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Medical devices for treatment-resistant hypertension

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Authors declare that they will not receive benefits or harms from the publication of this report. 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.

Mannone Tommaso declares that in the last three years he collaborated with Dephaforum s.r.l. and he received congressional reimbursement from Novartis, MSD and Pfizer.

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Abstract

Background: Treatment-resistant hypertension is a prevalent and life-threatening condition. At present, renal denervation is the most used non-pharmaceutical therapeutic approach. Optimal medical therapy (OMT) is the current standard.

Aim: To assess the potential benefits and risk of renal denervation for treatment-resistant hypertension in addition to OMT compared with OMT alone.

Methods: We ran searches of the national hospital discharge database to describe the level of use of renal denervation in Italy. We performed systematic review of evidence on effectiveness, safety, and economic impact of renal denervation.

Results: During 2010–2014, the total number of percutaneous renal denervation procedures per year ranged between 25 and 166. Five manufacturers are present on the Italian market. Available systems received the CE mark between 2011 and 2014 but none have received FDA approval. We included ten studies of six trials in the review and carried out a meta-analysis. We found no evidence of dominance or increased harms compared to OMT. One small trial reported dominance of carefully adjusted and supervised OMT. We included four economic evaluations – based on short-term clinical data – which reported dominance of renal denervation. Three were based on the same Markov model with assumptions of dominance of the procedure compared to OMT. We estimated average prospective cost of the procedure as € 6,129.90 (range € 3,821.15 – € 9,714.23).

Conclusions: Randomised controlled trial evidence shows no benefits of the procedure, but follow-up was limited to 6 months. This finding remains unexplained. Economic evaluations are unreliable as they are based on costs derived from publications, unrealistic assumptions of effectiveness, and contrived therapy regimes. Further investment in renal denervation should await the results of well-designed and adequately followed-up trials assessing the impact of renal denervation on major cardiovascular events compared to OMT. Good quality economic evaluations should be based on realistic assumptions.

Sintesi in italiano

Introduzione

Il presente report di HTA tratta le terapie non farmacologiche per il trattamento dell'ipertensione resistente. Le più recenti linee guida della Società Europea di Cardiologia (2013) individuano due approcci terapeutici non farmacologici per il trattamento dell'ipertensione resistente: la terapia di stimolazione dei barocettori carotidei e la denervazione transcatetere dell'arteria renale. Il comparatore selezionato per la presente valutazione è la terapia medica ottimale (TMO), approccio che comprende modifiche dello stile di vita (esercizio fisico, dieta, astinenza dal fumo) combinate a terapia farmacologica (almeno tre farmaci antipertensivi, uno dei quali è un diuretico, secondo la miglior dose tollerata).

La presente valutazione si concentra sui sistemi di denervazione renale transcatetere poiché la valutazione della terapia di stimolazione dei barocettori carotidei è stata effettuata nel 2015 dall'Agenzia Sanitaria e Sociale Regionale (ASSR) della Regione Emilia-Romagna (partner RIHTA, rete italiana per l'HTA). Il rapporto ASSR aveva concluso che *"la qualità e la quantità delle prove attualmente disponibili non è considerata sufficiente per stabilire efficacia e sicurezza del dispositivo. I principali elementi di incertezza non saranno chiariti dagli studi attualmente in corso in quanto finalizzati alla valutazione di esiti surrogati su periodi di osservazione brevi".* Il presente report di HTA presenta solo un aggiornamento dell'evidenza sulla terapia di stimolazione dei barocettori carotidei.

Obiettivi

Il report di HTA è stato sviluppato al fine di rispondere al seguente quesito di ricerca: *"Quali sono gli effetti dell'aggiunta della denervazione renale transcatetere alla TMO in pazienti con ipertensione resistente?"*

Metodi

Il presente report di HTA è stato costruito utilizzando un adattamento della versione 2.0 dell'applicazione *"Medical and surgical procedures"* del Core Model® di EUnetHTA. Le specifiche aree di indagine, denominate domìni e suddivise in quesiti denominati *Assessment Elements (AE)*, sono presentate sequenzialmente nei diversi capitoli del documento.

Sono stati sviluppati i seguenti domìni:

- Problema sanitario e uso corrente della tecnologia (CUR)

- Descrizione e caratteristiche della tecnologia (TEC)
- Aspetti regolatori (REG)
- Efficacia clinica (EFF) e Sicurezza (SAF);
- Costi e valutazione economica (ECO).

I relativi AE sono stati sviluppati, secondo pertinenza, effettuando ricerche su banche dati nazionali, indagini dirette presso i produttori della tecnologia in esame e loro siti web, revisione sistematica della letteratura clinica ed economica.

Risultati

Problema sanitario e uso corrente della tecnologia (CUR)

La prevalenza dell'ipertensione resistente ha stime che vanno dal 5% al 30% della popolazione totale di ipertesi (30-45% della popolazione generale). In Italia, nel periodo 2010–2014, il numero totale di procedure di denervazione renale per anno ha avuto valori compresi tra 25 (nel 2010) e 166 (nel 2013). L'età media dei 420 pazienti trattati era 61,35 anni e il 61,2% erano maschi. La diagnosi principale più frequentemente associata alla procedura di denervazione renale era ipertensione essenziale (65% dei casi).

L'analisi del database NSIS Flusso Consumi, diventato obbligatorio per le Regioni solo nel 2013, ha mostrato una probabile sottostima in termini di unità acquistate (cateteri per la denervazione renale) con costi unitari da € 3.224 a € 7.930.

Descrizione e caratteristiche della tecnologia (TEC)

La denervazione dell'arteria renale transcatetere consiste nella distruzione bilaterale delle fibre nervose che viaggiano lungo la parete dell'arteria renale a causa dell'aumento localizzato della temperatura provocato attraverso specifici cateteri per ablazione a radiofrequenza o ad ultrasuoni. La procedura è in genere eseguita in anestesia locale o sedazione cosciente, sotto guida fluoroscopica, all'interno di un laboratorio di cateterizzazione, da professionisti esperti in procedure endovascolari (cardiologi e/o radiologi interventisti). L'accesso percutaneo può essere eseguito attraverso l'arteria femorale o radiale. La procedura ha tempi caratteristici che dipendono dal sistema di ablazione utilizzato. Medtronic è il produttore che nel 2009 ha aperto la strada alla metodica con il sistema Symplicity. Ad oggi, cinque produttori sono presenti sul mercato italiano: Boston Scientific, Medtronic, ReCor Medical, St. Jude Medical e Terumo. Quattro sistemi di denervazione renale sono a radiofrequenza mentre solo uno è ad ultrasuoni. Le maggiori differenze tra i sistemi sono da ricercarsi nella conformazione del catetere (a cestello non occlusivo, a punta flessibile, a stent elicoidale, con elettrodi su palloncino).

Aspetti regolatori (REG)

I sistemi di denervazione renale transcatetere disponibili sul mercato italiano hanno ricevuto il marchio CE tra il 2011 e il 2014. Nessun sistema ha ancora ricevuto l'approvazione della FDA americana. In Italia non esiste un rimborso specifico per la procedura di denervazione renale transcatetere che viene quindi rimborsata utilizzando il codice DRG 120 - *"Altri interventi sull'apparato circolatorio"* associato ad una tariffa massima nazionale di € 6.876.

Efficacia clinica (EFF) e Sicurezza (SAF)

Terapia di stimolazione dei barocettori carotidei

Nessuno dei tre studi identificati come in corso nel 2015 all'interno del report di valutazione pubblicato da ASSR – Emilia-Romagna è stato completato o aveva pubblicato risultati preliminari. Due studi (NCT01471834 e NCT01679132) risultavano ancora in corso con completamento atteso entro Luglio 2016 e Settembre 2017. Lo studio ESTIM-rHTN (NCT02364310) risultava ancora in fase di reclutamento con completamento previsto a Novembre 2018. Un nuovo studio in corso è stato identificato: lo studio Nordic BAT (NCT02572024). Trattasi di uno studio randomizzato in doppio cieco finalizzato a studiare l'effetto della terapia di stimolazione dei barocettori carotidei rispetto alla terapia farmacologica in 100 soggetti. Tale studio sarà completato entro Novembre 2020.

Denervazione renale transcatetere

In totale sono state analizzate 10 pubblicazioni, riconducibili a 7 studi clinici, 6 dei quali randomizzati (887 pazienti in totale). Sono stati considerati i seguenti esiti: variazioni dei valori pressori sistolici e diastolici, mortalità (tutte le cause), mortalità cardiaca, eventi cardiovascolari maggiori (infarto del miocardio, collasso cardiaco, ictus). Nonostante l'entusiasmo iniziale legato ai risultati dei primi studi, l'analisi degli studi più recenti non ha mostrato alcuna riduzione significativa della pressione arteriosa, sistolica o diastolica, misurata ambulatorialmente (ambulatory setting) a 6 mesi di follow-up. Solo due studi hanno mostrato una riduzione dei valori di pressione diastolica alle misurazioni domiciliari durante 6 mesi di follow-up. Gli studi sono inoltre risultati affetti da notevole eterogeneità legata alle definizioni di ipertensione resistente, alle tecniche per la misura della pressione e ai livelli di aderenza alla terapia farmacologica da parte dei pazienti. Il periodo di follow-up degli studi non è stato considerato sufficientemente lungo per trarre conclusioni robuste sulla mortalità e sull'insorgenza di eventi cardiovascolari.

Costi e valutazione economica (ECO)

Quattro studi sono stati inclusi nella revisione sistematica della letteratura economica. Tutti gli studi erano delle analisi di costo-utilità e tre di essi hanno sviluppato anche un'analisi di costo-efficacia. La qualità generale degli studi è stata giudicata medio-alta. Nonostante sia risultata associata a maggiori costi, la procedura di denervazione renale transcatetere è apparsa più costo-efficace del trattamento standard grazie alle assunzioni di maggiore efficacia adottate nei modelli economici degli studi. L'analisi dei costi per il contesto italiano ha mostrato valori compatibili con quelli riportati nella letteratura internazionale. Il costo dei dispositivi per la denervazione renale sembra avere la maggiore incidenza sul costo totale della procedura, stimato nel range € 3,821 – € 9,709.

Conclusioni

In merito alla terapia di stimolazione dei recettori carotidei, restano invariate le conclusioni tratte nel 2015 dalla ASSR – Regione Emilia-Romagna.

Per quanto riguarda la denervazione renale transcatetere, una spiegazione per l'apparente mancanza di effetto nella riduzione dei valori pressori in soggetti ipertesi potrebbe ricercarsi proprio nelle caratteristiche anatomiche delle arterie renali della popolazione oggetto di studio, danneggiate dalla condizione stessa e nelle quali i meccanismi di regolazione pressoria potrebbero essere compromessi.

Diversi studi sono attualmente in corso per chiarire l'utilizzo della procedura di denervazione renale transcatetere. Tuttavia, la maggior parte di essi, non utilizza come comparatore lo standard di cura (TMO) bensì procedure simulate (*sham procedure*). Particolarmente attesi saranno i risultati dagli studi NCT01570777 (chiusura prevista entro il 2018) e NCT01888315 (chiusura prevista entro il 2021) finalizzati ad un confronto diretto della procedura di denervazione con la TMO.

Raccomandazioni

Si raccomanda di attendere i risultati degli studi clinici in corso prima di utilizzare o investire ulteriormente sulla denervazione renale transcatetere. I futuri studi economici sull'impatto della denervazione renale transcatetere dovrebbero essere basati su assunzioni di efficacia realistiche, supportate da dati provenienti da studi clinici di buona qualità.

Introduction

This document was developed following the EUnetHTA Core Model® application for "Medical and surgical procedures" version 2.0. The Core Model is divided into domains representing each a specific area of technology impact to be assessed. Each domain contains a series of research questions or Assessment Elements (AEs) identified by a capital letter and number (e.g., A0001). To test the Core Model applicability, an adapted model was elaborated by Agenas (see Appendix 1 for a full description). The use of the Core Model is mirrored in the structure of this report, where each chapter corresponds to a domain and reports the AEs considered for the assessment.

Treatment-resistant hypertension is the condition of interest in the present assessment. According to the latest ESH-ESC guidelines (2013), two non-drug therapeutic approaches are available for treatment-resistant hypertension: carotid baroreceptor stimulation therapy and renal artery denervation. Optimal medical therapy (OMT), defined as lifestyle modifications (such as exercise, diet and smoking abstinence) together with drug treatment (with at least three antihypertensive agents, one of which is a diuretic, at best tolerated doses) is the comparator selected for the present assessment.

The assessment focuses on renal denervation systems, as the assessment of carotid baroreceptor stimulation therapy has been carried out in 2015 by the Agenzia Sanitaria e Sociale Regionale (ASSR) of Regione Emilia-Romagna (partner of RIHTA, the Italian Regional HTA network). The ASSR report concluded that *"quality and quantity of presently available evidence is not considered sufficient to yet claim efficacy and safety of the device. Main uncertainties will not be resolved by results from presently ongoing studies, assessing only surrogate outcomes over a short period of time."*[1].

An evidence status update on carotid baroreceptor stimulation therapy was performed during the preliminary phases of the present assessment. None of the three studies identified as ongoing in 2015 by the ASSR – Emilia-Romagna report[1] were completed or had published preliminary results at the time of writing (June 2016). Two studies (NCT01471834 and NCT01679132) were still ongoing but not recruiting participants, and will complete in July 2016 and September 2017, respectively. The ESTIM-rHTN study (NCT02364310) is still recruiting and should be completed in November 2018. A new ongoing study was identified: the Nordic BAT study (NCT02572024), a randomised, double-blind, parallel-design clinical trial of 100 subjects, that examines the effect of baroreceptor stimulation therapy compared to continuous pharmacotherapy on blood pressure, as well as arterial and cardiac function and structure. The Nordic BAT study will be completed in

November 2020. No changes to the conclusions of the report on carotid baroreceptor stimulation therapy published by ASSR – Emilia-Romagna[1] can be made.

1. Report's objectives: policy and research questions

A HTA report was developed to answer the following:

Policy Question: What is the impact of the introduction and use of renal denervation systems in the management of subjects with treatment-resistant hypertension?

Research Question: What are the effects of adding renal denervation to OMT?

The following domains were developed within the present rapid HTA report:

- Health problem and current use of technology (CUR)
- Description and technical characteristics of technology (TEC)
- Regulatory aspects (REG)
- Clinical effectiveness (EFF) and Safety (SAF);
- Costs and economic evaluation (ECO).

For each investigated domain, the selected Assessment Elements (AEs) are listed in Appendix 2.

2. Health problem and current use of technology

Methods

The AEs of this domain were:

Assessment Element ID	Research question
A0001	A0001a: For which health condition is the technology proposed? A0001b: Which group of patients represents the target population for the technology? A0001c: For what purposes is the technology used?
A0002	What is the health condition in the scope of this assessment?
A0006	What are the statistics of incidence, prevalence, morbidity, and mortality of the health condition?
A0024	How is the health condition identified/diagnosed?
A0003	What are the known risk factors for the health condition?
A0004	What is the natural course of the health condition?
A0005	What are the symptoms for the patient at different stages of the health condition?
G0009	G0009a: Who decides which people are eligible for the technology? G0009b: On what basis is the eligibility for the technology decided?
A0018	What are the alternatives to the current management of the health condition?
A0011	What is the diffusion of the technology across the Italian regions?
B0001b	What is the comparator?
B0004b	Who performs or administers the comparator?
B0005b	In what context and level of care is the comparator used?

All the AEs selected within the domain were developed. The health condition of interest (treatment-resistant hypertension) was described using international and national literature. Specific searches were performed to identify the latest reviews and epidemiological studies. European and Italian guidelines were searched to define diagnosis and management of the condition.

The level of use of renal denervation in Italy was described by using information contained in the New Health Information System (NSIS) as the official source of the Ministry of Health that contains data validated and standardised for all the national territory. We selected hospital discharges "SDO" Database to analyse the level of use of the renal denervation procedures in Italy. The source of data for this study was database from 2010 to 2014 (SDO 2010-2014). There are no specific procedure codes for percutaneous renal denervation procedure. So, this procedure may be identified by no specific ICD-9-CM code 05.25 – *Periarterial sympathectomy*. We searched records discharges showing this code corresponding to principal or other procedures. Descriptive analyses were done on national and regional estimates on numbers of procedures performed. Hospital

discharge characteristics were estimated and tabulated. Data management and analyses were done using SAS Studio v.3 for servers (SAS Institute Inc, Cary, NC).

The volume of renal denervation systems purchased was presented by searching the national database "NSIS – Flusso Consumi", aimed to register all the medical devices acquisition events performed by public healthcare providers. Searches were performed from 2012, year in which the database was launched (as a pilot project), and 2015, latest year available. The analysis was limited to the number of renal denervation catheters purchased per year, at national level, and the average minimum and maximum acquisition price per single catheter registered during 2015.

Results

Percutaneous renal artery denervation is offered to patients with treatment-resistant hypertension with the aim of lowering blood pressure values by the interruption of the neurogenic reflexes involved in blood pressure control **(A0001)**.

Description of treatment-resistant hypertension

Hypertension, or high blood pressure, caused by the force that blood is exerting on the walls of the arteries is higher than desirable. According to the guidelines from the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC), hypertension is defined as values >140 mmHg of systolic blood pressure (SBP) and/or >90 mmHg of diastolic blood pressure (DBP)[2]. The same classification, first recommended in 2003, remained unchanged until now and is used in young, middle-aged and elderly subjects, whereas different criteria are adopted in children and teenagers.

Hypertension is universally considered the major cardiovascular risk factor due to its high prevalence in the general population and impact on cardiovascular mortality and morbidity[3]. Correlations between high blood pressure values and cardiovascular events such as stroke, myocardial infarction, sudden death, heart failure and peripheral artery disease, and end-stage renal disease, have been addressed in a large number of observational studies[4]. Hypertension is very often concomitant to additional cardiovascular risk factors, such as smoking, dyslipidaemia (high values of cholesterol and triglycerides), and obesity.

Hypertension can be managed with lifestyle modifications (such as exercise, diet and smoking abstinence) and antihypertensive drug treatment. However, in some patients, these approaches do not achieve the desired reduction. Treatment-resistant hypertension is defined as high blood pressure that remains above the goal of 140/90 mmHg despite the adoption of lifestyle changes

and a treatment with at least three antihypertensive agents (one of which is a diuretic) at best tolerated doses[2].

Treatment-resistant hypertension is the condition of interest in the present assessment **(A0002)**. Causes of treatment-resistant hypertension may be lifestyle factors (e.g., obesity or large weight gains), excessive alcohol consumption and high sodium intake, chronic intake of vasopressor or sodium-retaining substances, obstructive sleep apnoea, undetected secondary forms of hypertension and advanced and irreversible organ damage (particularly when it involves renal function or leads to a marked increase in arteriolar wall-lumen ratio or reduction of large artery distensibility)[2] **(A0003)**.

Epidemiology of treatment-resistant hypertension

Depending on the population examined and the level of medical screening, the prevalence of treatment-resistant hypertension ranges from 5 to 30% of the overall hypertensive population, with figures less than 10% probably representing the true prevalence[2] **(A0006)**. Overall, the prevalence of hypertension appears to be around 30–45% of the general population, with a steep increase with ageing[2]. 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[5] **(A0006)**.

Diagnosis of treatment-resistant hypertension

Usually patients do not experience symptoms that are associated with hypertension or treatment-resistant hypertension[6] **(A0005)**. Since treatment-resistant hypertension has multifactorial origin, its evaluation should verify the diagnosis of hypertension, excluding pseudo-resistant patients (e.g., white-coat hypertension), uncover any causes of secondary hypertension and clarify the cardiovascular risk, organ damage and related clinical conditions. A medical history should be included in the clinical evaluation, as should a family history with regard to hypertension, a physical examination, laboratory investigations and further diagnostic tests. Ambulatory blood pressure should be monitored regularly, not only to exclude spurious resistance but also to quantify the blood pressure elevation and the subsequent effect of the treatment modifications[2]. The evaluation of patients with treatment-resistant hypertension should be directed toward confirming actual treatment resistance[6] **(A0024)**.

Clinical course and prognosis of treatment-resistant hypertension

The natural course of treatment-resistant hypertension has been inadequately appraised. In general, if left untreated, hypertension will increase the risk of cardiovascular diseases, stroke, and renal failure in a population of subjects that frequently presents other cardiovascular risk factors, such as diabetes, obstructive sleep apnoea and left ventricular hypertrophy[7] **(A0004)**.

Management of treatment-resistant hypertension

Hypertension is usually diagnosed and managed in primary care **(B0005b)**. The ESH-ESC guidelines suggest that, for an effective management, a multidisciplinary approach is required: the general practitioner should take care of the majority of patients, involving other specialists (internists, cardiologists, nephrologists, endocrinologists and dieticians) when needed[2] **(B0004b)**.

Most resistant hypertensive patients require the administration of more than three drugs. It is recommended that physicians check whether the drugs included in the existing multiple drugs regimen have any blood pressure lowering effect, and withdraw them if their effect is absent or minimal[2]. Subgroup analyses of large-scale studies showed that all drug classes with mechanisms of action partially or totally different from those of the existing three drug regimens can lower blood pressure in some resistant hypertensive individuals[8]. Such approach is known as optimal medical therapy (OMT) and represents the standard of care for patients with treatment-resistant hypertension **(B0001b)**.

Two non-drug therapeutic approaches to treatment-resistant hypertension are mentioned within the latest ESH-ESC guidelines: carotid baroreceptor stimulation therapy and renal artery denervation (class of recommendation IIb, level of recommendation C)[2] **(A0018)**. Carotid baroreceptor stimulation therapy is administered by an implantable device that electrically activates the carotid baroreflex, which controls blood pressure by regulating nervous activity. Renal artery denervation consists of bilateral destruction of the renal nerves travelling along the renal artery and linked to blood pressure control, by ablation catheters of various design, inserted percutaneously through the femoral or radial artery.

According to the ESH-ESC guidelines, these approaches should be offered by experienced operators within hypertension centres and need to be considered only for resistant hypertensive patients, with clinic values ≥160 mmHg of SBP or ≥110 mmHg DBP and with blood pressure elevation confirmed by ambulatory blood pressure monitoring (class of recommendation I, level of recommendation C) **(G0009)**[2].

Current use of renal denervation in Italy

Percutaneous renal denervation hospital discharges

In the five years between 2010 and 2014, exploration showed that 420 Italian hospital discharges matched the procedure code (ICD-9CM 05.25). The annual number of estimated cases of percutaneous renal denervation was relatively small. Table 1 shows the trend of procedures carried out in Italy from 2010 to 2014: data show an increasing trend until 2013, when 166 procedures were carried out country-wide, the highest figure so far.

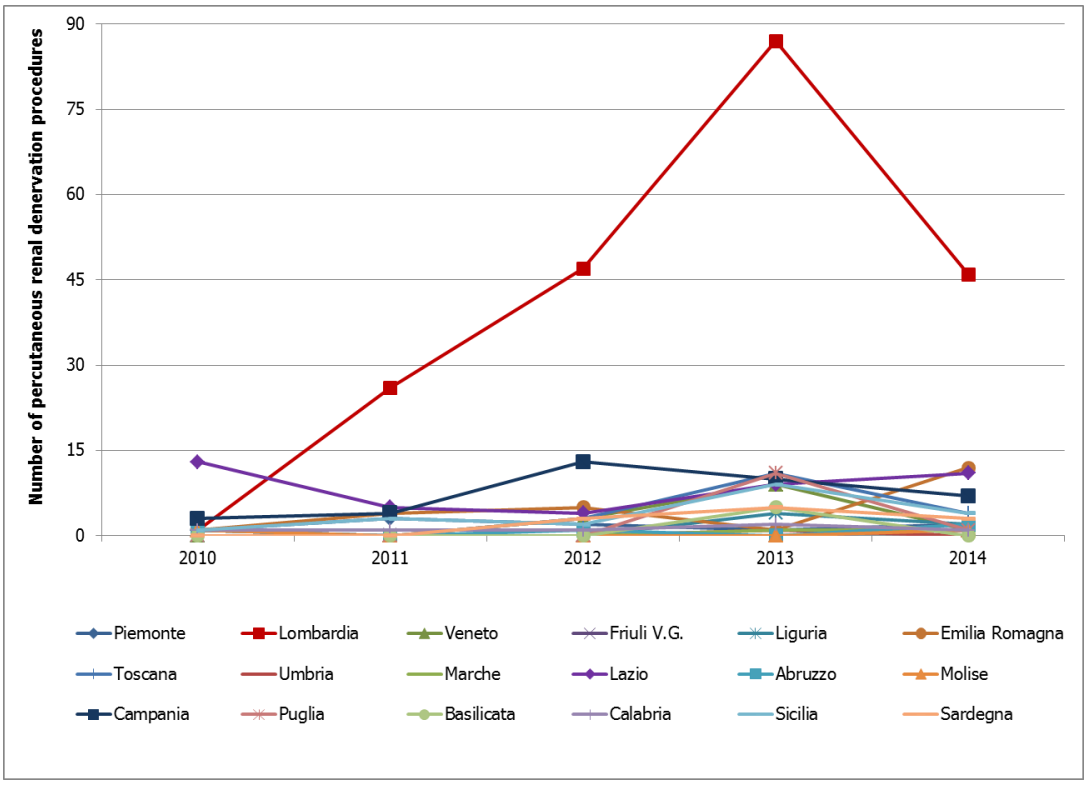
Table 1: Number of percutaneous renal denervation procedures (Italy, 2010-2014)

Year	2010	2011	2012	2013	2014	Total
Number of procedures	25	46	84	166	99	420

Source: *Agenas analysis based on SDO 2010 – 2014*

Figure 1 shows the trend of procedure number performed in Italian Regions in the five years under review. In all Regions less than 10 procedures per year were performed except for Lombardia. However, some Regions (Campania, Lazio, Emilia-Romagna) show outlier values in some years **(A0011).**

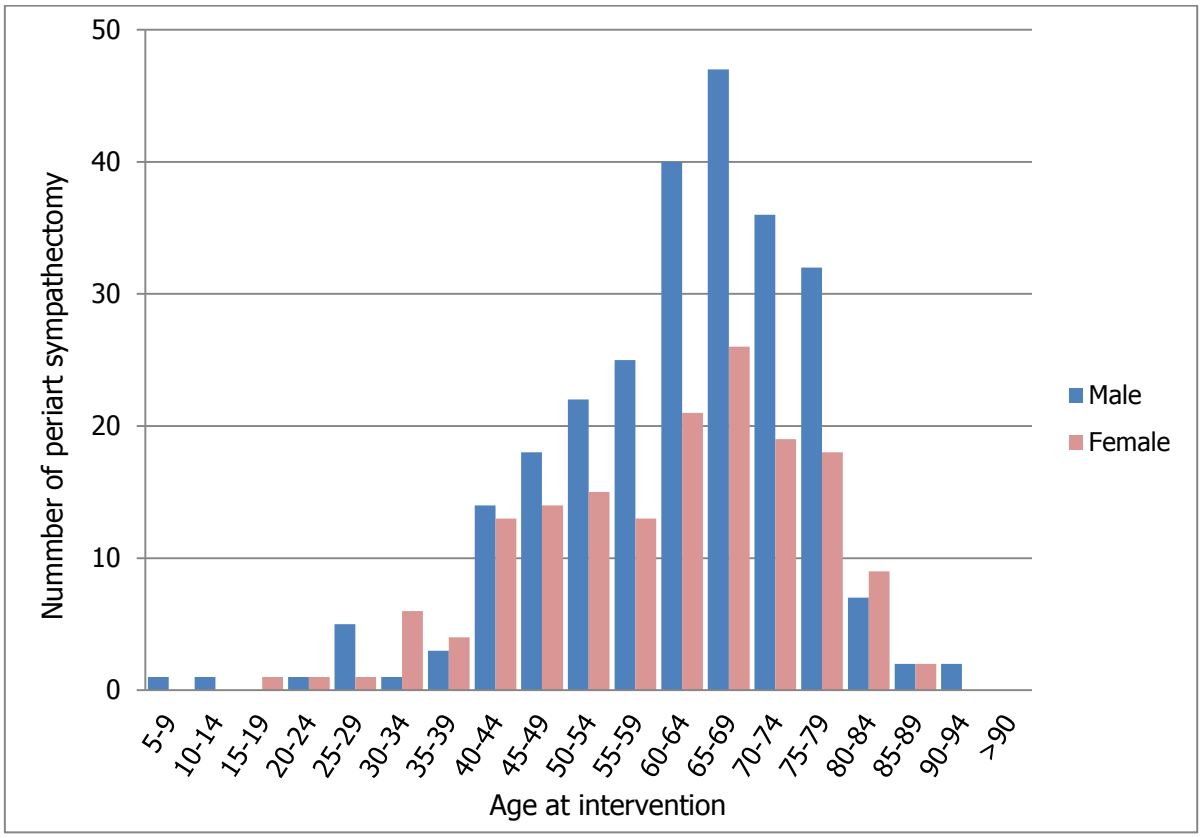
Figure 1: Number of percutaneous renal denervation procedures performed from 2010 to 2014 in the Italian Regions.



Source: *Agenas analysis based on SDO 2010 – 2014*

Based on the discharges recorded in the SDO database for period 2010-2014, 61.2% of 420 procedures were performed on males **(A0001b)**. The average age of patients was 61.35 years (SD: 13.82, median: 64, range: 5-90). Figure 2 shows the age distribution, per 5-year category, per gender.

Figure 2: Periarterial sympathectomy: age class distribution per gender (Italy, 2010-2014).



Source: *Agenas analysis based on SDO 2010 – 2014.*

417 patients out of 420 were admitted to hospital for at least one night. The mean length of stay was 4.9 days (SD: 5.3, median: 3, range: 1-59).

The 78.3% of 420 periarterial sympathectomies was recorded as a principal procedure. The most frequent 3-digit ICD9-CM codes of principal concomitant diagnosis with periarterial sympathectomy (principal or secondary procedure) was essential hypertension (65%) followed by hypertensive heart disease (8.33%) and secondary hypertension (3.09%) (see Table 2). The list of detailed codes (5 digit) of principal diagnosis can be found in Appendix 3.

Table 2: Most frequent 3-digit ICD9-CM of principal diagnosis associated to periarterial sympathectomy (ICD9-CM procedure code 05.25).

3 digits ICD9-CM codes of principal diagnosis	Number of cases	Percentage
Periarterial sympathectomy coded as principal procedure		
401 - Essential hypertension	236	56.19
402 - Hypertensive heart disease	35	8.33
405 - Secondary hypertension	13	3.09
404 - Hypertensive heart and renal disease	11	2.62
Other diagnosis	34	8.10
Periarterial sympathectomy coded as secondary procedure		
401 - Essential hypertension	37	8.81
440 - Atherosclerosis	11	2.62
Other diagnosis	43	10.24
Total	**420**	**100.00**

Source: *Agenas analysis based on SDO 2010 – 2014.*

Volume purchased

The total number of units purchased (i.e., catheters) by public healthcare providers showed an increase from 2012 (40 units) to 2013 (93 units) and then started to decrease up to 2015 (46 units). The average acquisition price ranged from a minimum of € 3,224.29 to a maximum of € 7,930.00.

Conclusions

Treatment-resistant hypertension is defined as high blood pressure that remains above the goal of 140/90 mmHg despite the adoption of lifestyle changes and a treatment with at least three antihypertensive agents (one of which is a diuretic) at best tolerated doses. Causes of treatment-resistant hypertension may be lifestyle factors (e.g., obesity or large weight gains), excessive alcohol consumption and high sodium intake, chronic intake of vasopressor or sodium-retaining substances, obstructive sleep apnoea, undetected secondary forms of hypertension, and advanced and irreversible organ damage. The prevalence of treatment-resistant hypertension ranges from 5 to 30% of the overall hypertensive population (estimated to be 30–45% of the general population).

OMT is currently the standard management strategy for patients with treatment-resistant hypertension. Two non-drug therapies for treatment-resistant hypertension are mentioned within the latest ESH-ESC guidelines[2]: carotid baroreceptor stimulation therapy and renal artery denervation. As already reported this assessment focuses on the renal denervation systems, as carotid baroreceptor stimulation therapy has been recently assessed by one of the RIHTA partners (ASSR Emilia-Romagna in 2015).

The total number of annual percutaneous renal denervation procedures ranged from 25 to 166 from 2010 to 2014. Patients were on average 61.35 years old and 61.2% of them were male. The most frequent principal diagnosis concomitant with periarterial sympathectomy was essential hypertension (65% of episodes).

Data from the "NSIS – Flusso Consumi" database may underestimate the real scenario both in terms of units purchased and acquisition price as the collection became mandatory for the Regions only in 2013.

3. Description and technical characteristics of technology

Methods

The AEs of this domain were:

Assessment Element ID	Research question
B0001	What is this technology?
B0003	What is the phase of development of the technology?
B0004	How is the technology used?
B0005	In which setting and level of care is the technology used?
B0007	Does the technology require additional/special equipment/tools or accommodation?
B0009	What disposables and supplies are needed to use the technology?
F0001	F0001a: Is the technology new/innovative? F0001b: Is the technology an add-on, a replacement or a modification of the standard mode of care?

All the AEs selected within the domain were developed. The technology (percutaneous renal artery denervation) and its technical characteristics were presented by using information gathered by a structured questionnaire sent to manufacturers (as described in Appendix 4) supplemented by *ad hoc* internet searches, manufacturers' websites, product brochures, instructions for use (IFU) documents, and regulatory bodies' databases.

Results

Percutaneous renal artery denervation implicates the interruption of the neurogenic reflexes involved in blood pressure control[2]. The procedure consists in the bilateral destruction of the renal nerves travelling along the renal artery wall by increasing local temperature using ablation catheters based on radiofrequency (RF) or other energy-delivery mechanisms (e.g., ultrasounds)[7] **(B0001)**.

Proof-of-concept of renal denervation therapy was published in 2009: 45 patients were treated across centres in Australia and Europe between 2007 and 2008[9]. The device used was the Symplicity Catheter System manufactured by Ardian, Inc. The company was acquired by Medtronic, Inc. in 2010. The device became commercially available in Europe in 2011. Since 2011 other companies have developed different catheter designs (Table 3) **(B0003)**. Today the procedure is considered an add-on to the standard management of treatment-resistant hypertension as treated patients are not requested to interrupt lifestyle modifications and OMT **(F0001)**.

The procedure is generally performed under fluoroscopic guidance, in a catheterisation laboratory, by professionals trained in endovascular procedures (typically, interventional cardiologists, interventional radiologists or vascular surgeons), and carried out using local anaesthesia, conscious sedation and anticoagulation **(B0005)**. The renal denervation system consists of a guiding catheter, an ablation catheter, and a generator. The guiding catheter is introduced via the femoral or the radial artery and advanced into each renal artery under fluoroscopic control. The ablation catheter, which is connected to the generator, is then advanced into the guiding catheter and delivers energy according to specific patterns. The number of ablations necessary and the time to generate the lesions varies according to the specific system being used[10] **(B0004)**.

Table 3: Percutaneous renal denervation systems registered within the Italian National Medical Devices Inventory and Database (Banca Dati e Repertorio Dispositivi Medici – BD/RDM). All the devices listed in the table are CE marked.

Renal denervation system	Manufacturer	BD/RDM registration number(s)*	On the market§
EnligHTN Multi-electrode Renal Denervation System	St. Jude Medical (now Abbot)	**529950**, **530067**, 951455, 529890, 951498, 610769	Yes
Iberis Renal Denervation System	Terumo	**978333**, **978372**, 978375	Yes
OneShot Renal Denervation System	Covidien	**604589**, **604590**, **604591**, 604567, **590441**, **590582**, **590587**, 590167	No
Paradise Ultrasound Denervation System (with Paradise and Radiance catheter)	ReCor Medical	**1047286**, 1047331, 1048135, 1047266, 1164738, **891936**, 891955, 891938, 891956, 891834 **1162030**, **1162847**, **1162848**, 1164738	Yes
Symplicity Renal Denervation System (with Flex§§ and Spyral catheter)	Medtronic	**308430**, **313927**, 308920, **519824 1065226**, 1064010	Yes
Vessix Renal Denervation System	Boston Scientific	802752, **1159154**, 1159107	Yes

**Registration numbers of all the components of the renal denervation systems; catheters' registration numbers are marked in bold.*

§Italian market.

§§Symplicity Flex catheter is the first generation catheter and, even if still on the market, it is not promoted anymore by the manufacturer.

***Source:** Data from BD/RDM database (accessed on 10th May 2016). Devices are listed in alphabetical order by device name.*

Equipment and tools needed for the renal denervation procedure are the ones typically used for an endovascular procedure with percutaneous femoral/radial artery access **(B0007)**.

The main features and technical characteristics of the renal denervation systems available on the Italian market are presented in Table 4. The special features of the different ablation catheters are

briefly summarised in the following paragraphs together with the specific equipment and tools needed for the procedure.

Table 4: Technical characteristics of the percutaneous renal denervation systems available on the Italian market. Adapted from[11] and supplemented by ad hoc internet searches on specific systems. Devices are listed in alphabetical order by device name.

Device name	Energy	Design and array	Number of electrodes	Energy delivery time	Treatment time	Guide size
EnligHTN	Unipolar RF	Basket; Multi-array	4	60 s	4 min	8 Fr
Iberis	Unipolar RF	Flexible tip; Single	1	n.a.	n.a.	6 Fr
Paradise/Radiance	Ultrasound	Balloon; Circumferential	1	30 s	3 min	7 Fr 6 Fr
Symplicity Spyral	Unipolar RF	Helical; Multi-array	4	60 s	2 min	6 Fr
Vessix Reduce	Bipolar RF	Balloon; Multi-array	8	30 s	2 min	8 Fr

Key: *Fr, French; min, minutes; RF, radiofrequency; s, seconds; n.a., not available.*

EnligHTN (St. Jude Medical)

The EnligHTN renal denervation system has a multi-electrode ablation catheter characterised by a non-occlusive basket design that permits simultaneous ablations. The catheter is provided with a deflectable atraumatic tip. Once the basket is expanded, it causes the electrodes to make contact with the artery walls. The basket is collapsed for removal or repositioned for additional ablations[11]. Dedicated equipment and tools necessary for the renal denervation procedure are presented in Table 5.

Table 5: Dedicated equipment/tools needed for a renal denervation procedure performed with EnligHTN Multi-electrode Renal Denervation System (St. Jude Medical).

Item	Description	Use
Generator	To perform ablation catheter activation according to specific algorithm	Re-usable
Guiding catheter	To allow the ablation catheter to reach the site of treatment	Single use
Ablation catheter	To perform localised ablation in the renal artery wall	Single use
Grounding patches	To connect the electric circuit with the ground	Single use
Electrophysiology cable	To connect the ablation catheter with the adapter cable	Single use
Adapter cable	To connect the electrophysiology cable with the generator	Re-usable

Source: *Manufacturer.*

Iberis (Terumo)

The Iberis ablation catheter consists of a single electrode mounted on a flexible tip. The thin diameter allows access from the radial artery as well. Several localised ablations are repeated to complete the procedure[11]. Dedicated equipment and tools necessary for the renal denervation procedure are presented in Table 6.

Table 6: Dedicated equipment/tools needed for a renal denervation procedure performed with Iberis Renal Denervation System (Terumo).

Item	Description	Use
Generator	To perform ablation catheter activation according to specific algorithm	Re-usable
Guiding catheter	To allow the ablation catheter to reach the site of treatment	Single use
Ablation catheter	To perform localised ablation in the renal artery wall	Single use
Foot pedal	To control the generator by a foot switch	Re-usable
Grounding patch	To connect the electric circuit with the ground	Single use

Source: *Instructions for use document.*

Paradise and Radiance (ReCor Medical)

The Paradise and Radiance ultrasound balloon catheters deliver ultrasound energy to the wall of the renal artery while simultaneously cooling the endothelium. The control unit inflates the sterile water and contrast-filled balloon positioning the transducer in the centre of the artery[11]. The two catheters mainly differ by the diameters, being Radiance specific for radial artery access. Dedicated equipment and tools necessary for the renal denervation procedure are presented in Table 7.

Table 7: Dedicated equipment/tools needed for a renal denervation procedure performed with Paradise Ultrasound Denervation System (ReCor Medical).

Item	Description	Use
Generator	To perform ablation catheter activation according to specific algorithm	Re-usable
Cartridge	To manage the balloon inflation	Single use
Ablation catheter	To perform localised ablation in the renal artery wall	Single use
Connection cable	To connect the cartridge to the generator	Single use

Source: *Instructions for use document.*

Symplicity Spyral (Medtronic)

The Symplicity Spyral ablation catheter consists of a multi-electrode array mounted on a nitinol shaft in a helical configuration. The catheter is delivered using a monorail system that straightens the helical configuration: once the wire is removed, the catheter becomes helical and conforms to the arterial surface[11]. Dedicated equipment and tools necessary for the renal denervation procedure are presented in Table 8.

Table 8: Dedicated equipment/tools needed for a renal denervation procedure performed with Symplicity Renal Denervation System (Medtronic).

Item	Description	Use
Generator	To perform ablation catheter activation according to specific algorithm	Re-usable
Guiding catheter	To allow the ablation catheter to reach the site of treatment	Single use
Ablation catheter	To perform localised ablation in the renal artery wall	Single use
Grounding pad	To connect the electric circuit with the ground	Single use
Guiding wire	To facilitate catheter placement during peripheral intravascular procedures	Single use
Foot pedal	To control the generator by a foot switch	Re-usable
Generator cart	To host the generator unit	Re-usable

Source: *Manufacturer.*

Vessix Reduce (Boston Scientific)

The Vessix Reduce ablation catheter consists of a balloon-based multi-electrode array. The electrodes are made of gold and mounted on the balloon's surface: once the balloon is expanded, the electrode come in contact to the artery wall. Several balloon sizes are available to allow treatment of both main and accessory renal arteries[11]. Dedicated equipment and tools necessary for the renal denervation procedure are presented in Table 9.

Table 9: Dedicated equipment/tools needed for a renal denervation procedure performed with Vessix Renal Denervation System (Boston Scientific).

Item	Description	Use
Generator	To perform ablation catheter activation according to specific algorithm	Re-usable
Guiding sheath	To allow the ablation catheter to reach the site of treatment	Single use
Ablation catheter	To perform localised ablation in the renal artery wall	Single use
Diagnostic catheter	To perform aortography and renal artery angiography	Single use
Guiding wire	To facilitate catheter placement during peripheral intravascular procedures	Single use

Source: *Manufacturer.*

Conclusions

Percutaneous renal artery denervation consists in the bilateral destruction of the renal nerves travelling along the renal artery wall by increasing local temperature using ablation catheters based on RF or ultrasounds. The procedure is typically performed under fluoroscopic guidance, in a catheterisation laboratory, by professionals trained in endovascular procedures (e.g., interventional cardiologists and interventional radiologists), using local anaesthesia, conscious sedation and anticoagulation. Renal arteries are accessed by the femoral or radial artery, using standard percutaneous endovascular access manoeuvres. Procedure time varies with the system being used, according to the number of ablations necessary and the time to generate the lesions.

Since 2009, when the first patients were treated, the manufacturers developed renal denervation systems following different concepts. Medtronic pioneered the field with its Symplicity renal denervation system. As of today, five manufacturers are present on the Italian market: Boston Scientific, Medtronic, ReCor Medical, St. Jude Medical, and Terumo. Four renal denervation systems perform RF ablation while one uses ultrasound energy. Among the RF-based systems, one has bipolar electrodes and does not require the patient to be connected to the ground. Ablation catheters play a key role in the procedure and several designs have been proposed (non-occlusive basket, flexible tip, helical stent, and balloon). Other than the standard equipment and tools necessary for an endovascular procedure with percutaneous femoral/radial artery access, additional devices necessary for a renal denervation procedure are those related to the specific renal denervation system being used.

4. Regulatory aspects

Methods

The AEs of this domain were:

Assessment Element ID	Research question
A0020	What is the marketing authorisation status of the technology?
A0021	What is the reimbursement status of the technology across countries?
I0016	Does the technology need to be listed in a national/EU database?

All the AEs selected within the domain were developed. The regulatory status of the identified devices (CE marking and FDA approvals) was described by using information gathered by a structured questionnaire sent to the manufacturers (as described in Appendix 4) supplemented by *ad hoc* internet searches on regulatory bodies' websites and databases, and manufacturers' press releases.

Results

Approval

EnligHTN, St. Jude Medical's renal denervation system received the CE mark in 2011 and has been on the Italian market since 2012. The catheter has not been changed from its introduction but a new generator allowing simultaneous ablation with lower temperature has been developed. In the USA the EnligHTN denervation system is limited to investigational use and not available for sale. At the time of our survey (April 2016) the manufacturer stated that an investigational device exemption (IDE) study would start at the end of 2016, involving hospitals worldwide (Appendix 4) **(A0020)**.

Iberis is Terumo's renal denervation system and received the CE mark in 2013[12] (on the Italian market since 2013). In the USA, the Iberis renal denervation system is limited to investigational use and not available for sale (details on the FDA approval status were not found and no information has been provided by the manufacturer) **(A0020)**.

Paradise is ReCor Medical's renal denervation system provided with two specific catheters for femoral and radial access, Paradise and Radiance. The two catheters received the CE mark in 2012 and 2013, respectively, and are on the Italian market since 2013 (Paradise) and 2014 (Radiance). In the USA, Paradise and Radiance are limited to investigational use and not available for sale; in

April 2016 the manufacturer announced the enrolment of the first subjects in the FDA IDE-approved clinical trial[13] **(A0020)**.

Symplicity Spyral is Medtronic's latest generation renal denervation system. It received the CE mark in 2013 and has been on the Italian market since 2014. A previous system, Symplicity Flex, was available to the Italian market from 2010 (CE marked in 2008). The new system mainly differs for a multi-electrode design, reduced ablation time, and catheter diameter (Appendix 4). In the USA, the Symplicity Spyral renal denervation system is limited to investigational use and not available for sale; in April 2015, the manufacturer announced that its global Spyral HTN programme received IDE approval by the FDA[14] **(A0020)**.

Vessix Reduce is the Boston Scientific's latest generation renal denervation system. It received the CE mark in 2014. A previous generation catheter, Vessix (Vessix Vascular), has been available on the Italian market since 2013 (Vessix Vascular was acquired by Boston Scientific in 2012). The two generations mainly differ for the catheter guide (the newest has a smaller size). In the USA, the Vessix renal denervation system is limited to investigational use and not available for sale. The manufacturer stated that in December 2014, FDA gave authorisation for the REINFORCE study (NCT02392351). The first patient was enrolled in April 2015. At time of writing (April 2016), in the USA there are 15 active sites in the REINFORCE study (Appendix 4) **(A0020)**.

Table 10: Approval details of the renal denervation catheters currently available on the Italian market.

Renal denervation catheters	CE mark	Indications	Contraindications
EnligHTN	2011	*Indicated for use in renal denervation procedures for the treatment of resistant hypertension*	*- Patients with an active systemic infection.* *- Patients with renal artery stenosis greater than 30%.* *- Patients with prior renal angioplasty, indwelling renal stents and/or aortic stent grafts.* *- Patients with blood clotting abnormalities.*
Iberis	2013	*Indicated for use in renal denervation procedures for the treatment of resistant hypertension*	*- Patients with an evident tendency to bleeding and blood disorders such as thrombocytopenia, severe anaemia, etc.* *- Chronic renal dysfunction.* *- eGFR <45 mL/min/1.73 m^2 (MDRD equation).* *- Type I diabetes mellitus.* *- Anatomically or haemodynamically significant renal artery abnormalities or previous surgery.* *- Renal artery diameter <4 mm.* *- Tortuosity of the renal arteries.* *- Aneurysm of the renal artery.* *- Patients under 18 years of age.* *- Pregnancy.*
Paradise Radiance	2012 2013	*Indicated for percutaneous renal denervation.*	*Paradise:* *- Renal arteries diameter < 4 mm and > 8mm.* *- Renal artery stenosis.* *- Iliac/femoral artery stenosis precluding insertion*

			of the Paradise Catheter. *- Less than 18 years of age.* *- Pregnant.* *Radiance:* *- Renal arteries diameter < 4 mm and > 8mm.* *- Renal artery stenosis.* *- Radial and brachial artery stenosis precluding insertion of Radiance Catheter.* *- Radial artery with AV fistula.* *- Radial artery with no pulse.* *- Patient with renal artery not reachable by a 125 cm guide catheter working length via transradial access.* *- Less than 18 years of age.* *- Pregnant.*
Symplicity Spyral	2013	*Intended to deliver low-level radio-frequency energy through the wall of the renal artery to denervate the human kidney; Treatment of uncontrolled hypertension.*	*- The catheter has not been evaluated in patients who are pregnant, nursing, plan to become pregnant, and in patients with Type I diabetes mellitus, prior renal angioplasty, indwelling renal stent, aortic grafts, or abnormal renal anatomy.* *- Avoid use of the catheter in individuals in whom a reduction in blood pressure would be considered hazardous (such as those with hemodynamically significant valvular heart disease).* *- Implantable pacemakers and implantable cardioverter/defibrillators (ICDs) may be adversely affected by RF ablation. Consider deactivating ICDs during ablation, having temporary external sources of pacing and defibrillation available during ablation, and performing a complete analysis of the implanted device's function after ablation.* *- Avoid treating in arteries with a diameter less than 3 mm or greater than 8 mm.* *- Avoid treating in arteries with significant disease or with flow-limiting obstructions.*
Vessix Reduce	2014	*Indicated for use in percutaneous renal denervation procedures for the treatment of resistant hypertension*	*- Not indicated for use in arteries other than the renal one.* *- Not indicated for use in renal arteries in which a stent has been implanted or presenting calcifications.*

Source: *Catheters' instructions for use documents and technical specifications sheets. Devices are listed in alphabetical order by device name.*

Reimbursement

Generic codes are used across the European countries to reimburse percutaneous renal denervation (no specific procedure codes have been issued yet). In Italy, the percutaneous renal denervation procedure is reimbursed by using the DRG code 120 – *"Other circulatory system or procedures"*. The maximum national fee linked to this DRG code is EUR 6,876[15] **(A0021)**.

Like all the medical devices for sale to Italian public hospitals, renal denervation systems must be registered within the Italian National Medical Devices Inventory and Database (Banca Dati e Repertorio Dispositivi Medici – BD/RDM) **(I0016)**.

Conclusions

The renal denervation systems available on the Italian market received the CE mark between 2011 and 2014. None of them have received FDA approval at time of writing (May 2016). Studies are ongoing for some of the systems. In Italy, as there is not specific reimbursement for medical devices, renal denervation is reimbursed through the tariff for "other" interventions on the circulatory system.

5. Clinical effectiveness and safety

Methods

The AEs of "Clinical effectiveness" domain were:

Assessment Element ID	Research question
D0001	What is the effect of the intervention on all cause mortality?
D0002	What is the effect on the disease-specific mortality?
D0005	D0005a: How does the technology affect symptom frequency of the target condition? D0005b: How does the technology affect symptom severity of the target condition? D0005c: How does the technology affect symptom duration of the target condition?
D0006	D0006a: How does the technology affect the progression of the target condition? D0006b: How does the technology affect the recurrence of the target condition?

The AEs of "Safety" domain were:

Assessment Element ID	Research question
C0001	What harms are associated with the use of the technology?
C0002	Are the harms related to the exposure to the technology?
C0060	How does the safety profile of the technology vary between different generations, approved versions or products?
C0061	Can different organizational settings increase or decrease harms?

Some of the AEs selected within the two domains were developed according to available evidence. Electronic searches were performed between 20-25 April 2016 on MEDLINE, Embase, and Cochrane Library, according to the search strategy presented in Appendix 5. The PICO framework and inclusion criteria defined for the present HTA report are presented in Table 11.

Data extraction and management

Two authors independently assessed titles and abstracts of all retrieved citations according to the defined inclusion criteria. Data extraction was performed using a standardised sheet developed by the authors.

Statistical analyses

A meta-analysis of continuous outcome measurements (in mmHg) used to assess the effects of treatment expressed as mean difference (MD) and standard deviation (SD) was performed. Where standard deviations were not available, confidence intervals for means were used to obtain standard deviation values. The standard deviation for each group was obtained by dividing the length of the confidence interval by 3.92 (where the 95% confidence interval is 3.92 standard errors wide; 3.92 = 2 × 1.96), and then multiplying by the square root of the sample size (Cochrane Handbook 7.7.3.2)[16]. For potential harms, dichotomous outcomes results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Analyses were performed according to an intention-to-treat principle. For missing data, trial authors were contacted. Heterogeneity was evaluated using a Chi^2 test with N-1 degrees of freedom, with an alpha of 0.10 used for statistical significance and with the I^2 test[16]. Source of heterogeneity were sought by assessing the participants, the intervention, the comparison group, and the outcomes and by visually assessing the forest plots. Review Manager (Revman 5.3) was used for data synthesis. Data were pooled using both the random-effects model and the fixed-effect model to ensure robustness of analyses. No subgroup analyses were performed because of lack of reported data but stratification by BP measurement settings. A table of findings presenting results coming from selected studies was created.

Assessment of methodological quality of included studies

Methodological quality of included studies was assessed independently by two authors by using the Cochrane risk of bias tool[16].

Table 11: PICO framework and inclusion criteria defined for the present HTA report "Medical devices for treatment-resistant hypertension".

PICO	
Population	People aged 18-75 with office or continuous monitoring hypertension (>140/90 mm Hg) treated with OMT (three or more agents one of which must be a diuretic) and lifestyle changes.
Intervention	Transcatheter renal artery denervation.
Comparison(s)	Optimal medical therapy (OMT).
Outcome(s)	Effectiveness outcomes: *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).*
Design of study	HTA reports, systematic reviews, and randomised controlled trials (RCTs).

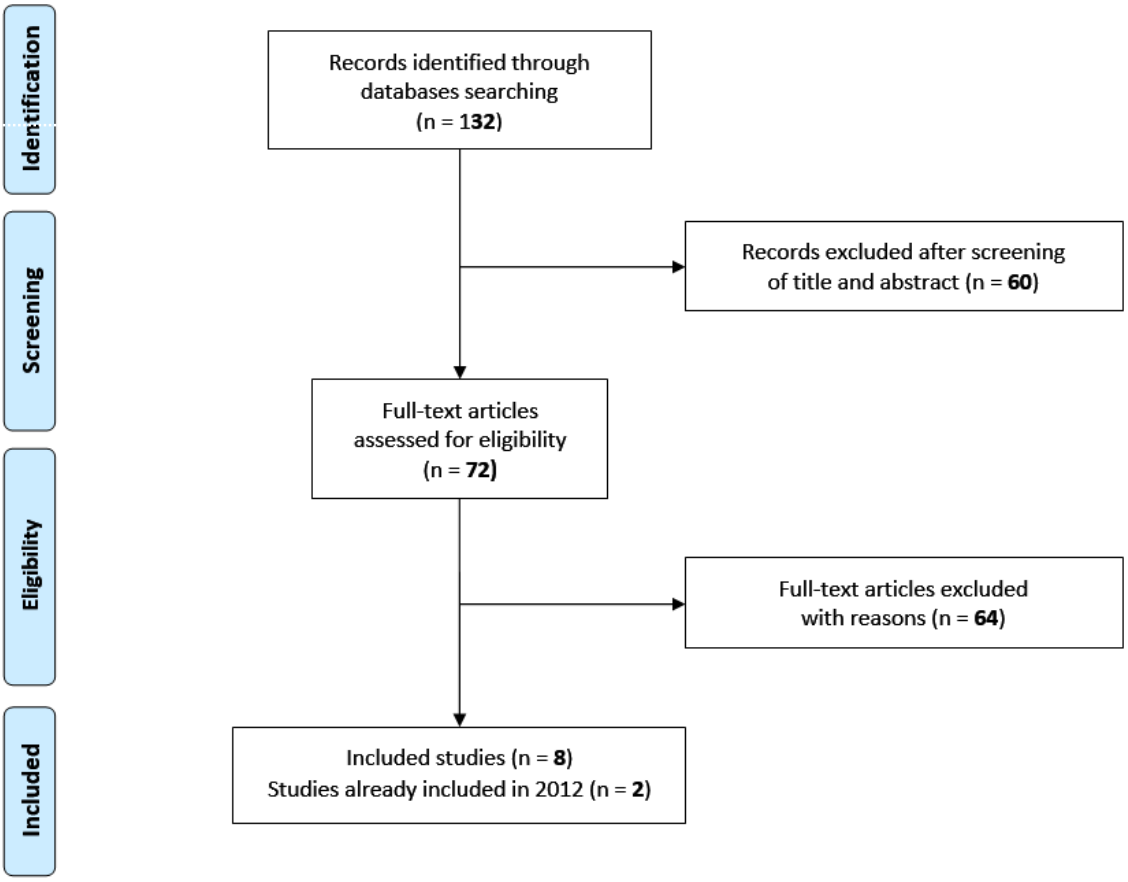
Results

Our searches identified 132 studies of possible interest. Of these, 60 were excluded on the basis of their title and/or abstract content. A further 44 were excluded because they were reports of registries (n = 5), research synthesis reports (n = 30) with search dates preceding our own, and protocols of studies (n = 9). A further 28 studies were assessed. Of these, 2 were not retrievable[17], one had been conduct in people with heart failure[18], one was an abstract of a methodological study[19], one was an editorial[20 21], three were non randomised studies[22-24], five had interventions or populations not fitting our inclusion criteria[25-29], one was an economic model[30].

Of the remainder, three studies were part of the SYMPLICITY HTN-2 trial publication group: Esler et al. 2010[31] is the primary publication while Esler et al. 2012[32] and Esler et al. 2014[33] report follow-up data at 12 and 36 months respectively.

The SYMPLICITY HTN-3 trial publication group consisted of Bhatt et al. 2014[34] which we considered the primary publication, Bakris et al. 2015[35] and Bhatt et al. 2015[36] reporting results at 12 and 24 months respectively. However other studies in this group, Bhatt et al. 2014 (Journal of Vascular Surgery)[37], Bakris et al. 2014[34], and Kandzari et al. 2015[38] reported further analyses of SYMPLICITY HTN-3 trial to explore the reasons of some of its findings and Kario et al. 2015b[39] reported an analysis of the Japanese arm of SYMPLICITY HTN-3 trial but did not report any new data. In summary, we included 8 new studies and 2 studies already included in the 2012 review: Esler et al. 2012[40] and Esler et al. 2014[33] (Esler et al. 2010[31] reporting the SYMPLICITY HTN-2 NCT00888433 trial, had already been included in the previous version of the review together with Mahfound et al. 2011[41]), Azizi et al.[42] reporting the DENER-HTN trial (NCT01570777), Bhatt et al.[36] reporting the SYMPLICITY HTN-3 trial (NCT01418261), with Bakris et al. 2015[35] and Bhatt et al. 2015[36] reporting original follow-up data, Desch et al. 2014[43] (NCT01656096) and Fadl Elmula et al. 2014[44] (NCT01673516) (see flow chart Figure 3 and Table 12 for characteristics of the studies).

Figure 3: Study screening process for effectiveness and safety of transcatheter renal artery denervation according to PRISMA. Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.



775 **Table 12:** Characteristics of included studies (studies included in the 2012 review are marked with *).

Study	Year	Objective	Study design	Participants		Outcomes		Follow up	Funding
				Intervention group/ Device	*Control group/ Control intervention*	*Primary*	*Secondary*		
*Esler et al. [SYMPLICITY HTN-2 trial] NCT00888433	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)* *At 36 months in 40/52 there was a difference of SBP/DBP -33 mmHg (95% CI: -40 to – 25) and -14 mmHg (95% CI: -17 to - 10 respectively* *Simplicity*	*Number: 54* *Age: 58 (SD 12)* *Antihypertensive drugs: 5.3 (1.8)* *SBP/DBP: 178(SD16)/98(SD17)* *At 30 months no control data were reported because all 30 subjects for whom data were available had crossed over to RD at 6 months OMT*	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 and 12 and 36 months reported in Esler 2012 and 2014 respectively	Medtronic Inc
*Mahfoud et al. SIMPLICITY HTN-1	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
Azizi et al. [DENERHTN trial] [NCT 01570777]	2015	To assess the effects of adding radiofrequency-based renal denervation to a standardised stepped-care antihypertensive	RCT	*Number: 53 (ITT)* *Age: 55.2• (±10.8)* *Antihypertensive drugs: Indapamide, ramipril and amplodipine taken by at least 80% of*	*Number: 53 (ITT)* *Age: 55.2• (±10.1)* *Antihypertensive drugs: Indapamide, ramipril and amplodipine taken by at least 80% of*	Mean change in daytime ambulatory SBP from baseline to 6 months	(a) Mean changes in all other BP variables from baseline to 6 months in ambulatory, home, and office settings (b) Proportion of patients with controlled BP at 6 months	6 months	Government

		treatment (SSAHT) on ambulatory blood pressure in patients with resistant hypertension		*participants. All at least on triple therapy* *SBP/DBP: 159.3 (±22.7)/93.3 (±16)*	*participants. All at least on triple therapy* *SBP/DBP: 155.9 (±21.9)/91.4 (±13.8)*		(<135/85 mmHg by daytime, <120/70 mmHg by night-time, and <130/80 mmHg by 24-h ABPM) (c) adherence to antihypertensive medication by three categories according to the MMAS-8 score at 6 months (d) mean changes in eGFR from baseline to 6 months (e) incidence of acute adverse events of the procedure (f) incidence of all adverse events from baseline to 6 months		
Bhatt et al. [SYMPLICITY HTN-3 trial] NCT01418261	2014	To assess the effect of renal denervation or a sham procedure on Ambulatory BP measurements 6 months post-randomization compared with OMT	RCT	*Number: 364 (ITT)* *Age: 57.9 (±10.4)* *Antihypertensive drugs: All participants on OMT including 99.7% on diuretic* *SBP/DBP 179 (± 16.1)/96.5 (± 16.6)* *Office SBP: -14.13 (±23.93)* *Simplicity*	*Number: 171 (ITT)* *Age: • 56.2 (±11.2)* *Antihypertensive drugs: All participants on OMT including 100% on diuretic* *SBP/DBP 180.2 (± 16.8)/98.9 (± 15.8)* *Office SBP: - 11.74 (±25.94)* *Sham procedure*	Change in office SBP at 6 months	Change in ambulatory BP at 6 months	at 12 months there was no difference, and 24 months data are not yet available (see note) Bakris 2015 [35] and Bhatt 2015[36]	Medtronic
Desch et al. [NCT NCT01656096]	2015	To test the hypothesis that RSD is superior to a sham intervention in patients with only mild resistant arterial hypertension. This was a consequence of the SIMPLICITY trial negative findings, when one explanation could be the severity of hypertension in the SIMPLICITY participants	RCT	*Denominator: 35* *Age: 64.5 (±7.6)* *Mean number of OMT medications 4.4 (±1.3)* *SBP/DBP 144.4 (±4.8)/80.6 (±7.8)* *SBP: -7.0 (-10-8) to -3.2)* *DBP: -2.8 (-4.8 to -*	*Denominator: 36* *Age: 57.4 (±8.6)* *Mean number of OMT medications: 4.3 (±1.3)* *SBP/DBP 143.0 (±4.7)/ 82.9 (±7.3)* *SBP: - 3.5 (-6.7 to -0.2)* *DBP: 2.1 (-39 to -0.2)* *Sham procedure*	Change in 24-hour systolic BP at 6 months between groups in the ITT population	NR	6 months	University of Leipzig, Heart Center

				0.09) *Symplicity Flex Catheter (Medtronic)*					
Fadl Elmula et al. NCT01673516	2014	To investigate the BP-lowering effect of RDN compared with clinically adjusted drug therapy in patients with true treatment resistant hypertension (i.e. high pharmacological compliance)	RCT	*Denominator: 10* *Age: 57 (±10.9)* *Office baseline: SBP/DBP 156 (12.6)/91 (14.9)* *Office SBP: -8 (±15) mmHg at 6 months* *DBP change is not reported clearly but appears to be – 2 mmHg* *Simplicty*	*Denominator: 9* *Age: 62.7 (±5.1)* *Office baseline: SBP/DBP 160 (12)/89 (12.7)* *Basic DBP 89 (±12.7Office SBP – 28 (±13) mm Hg at 6 months* *DBP change is not reported clearly but appears to be – 11 mmHg* *Adjusted OMT*	Change in office SBP	NR	Trial stopped at 6 months for dominance of control intervention	Oslo University

776 ***Key:*** *RCT = Randomised Clinical Trial; CCT = Controlled Clinical Trial; SD = standard deviation; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; ITT = Intention to*
777 *Treat population; OMT = Optimal Medical Therapy; RSD = Renal sympathetic denervation.*

778 ***Note on SYMPLICITY HTN-2 trial publication group****: Esler 2010 is the primary publication. Esler 2012 and 2014 report follow-up data at 12 and 36 months respectively.*

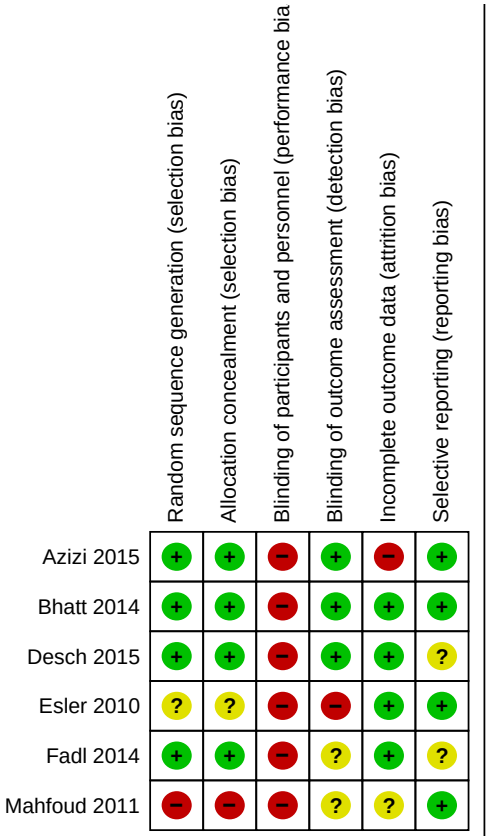
779 ***Note on SYMPLICITY HTN-3 trial publication group:*** *Bhatt et al 2014 (NEJM) is considered the primary publication of the SYMPLICITY HTN-3 trial. Bakris 2015 and Bhatt*
780 *2015 reported results at 12 and 24 months (expected) respectively and Bhatt 2015(a) reported further BP analyses results. Bhatt et al 2014 (Journal of Vascular Surgery) did not*
781 *provide additional original data. Kandzari 2015 is a further analyses of SYMPLICITY HTN-3 trial to explain some of its findings - no new data reported. Kario 2015b reports an*
782 *analysis of the Japanese arm of SYMPLICITY HTN-3 trial but no new data are reported.*
783

Assessment of methodological quality of included studies

The included studies were assessed using the Cochrane risk of bias tool. Figure 4 reports the assessments by risk of bias domain and by trial.

- *Allocation concealment:* Of the 6 included trials, four used central randomisation and were judged to be at low risk of selection bias[34 42-44], one randomised trial did not describe the method used to conceal allocation and was judged to be at unclear risk of bias[31]. The remaining study was a controlled trial with no randomisation and was then judged at high risk of selection bias[41].
- *Blinding of participants and personnel:* All studies were deemed at high risk of performance bias due to the nature of the intervention. However, two trials used sham control to mask participants in the control group. In one trial investigators attempted masking participants by administering saline infusion to patients to simulate administration of intravenous pain medication and invasive examination[43] whereas in the second trial patients in the sham-procedure group remained on the catheterization laboratory table for at least 20 minutes prior to removal of the introducer sheath[34].
- *Blinding of outcome assessor:* Three trials reported blinding the outcome assessor and were considered at low risk of detection bias[34 42 43]. Two trials did not describe the blinding of the outcome assessors[41 44] whereas the remaining trial did not perform any blinding and was this deemed to be at high risk of detection bias[31].
- *Incomplete outcome data:* Four trials were rated at low risk of attrition bias[31 34 43 44]; one trial was deemed at high risk of attrition because while no missing data or loss to follow-up occurred in the control group, 17% in the experimental group were not included in analysis either because they did not receive RD (n = 7) or had missing data (n = 2)[42]. One trial reported the same mean ages of participants by arm[42].
- Selective outcome reporting: one study[44] did not explicitly report the outcome mortality and was rated as unclear risk of bias.

Figure 4: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

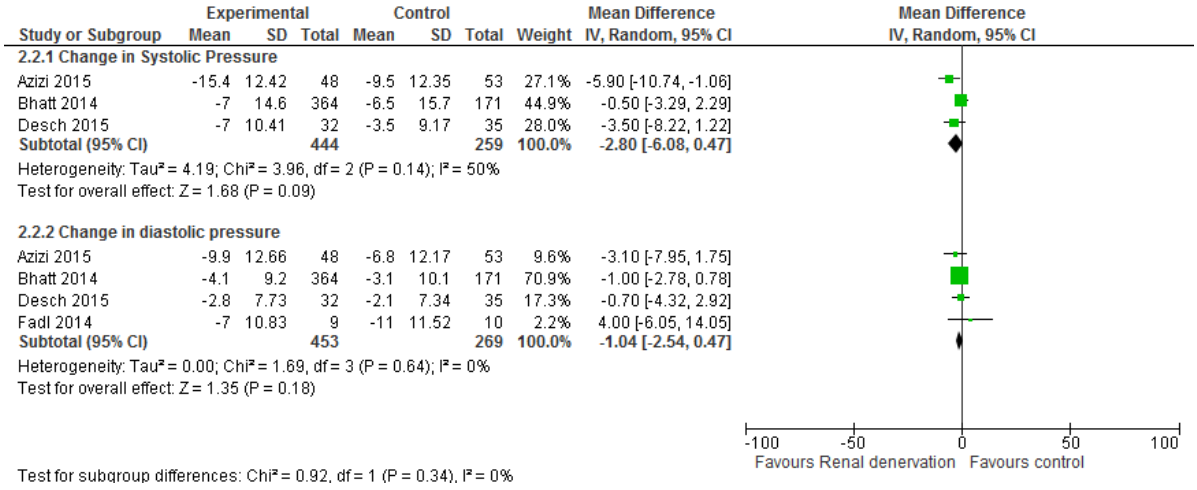


Effectiveness outcomes

Change in average measurements of systolic and/or diastolic blood pressure (D0005) (D0006)

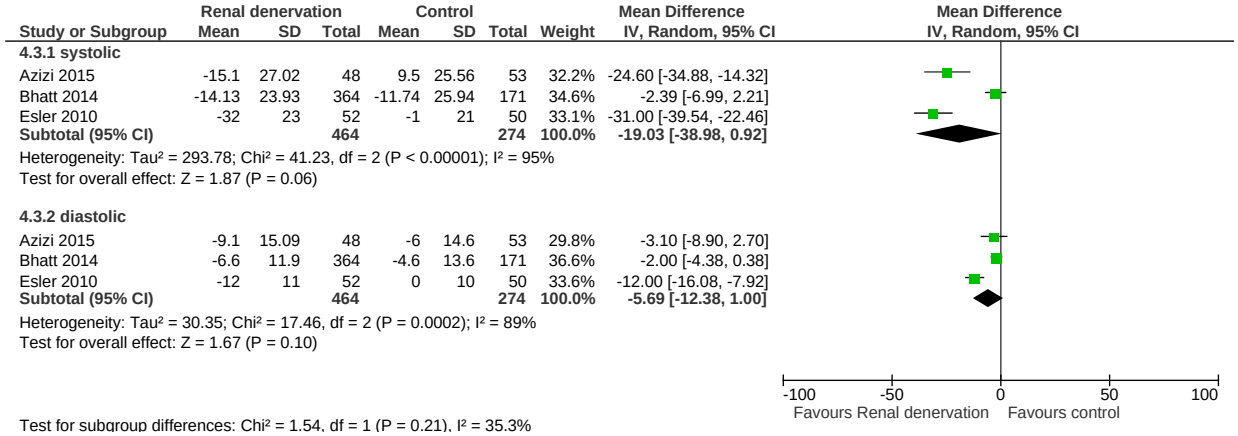
- *Ambulatory setting (Figure 5):* Four trials comprising 722 participants provided data on change in an ambulatory setting at 6 months follow-up[34 42-44]. Pooling the data of the studies that uniformly used standard criteria (systolic BP >160 mmHg) to define resistant hypertension, the results showed that patients that received RD did not experience any reduction in systolic [WMD -2.80 [95% CI -6.08 to 0.47); I^2 50%, P = 0.14] and diastolic pressure [WMD -1.04 [95% CI -2.54 to 0.47); I^2 0%, P = 0.64] when compared to the control group. The trial by Fadl Elmula et al.[44] was excluded from the meta-analysis of systolic changes because it used the European Society of Hypertension guidelines definition for resistant hypertension (systolic BP >140 mmHg). However, the results did not show any effect (WMD 9.00 95% CI -4.67 to 22.67).

Figure 5: Change in ambulatory blood pressure values (in mmHg) at 6 month follow up.



- *Office setting (Figure 6):* Five trials evaluated the change in blood pressure values in an office setting. Two of these trials reported data at a 3 months follow-up and results were in favour of RD for both systolic [WMD -21.66 (95% CI -28.85 to -14.48); I^2 0%] and diastolic blood pressure values [WMD -9.00 (95% CI [-16.65, to -1.35); I^2 0%][31 41]. Three trials reported outcomes at 6 months follow-up[31 34 42]. Results were however extremely heterogeneous (I^2 = 95% for systolic blood pressure).

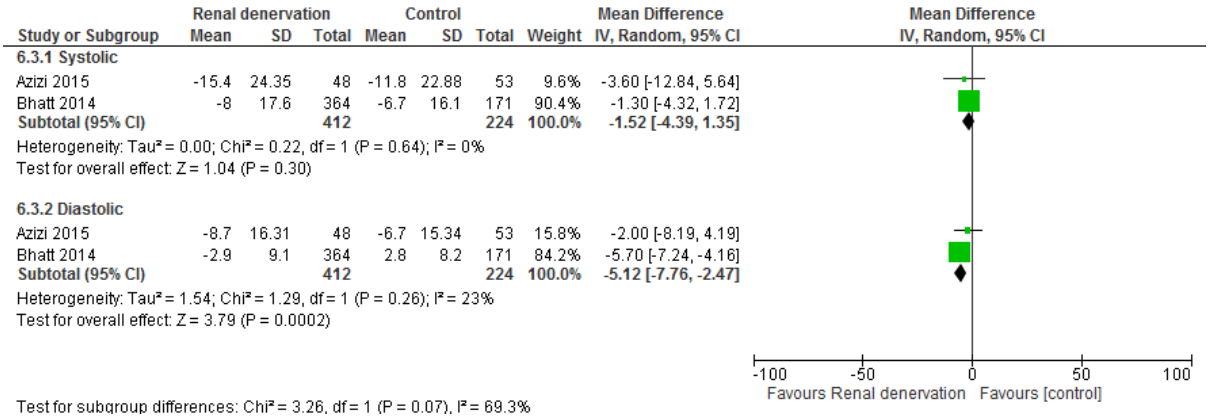
Figure 6: Change in office blood pressure values at 6 month follow-up.



- *Home setting (Figure 7):* Only two trials reported blood reduction measurement at 6 months follow-up in a home setting[34 42]. Pooling the data, the results showed significant

difference between the two groups in diastolic pressure [WMD -5.12 (95% -7.76 to -2.47); I^2 23%, P = 0.26] favouring renal denervation but not in systolic pressure [WMD -1.52 (95% -4.39 to 1.35); I^2 0%, P = 0.64].

Figure 7: Change in home setting blood pressure values.



All-cause mortality (D0001)

No death occurred at 3 months follow-up in Mahfoud et al.[41]. Bhatt et al.[34] reported 3 deaths (2 in the RD group) at 6 months follow up. The difference was not statistically significant. No death occurred in three trials at 6 months follow-up[31 42 43]. In Fadl Elmula et al.[44] no clear information was reported regarding mortality.

Major cardiovascular events (D0005)

Two myocardial infarction events were recorded by Azizi et al.[42] (one in each group); 9 by Bhatt et al.[34] (6 in the RD group); one occurred in the RD in Fadl Elmula et al.[44]; in Esler et al.[31] two patients received coronary stent for angina (one in each group).

Heart failure was reported only by Bhatt et al.[34] where 6 events in the RD group and 3 in the control were recorded.

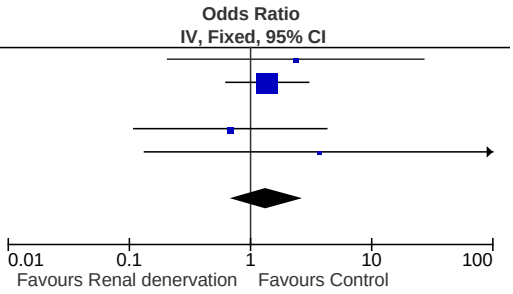
Six strokes were reported by Bhatt et al.[34] (of which 5 in the RD group) whereas in Azizi et al.[42], one event was recorded in the RD group. In Bhatt et al.[34] an embolic event that resulted in an organ damage was reported in the RD group. Esler et al.[31] recorded one transient ischaemic attach in each group of participants. Six events of atrial fibrillation requiring hospitalization were reported by Bhatt et al.[34] (5 events in the RD group).

Desch et al.[43] reported that no cardiovascular event occurred. Overall the proportion of major cardiovascular events was higher in the RD group (6.1%) than in the control group (4.0%) but with no statistical difference: OR 1.36 (95% CI 0.69 to 2.67 fixed effects model) (Figure 8). No cardiovascular event occurred in Mahfoud et al.[41] (personal communication).

Figure 8: Major cardiovascular events reported at 6 months follow-up.

Study or Subgroup	Renal denervation Events	Total	Control Events	Total	Weight	Odds Ratio IV, Fixed, 95% CI
Azizi 2015	2	46	1	53	7.7%	2.36 [0.21, 26.95]
Bhatt 2014	25	352	9	171	74.5%	1.38 [0.63, 3.02]
Desch 2015	0	35	0	36		Not estimable
Esler 2010	2	49	3	51	13.6%	0.68 [0.11, 4.26]
Fadl 2014	1	9	0	10	4.1%	3.71 [0.13, 103.11]
Total (95% CI)		**491**		**321**	**100.0%**	**1.36 [0.69, 2.67]**
Total events	30		13			

Heterogeneity: Chi² = 1.09, df = 3 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.38)



Insufficient data were reported to answer **(D0002)**.

Adverse events (C0001)

Although no safety outcome was explicitly reported in Mahfoud et al.[41], 1 patient out of 37 in the denervation group developed a pseudoaneurysm at the femoral access site that was treated without further sequelae. No other complications were observed either in the denervation or in the control group. Azizi et al.[42] reported three renal denervation-related adverse events: lumbar pain in two patients and mild groin haematoma in one patient. Bhatt et al.[34] reported one vascular complication requiring treatment and one new renal-artery stenosis of >70% occurring in the RD group. Esler et al.[31] 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. Fadl Elmula et al.[44] reported that 4 patients had mild-to-moderate hematomas at the femoral access site; one patient had bradycardia and received atropin injection during the procedure. Desch et al.[43] reported no occurrence of adverse events.

Insufficient data were reported to answer the AEs **C0060** and **C0061**.

Forthcoming evidence

Several studies on renal denervation were identified by our searches on Clinicaltrial.gov database (see Appendix 6). Three studies were registered as "active, not recruiting". One of them, DENER-HTN (NCT01570777) was aimed at comparing renal denervation with optimised medication regimen in 121 subjects; results are awaited within April 2018.

Nine studies were registered as "open". Only three of them are aimed at comparing renal denervation with usual care (standard antihypertensive drug treatment) while the remaining studies are using sham comparators. The INSPiRED study (NCT01505010) aimed to enrol 240 subjects and give results by April 2016 but no results have been posted (information on are updated to February 2015) and no studies referring to it have been identified. The study NCT01888315 aims to enrol 1,000 subjects and use four different renal denervation systems; results are expected in 2021. No completion date has been provided for study NCT01850901, aiming to enrol 300 subjects.

Conclusions

In general, all trials reported negative results regardless of funders apart from the earlier SYMPLICITY HTN-2 trial. Like the manufacturers, we cannot give reasons for such demonstrable lack of effect, as trials with and without control sham procedures and different levels of pharmacological attention to titration and compliance all reported no evidence of dominance of transcatheter renal denervation. In one case (the small trial by Fadl Elmula et al.[44]) dominance of carefully adjusted and supervised OMT was reported.

6. Costs and economic evaluation

Methods

The AEs of this domain were:

Assessment Element ID	Research question
E0001	Can you identify what types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?
E0002	Can you quantify what amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?
E0009	What were the measured and/or estimated unit costs of the resources used by the assessed technology and its comparator(s)?
E0005	What is(are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)?
E0006	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?
E0010	What are the uncertainties surrounding the inputs and economic evaluation(s) of the technology and its comparator(s)?
E0012	To what extent can the model estimates of inputs, outcomes, or economic evaluation(s) be considered as providing valid descriptions of the technology and its comparator(s)?
G0007	What are the likely budget impacts of implementing the technologies being compared?

All the AEs selected within the domain were developed. We carried out a systematic review to answer cost and economic AEs, updating the systematic review produced by Agenas in 2012[45]. Italian and international scientific literature was searched to identify and analyze the economic implications of using the transcatheter renal artery denervation (RDN) in patients with resistant hypertension despite adherence to an optimal medical therapy (OMT).

The electronic bibliographic databases PubMed, Embase, and Cochrane Library were searched (20-25 April 2016) according to the search strategy reported in the Appendix 7. The keywords related to the *Population*, *Intervention* and *Comparator* reported in the EFF and SAF chapter (Chapter 5) were combined with the following keywords: cost-utility, cost-effectiveness, cost-minimization, cost analysis, economic evaluation, economic analysis, economic aspect, economic assessment, ICER, health care cost, budget impact analysis. We included all types of economic analysis: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), cost-consequences analysis (CCA) and cost-minimization analysis (CMA) comparing the use of renal denervation procedure plus optimal medical therapy to the optimal medical therapy alone. Cost analyses which reported insufficient details or full economic evaluations which did not provide an estimate of cost-effectiveness were excluded. One author (MC) screened the title or abstract of

studies yielded from literature searches to identify the potential eligible studies. The full text of such studies was analysed to select those to be included in the analysis, according to the inclusion criteria stated above. Evidence references were managed using the software EndNote (X7.2). Economic data from included economic studies were extracted by using an *ad hoc* form. The results were tabulated and described in narrative way. The assessment of the methodological quality was carried out using the checklist for economic evaluations of health programmes[46].

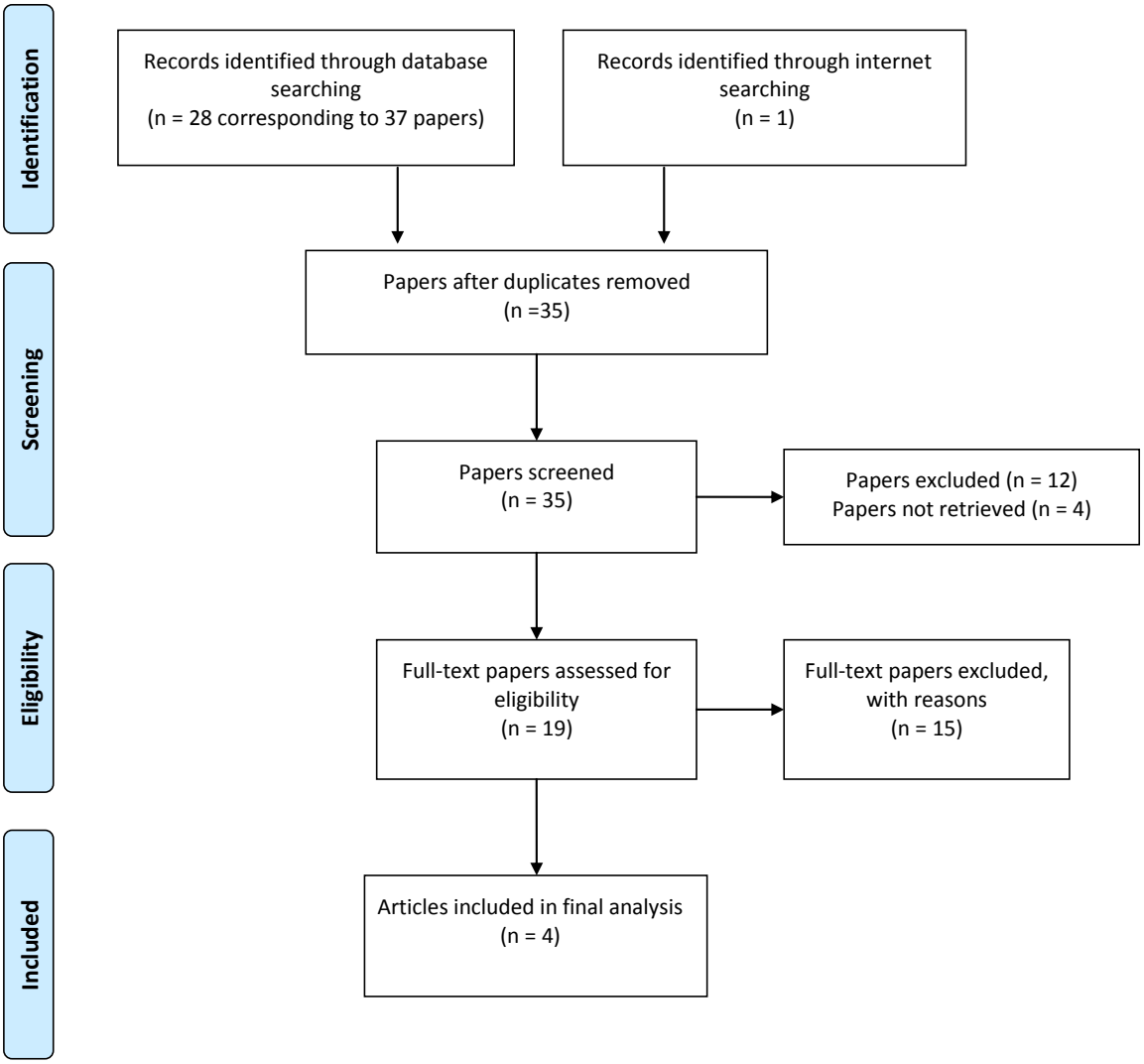
We aimed to develop a decisional analytic model to estimate the costs of the different interventions. However given the lack of efficacy evidence resulting from our systematic review (see Chapter 5) and the findings about the current use of RDN in Italy (which showed a quite small number of estimated cases of RDN per year) we decided not to develop a comparative decisional analytic model but performed a cost analysis of the RDN procedure from the Italian National Health System (NHS) viewpoint. For the same reason we did not estimate the budget impacts of implementing RDN and its comparator **(G0007)**. We estimated the cost of the RDN using data from the 2012 Agenas previous systematic review[45] and data collected from other sources (clinical experts, manufacturers). The estimation of the cost of RDN is based mainly on data provided by manufacturers through a questionnaire that was sent to the 3 manufacturers Agenas met on the 8th of April 2016.

Part of the questionnaire collected economic data on specific products. The findings of the economic analysis were investigated comparing its content with results from the clinical effectiveness and safety domains.

Results

The systematic searches of electronic databases yielded 29 records corresponding to 37 papers while one more paper was retrieved from a non-systematic free text search. After removing 3 duplicates, 35 potentially relevant papers were screened on the basis of the title and abstract (if available). Twenty-three papers were judged to be relevant for the analysis and the full text was retrieved for 19 of them. According to our predefined inclusion criteria, 4 full economic evaluations were included[47] [48] [49] [50]. The PRISMA flow-chart describing the inclusion process of the economic studies is shown in Figure 9. The included and excluded papers along with the reason for exclusion are reported in Appendix 8 and Appendix 9, respectively.

Figure 9: Study screening process for economic studies of transcatheter renal denervation according to PRISMA. Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.



An overview of the 4 evaluations included in our economic review is reported in Table 13. All the included studies were cost-utility analyses and three of them performed also a cost-effectiveness analysis. All the studies developed a Markov model to evaluate the cost-effectiveness of the RDN procedure plus OMT versus OMT alone in resistant hypertensive patients. The definition of resistant hypertension reported in the included studies was similar, namely a condition where blood pressure remains elevated and above the goal range in spite of optimal medical therapy with 3 or more antihypertensive agents, including a diuretic, at maximal recommended or tolerated dose. This goal range was explicitly reported in Gladwell et al.[47] to be 100-140 and 60-90 mmHg for Systolic and Diastolic Blood Pressure respectively. Different terms were used to indicate optimal medical therapy e.g. standard of care (SoC), best medical therapy (BMT); however all terms

996 referred to a pharmacological therapy comprising 3 or more antihypertensive medications. Two of
997 the studies were based on the Markovian model first created by Geisler et al.[49], adapted to the UK
998 by Gladwell et al.[47], and to the Dutch setting by Henry et al.[48] The economic models were
999 designed to follow the entire life of patients using a cycle length of 1 month[47 49] or of 1 year[50]. One
1000 study considered a shorter time horizon (10 years)[49]. Most of the studies (3/4) adopted the payer
1001 perspective and the last one the societal perspective. Competing interests (COI) were disclosed in
1002 all studies. Two studies reported manufacturer funding.
1003

Table 13: Included economic studies – General information.

Study	Country	Objective	Economic analysis and modelling	Time horizon/Perspective	Intervention	Comparator	Funding/COI
Geisler, 2012	USA	*To develop a decision-analytic model to predict long-term cardiovascular consequences and to ultimately assess the cost-effectiveness based on long term clinical benefits of RDN compared to SoC alone*	CEA/CUA - Markov model (34 health states to represent the disease's progression; cycle length=1 month)	Patient's lifetime (10 years)/Societal perspective	RDN+SoC	SoC	NR/declared
Dorenkamp, 2013	Germany	*To determine the benefits, costs and cost-effectiveness of catheter-based RDN for treatment of resistant hypertension (RHyp)*	CEA/CUA - Markov model (two arms with a cycle length=1 year and half cycle correction)	Lifetime/Payer (German statutory health and nursing care insurance system)	RDN+BMT	BMT	NR/declared
Gladwell, 2014	UK	*To estimate the cost-effectiveness of RDN for patients in the UK with diagnosed resistant hypertension, expressed as a standard cost per QALY ratio*	CUA - modified Markov model (34 health states to characterize disease progression; event history-based transition probabilities)*	Patient's lifetime/UK Health payer	RDN+Soc	SoC	Medtronic Ltd./declared
Henry, 2015	The Netherlands	*To consider the cost-effectiveness (cost per life-year gained (LYG) and cost per quality-adjusted life gained (QALY)) of RDN therapy for patients with resistant hypertension in the Netherlands compared to SoC*	CEA/CUA - Markov model (34 health states to represent the disease's progression; cycle length=1 month)**	Patient's lifetime/Healthcare payer in the Netherlands	RDN+SoC	SoC	Medtronic Ltd./declared

** Based on the model by Geisler et al.*[49]

*** Based on the model by Gladwell et al.*[47]

Key: *COI, conflict of interest; RDN, renal denervation; SoC, standard of care; CUA, cost-utility analysis; CEA, cost-effectiveness analysis; NR, not reported; BMT, best medical therapy; QALY, quality-adjusted life year.*

Description of the available evidence

All studies except the one by Dorenkamp et al.[50] were based on the economic model developed by Geisler et al.[49]. This is a Markov model comprising 34 health states, with 1-month cycle length, to represent the progression of the disease throughout patients' lifetime (base-case). A simulated cohort of hypertensive resistant patients with the same clinical characteristics of the Symplicity HTN-2 trial population[1] was followed for the two treatment options investigated (RDN+SoC or SoC alone). The estimated effects of both treatment options (RDN and SoC) were based on results of the Symplicity HTN-2 trial. The model used the reductions in SBP observed in the randomized controlled trial and applied associations, derived from the published literature, between SBP and clinical events[2] to estimate their number by type[49]. Specifically the transition probabilities used in the model were derived from the Framingham risk equations (for cardiovascular event probabilities), the PROCAM (Prospective Cardiovascular Münster Heart Study) risk equation (for myocardial infarction incidence) and from a cohort study by Hsu et al. (for the estimated ESRD incidence)[51 52]. Mortality rates and utility values (adjusted for different age groups) were based on the most recent published evidence. Context specific utility values and mortality rates, if available, were used in the economic analyses based on the model by Geisler et al.[48 49].

The remaining study, Dorekamp et al.[50], developed a Markov model structured in two arms (RDN+BMT or BMT alone) with 1 year cycle length and half cycle correction, able to follow a cohort of patients with resistant hypertension during their entire life (base-case). The simulated cohort was comprised of men and women with baseline SBP ≥160 mmHg despite compliance with at least 3 antihypertensive drugs (including 1 diuretic) and with an age ranging from 30 to 100 years or death. The efficacy of RDN was estimated as the reduction in the risk of clinical events (MI, angina, stroke, HF, ESRD) and death (CVD/non-CVD) associated to hypertension (blood pressure levels). Systolic BP reduction in base-case was based on the findings of Symplicity trials[9] [31 53]. Probabilities of clinical events and death occurring during the 1st year after RDN were estimated using the Systemic Coronary Risk Evaluation (SCORE) risk estimation system (CHD and stroke) and from a published study (ESRD)[54] starting from the incidence of primary CVD events and ESRD events recorded in the German/North European registries and in German QuaSi-Niere

[1] The cohort had a mean Systolic blood pressure (SBP) equal to 178±18 mmHg at baseline, was on average on 5 medications, had a mean age of 58 (55 to 61) years, was comprised for 43% of women, had a diabetes mellitus prevalence of 34%, and a current smoker prevalence of 16%.

[2] The clinical endpoints of interest were: stroke, myocardial infarction (MI), coronary heart disease (CHD), heart failure (HF), end-stage renal disease (ESRD), cardiovascular (CVD) mortality, all-cause mortality.

renal registry respectively. Subsequent events, as well as mortality rates both within and after the 1st year were drawn from large registries or/and randomized controlled trials. Utility values were obtained from published evidence.

One important issue is that in all trial clinical benefits associated with RDN are measured in terms of SBP reductions, an intermediate endpoint. There is a lack of trials comparing hard clinical endpoints in patients treated with RDN versus OMT. As a consequence all economic models relied on the assumption that the lower SBP levels after RDN would translate into reductions in event rates derived from published studies[50].

The included studies did not report detailed information about the typology, quantities and unit costs of the resources used to realize the RDN procedure, so we found no available evidence to answer AEs **E0001**, **E0002** and **E0009**. This is because all the included models were aimed at estimating the economic impact of a cohort of patients treated with the RDN in reducing cardiovascular events and deaths compared to the standard of care (SoC) during patients' lifetime. The economic models were populated with cost data estimating the clinical management of patients in chronic health states as well as acute events (e.g. stroke, MI), anti-hypertensive pharmacological treatments (SoC) and RDN. Cost data were derived mainly from national administrative databases and also from a literature search.

In Geisler et al.[49] direct medical costs of the treatments were measured in 2010 US Dollars and were derived from published studies, context data and device manufacturers. Cost input parameters used in the model developed by Dorekamp et al.[50] were derived from multiple sources including: German DRG (version 2012), German pharmaceutical price lists, and German fee schedules for doctors and outpatient visits. Health care costs comprised hypertension therapy (RDN or BMT), adverse CVD events and ESRD, and are expressed in Euros for the year 2012. In Gladwell et al.[47] direct medical costs and social care costs were expressed in 2012 UK Pounds and were derived from UK costs data (hospital-based care and ad hoc systematic searches to calculate the costs of the clinical management of patients in chronic health states and the costs of acute clinical events), from the British National Formulary (economic burden of the anti-hypertensive pharmacological treatments), from the manufacturers (cost of the RDN procedure). The economic model by Henry et al.[48] used costs data taken from the Netherlands costs data and literature (clinical management of patients in health states and the anti-hypertensive pharmacological treatments), from the manufacturer (the RDN procedure, including both the procedure and material costs and the screening phase resources). Direct medical costs of treatments and consequences were expressed in 2012 Euros. The findings of the included studies with respect to

the total costs of the comparative treatments resulting from the base-case analysis are reported in Table 14.

We found out that RDN results to be associated with increased healthcare costs during the entire life of patients compared to the standard of care when considering discounted costs. However it appears to be cost saving in two undiscounted analyses in which negative incremental costs are reported[48 49]. As stated by the authors of the included studies, such additional costs are mainly due to the higher initial costs of the RDN procedure.

Efficacy results were measured in life years gained (LYs), quality adjusted life years (QALYs) and median survival in the 4 included economic evaluations. The analysis of the efficacy findings showed that patients undergone RDN gained more life years/median survival as well as higher QALYs compared to those treated with standard of care alone (see Table 14) **(E0005)**. As reported by the authors, the additional health benefit of RDN was associated with the reductions in the risk of clinical events and death, *"resulting in patients spending less time in severe health states with low HRQoL (health related quality of life)"*[48].

The base-case incremental cost-effectiveness ratios (ICERs) reported by all the economic models were under the willingness to pay (WTP) threshold established in the country of reference. The ICER per QALY varied from US Dollars 3,071[49], well below the WTP threshold equal to US Dollars 50,000, to UK Pounds 4,805[47] which is substantially below the NICE WTP thresholds (UK Pounds 20,000-30,000) or to €2,914[48] under the conventional threshold levels used by Zorginstituut Nederland (€10,000-80,000). Finally the ICER per QALY estimated by Dorekamp et al.[50] ranged from €1,512 in men 50 years of age (€1,560 for women) to €62,417 in men 90 years of age (€126,633 for women). ICERs were below the WTP threshold - set at an internationally accepted level of €25,000 to €35,000 – for patients up to 85 years of age[50]. Hence RDN was cost-effective compared to standard of care (see Table 14) **(E0006)**. An analysis by age groups showed that ICER increases with increasing age, due to lower incremental health benefits; specifically the shorter survival time after RDN procedure and smaller assumed reduction in CVD events and death (resulting in lower QALY gains). Consequently, RDN seems to be generally more favourable in younger patients[50].

1099 Table 14: Studies results (base-case) – efficacy, costs, cost-effectiveness.

Study	Cost results		Efficacy results [0005]				Discount rate	Differences in costs and results [0006]	
	Intervention	Comparator	Intervention		Comparator				
Geisler, 2012	Incremental Costs: 2,013US$ (discounted) -1,769US$ (undiscounted)		Median survival: 18.37	QALY: 13.17	Median survival: 17.07	QALY: 12.07	3% costs and benefits per year	ICER (US$/LY): 2,715	ICER (US$/QALY): 3,071
Dorenkamp, 2013	50y M: 32,349€ 60y M: 29,738€ 70y M: 25,434€ 80y M: 17,436€ 85y M: 15,121€ 90y M: 11,605€ 50y W: 31,325€ 60y W: 29,005€ 70y W: 24,584€ 80y W: 17,076€ 85y W: 14,026€ 90y W: 10,729€	50y M: 30,474€ 60y M: 27,149€ 70y M: 22,601€ 80y M: 14,065€ 85y M: 11,703€ 90y M: 7,860€ 50y W: 29,593€ 60y W: 26,961€ 70y W: 22,113€ 80y W: 13,908€ 85y W: 10,612€ 90y W: 6,930€	LY gained: 50y M: 15.69 60y M: 12.99 70y M: 9.72 80y M: 6.27 85y M: 4.69 90y M: 3.47 50y W: 17.91 60y W: 15.12 70y W: 11.58 80y W: 7.35 85y W: 5.36 90y W: 3.83	QALY: 50y M: 14.52 60y M: 11.91 70y M: 8.84 80y M: 5.74 85y M: 4.26 90y M: 3.17 50y W: 16.86 60y W: 14.12 70y W: 10.76 80y W: 6.85 85y W: 4.98 90y W: 3.56	LY gained: 50y M: 14.50 60y M: 12.00 70y M: 9.04 80y M: 5.94 85y M: 4.46 90y M: 3.35 50y W: 16.84 60y W: 14.25 70y W: 10.98 80y W: 7.07 85y W: 5.18 90y W: 3.74	QALY: 50y M: 13.28 60y M: 10.93 70y M: 8.18 80y M: 5.45 85y M: 4.08 90y M: 3.11 50y W: 15.75 60y W: 13.24 70y W: 10.18 80y W: 6.61 85y W: 4.85 90y W: 3.53	3% costs and benefits annually	ICER (€/LY): 50y M: 1,576 60y M: 2,615 70y M: 4,166 80y M: 10,215 85y M: 14,861 90y M: 31,208 50y W: 1,619 60y W: 2,349 70y W: 4,118 80y W: 11,314 85y W: 18,967 90y W: 42,211	ICER (€/QALY): 50y M: 1,512 60y M: 2,642 70y M: 4,292 80y M: 11,624 85y M: 18,989 90y M: 62,417 50y W: 1,560 60y W: 2,323 70y W: 4,260 80y W: 13,200 85y W: 26,262 90y W: 126,633
Gladwell, 2014	11,770UK£ (discounted) 16,965UK£ (undiscounted)	8,810UK£ (discounted) 14,678UK£ (undiscounted)	Incremental LY: 0.5 (discounted) – 1.07 (undiscounted) Incremental QALY: 0.62 (discounted) – 1.19 (undiscounted)				3.5% costs and benefits per annum	ICER (UK£/LY): 5,887 (discounted) 2,146 (undiscounted)	ICER (UK£/QALY): 4,805 (discounted) 1,916 (undiscounted)
Henry, 2015	23,461€ (discounted) 38,190€ (undiscounted)	20,861€ (discounted) 38,226€ (undiscounted)	Incremental LY: 0.78 (discounted) – 1.09 (undiscounted) Incremental QALY: 0.89 (discounted) – 1.20 (undiscounted)				4.0% costs 1.5% benefits per annum	ICER (€/LY): 3,335 (discounted) -33 (undiscounted)	ICER (€/QALY): 2,914 (discounted) -30 (undiscounted)

1100 ***Key:*** *NR, not reported; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; y, year; M, men; W, women; LY, life year.*

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Deterministic, probabilistic and scenario analyses were performed in all studies to assess the uncertainty in the values of the model parameters and to test the robustness and generalizability of the model results **(E0010)**. The base-case scenario tested by Dorekamp et al.[50] included patients aged 60 years which is the mean age of patients in the Symplicity trials. The findings of the deterministic analyses from the 4 studies included are consistent. ICER values were sensitive to: expected lowering effect on SBP with RDN, costs of RDN procedure and baseline SBP. Probabilistic analyses showed that the ICER remains well below the accepted WTP thresholds. In particular the probability that RDN would be cost-effective compared to standard of care:

- ranges from 97% (WTP = US Dollars 30,000 per QALY) to 99.6% when considering WTP = US Dollars 50,000 per QALY[49];
- remains 95% up to an age of 76 and 75 years in men and women respectively at a WTP = €25,000/QALY[50];
- is equal to 100% for a WTP >€12,000/QALY[48].

Finally, scenario analyses were performed in 3 studies[47 48 50] while the remaining study[49] carried out a threshold analysis. One scenario investigated by all the studies assumed smaller treatment effects of RDN in terms of SBP reduction. Assumptions, parameters and results of scenario analyses are represented in Table 15.

Table 15: Scenario analyses

Scenario assumption	Study	Base-case parameters	Scenario Parameters	Study results
Decreased SBP effects after RDN	Dorekamp, 2103	RDN arm → ΔSPB= -20.00 mmHg [Assumption based on Symplicity trials[31 53]]	RDN arm → ΔSBP= -10 mmHg	*"We found even a 10 mmHg decrease to be cost-effective"* (ICER<€8,000 per QALY).
	Gladwell, 2014	RDN arm → ΔSPB= -32.00 mmHg[31]	RDN arm → ΔSPB= -14.13 mmHg[38]	At lower treatment effect, RDN is still cost-effective (ICER=UK£18,849 per QALY). *"Furthermore, RDN results to be cost-effective at the threshold value of UK£30,000 up to a reduction in SPB from baseline of approximately 10 mmHg (…)"*.
	Henry, 2015		RDN arm → ΔSPB= -14.13 mmHg[34]	The ICER for RDN would be equal to €17,270/QALY so *"within the band of acceptable cost-effectiveness thresholds used in The Netherlands"*.
Increased SBP effects after RDN	Dorekamp, 2103	RDN arm → ΔSPB= -20.00 mmHg [Assumption based on Symplicity trials[31 53]]	RDN arm → Δ- SBP = 30 mmHg	*"(…) it resulted in an even better cost-effectiveness of RDN"*.
Shorter duration of RDN effects	Gladwell, 2014	Base-case effect of RDN was assumed to be maintained and continued over time	Retreatment with RDN every 10 years	Discounted ICER increased to UK£11,682/UK£14,312 (per LY/QALY) *"(…) comfortably below the NICE cost-effectiveness thresholds"*.
	Henry, 2015		Waning in RDN effect by 1 mmHg per year and re-treatment after 10 year	*"RDN therapy remains cost-effective with an ICER value of €9,056"*.
Increased age of patients undergoing RDN	Henry, 2015	Average patients age = 58 years[31]	Patients aged >58 years	*"The ICER for RDN falls below €10,000/QALY up to the age of 75"*.
	Dorekamp, 2103	Patients age = 60 years [Assumption based on Symplicity trials[31 53]]	Patients aged >80 years	*"ICER exceeded €35,000 per QALY and thus RDN may only be considered cost-effective at higher WTP thresholds"*.
Considering non-responder rate to RDN	Dorekamp, 2103	NR	Non-responder rate = 30%	*"RDN remained cost-effective even if 30% of patients did not respond to therapy and blood pressure levels persisted at initial elevated systolic levels"* (ICER<€6,000 per QALY).
Decreasing and increasing discounting rates	Dorekamp, 2103	Discount rate = 3% per annum	Discount rate=0% and 5% per annum	NR

Key: *SBP, systolic blood pressure; RDN, renal denervation; Δ, variation; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; WTP, willingness to pay; NR, not reported.*

Scenario analyses showed that RDN was cost-effective even changing the values of parameters. The threshold analyses by Geisler et al.[49] showed that although ICER increases with smaller SBP reductions after RDN it remains cost-effective at the WTP threshold of US Dollars 50,000 per QALY up to a treatment effect less than 11.1 mmHg. In addition authors highlighted that SBP reduction would need to decrease by more than 3 mmHg per year for ICER to exceed the WTP threshold. Finally even assuming that RDN is performed 3 times, every 10 years, it would remain cost effective with an ICER of US Dollars 19,869 per QALY[49].

The authors of the economic studies included in our analysis were all in agreement that RDN is a cost-effective treatment strategy in patients with resistant hypertension in which a significant reduction in systolic blood pressure up to 11 mmHg has been achieved as it might be associated with substantial reductions in cardiovascular morbidity and mortality. Age groups analysis by Dorekamp et al.[50] showed also that RDN provide better cost-effectiveness ratios in younger patients.

Assessment of methodological quality of the studies

We evaluated the quality of the included studies using the checklist for economic evaluations of health programmes[46]. The checklist was grouped in ten sections under three headings: Study design (7 items), Data collection (14 items) and Analysis and interpretation of results (14 items) comprising a total of 35 items. Each item could be answered with 4 options: "yes", "no", "not clear" or "not appropriate". The sections included in the headings are the following: study question, selection of alternatives, form of evaluation (Study design), effectiveness data, benefit measurement and valuation, costing, modelling (Data collection) and adjustments for timing of costs and benefits, allowance for uncertainty, presentation of results (Analysis and interpretation of results).

Based on the checklist, all studies were of medium-high quality, meeting, partially or completely, at least 21 of the 35 items. Henry et al.[48] was the study with high positive answers (26/35) while the lowest positive answer rate was for Geisler et al.[49] (21/35). In all studies the unmet items (with "no" answer) were related to the costing section, specifically the quantification of resources used and the methods for the measurement of quantities and unit costs.

Analysis of the evidence

Based on our systematic review of economic evaluations RDN was a cost-effective option in resistant hypertensive patients. The models showed that although RDN produced higher costs

compared to the SoC, the longer survival and lower assumed risk of clinical and cardiovascular events and deaths associated with RDN more than offset its high initial procedural costs.

However the clinical effectiveness findings on RDN from our systematic review (see Chapter 5) undermine the conclusions drawn by economic evaluations. The majority of included studies comparing RDN versus OMT reported a lack of additional effects associated with RDN, so it is unclear how such a treatment could be cost-effective. To answer this crucial issue we conducted a more critical and careful analysis on the assumptions underlying the economic models assessed. In particular we focused on the clinical parameters used as inputs of the economic models.

The premise of our analysis is that we found no study assessing hard clinical endpoints (e.g. cardiovascular mortality, all causes mortality, stroke, etc.) in the cohort of patients who had either undergone RDN or were treated with OMT at long term follow up. The clinical benefits of both RDN and OMT were measured using a surrogate clinical outcome, namely the SBP reduction from baseline. On the basis of the SBP reductions resulting from the treatments and observed in the RCTs, the associated probabilities/risks of the occurrence of acute clinical events and CVD/non CVD death were extrapolated using multivariate risk equations or were derived from published evidence[3]. Therefore the clinical parameters used as inputs of the economic models were based on several assumptions and extrapolated using multivariate risk equations. The assumptions on the clinical characteristics of the cohorts and the treatments' effect on SBP used to populate the models are reported in Table 16.

Deterministic sensitivity analyses performed within the studies showed that models' results are mainly sensitive to the effect size of RDN in terms of SBP reduction. The majority of the economic studies included (3/4) assumed a SBP reduction equal to the SBP reduction recorded in the Symplicity HTN-2 trial at 6 months follow up (-32 mmHg). The remaining study assumed a SBP reduction of 20 mmHg based on the results of the more recent Symplicity HTN-1 trial[40]. However two issues need to be considered:

- the uncertainty around RDN effect size as well as the duration due to the lack of long-term data and the recent results from the HTN-3 clinical trial[34];
- the lack of additional effects associated with RDN resulting from our systematic review.

[3] A more detailed description of the models' structure is reported in the previous paragraph.

Table 16: Assumptions underlying the economic models

Study	Cohort clinical characteristics	SBP reduction
Geisler, 2012	- Cohort was assumed to have the same clinical characteristics of the Symplicity HTN-2 trial population. - Cohorts were assumed not to include patients with prior cardiovascular events, manifest CHD or ESRD. - Patients in both cohorts were assumed to be maintained on the antihypertensive medications from their baseline.	- SBP reduction was assumed to be equal to 32 mmHg after RDN based on the Symplicity HTN-2 trial results at 6-month follow up. - The treatment effect of RDN was assumed to be maintained and continued over the lifetime horizon.
Gladwell, 2014	- Cohort was assumed to have the same clinical characteristics of the Symplicity HTN-2 trial population. - Cohorts were assumed to not include patients with prior cardiovascular events, manifest CHD or ESRD.	- SBP reduction was assumed to be =32 mmHg after RDN based on the Symplicity HTN-2 trial results at 6-month follow up. - The treatment effect of RDN was assumed to be maintained and continued over time. - Patients allocated to the SoC arm were assumed to have a continuing SBP=178 mmHg.
Henry, 2015	- Cohort was assumed to have the same clinical characteristics of the Symplicity HTN-2 trial population. - Patients allocated in the RDN arm were assumed to remain on the same pharmacological treatment after RDN.	- SBP was assumed to decrease by 32±23 mmHg within the RDN group and SBP was assumed to increase by 1±21 mmHg in the Soc group based on the Symplicity HTN-2 trial results at 6-month follow up. - The treatment effect of RDN was assumed to be maintained and continued over a patient's lifetime. - Patients allocated to the SoC arm were assumed to have a continuing SBP of 178 mmHg.
Dorenkamp, 2013	- Patients enrolled were assumed to be free from prior CVD or renal disease. - Patients allocated in both RDN and BMT groups were assumed to remain on the same 3-drug therapy.	- RDN was assumed to result in sustained SBP reduction=20 mmHg. - In BTM arm the elevated SBP was assumed to remain unchanged. - The reduction in SBP associated with RDN was maintained over the lifetime of the patient. – Beneficial effects of RDN, other than those consequent to blood pressure reduction, were not included in the model.

Our meta-analysis did not show any effect of RDN on SBP at 6-months follow up in the ambulatory setting [WMD -2.80 (95% CI -6.08 to 0.47); I^2 50%, P = 0.14] as well as in the home setting [WMD -1.52 (95% CI -4.39 to 1.35); I^2 0%, P = 0.64]. The pooled estimate of SBP reduction in the office setting suggested a relevant but not statistically significant effect of RDN over SoC for this outcome at 6-months follow up [WMD -19.03 (95% CI -38.98 to 0.92]. The main reason of

the last finding may be due to the sizeable heterogeneity of results ranging from a SBP reduction of 2.39 mmHg[34] to 31.00[31] after RDN (see Chapter 5).

As already described the probabilistic and scenario analyses undertaken to test the models assessed the cost-effectiveness of RDN at lower treatment effect (see Table 15) up to a SBP reduction equal to 10 mmHg. However the available evidence did not confirm an actual incremental effect of RDN over SoC in terms of SBP reductions. Another issue to be considered is the duration of RDN effect since the economic analyses were conducted using a life-time horizon. All models were based on the assumption that the short-term effect of RDN was maintained and continued over the lifetime horizon (see Table 16). However the lack of long-term data and the results from the HTN-3 clinical trial[34] make it impossible to confirm this assumption.

To populate the economic models extrapolations were required well beyond the length of available data from RCTs. Hence the findings from the economic models rely heavily on the predictive equations; over all the multivariate risks equations used to estimate the probabilities of acute clinical events and deaths. As regards the Framingham risk equations, Henry et al have stated that there is evidence that such risk equations, based on a US population, could *"overestimate the risk of cardiovascular events in European populations*". So *"(…) the true predictive power of Framingham risk equations in this resistant hypertension population is unknown"*[48]. Hence the clinical benefits of RDN could be uncertain and that could be reflected in economic evaluations.

Based on the deterministic analyses, ICERs were sensitive to the baseline SBP. The economic models assumed that the cohort of patients have the same clinical characteristics of the Symplicity HTN-2 trial population with a mean baseline SBP = 178 mmHg - in spite of the concurrent use of 3 antihypertensive agents, including a diuretic, at maximum tolerated dose - which is higher than the defined SBP value for resistant hypertension (>140 mmHg)[2]. Such a higher SBP level at baseline could overestimate the actual effect of RDN in terms of SBP reduction in the real world.

The models relied on the assumption that in the SoC/OMT cohort the SBP levels remain unchanged according to the findings from Symplicity HTN-2 trial[31]. However one small trial[44] reported dominance of carefully adjusted and supervised OMT versus RDN in which greater attention was to titration and compliance of patients to pharmacological treatments. All 4 groups of modellers did not allow for this real-world occurrence, when therapy is changed according to patients' responses to it.

Finally for unexplained reasons the effects of RDN on diastolic blood pressure, which is part of the definition of hypertension, were not taken into consideration.

Cost analysis

To estimate the cost of the RDN procedure in the Italian context we performed a search of published studies reporting Italian cost data. In addition we submitted a questionnaire to manufacturers Agenas met in face-to-face meetings asking for information including cost data in our country (see Appendix 4).

The clinical care pathway of patient treated with renal denervation is structured in three main phases: pre-intervention, intervention and follow up. For each phase we identified the typology of resources needed, the number of units to be used and the unit costs. Data referring on resource use and quantities were derived mainly from the previous systematic review on renal denervation by Agenas[45], manufacturers and clinical experts. The unit costs and ranges were collected mostly from national legislative sources and (if missing) from the micro-costing analysis performed in the Veneto Region[45]. The cost of the devices was provided by manufacturers who filled in the questionnaire. Given the prices provided we estimated the mean cost of the renal denervation catheter to calculate the overall cost of the RDN procedure. The lowest and highest prices (range values) of the RDN catheter were used to carry out further costing analyses. The procedural times needed to perform the RDN, according to the manufacturers, were very similar ranging from 23 to 30 minutes (up to 60 minutes for the first procedure). We considered 30 minutes as average procedural time. Results of cost analysis are reported in Table 17.

Table 17: Cost analysis - resources use and costs

Item	Number of units	Unit cost (range)§	Comment
Pre-intervention phase			
Specialist visit	1	€12.91 (11.90-18.00)	Ambulatory tariff, code 89.01[15]
Complete abdominal CT scan (with or without contrast)	1	€158.04 (158.00-279.20)	Ambulatory tariff, code 88.01.6[15]
24-hour ambulatory blood pressure	1	€41.32 (41.00-52.80)	Ambulatory tariff, code 89.61.1[15]
Creatinine test	1	€1.60 (1.60-3.60)	Ambulatory tariff, code 90.16.4[15]
Cistatine C test	1	€15.20	Ambulatory tariff, code 90.13.A[45]
Urine test	1	€2.17 (2.05-3.00)	Ambulatory tariff, code 90.44.3[15]
Haemoglobin test	1	€7.41 (7.40-13.60)	Ambulatory tariff, code 90.28.1[15]
Intervention phase			
Arteriography	1	€216.40	Ambulatory tariff, code 88.45[45]

Operating room time	60 min (mean time including patient preparation)*	€559.10/h	Full cost[45]
Procedural time	30 min*		Mean time (from manufacturers)
Cardiologist/radiologist/vascular surgeon	1/2 for 30 min*	€62.06/h	Full cost[45]
Nurse	1/2 for 60 min*	€26.32/h	Full cost[45]
Radiology technician	1/2 for 30 min*	€ 26.10/h	Full cost[45]
Anaesthesiologist	0/1 for 30 min*	€62.06/h	Assumption**
Analgesia droperidol, morphine sulphate		€4.30	Full cost[45]
Cardiology ward	1/2 d*	€95.40/d	Full cost[45]
Renal denervation catheter	1	€4,700 (2,500-8,000)	Mean price (from manufacturers)
Follow up phase			
Creatinine test (1 week and 6 months)	2	€1.60 (1.60-3.60)	Ambulatory tariff, code 90.16.4[15]
Potassium test	1	€1.02 (1.00-2.00)	Ambulatory tariff, code 90.37.4[15]
Sodium test	1	€1.02 (1.00-2.00)	Ambulatory tariff, code 90.40.4[15]
Arterial ultrasound scan	1	€68.40	Ambulatory tariff, code 887451 (Veneto Region)[15]
24 hours ambulatory blood pressure	1	€41.32 (41.00-52.80)	Ambulatory tariff, code 89.61.1[15]
Specialist visit	2/3	€12.91 (11.90-18.00)	Ambulatory tariff, code 89.01[15]

[$] Ranges, representing the min and max charge applied in the Italian Regions, were taken from the document by Morandi I., (Agenas). "Prestazioni specialistiche ambulatoriali. Confronto tra le tariffe nazionali ex DM 18.10.2012 e le tariffe regionali vigenti al 31.12.2014" [http://www.agenas.it/prestazioni-specialistiche-ambulatoriali-confronto-tra-tariffe] with the exception of the cost of renal denervation catheter.

* Data provided by manufacturers.

** We assumed for anesthesiologist the same fee of the other specialist physicians.

Key: *DM, ministerial decree; DGR, Regional decree; CT, computed tomography; min, minutes; h, hour(s); d, day(s).*

The total cost of the pre-intervention phase is €238.65, ranging from €237.15 to €385.40 considering the minimum and maximum regional ambulatory tariff. To be noted that the highest costs occur in the intervention phase. Considering the average cost of the catheter (€4,700) the total cost of this phase ranges from €5,645.60 to €5,842.43 depending on the staff involved in the procedure. Assuming consumption to be the mean number of units for each resource, the intervention phase costs €5,744 on average. At the lowest cost of the device (€2,500) the intervention phase average cost decreases to €3,544.20 (range: €3,445.60-€3,642.43) whereas it amounts at €9,044.02 (range: €8,945.60-€9,142.43) when considering the highest device cost equal to €8,000. The cost of the device accounts for 72%-88% of the total interventional costs.

Finally the total costs incurred in the follow up phase are equal to €140.78 (range[4]: €138.40-€168.40) when considering 2 specialist visits at follow up. Follow up costs increase at €153.69 (range[5]: €150.30-€186.40) if 3 specialist visits are planned. In conclusion the overall cost of RDN procedure is on average €6,129.90 with a range from a minimum value of €3,821.15 to a maximum value of €9,714.23 (Table 18).

Table 18: RDN costs - summary

Phase	Average cost	Range (Min-Max)	Notes
Pre-intervention	€238.65	€237.15-€385.40	*Range values are based on different regional ambulatory tariffs*
Intervention	€5,744.02	€3,445.60-€9,142.43	*Range values are measured according to different cost of catheters and the resources used in the procedure*
Follow up	€147.24	€138.40-€186.40	*Range values are based on different regional ambulatory tariffs and the number of follow up visits*
Total	**€6,129.90**	**€3,821.15-€ 9,714.23**	

Pre-intervention and follow up costs are marginal accounting for at least 2% (up to 10%) and 1% (up to 5%) of the overall costs associated to RDN procedure respectively. The higher costs are incurred in the intervention phase which accounts for at least 86% (up to a maximum of 96%) of the overall costs. The device is the highest cost item and represents at least 59% of the overall costs (up to a maximum of 86%).

Conclusions

The analysis of the available economic evidence showed that all the economic models are based on short term findings and assumptions that haven't been proved yet by clinical trials; so results from existing economic evaluations should be interpreted and used with caution. Further economic studies based on final clinical outcomes as well as long term clinical data are needed. Such

[4] The range values of the total costs at follow up are estimated on the basis of the minimal and maximal regional ambulatory tariff.

[5] The range values of the total costs at follow up are estimated on the basis of the minimal and maximal regional ambulatory tariff.

analyses should be able to estimate the consequences of RDN in terms of acute clinical events and CVD/non CVD death with more reliability.

The cost of the RDN procedure within the Italian National Health System was estimated on the basis of the clinical care pathway of patient treated with RDN. The overall cost of RDN was on average €6,133 – consistent with the included economic studies - ranging from a minimum value of €3,821.15 to a maximum value of €9,709.14. The device accounts for the most part of the overall RDN cost.

7. Discussion

Transcatheter renal denervation is mentioned in the latest ESH-ESC guidelines as one of the two non-drug therapies for treatment-resistant hypertension *(class of recommendation IIb, level of recommendation C).* The present HTA report focused on the impact of the introduction and use of renal denervation systems in the management of subjects with treatment-resistant hypertension. Since OMT is currently the standard management strategy for such patients, it was selected as comparator for the analyses.

As of today, five manufacturers are present on the Italian market of renal denervation systems (Boston Scientific, Medtronic, ReCor Medical, St. Jude Medical, and Terumo). Ablation catheters are available in different designs and offer different performance in terms of ablation time.

From 2010 to 2014, the total number of percutaneous renal denervation procedures was 420 (annual procedures ranged between 25 and 166). Patients were on average 61.35 years old and 61.2% of them was male.

Using data from published literature, we summarised the evidence of the effects of adding renal denervation to OMT in refractory hypertension. Overall, we identified and examined 10 publications reporting 7 trials, 6 of which were randomised. The review's outcomes were: change in average measurements of systolic and/or diastolic blood pressure; all causes mortality; cardiac mortality; as well as major cardiovascular events including myocardial infarction, heart failure, and stroke.

Despite initial enthusiasm with the results of the first two trials[31 41], the results of our meta-analysis do not show any significant reduction of either systolic or diastolic blood pressure at 6 months' follow-up in an ambulatory setting. In an office setting, pooled data in meta-analysis at 6 months' follow-up were compromised by a highly significant heterogeneity. In a home setting, the results from only two studies at 6 months' follow-up showed a reduction in diastolic pressure in favour of renal denervation but not in systolic pressure.

The heterogeneity of the results from the included trials may have different explanations. While the OSLO study showed a higher decrease in the control group than in the denervation group[44], at the other end of the spectrum the SYMPLICITY HTN-2 trial[31]) reported an impressive reduction in office measurement (33 mmHg for systolic and 12 mmHg for diastolic). One important reason for this diversity can be attributed to the criteria used to define resistant hypertension. For example, in the OSLO study the average systolic/diastolic pressure values at entry were much lower [156 (12.6) / 91 (14.9) mmHg] than the corresponding values in the SYMPLICITY HTN-2 trial [178 (SD18) / 97 (SD16) mmHg]. The SYMPLICITY HTN-2 trial had similar basic characteristic with SIMPLICITY HTN-

1 trial[41] and showed similar impressive results in favour of renal denervation. However, these results were not observed in the SYMPLICITY HTN-3 trial that had similar pressure values to the two previous trials. Unlike these trials, the SYMPLICITY HTN-3 was at low-risk of bias and the sample size was large enough. Other reasons of heterogeneity may include the interventions used in the control group, the technique used for blood pressure measurement, and adherence of patients to medication. Assessing overall and cardiac mortality, no death occurred in the trials except in one[34] (2 in the denervation group and 1 in the control group). However, the time of follow-up was not sufficient to reach a robust conclusion. With the exclusion of two trials[41 43] in which no events occurred, all the trials reported the occurrence of cardiovascular events. In general, the proportion of such events in these trials was similar between the groups under comparison. Of notice is the incidence of 5 atrial fibrillation events that occurred in the denervation group against none in the control group (although there was no statistically significance)[34]. The main limitation of all the included trials is that the time of follow-up was not sufficient to reach a robust conclusion on the occurrence of cardiovascular events. The frequency of adverse outcomes was higher in the denervation groups that in the control groups but the differences were not statistically significant.

One explanation for the apparent lack of effect could be the testing and use of RDN in a population who have renal arteries which are damaged by the very high blood pressure, refractory in most cases to treatment. In such patients the endothelium is likely to have been extensively damaged and any pressure control pathways already compromised.

Results from currently running studies, especially for NCT01570777 and NCT01888315 may clarify the real effectiveness of renal denervation in comparison with OMT.

The available economic evidence shows that RDN is a cost-effective option in resistant hypertensive patients. However this finding was inconsistent with the lack of additional effects associated with RDN from clinical studies comparing RDN with OMT. To explain this crucial issue we analysed in more detail the clinical parameters underlying the economic models, comparing them with the results of available clinical evidence. In the economic evaluations the clinical benefits of both RDN and OMT were always measured exclusively as SBP reduction from baseline or reduction in events linked to a reduction of SBP. SBP is an incomplete surrogate clinical outcome. Sensitivity analyses showed that the results of the economic models are mainly sensitive to the effect size of RDN in terms of SBP reduction. The majority of the economic studies assumed a SBP reduction equal to 32 mmHg as resulted from the Symplicity HTN-2 trial at 6-months follow up. However the lack of long-term data and the recent results from the HTN-3 clinical trial[34] undermine this assumption. Our systematic review did not confirm an incremental effect of RDN over OMT in terms of SBP

reductions. In addition the assumption that the short-term effect of RDN was maintained and continued over the lifetime horizon was not confirmed by the lack of long-term data and the results from the HTN-3 clinical trial[34]. The multivariate risks equations used to estimate the probabilities of events occurring well beyond the length of available data from RCTs are based on specific populations that could not be representative of European or Italian populations. The SBP level at baseline assumed in the models – higher than the defined SBP value for resistant hypertension - could overestimate the actual effect of RDN in terms of SBP reduction in the real world. The models assumed that in the OMT cohort the SBP levels remain unchanged according to the findings from Symplicity HTN-2 trial. However one small trial reported dominance of carefully adjusted and supervised OMT versus RDN when greater attention was paid to drug titration and compliance of patients to pharmacological treatments. All models did not allow for this real-world occurrence, when therapy is changed according to patients' responses to it. Finally, for unexplained reasons, the effects of RDN on diastolic blood pressure, which is part of the definition of hypertension, were not taken into consideration. The costs of the procedure in Italy are similar to the costs reported in the included studies. The greatest cost accrued in the procedure is that of device purchase.

8. Recommendations

We recommend awaiting the results of well-designed and adequately followed up trials assessing the impact of RDN on major cardiovascular events before investing further and using the technology. Such trials should be followed by good quality economic evaluations based on realistic assumptions.

List of acronyms and abbreviations

AE: Assessment element

BMT: Best medical therapy

CBA: Cost-benefit analysis

CCT: Comparative controlled trial

CE: Conformité Européenne

CEA: Cost-effectiveness analysis

CHD: Coronary heart disease

CMA: Cost-minimization analysis

COI: Competing interests

CRD: Centre for Reviews and Dissemination

CUA: Cost-utility analysis

CVD: Cardiovascular

DBP: Diastolic blood pressure

ESRD: End-stage renal disease

EU: European Union

FDA: United States Food and Drug Administration

ICD-9-CM: International Classification of Diseases - 9th Edition-Clinical modification

HF: Heart failure

HTA: Health Technology Assessment

HRQoL: Health related quality of life

ICD: International Statistical Classification of Diseases and Related Health Problems

ICER: Incremental cost-effectiveness ratios

LY(s): Life year(s)

MeSH: Medical Subject Headings

MI: Myocardial infarction

NR: Not reported

OMT: Optimal medical therapy

QoL: Quality of life

QALY: Quality-adjusted life year.

R-AMSTAR: Revised Assessment of Multiple Systematic Reviews

RCT: Randomised controlled trial

RDN-RD: renal artery denervation

SBP: Systolic blood pressure

SoC: Standard of care

WTP: Willingness to pay

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