current clinical activity* - What type of acquisition procedure are used? Please, specify if the catheter is rented, acquired for free, acquisition by tender:

_____

6. *Current clinical activity* – What are the activity volumes of the radioablation in the last 12 months in your institution?

Total number per year_____

7 *Current clinical activity* – What is the total annual expenditure for the catheter based radioablation in the last 12 months in your institution?

Total expenditure per year_____

8. *Research activity* – what are the inclusion criteria of patients undergoing catheter based radioablation according to the approved clinical protocol?

9. *Research activity* – what are the exclusion criteria of patients undergoing catheter based radioablation according to the approved clinical protocol?

10. *Research activity* – study timelines

- What is the study start date?

_____

- How long is the enrolment period?

_____

- What is the follow-up of the study?

_____

11. *Research activity* – which outcomes do you collect in the clinical trials according to the approved protocol?

12. *Research activity* – in your institution, how many patients are estimated to be enrolled in the clinical trial according
to the approved protocol?

13. *Centre characteristics* – what are the required characteristics of the centre implementing a catheter based radioablation? (please refer to type operating room, type of healthcare figures involved, structural needs etc)

Angiographic suite with solid state fluoroscopic imager for high-resolution angiography.

On site Vascular surgery

14. *Procedure characteristics* – what is the average resource consumption for a catheter based radioablation procedure?

- operating room occupation _____ minutes
- healthcare personnel type (please differentiate among clinician, nurse, technician etc and specify number and
- average working time)

  _____
  _____
  _____
  _____
- materials required (please specify type and number of durables require during procedure):_____
  _____
  _____
  _____
- drugs used during procedure (please specify name of drug and dosage during procedure):_____
  _____
  _____
  _____

15. *Procedure codes*– Please report:

- what are the diagnosis codes related to the procedure? (please , specify the ICD9-CM version you refer to):
  _____
  _____
  _____
  _____
- what are the procedure codes related to renal ablation? (please , specify the ICD9-CM version you refer to):
  _____
  _____
  _____
  _____
- what are the DRG codes relative to renal ablation? (please , specify the ICD9-CM version you refer to):
  _____
  _____
  _____
  _____

RENAL ARTERY ABLATION SURVEY

Please fill this questionnaire and send it to teresa.gasparetto @.regione.veneto.it

1. Place of completion of questionnaire	Clinica Medica 4, Dipartimento di Medicina PADUA UNIVERSITY
2. Date of completion of questionnaire	April 11, 2012

1. Is the denervation of renal artery by catheter based radioablation used in your hospital?

– *Current clinical activity* - Clinical practice ☒ Yes go to question 2-7 No
– *Research activity* - Clinical trials ☒ Yes go to question 8-12 No

2. *Current clinical activity* – what kind of patients undergo catheter based radioablation? Please, report patients clinical characteristics

PATIENTS WITH RESISTANT HYPERTENSION ACCORDING TO 2007 ESH/ESC GUIDELINES

3. *Current clinical activity* - please describe follow-up activities after radioablation:

- How many specialist visits are performed at 1-year follow-up?

3 PATIENTS.

- Are antihypertensive drugs required? If yes, which one do you prescribe? Please report name of drug, dosage and duration of therapy?

YES, SAME AS BEFORE THE DENERVATION PROCEDURE.

- Which clinical exams do you prescribe at 1-year follow-up? (i.e. creatinine, renal functioning ect.)

CREATININE, SERUM POTASSIUM, SODIUM; RENAL ARTERY DUPLEXULTRASOUND, 24 HOURS AMBULATORY BLOOD PRESSURE MEASUREMENT (ABPM).

4. *Current clinical activity* - What is the purchasing price of the catheter ? Please, report price excluding VAT:

UP TP NOW THEY HAVE BEEN PROVIDED FOR FREE BY MEDTRONIC.

5 *Current clinical activity* - What type of acquisition procedure are used? Please, specify if the catheter is rented, acquired for free, acquisition by tender:

THE DEVICE WAS BORROWED. THE CATHETERS WERE GIVEN FOR FREE FOR COMPASSIONATE USE.

6. *Current clinical activity* – What are the activity volumes of the radioablation in the last 12 months in your institution?

Total number per year__3___

7. *Current clinical activity* – What is the total annual expenditure for the catheter based radioablation in the last 12 months in your institution?

Total expenditure per year _____UNKNOWN_____

8. *Research activity* – what are the inclusion criteria of patients undergoing catheter based radioablation according to the approved clinical protocol?

WE WILL PARTICIPATE TO THE GLOBAL SYMPLICITY REGISTRY.

MOREOVER, WE HAVE PLANNED A TRIAL WHICH WILL ENROLL PATIENTS WITH:

- RESISTANT HYPERTENSION DIAGNOSIS;
- DAYTIME SYSTOLIC BLOOD PRESSURE (SBP) ≥ 135 mmHg AND DIASTOLIC BLOOD PRESSURE (DBP) ≥ 85 mmHg, OR NIGHTTIME SBP ≥ 120 mmHg OR DBP ≥ 70 mmHg.

9. *Research activity* – what are the exclusion criteria of patients undergoing catheter based radioablation according to the approved clinical protocol?

- INELEGIBLE RENAL ARTERY ANATOMY;
- CALCULATED GFR ≤ 35 ML/MIN/1.73 M^2 (MDRD FORMULA);
- CURRENT OR PLANNED PREGNANCY;
- UNSTABLE CLINICAL CONDITIONS.

10. *Research activity* – study timelines

- What is the study start date?

PENDING APPROVAL FROM THE ETHICS COMMITTEE (SUBMISSION PLANNED)

- How long is the enrolment period?

24 MONTHS

- What is the follow-up of the study?

24 MONTHS

11. *Research activity* – which outcomes do you collect in the clinical trials according to the approved protocol?

PARTICIPATION TO THE GLOBAL SYMPLICITY REGISTRY (OBSERVATIONAL STUDY).

ONSITE TRIAL:

- REDUCTION OF SBP OR DBP AT 6 MONTHS (ABPM) AFTER DENERVATION;
- - PERCENTAGE OF PATIENTS ACHIEVING TARGET SBP OR DBP 6 MONTHS AFTER DENERVATION.

12. *Research activity* – in your institution, how many patients are estimated to be enrolled in the clinical trial according to the approved protocol?

50 PATIENTS

13. *Centre characteristics* – what are the required characteristics of the centre implementing a catheter based radioablation? (please refer to type operating room, type of healthcare figures involved, structural needs etc)

– HAEMODYNAMIC LAB – EXPERIENCED INTERVENTIONAL RADIOLOGISTS/CARDIOLOGISTS – TRAINED TECHNICIANS ND NURSES

14. *Procedure characteristics* – what is the average resource consumption for a catheter based radioablation procedure?

- operating room occupation _____40_____ minutes
- healthcare personnel type (please differentiate among clinician, nurse, technician etc and specify number and average working time):

  - 2 INTERVENTIONAL CARDIOLOGISTS/RADIOLOGISTS, 40 MINUTES;

  - 2 NURSES, 120 MINUTES;

  - 1 TECHNICIAN, 40 MINUTES.
- materials required (please specify type and number of durables require during procedure):
- drugs used during procedure (please specify name of drug and dosage during procedure):

  DRUGS FOR NEUROLEPTOANALGESIA:

  - MORPHINE SULPHATE (6 – 12 MG).

15. *Procedure codes* – Please report:

- what are the diagnosis codes related to the procedure? (please , specify the ICD9-CM version you refer to): NOT APPLICABLE
- what are the procedure codes related to renal ablation? (please , specify the ICD9-CM version you refer to): NOT APPLICABLE
- what are the DRG codes relative to renal ablation? (please , specify the ICD9-CM version you refer to): NOT APPLICABLE

Glossary

Case-control study

Observational study in which groups from the same population with (cases) and without (controls) a specific outcome of interest, are compared to evaluate the association between exposure to an intervention and the outcome.

Catheter arteriography

Catheter arteriography radiography of vessels after introduction of contrast material through a catheter inserted into an artery

CINAHL

The Cumulative Index to Nursing and Allied Health Literature, is the most comprehensive resource for nursing and allied health literature. While starting out as a single bibliographic database, CINAHL has expanded to offer four databases including two full-text versions. CINAHL is owned and operated by EBSCO Publishing, with the Cinahl editorial team continuing to work out of the offices in Glendale, California. The CINAHL databases are available on EBSCOhost®, one of the most-used research platforms available.

Cochrane Library (CLIB)

The Cochrane Library is a collection of databases, published on disk, CD-ROM and internet by the Cochrane Collaboration. It is published quarterly and includes: regularly updated reviews of the efficacy of health assistance; structured evaluations and abstracts of systematic reviews published in the principal journals; bibliographic information about over 446,000 controlled clinical studies; a manual, a glossary and other references on the methodology of systematic reviews; information about Collaborative Review Groups and other Cochrane Collaboration bodies; references to Internet for further information about the efficacy of health interventions.

Cohort study

Observational study in which a defined group of participants is followed over time and comparison is made between those who did and did not receive an intervention.

Controlled Before-and-after study

Comparison of outcomes in study participants before and after the introduction of an intervention. The before-and-after comparisons may be in the same sample of participants or in different samples.

CRD York

This is a department at the University of York which handles the management of the following databases: DARE (Database of Abstracts of Reviews of Effects) which contains the abstracts of systematic reviews further to the works and protocols of Cochrane reviews and protocols; NHS EED (NHS Economic Evaluation Database) which contains the abstracts of economic assessment studies; and the Health Technology Assessment (HTA) Database which contains the details of all the HTA assessments completed or in course at the international level.

EMBASE

The bibliographic database specialised in medical literature with particular attention to the pharmacology and toxicology sector. It is produced by Elsevier Science and contains more European literature with respect to Medline.

Guidelines

Clinical guidelines are recommendations on the appropriate treatment and care of people with specific diseases and conditions based on the best available evidence. Guidelines help healthcare professionals in their work, but they do not replace their knowledge and skills.

MedLine

The electronic database produced by the National Library of Medicine (USA). It covers the international biomedical literature from 1966 to date in the medicine, nursing, dentistry, veterinary medicine, health organisation sectors. Since June 1997 MEDLINE can be consulted free on the Web via the PubMed service, with daily updates of the data.

Radiofrequency ablation (radiofrequency catheter ablation)

Destruction of an accessory conduction pathway or other troublesome area by means of unmodulated high frequency alternating current delivered by a bipolar or unipolar catheter. The current causes heat with tissue destruction and formation of scar tissue to block the pathway. Transvenous radiofrequency ablation is an attractive option to surgery, and it is called also catheter ablation.

Randomized Controlled trial (RCT)

Clinical trial which randomizes eligible participants to two or more groups, treats according to assignment, and compares the groups with respect to outcomes of interest. Participants are allocated to groups using both randomisation (allocation involves the play of chance) and concealment (ensures that the intervention that will be allocated cannot be known in advance).

X-ray fluoroscopy

An x-ray imaging technique used to the visual examination of a part of the body or the function of an organ. The technique offers continuous imaging of the motion of internal structures and immediate serial images. It is invaluable in many clinical procedures, such as intrauterine fetal transfusion and cardiac catheterization.

Web of science

Web of Science is an electronic bibliographic database, searching over 12,000 journals and 120,000 conference proceedings across the sciences, social sciences, and arts and humanities to find the high quality research most relevant to your area of interest.