Joint Position Paper on Renal Denervation of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) and the European Society of Hypertension (ESH)

[1]Jonathan Moss, [2]Anna-Maria Belli, [3]Antonio Coca, [4]Michael Lee, [5]Giuseppe Mancia, [6]Jan Peregrin, [7]Josep Redon, [8]Jim Reekers, [9]Costas Tsioufis, [10]Dierk Vorwerk, [11]Roland E. Schmieder

1 Jonathan Moss
Interventional Radiology Unit, North Glasgow Hospitals, Gartnavel General Hospital, Glasgow, United Kingdom,
✉ Jonathan.Moss@glasgow.ac.uk

2 Department of Radiology, St George's Hospital, United Kingdom,
Anna.belli@stgeorges.nhs.uk

3 Hypertension and Vascular Risk Unit.Department of Internal Medicina.Hospital Clínic (IDIBAPS), University of Barcelona, Barcelona, Spain
acoca@clinic.ub.es

4 Department of Radiology, Beaumont Hospital, Dublin, Ireland
mlee@rcsi.ie

5 University of Milano-Bicocca, Milan, Italy
giuseppe.mancia@unimib.it

6 Department of Diagnostic and Interventional Radiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic
Jan.Peregrin@seznam.cz

7 Research Institute INCLIVA, University of Valencia and CIBERObn, ISCIII, Madrid, Valencia, Spain
josep.redon@uv.es

8 University of Amsterdam Department of Radiology, G1.206, Academic Medical Centre, Amsterdam, Netherlands
j.a.reekers@amc.uva.nl

9 National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece
ktsioufis@hippocratio.gr

10 Institute of Radiology, Klinikum Ingolstadt, Ingolstadt, Germany
dierk.vorwerk@klinikum-ingolstadt.de

11 University Hospital Erlangen, Nephrology and Hypertension, Erlangen, Germany
Roland.Schmieder@uk-erlangen.de

Introduction

Renal denervation (RDN) was reported as an exciting new development for the treatment of resistant hypertension (RHTN) in 2009 [1]. This minimally invasive technique gained rapid acceptance across the globe although the majority of procedures were carried out in one country (Germany). The Symplicity HTN-2 randomised trial [2] added further supportive evidence (both efficacy and safety) and by late 2013 no fewer than 60 companies were investing in the technology. The global potential is obvious with between 5-10% of hypertensive patients (a third of the world population) falling into the "resistant" category. The Simplicity HTN-3 [3] was designed and delivered as a regulatory study to satisfy the demands of the FDA for the US market. It was the largest study to date (n=535) and was novel in several respects, being single-blinded with a sham arm and using ambulatory blood pressure (ABPM) as an entry and outcome measure. The initial results of this trial were released by Medtronic (the funder and manufacturer) in the form of a press release in January 2014 stating that although the study had met its safety endpoint, the efficacy primary endpoint of reduction in office blood pressure had not been met. The peer-reviewed paper was published in the NEJM in March of the same year [3]. It is difficult to exaggerate the fallout from this trial and its effect across the globe was almost immediate and perhaps also exaggerated. There has been much criticism and praise of HTN-3 and a wide range of opinions persist. The aftermath has included a failure of FDA approval, a continued moratorium on routine use throughout

many parts of the world, an estimated reduction in procedural activity of 84% [4] across Western Europe and withdrawal of devices from the market by two of the seven leading manufacturers.

This joint position paper by the two societies attempts to review the evidence and provide some guidance and forward direction for this new and potentially still valuable technique.

A review article of this Joint Position Paper has been published concurrently in the CardioVascular and Interventional Radiology (CVIR) and the Journal of Hypertension. Permission to reproduce this review article can be granted by one of the two copyright holders.

Executive Summary

- Resistant hypertension is a subset of uncontrolled hypertension accounting for 5-10% of all patients with hypertension. Resistant to conventional treatment, these patients are a very high-risk group and any effective treatment should lead to a marked reduction in cardiovascular morbidity and mortality.

- Renal denervation is a new minimal invasive treatment option for this group.

- There do not appear to be any major safety issues although this may reflect limited and incomplete long-term follow-up. Isolated cases of renal artery stenosis sometimes with worsening renal function have been recently published. Further long-term follow-up is mandatory and should include dedicated renal artery imaging such as magnetic resonance angiography.

- The evidence for efficacy is mixed with conflicting results. Initial single-arm studies and early non-blinded randomised trials (Symplicity HTN-2) showed a significant reduction in office BP at 6 months in the majority of patients treated. Three-year follow-up of some of these studies has shown sustained benefit. There was no blinding, no sham arm and no routine use of ambulatory blood pressure (ABPM) in these studies.

- The Symplicity HTN-3 FDA regulatory randomised trial included a sham arm and used ABPM in the largest trial to date (n=535). Therefore it addressed many of the shortcomings of the earlier trials. The results published in March 2014 showed a failure to achieve the primary efficacy outcome in reducing office blood pressure at 6 months compared to the sham procedure. The safety endpoint was met with a major adverse event rate of 1.4%.

- The HTN-3 trial was well designed but has been criticised in several respects. One hundred and eleven different interventionists treated the 364 patients in the active arm (34% of operators only carried out a single procedure). The majority of patients did not have a successful 4 quadrant ablation.

- The anatomical studies of human renal nerve anatomy are limited and inconsistent and further research is needed to guide RDN devices for the future.

- RDN is currently severely hampered by having no easy method to measure the completeness of denervation, which largely remains a “blind technique”.

- Subgroup analyses of the HTN-3 cohort suggest that RND may be of more benefit in the Caucasian population than the African-American.. Further research into this and other phenotypes, that may benefit, is needed.

- Variations in the use of aldosterone antagonists and change of medication in HTN-3 may have introduced confounders and also overall drug compliance in both groups is questioned.

- As a result of HTN-3 there has been a dramatic reduction in the use of RDN in all countries in the order of 80% and two major companies have withdrawn from the market.
- The guidance technologies applicable to RDN (for example ultrasound) continue to evolve and may offer a more effective denervation in the future.

- This group remains interested in RDN although accepting high-quality research is needed before widespread adoption of this expensive technology. This research should include sham arms, use of ABPM to select and monitor patients, objective assessment of drug compliance and long-term assessment of the renal artery and renal function. These trials should be conducted in high-volume specialist centres with the appropriate physician expertise in hypertension management supported by well-trained and audited interventionists.

- There are insufficient data to inform on the role of RDN in other conditions such as cardiac and renal failure and again further research is encouraged.

Methodology

CIRSE and the ESH produced this joint position paper using the following process. The formal decision of the two societies to draft a multidisciplinary joint position paper was taken in November 2013, following discussion on potential benefits of a joint statement on the occasion of the CIRSE Annual Meeting 2013 in Barcelona.

Both societies identified and nominated recognised experts as members of the joint writing group for the document. In the case of CIRSE, the Renal Denervation Task Force, an already established group of senior interventional radiologists and CIRSE members with significant experience in performing renal artery denervation, represented the society in the working group. In the case of ESH, the eminent members of the joint writing group were selected by the society's council, based on their expertise.

In a workshop in early January 2014, the group agreed on the purpose and structure of the document, as well as its main contents, based on a preceding conceptualisation of documents of relevance and timelines.

Shortly after the workshop, the announcement that SYMPLICITY HTN-3, the US-based pivotal trial in renal denervation for treatment-resistant hypertension, failed to meet its primary efficacy endpoint raised serious concerns among experts regarding the future utility of this therapy. In order to include all relevant data in the position paper and avoid hasty conclusions, the joint writing group decided to postpone the drafting process until the publication of the full HTN-3 results. Following the publication of the results, a new timeline for the drafting process was set.

In the drafting process, an in-depth literature review was performed using electronic medical literature databases. A critical review of currently available position statements, peer-reviewed articles and regulatory documents in the field of renal denervation was performed with regard to methodology, results and conclusions. The qualitative weight of these articles was evaluated and used to write the document such that it contains evidence-based data, when available. In addition, manufacturers of currently CE-marked RDN devices were contacted by email and requested to provide information on their currently marketed devices, as well as ongoing and planned studies in the field of RDN as of May 2014. This information was checked against other available sources and publications.

All chapters were submitted by August 2014, and a first draft version of the document was compiled and circulated among all authors for further input and criticism during a 1-month comment period. A second drafting workshop was held at the CIRSE Annual Meeting in September 2014 in Glasgow. In this meeting, the group jointly reviewed the draft document and discussed all comments and suggested changes from the authors. All agreed changes and edits were implemented and a second version of the joint position paper was circulated for review by the group in June 2015.

In a teleconference in September 2015, the authors agreed on several revisions to be made to create the final document, including the inclusion of the most recent trials, thereby extending the stopping date for data and CE-marks to September 2015. The agreed edits were again implemented and circulated for a third critical review by the group in December 2015. Agreement was reached on all statements in this document without the need for utilising modified Delphi consensus techniques. Prior to its publication, the CIRSE Executive Board and the ESH Council endorsed the document.

The drafting process of this joint position paper allowed for an extensive exchange among interventional radiologists and hypertension specialists, and achieved a consensus document all authors agreed with. However, the negative results of the first randomised controlled trial with sham control of this therapy that were published during the drafting process had a significant impact on the ongoing assessment. The publication of this position paper intervenes at a point in time where renal artery denervation seems to have lost its momentum in Europe, but the joint writing group deems it all the more important to give a comprehensive account of this therapy, including the potential benefits and urgent need for more clinical data.

Rationale

Several pathophysiological data support the concept that renal denervation has a blood pressure (BP) lowering effect, giving this procedure a good rationale. Evidence in both animals and man show that sympathetic nerve fibres to the kidney exert a "tonic" vasoconstrictor influence on afferent and efferent arterioles, thus raising vascular resistance at a site that accounts for 20-25% of the total resistance of the entire systemic circulation [5, 6]. Furthermore, both via their haemodynamic effects and via a direct influence on the juxtaglomerular cells, efferent sympathetic nerves continuously stimulate renin release, with an increased production of angiotensin II, adding to the vasoconstriction and favouring sodium and water retention [7-9]. The latter is further enhanced by a direct influence of renal efferent nerves on tubular cells, increasing sodium reabsorption [10]. All this is likely to be more pronounced in hypertension, which is characterised by a sympathetic activation proportional to the BP increase [11, 12], with a further elevation of nerve traffic in treatment resistant hypertension [13]. It may be even more pronounced in heart failure in which sympathetic activation and neural renal vasoconstriction are especially marked [14].

Renal sympathetic nerves also include afferent fibres originating from receptors in the kidney and renal pelvis. These connect to the spinal cord and brain and cause, when stimulated, a marked blood pressure increase, a striking vasoconstriction of several regional beds and alterations of contralateral renal function [10, 15, 16]. Most importantly, the effects of afferent renal fibres is not confined to their stimulation (sometimes obtained in a non-physiological fashion such as electrically)

because both renal denervation and selective section of afferentrenal fibres where they enter the spinal cord (posterior root rhizotomy) has been found to delay or prevent the BP rise in experimental models of hypertension [9], documenting the continuous nature of their excitatory neural influence.

Patient Selection

This has been recently reported in the 2013 ESH/ESC hypertension guidelines [[17] and the reader is referred to that document]. RDN is currently restricted to patients with true essential resistant hypertension, i.e. those who maintain office systolic blood pressure (SBP) ≥ 160 mmHg or office diastolic blood pressure (DBP) ≥ 110 mmHg, with 24h-ambulatory BP levels >= 130/80 mmHg, despite treatment with ≥ 3 antihypertensive drugs at full dose, including a thiazide diuretic.

Figure 1: Causes of Resistant Hypertension

Resistant hypertension due to incorrect diagnosis or inadequate treatment

Apparent Resistant Hypertension
· Non compliance with treatment
· White coat hypertension
· Inadequate drug combinations or drug doses

True Resistant Hypertension
· Medication and illicit drugs use
- Drugs (weight loss medicines, ...)
- Herbal medicines
- Illicit drugs (cocain, ...)

· Associated clinical factors
- Excessive salt and alcohol consumption
- Obesity
- Obstructive sleep apnea

· Identifiable causes
- Primary aldosteronism
- Renovascular disease
- Chronic kidney disease
- Pheochromocytoma, Cushing‘s
- Aoritic coarctation

· No identifiable causes:
“Essential” Resistant Hypertension

The evaluation, confirmation of the indication and follow-up of patients after RDN should be performed in hypertension clinics at specialised centres and the RDN procedure must be performed by experts in renal arterial intervention. Evaluation by the hypertension clinic is essential, because of all the patients referred for RDN with a diagnosis of apparent resistant HT, around 70% are excluded for various reasons, most commonly the normalisation of BP after correct adjustment of the initial treatment prescribed, detection of a white coat effect, detection of secondary causes of HT, and anatomical abnormalities of the renal arteries [18, 19].

It would be desirable to have predictors of efficacy of the response to RDN (usually defined as a decrease of ≥ 10 mmHg in office SBP). Unfortunately, only the magnitude of baseline SBP levels is determinant of the magnitude of the BP reduction after RDN [20, 21]. Recent reports indicate that impaired baroreflex sensitivity [22] or increased plasma noradrenaline [23] may be predictors of BP response to RDN, although the sensitivity and specificity of these predictors requires confirmation in large cohorts.

For all these reasons, the evaluation protocol of patients eligible for RDN should be strict and systematic, with two main objectives:

1. To confirm that patients referred with apparent resistant HT are true essential resistant HT patients and to exclude patients with pseudoresistant HT due to a white coat effect or who do not comply with prescribed treatment, and patients with true resistant HT due to secondary causes of HT or concomitant clinical conditions leading to a reduction in the effect of anti-hypertensive drugs [17-19, 24, 25]. Figure 1 summarises the causes of resistant HT and Table 1 shows the list of tasks to be performed in patients eligible for RDN.

2. To determine the anatomy of the renal arteries and confirm they are suitable for RDN [18, 19].

Assessment of renal arteries prior to renal denervation

It is essential to image (MRA or CTA) the renal arteries prior to RDN. The main aim of imaging is two-fold, firstly to exclude renal artery stenosis and secondly to determine if the arteries fulfil the anatomic criteria for the particular device to be used. Imaging requirements for RDN:

- Single renal artery
- Renal artery diameter ≥ 4mm
- 2cm main renal artery from ostium before branch vessel
- No significant renal artery stenosis
- No previous renal angioplasty or stent

Multiple renal arteries are found in approximately one third of the patients. Early branching (< 2 cm from the aorta) was seen in 21% of the left renal arteries and in 15% of right renal arteries [26]. It is not surprising therefore that a significant

minority of patients (10-20%) referred for RDN are excluded because of anatomical constraints. This may change with evolving technology.

Table 1: List of tasks in the selection of patients by the expert team in managing resistant hypertension (hypertension unit)

- Confirmation of office systolic blood pressure ≥ 160 mmHg, mean of 3 visits, and/or diastolic blood pressure ≥ 110 mmHg.
- Confirmation of current anti-hypertensive treatment with appropriated doses of 3 or more drugs with different mechanisms of action, one of which is a thiazide (or loop) diuretic. If possible, response to spironolactone at a dose of 25-50 mg/d should be observed for a month before RDN is indicated.
- Confirmation of true resistant hypertension by 24-ABPM levels >= 130/80 mmHg (rule out white coat HT)
- Rule out non-compliance with therapy.
- Rule out excessive salt intake (Na + excretion/24h> 300 mmol) and alcohol intake (pure alcohol intake > 30 g/day; or > 15 g/day in women).
- Rule out consumption of pressor substances or drugs
- Rule out secondary hypertension

Recommendations for Follow-up

After RDN, patients require follow-up to assess reduction of BP levels and cardiovascular risk as well as changes in renal function. Moreover, since the procedure is still relatively new and under evaluation, additional data has to be collected in a prospective way to better understand the potential benefits and caveats. The need for long-term data collection cannot be over-emphasised. It is necessary to check the efficacy of RDN not only in terms of BP values, metabolic parameters and renal function but also the impact on hypertension-induced organ damage and glucose metabolism. Information about systemic or local unwanted effects should be systematically included. Careful evaluation of anti-hypertensive drug treatment to reduce the pill burden, if possible, as well as monitoring adherence is part of clinical follow-up. Assessment of the long-term impact in CV (coronary heart disease, heart failure, atrial fibrillation, sudden death and stroke) and renal events (eGFR changes, ESRD) is also essential. The balance between what ideally should be measured and what is reasonably achievable from a patient perspective is always difficult. An ideal follow-up scenario is shown in Table 2.

6.1. Monitoring BP Values

Measurement of BP values after the RDN procedure should include office and out-of-office BP as a minimum. Average 24-hour, awake or nocturnal BP measured with ABPM as well as the average of self-BP measurement at home have a better relationship with the presence of hypertension-induced organ damage, left ventricular hypertrophy, urinary albumin excretion, estimated glomerular filtration rate and signs of cerebral small vessel disease when compared to office BP counterparts [27].

6.2. Monitoring Renal Function

The absence of significant changes in GFR, calculated by different equations, after RDN is reassuring [3, 28]. However, long-term monitoring of renal function is essential.

6.3. Monitoring Glucose Metabolism

Increased central sympathetic activity is a main contributor to the pathophysiology of several important chronic cardiometabolic diseases, including diabetes and the metabolic syndrome. Indeed, several recently published pilot studies and case reports suggest beneficial effects of RDN on glucose metabolism in patients with resistant hypertension. RDN improved glucose metabolism and insulin sensitivity assessed by fasting glucose, insulin and C-peptide [29]. Likewise, homeostasis model assessment-insulin resistance (HOMA index) decreased as well as the 2-hour glucose levels during an oral glucose tolerance test. In patients with impaired fasting glucose or diabetes, it is suggested glucose metabolism be monitored (Table 2).

6.4. Monitoring Hypertension-Induced Organ Damage

Hypertension-induced mortality and morbidity is produced through the impact on the heart, the central nervous system, the vessels and the kidneys. Evaluation of early target organ damage (TOD) in these organs is an important step in a risk stratification strategy to reduce cardiovascular and renal damage [30]. The reappraisal of the 2009 ESH guidelines [31] and the 2013 ESH-ESC Guidelines [17] encouraged repeated TOD assessment during follow-up.

The presence of TOD upgrades the risk category for a given BP value and other CV risk factors [17]. There is a consensus that if TOD is present in several organs, this has an additive prognostic value of increased cardiovascular risk. A table of TOD was included in the 2013 guidelines, although some of them, such as the ankle/brachial index indicate advanced organ damage and others are not routinely available. Based on availability, cost and clinical significance, left ventricular mass assessment, urinary albumin excretion and glomerular filtration rate are the minimum recommended.

Several studies have shown that regression of asymptomatic TOD during treatment reflects reduction of morbid and fatal CV events, offering valuable information about whether patients may be effectively protected by the treatment strategy (Table 2).

6.5. Clinical Monitoring

Clinical monitoring includes assessment of anti-hypertensive medication and their systemic or local side effects. The decision to reduce or stop a drug after a significant office BP reduction requires out-of-office BP (Home or 24-hour ABPM) confirmation. If confirmed, deciding which drug to withdraw is not easy and depends on several factors such as tolerance of the drug, presence of side effects and patient preference. It is recommended to start by withdrawing one of the drugs which share mechanisms of action.

The role of drug adherence is particularly relevant in clinical situations in which drug therapies do not provide the expected results. Adherence assessment is complex and time consuming. Methods include retrospective analysis of prescription refill records, analysis of chemical markers of drug exposure, automatic electronic time-stamping and compilation of events more or less strongly linked to the act of medication (e.g. package opening, dosage form dissolution). Other methods, such as questionnaires, interviews and periodic counts of patients' returned, untaken doses, are subject to many uncertainties and easy manipulation by patients [32]. For routine practice, simple questionnaires and interviews are the most suitable (Morinsky test).

6.6. Monitoring Renal Arteries

Considering the endothelial injury after the impact of the different systems used for RDN, it is remarkable how little evidence there is of long-term damage to the vessel. The incidence of renal artery stenosis was about 1% at six months in the Symplicity HTN-3 and at 3 years in Symplicity HTN-2.

Several cases of significant, de novo renal artery stenosis have been reported 3 to 6 months after RDN and beyond 6 months with different renal ablation systems [33-41]. The diagnosis is often made following a rise in blood pressure and a decrease in renal function and/or repeated pulmonary oedema. Only in three small RDN cohorts has routine renal CT angiography been performed. In those studies the prevalence of renal artery stenosis ranged from 6.6% to 18% [19]. In the absence of routine renal artery imaging it is likely that asymptomatic renal artery stenosis may be overlooked. Therefore some form of non-invasive renal imaging should be undertaken routinely between 6-12 months and thereafter annually until the safety of RDN can be firmly established.

6.7. Monitoring Reduction in Sympathetic Activity

The sympathetic nervous system is notoriously difficult to

Table 2: Suggested ideal follow-up protocol for patients undergoing RDN

	1st week	2nd week	3rd week	4th week	3rd month	6th month	Yearly
Symptoms	X	X	X	X	X	X	X
Adherence	X	X	X	X	X	X	X
Office BP	X	X	X	X	X	X	X
Home BP				X	X	X	X
24h ABPM				X		X	X
Aortic BP*				X		X	X
Glucose	X			X		X	X
HbA1c				X		X	X
Creatinine	X			X	X	X	X
Potassium	X			X	X	X	X
EKG				X		X	X
Echo-C						X	X
UAE				X		X	X
CWT							
cfPWV*				X		X	X
Renal artery imaging						X	X

EKG: electrocardiogram, Echo-C: echocardiogram, UAE: urinary albumin excretion (albumine/creatinine ratio) in first voiding urine, CWT: carotid wall thickness, cfPWV: carotid-femoral pulse wave velocity

monitor and there are no readily available tools to help guide the RDN procedure.

Assessment of sympathetic activity after or during RDN is currently only available within research studies. Using microneurography, Dimitriadis [42] did not observe a reduction in the muscle sympathetic nerve activity (MSNA) 6 months after RDN and no correlation was found between BP reduction and MSNA activity.

An indirect method to assess sympathetic activity is baroreceptor sensitivity. One study suggested low baseline baroreceptor sensitivity may predict a better response to RDN [43].

Rapid Technological Change

Few procedures in the medical device world have witnessed a similar explosion in development as renal denervation. It has recently been estimated that at least 60 companies are working in this area with either an approved or prototype device.

For the purposes of this document they have been divided into those with a CE mark for sale in Europe and those without that certification. None of the devices currently have FDA approval for sale in the USA. Although there are several published studies on RDN using some of these devices, only the Symplicity device (Medtronic Inc.) has randomised controlled trial data (HTN2 & 3). Much of the data has been presented at conferences but is currently not in the peer-reviewed literature.

CE-marked devices
As of June 2015 there are six companies with seven approved devices for use in Europe. These are detailed in Table 3. Two companies (Covidien and Cordis) have withdrawn their devices from the market following the publication of the HTN -3 trial. All but one use RFA as the energy source, with the Paradise device (ReCOR medical) using high-intensity non-focused ultrasound. The RFA devices have evolved since the first single electrode device (Symplicity, Medtronic Inc.). The main focus of change is in using multi-electrode devices, allowing a faster and possibly more effective denervation. RFA is usually delivered using monopolar probes with the exception of the Vessix device (Boston Scientific) which uses multiple bipolar electrodes. There have been no head-to-head comparisons of any of the devices, making it difficult to measure the value of the individual modifications.

Non-CE-marked devices
There are many devices in this category and we make no attempt to include them all. Some use alternative energy sources, such as ultrasound including low intensity focused US (Kona Medical) where there is no need to insert a device or needle. Cryotherapy relies on cooling the nerves to produce damage. Other methodologies include drugs (guanethidine (Mercator Med Systems, Inc.), Vincristine, Paclitaxel), and chemicals or toxins e.g. alcohol (Ablative Solutions, Inc.) and Botox (Apex Nano Therapeutics, Inc.). Usually the drug or chemical is applied from the lumen of the renal artery either using porous angioplasty balloons or balloons containing small micro-needles which penetrate the arterial wall to allow delivery to the periadvential tissue.
There is very little data on these devices, and much of it is held by individual companies and not yet in the public domain.

Company Perspective
All the CE-marked device companies were contacted seeking their view on the future of RDN. Individual responses are not cited here but all remain cautiously optimistic, emphasising the need for more research and also to explore other indications, e.g. cardiac failure and renal insufficiency.

In 2015 several new company-funded trials have been announced. Medtronic Inc. has two global prospective, randomised, sham-controlled trials to be conducted simultaneously. One (Spyral HTN-ON MED) is testing RDN whilst on anti-hypertensive treatment and the other (Spyral HTN-ON MED) off anti-hypertensive treatment. These small trials of approximately 100 patients will help inform a pivotal study to gain FDA approval. Boston Scientific has commenced a randomised, sham-controlled trial (Reduce HTN:Reinforce) again with approximately 100 patients. These trials will begin to report early results in 2016.

Table 3: CE-marked devices and RDN studies by company (June 2015)

Boston Scientific

Vessix CE - 2012
Radiofrequency 4-8 balloon-mounted electrodes (4-7 mm balloon diameters). Bipolar
8F system Simultaneous 30 second burns. Low energy 1W.

Study	Study descriptions and numbers	Status
REDUCE-HTN FIM + PMS	Treatment of Resistant Hypertension Using a Radiofrequency Percutaneous Transluminal Angioplasty Catheter (REDUCE-HTN), international, multi-centre, single-arm, open-label, prospective, first-in-man and post-market follow-up study. Follow-up through 2 years. N=146.	Completed.

Vessix Reduce Catheter CE - 2014
Radiofrequency 4-6 balloon-mounted electrodes (4-7 mm balloon diameters). Bipolar
7F system Simultaneous 30 second burns. Low energy 1W.

Study	Study descriptions and numbers	Status
REDUCE-HTN FIM + PMS	Treatment of Resistant Hypertension by Renal Denervation in China (REDUCE-HTN-CN); prospective, multi-center, single cohort study for the percutaneous therapeutic treatment of medication-resistant hypertension in China. N=60.	Ongoing.
REDUCE HTN: REINFORCE	Prospective, multicenter, single blinded, randomized, controlled, pilot study. Sham arm. N=100.	Recruiting..
REDUCE-HTN US Study	Under development and discussion with regulatory authorities.	Recruiting..

Boston Scientific continues to invest in clinical research, including research on possible benefits for hypertension patients with high risk co-morbidities such as chronic kidney disease, heart failure, diabetes, obesity and atrial fibrillation.

Covidien
OneShot CE - 2012
Radiofrequency Irrigated balloon system. Unipolar
7F system Single two-minute burn

Study	Study descriptions and numbers	Status
RAPID	Rapid Renal Sympathetic Denervation for Resistant Hypertension (RAPID),	Closed.
RAPID II	Rapid Renal Sympathetic Denervation for Resistant Hypertension II (RAPID II); global, multi-centre, prospective, randomised, controlled study of the safety and effectiveness of renal denervation with the OneShot Renal Denervation System in patients with uncontrolled hypertension.	Closed.
OneShot Renal Denervation Registry		Closed; Patients in follow-up phase.

RDN programme and OneShot registry discontinued Jan 2014.

Medtronic
Symplicity Flex CE - 2010
Radiofrequency Single electrode catheter. Unipolar
4F catheter, 6F guide compatible system 6-8 two-min ablations

Study	Study descriptions and numbers	Status
SYMPLICITY HTN-1	Renal Denervation in Patients With Refractory Hypertension (SYMPLICITY HTN-1); investigate the clinical utility of renal denervation in the treatment of refractory hypertension. N=153.	Completed; results through 3 years published.
SYMPLICITY HTN-2	Renal Denervation in Patients With Uncontrolled Hypertension (SYMPLICITY HTN-2); international, multi-centre, prospective, randomised, controlled study of the safety and effectiveness of renal denervation in patients with uncontrolled hypertension. N=106.	Completed;results through 3 years published
SYMPLICITY HTN-3	Renal Denervation in Patients With Uncontrolled Hypertension (SYMPLICITY HTN-3); multi-centre, prospective, single-blind, randomised, controlled study of the safety and effectiveness of renal denervation in subjects with uncontrolled hypertension. N=535.	Active, not recruiting, results through 6 months published
SYMPLICITY HTN-4	Renal Denervation in Patients With Uncontrolled Hypertension – (SYMPLICITY HTN-4); international, multi-centre, prospective, blinded, randomised, controlled trial in subjects with uncontrolled hypertension.	Active, not recruiting.
HTN-India	Single-arm Study of Symplicity™ Renal Denervation System in Patients With Uncontrolled HyperTensioN in India (HTN-India); multicentre, prospective trial to evaluate efficacy and safety of renal denervation in the treatment of uncontrolled hypertension. N=40.	Terminated.
HTN-J	Renal Denervation by Symplicity™ System in Patients With Uncontrolled Hypertension (HTN-J), multi-centre, prospective, randomised controlled study to determine if RDN with the SYMPLICITY system is safe and effective treatment for uncontrolled hypertension. N=100.	Active, not recruiting.

Symplicity Spyral CE - 2013
Radiofrequency 4 electrodes catheter. Unipolar
4F catheter, 6F guide compatible system Single ablation 1 min

Study	Study descriptions and numbers	Status
Symplicity Spyral Catheter Feasibility Study	Symplicity Spyral Catheter Feasibility Study; international, multi-centre, prospective, open-label study of the evaluate safety and efficacy of multi-electrode radiofrequency renal denervation in patients with uncontrolled hypertension. N=50.	Active, not recruiting, results through 6 months published.
Global Symplicity Registry	Observational, open-label study with planned follow-up to 5 years including subjects treated with either single electrode or multi-electrode catheter. N=5000.	Active, results through 6 months published on first 1000 subjects.
SYMPLICITY HF	Renal Denervation in Patients With Chronic Heart Failure & Renal Impairment Clinical Trial (SymplicityHF); international, prospective, open-label study to determine safety response to renal denervation in patients with systolic heart failure. N=40.	Active.

Study	Study descriptions and numbers	Status
SPYRAL HTN-ON MED Study	Interventional, single-blinded randomised Phase 2 Trial to test efficacy and safety of renal denervation in the presence of three standard anti-hypertensive medications. Sham arm. N=100.	Recruiting.
SPYRAL HTN-OFF MED Study	Interventional, single-blinded randomised Phase 2 Trial to test efficacy and safety of renal denervation in the absence of anti-hypertensive medications. Sham arm. N=200.	Recruiting..
SYMPLICITY AF	Renal Nerve Denervation in Patients With Hypertension and Paroxysmal or Persistent Atrial Fibrillation (Symplicity AF), multi-centre, randomised feasibility study of pulmonary vein isolation versus pulmonary vein isolation combined with renal denervation to characterise safety and effectiveness in an atrial fibrillation population with hypertension. N=245.	Recruiting.

Medtronic's renal denervation technology remains available in countries with current regulatory approval and Medtronic plans to expand the availability of their multi-electrode Symplicity Spyral™ technology.
Clinical decisions should be made on the basis of the totality of available evidence, including the experience of clinicians.
Further investigation is warranted. Consultation is sought with the regulatory bodies of various countries.

ReCor
Paradise System CE - 2012
non-focused ultrasound, balloon mounted system. Radial artery access with Radiance catheter
7F system Single two-minute burn

Study	Study descriptions and numbers	Status
REALISE	REnAL denervatIon by ultraSound Transcatheter Emission (REALISE); single-arm, open-label, prospective, first-in-man study. N=20.	Recruiting.
ACHIEVE	TrAnsCatHeter Intravascular Ultrasound Energy deliVery for rEnal Denervation; single-arm, open-label, prospective, post-market follow-up study to be conducted on fifty (50) eligible patients with a twelve-month follow-up period. N=50	Active, not recruiting.

ReCor has a strong conviction that the Paradise system is well differentiated from RF-based approaches, provided reliable, safe and complete denervation and that renal denervation had the potential to become a key component of hypertension therapy.

Terumo
Iberis CE - 2013
Radiofrequency Single electrode catheter system Radial artery access
4F 6-8 single burns

Study	Study descriptions and numbers	Status
IBERIS HTN	Rapid Renal Sympathetic Denervation for Resistant Hypertension (RAPID),	Recruiting..
Allegro-HTN	Renal denervation in patients with uncontrolled hypertension: multi-centre, prospective, randomised, controlled study of safety and efficacy.	Recruiting.

More research necessary to explore the benefits and scientific value of RDN in patients with hypertension.
Plan to expand RDN programme with the ongoing trial in China, and upcoming registry in Europe, Latin America and Australia.

St. Jude
EnligHTN CE - 2012
Radiofrequency 4 electrode basket catheter system. Unipolar
8F compatible system 4 separate burns then catheter rotated for 4 more burns. The generators has a diagnostic test mode to evaluate electrode contact before proceeding with ablation.

Study	Study descriptions and numbers	Status
EnligHTN I	Prospective, multi-centre, first-in-human safety and efficacy study of renal artery ablation in resistant hypertension. N=46.	Completed; follow-up completed at 24 months as presented at EuroPCR May 2014. 6-month results published in European Heart Journal June 2013. 1-year results published Hypertension: June 16, 2014.
EnligHTN II	International prospective, non-randomised, multi-centre post-market study to further evaluate safety and performance of the EnligHTN™ System in Resistant and Uncontrolled HTN population.	Recruiting; 1 Month follow up for 100 patients reported at EuroPCR 2014 Continuing to enrol and follow patients.

EnligHTN Generation 2 CE - 2013
Radiofrequency 4 electrode basket catheter system. Unipolar
8F compatible system 4 simultaneous burns then catheter pulled-back and rotated for 4 more burns. The new generator requires the diagnostic test mode to evaluate electrode contact before proceeding with ablation.

Study	Study descriptions and numbers	Status
EnligHTN II	International, prospective, non-randomised, multi-centre post-market study to further evaluate safety and performance of the EnligHTN™ System in Resistant and Uncontrolled HTN population.	Recruiting; 1-month follow-up for 100 patients reported at EuroPCR 2014. Continuing to enrol and follow patients.
EnligHTN III	Prospective, multi-centre, first-in-human safety and efficacy study of next generation device. N=39.	Completed. 6M follow-up reported at EuroPCR 2014.
EnLiven	International, multi-centre RCT using the EnligHTN renal denervation system.	Planning stages.

St. Jude believes in the potential of RDN to dramatically improve the lives of patients with drug-resistant hypertension.
Assess and revise their clinical strategy as appropriate in collaboration with a global board of hypertension and renal denervation experts.

New Evidence (efficacy)

In the last year several clinical controlled trials have been published analysing the efficacy of renal denervation in patients with treatment-resistant hypertension. In the 2013 guidelines of the European Society of Hypertension and European Society of Cardiology [17] the recommendation of treatment strategies in hypertensive patients with resistant hypertension were that in case of ineffectiveness of drug treatment, invasive procedures such as renal denervation and baroreceptor stimulation may be considered. Until more evidence is available on the long-term efficacy and safety of RDN and baroreceptor stimulation, it is recommended that these procedures remain in the hands of experienced operators and diagnosis and follow-up restricted to hypertension centres. Do we need to reconsider these recommendations after publication of Symplicity HTN-3 trial?

Long-term follow-up of Symplicity HTN-1 and HTN-2
Symplicity HTN-1 [1] is an open-label study that enrolled 135 patients of whom 111 consented to follow-up for 36 months. Eligible patients had severe treatment-resistant hypertension (systolic BP ≥ 160 mmHg, at least on 3 anti-hypertensive drugs, including a diuretic, at optimal doses). In 88 patients 36 months' follow-up was obtained. From a mean BP of 175/98 mmHg at baseline, office BP dropped by -32/-14 mmHg after 36 months, with a response rate of 93% at 36 months (fall in office blood pressure >10 mmHg). The absence of any relapse or attenuation of the anti-hypertensive effect suggests there is no evidence of functional re-innervation at 3 years. Most strikingly, office blood pressure fell further and the portion of controlled (< 140 mmHg) or at least to some extent controlled patients (140-159 mmHg) reached nearly 50% and 85%, respectively, at 36 months. This single arm, longitudinal study indicates that changes in blood pressure persist long-term in patients with treatment-resistant hypertension after RDN.

Periprocedural complications included groin haematoma, one renal artery dissection before energy delivery and 2 cases of temporary acute renal failure which fully resolved. There were 15 hypertensive events requiring hospitalisation and 3 deaths during the follow-up period.

The long-term follow-up data of Symplicity HTN-2, a randomised open clinical trial have been recently published [44]. 106 subjects with treatment-resistant hypertension were randomised to renal denervation or medical therapy alone. After 6 months, 37 control subjects crossed over to RDN. 40 subjects in the original RDN group and 30 from the cross-over group were followed up for 3 years. The systolic and diastolic blood pressure reduction at 36 months for the initial RDN group was -33/-14 mmHg, starting from baseline blood pressure 178/97 mmHg. In the cross-over group, baseline blood pressure increased throughout the first 6 month (waiting) period to 191/100 mmHg, but dropped by -33 mmHg at 36-month follow-up visit. Thus, renal denervation resulted in a sustained lowering of blood pressure during 3 years in a selected population of subjects with severe treatment resistant hypertension without serious safety concerns.

Both Symplicity HTN-1 and HTN-2 studies used the Symplicity Flex® catheter. Non-randomised data on some of the other CE-marked devices have been published (Figure 2). The fall in office blood pressure 6 months after renal denervation in these studies varied from 20-30 mmHg systolic. Data from the Global Symplicity Registry reported a change in office BP at 6 month of -11.6 mmHg systolic (N=998 subjects) [54]. If Symplicity HTN-3 inclusion criteria were applied to the registry data, those 323 subjects (similar to Symplicity HTN-3) showed a reduction in systolic office blood pressure of 20.3 mmHg. Thus, taking all this new evidence together, in addition to the first 6-month follow-up data of Symplicity HTN-1 and 2, there is good evidence that renal denervation results

Figure 2: Proof of Concept Studies

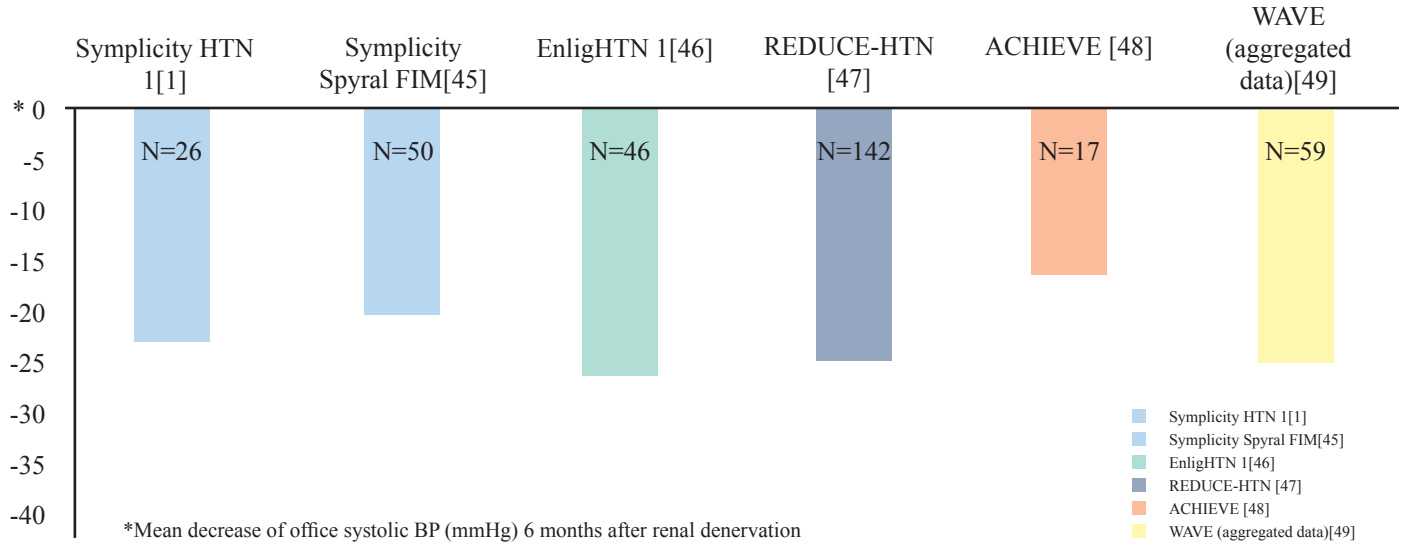
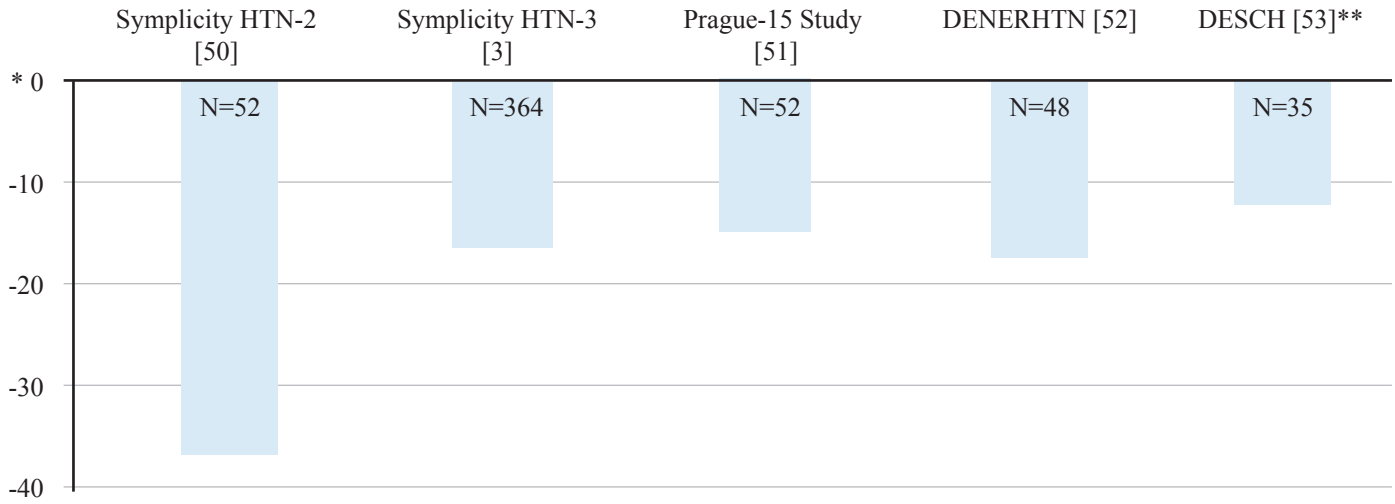


Figure 3: Randomised controlled studies



*Mean decrease of office systolic BP (mmHg) 6 months after renal denervation

** No office data provided, -9.9 mmHg refers to daytime BP

on average in a decline in office systolic blood pressure of < 20 mmHg and that this is maintained over a longer period of follow-up albeit in a smaller patient group.

Symplicity HTN-3 trial

The Symplicity HTN-3 study is a prospective, randomised (2:1), masked (sham) procedure, single-blind study, which aimed to establish the safety and efficacy of RDN [3]. It was primarily a regulatory trial to satisfy FDA requirements in the USA. Inclusion criteria were similar to the Symplicity HTN-1 and 2, i.e. systolic office blood pressure > 160 mmHg, 3 anti-hypertensive drugs including one diuretic and (new criteria) automated 24-hour ambulatory blood pressure ≥ 135 mmHg. Before randomisation, patients were receiving a stable anti-hypertensive regimen for at least 2 weeks involving maximum tolerated doses of at least 3 anti-hypertensive drugs, including a diuretic. The first primary objective, the safety endpoint – a composite of all-cause mortality, end-stage renal disease, embolic events resulting in end-organ damage, renal artery or other vascular complications, hypertensive crises at 30 days and new renal artery stenosis of > 70% at 6 months was met. This composite safety endpoint was observed in 1.4% of patients in renal denervation and 0.6% in the control (sham) group, without any significant difference between the two groups (p=0.67). These data therefore support the concept that RDN appears to have no significant short-term (6 months) safety concerns.

However, the primary efficacy endpoint, a difference in office systolic blood pressure between groups of ≥ 10 mmHg, was not achieved. Office systolic blood pressure dropped by -14.1 in the denervation and -11.7 in the control (sham) group respectively, the difference not reaching statistical significance. Since randomisation was stratified for ethnicity and centre, the pre-specified subgroup analysis for ethnicity deserves specific attention. Changes in office systolic blood pressure in the African-American subgroup did not achieve significance largely due to the large drop in blood pressure in the sham group (-17.8 mmHg). In the non-African-American subgroup (of which more than 95% were Caucasians) a significant difference in office systolic blood pressure was observed (-15.2 in the denervation and -8.6 mmHg in the control (sham) group, p=0.012). There was no significant reduction in ABPM between the main groups or any of the subgroups.

How do we reconcile these discrepant results in systolic blood pressure reduction after renal denervation? Symplicity HTN-3 is a well-designed study, but the execution of the study has been questioned. Now, some months after publication of Symplicity HTN-3, data have emerged suggesting incomplete renal denervation in many patients. Symplicity HTN-3 was a US trial with 88 sites and no fewer than 111 operators performing the procedure. The procedure-per-operator ratio is approximately 3.3 and deserves comment. 34% of the interventionists carried out only one single procedure. Proctoring in the study sites was largely undertaken by non-clinical staff. The mean number of ablation attempts (energy application) per artery was 4.7, whereas in Symplicity HTN-1 this figure was 8.6. In Symplicity HTN-3 we have also learned that with increasing numbers of RF ablations, there was greater lowering of BP lowering (p for trend = 0.01).

In Symplicity HTN-3 only a small proportion of patients (N=19) had successful ablation across all four quadrants of the renal artery [55]. Perhaps not surprisingly, successful four-quadrant ablation in both renal arteries was associated with the greatest BP drop (office systolic) of 24.3 mmHg; with one artery four-quadrant ablation, this reduced to 16.1 mmHg; and with no four-quadrant ablation, a reduction of 14.2 mmHg.

Effect of renal denervation on 24-hour ambulatory blood pressure

24-hour ambulatory blood pressure reflects the pressure load imposed on the cardiovascular system more accurately than office blood pressure and is now recommended as primary efficacy criteria [56]. Moreover, 24-hour ABPM is not sensitive to the white coat effect. Symplicity HTN-3 did not demonstrate a significant difference between groups for ABPM. The modest ABPM reduction of only 6.75 mmHg may be explained by the technical limitations alluded to in the previous paragraph. The difference in nocturnal ambulatory systolic blood pressure changes between groups was -3.3 mmHg and of borderline significance (p=0.06)

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In the Symplicity HTN-2 trial 20 subjects had 24-hour ABPM before and after renal denervation and blood pressure dropped -11/-7 mmHg in the RDN group (without any change in the control group). Accordingly, in 206 patients followed up for 6 months 24-hour ABPM decreased by 10.2 mmHg in patients with true resistant hypertension, which is similar to the 24-hour blood pressure decline observed in Symplicity HTN-2. The modest decrease in 24-hour ambulatory systolic blood pressure in the denervation group of Symplicity HTN-3 may be related first to the procedural difficulties discussed above, and to the surprisingly large decrease in the control (sham) group (-4.8 mmHg). This is much greater than that seen in double-blind randomised placebo-controlled trials evaluating anti-hypertensive drugs, where it is no greater than 2 mmHg.

The French DENER HTN study, a prospective open-label randomised trial with blinded endpoint evaluation used ambulatory blood pressure as primary objective. After standardised triple run-in phase, renal denervation effected greater blood pressure response (-5.9/-6.3 mmHg) than the control group, at similar anti-hypertensive standardised medication at follow-up [52].

In addition to 24-hour ABPM, integrated effects of blood pressure reduction after renal denervation can be assessed by examining intermediate endpoint parameters before and after renal denervation.

Effects on renal denervation and hypertensive organ damage

Several prospective observational studies have shown that blood pressure reduction following renal denervation is accompanied by reduction of early target organ damage. All these studies lack either a control group or a sham procedure, but nevertheless, deserve attention since the target organ damage has been evaluated in a blind fashion (PROBE design). Two studies focused on changes of left ventricular mass after renal denervation and consistently observed significant falls in left ventricular mass at the 6-month timeline. Interestingly, ejection fraction in patients with impaired systolic function significantly increased after renal denervation, and left ventricular circumferential strain as a surrogate of diastolic function also improved [56]. At least three research groups reported changes of pulse wave velocity and augmentation index improvements after renal denervation, in parallel to the fall in systolic blood pressure. This would indicate that vascular changes in the macrocirculation were improved 6 months after renal denervation. New reports in the retinal microcirculation indicate that early vascular remodelling is reversed to some extent after renal denervation.

In a further analysis of 100 patients with resistant hypertension, the rate of albuminuria improved by 8% and microalbuminuria decreased by 7% ($p<0.001$) [57]. In accordance, albuminuria decreased significantly by 4.5% in patients with resistant hypertension, who had baseline micro- or microalbuminuria. In comparison to the years prior to renal denervation, renal function was preserved in patients with chronic kidney disease and resistant hypertension [58].

Taken together, these studies support the notion that renal denervation is associated with a reduction in early target organ damage. It remains to be elucidated whether this is causally related to a reduction in blood pressure alone or due to the reduced sympathetic outflow to the target organs. None of these trials aimed to separate these two effects, but support the observation that patients with treatment-resistant hypertension have a lower integrated pressure load on the cardiovascular and renal system after renal denervation.

RDN Treatment Centre Criteria

The results of the HTN-3 trial have facilitated our understanding of the requirements needed for potential RDN centres. Patient selection, exclusion of other causes of apparent resistant hypertension, drug compliance and titration have already been discussed in this document. However a major criticism of HTN-3 has been the large number of low-volume operators, many of which had little experience of RDN. One way to address these shortcomings is to limit this technology to a smaller number of high-volume sites where expertise is either already present or can be rapidly acquired. A multidisciplinary approach is essential and at a minimum should include several core specialties (hypertension, interventional radiology/cardiology, nephrology). Other support requirements include imaging, vascular surgery and endocrinology. Furthermore as more research is clearly needed, centres should be capable of supporting quality research programmes and contributing data to national and international registries.

Unmet Data Needs

There are several significant knowledge gaps in the field of renal denervation. These include renal nerve anatomy, indicators of successful denervation and clinical or phenotypic predictors of success. One of the acknowledged failings of published RDN trials and registries is the lack of convincing predictors of blood pressure response and procedural success [59-61].

Poor or non-compliance with drug therapy has a substantial impact on RDN efficacy and should be thoroughly investigated. Several analyses have shown that the higher the baseline BP, the better the response to RDN. A possible explanation however is the "regression to the mean" phenomenon [59-61]. Older age and use of vasodilators in the recent Symplicity HTN-3 seemed linked to poorer use of aldosterone antagonists to better BP response [3]. Promising findings are related to baseline baroreceptor sensitivity with the hypertensives with the more dysfunctional baroreceptors being responsive to RDN [62].

In the largest clinical trial, the Symplicity HTN-3, the number of ablation points (8 per artery) and the circumferential pattern were strongly related to the range of BP drop, implying that more complete ablation is required to improve efficacy [62]. In the light of recent histopathological data, the segment of the renal arteries with the highest density of nerve fibres and in close proximity to the lumen should be identified for successful and more complete ablation in terms of device design and energy delivered [59-61]. A large human autopsy study has shown the highest density of nerves lies in the proximal renal artery, gradually reducing in both depth and number further distally. There is much variation however and it is unclear how and where the energy for denervation should be delivered to maximise the chance of effective denervation [63]. Electrical stimulation of the renal arteries has been proposed as a marker of RDN success [64] but these results have not been replicated [65]. Although needing validation in larger studies, there is evidence that RDN causes an increase in renal blood flow as well as a reduction in renal resistive index assessed by Doppler flow wire directly after the procedure [66].

Responsible behaviour

If RDN Had Been a Drug – medical device market approval in context

Compared to new medicines, medical devices in Europe are subject to far less scientific scrutiny through technical and clinical testing before their general introduction into the healthcare market. This regulatory environment fostered the rapid development and market approval (CE-marking) of various RDN technologies on the continent in the period 2010-2013. In the light of the HTN-3 trial results it seems justified to raise the question whether this streamlined approval process, whilst providing adequate data on relative safety in clinical use, may not demonstrate the required medical efficacy.

This section briefly outlines the regulatory requirements for drugs entering the European market (via EMEA or national drug regulatory agencies) and for medical devices entering the US market (FDA authorisation). These are compared with requirements to introduce a medical device into the European market (CE-mark approval) and the scientific evidence that was required for renal denervation technology when it gained authorisation under this system. The following discussion of the appropriateness of European device regulation by example of renal denervation technology illustrates the relative advantages and disadvantages of the current regulatory environment and highlights the need for responsible clinical behaviour of all medical professionals involved with new devices and procedures.

European Market Authorisation of a Medicine

Pharmaceutical manufacturers are subject to increasingly harmonised and detailed European legislation, including the rules governing medicinal products in the European Union and the Clinical Trials Directive.

In order for a medicinal product to be granted a marketing authorisation in Europe, applicants may apply either via national regulation agencies before seeking mutual recognition in other EU States, or via the centralised procedure of the European Medicines Agency (EMEA), which remains subject to certain restrictions .

The EMEA requires a pre-submission notification at least seven months before the application, containing detailed information on the medicinal product and a request to be admitted via the centralised procedure. The dossier submitted by the applicant includes detailed information on the drug's composition, clinical and pharmacological properties, pre-clinical and clinical data on safety and efficacy.

As regards the required pre-clinical data for proving the safety of a new medicinal product, randomised clinical trials play a vital role in the market authorisation process. All applicants must carry out clinical trials in accordance with European clinical trials legislation and comply with ethical principles such as international standards of good clinical practice (GCP) and the Declaration of Helsinki.

Introducing a Medical Device in the European Union

Whilst medicines are regulated by issue of a licence in the European Union, medical devices are approved according to guidelines by public and private sector organisations designated as "notified bodies" who issue the CE mark.

The introduction of new medical devices in Europe has been less well scrutinised in the past, but is important to ensure that patients receive high standards of care, whilst retaining access to the newest technology available. European Union legislation obliges manufacturers to ensure that their devices are "designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients" [67]. New devices must meet essential requirements such as biological safety, clinical data, technical specifications, risk management and sterilisation.

However, there is no legislation to guide the precise nature of clinical data required to obtain a CE mark; so long as the device is shown to be safe in humans, there are no recommendations about the level of evidence required for such new devices or new procedures.

Market Authorisation of a Medical Device in the US
Before a medical device can access the US market, it has to undergo the stringent controls of the US Food and Drug Administration (FDA).

Depending on the medical use and generic type of device, new products are assigned to one of three classes (with increased requirements and regulatory control from Class I to Class III). If a device is either not substantially equivalent to an already classified device or found to be a high-risk device, it requires Premarket Approval (PMA). This is the strictest and most demanding of market approval processes, requiring both non-clinical laboratory studies conducted in compliance with the Good Laboratory Practice for Nonclinical Laboratory Studies, and clinical investigations. In the clinical investigations section of the PMA, applicants have to provide "study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations" [68]. Randomised controlled trials are essential in this context.

Symplicity HTN-3 was the first study carried out on an RDN system in an effort to obtain FDA approval. However, because the RDN system failed to reach its efficacy endpoint, it failed to gain FDA approval, despite the fact that it had been on widespread release in Europe.

RDN, its Evidence-base & Responsible Behaviour
Thus, the European system of medical device approval places much responsibility on the individual doctor in deciding which medical device is best suited to be used in clinical care since the evidence-base may not always be available or conclusive. To a degree, it is appropriate that this is determined by healthcare professionals involved in the care of patients on a daily basis. However, physicians and patients are susceptible to accelerating the use of new devices and procedures if they are desperate for treatment and feel they have few or no alternatives. This may have been the case with renal denervation where patients were taking multiple drugs to little avail and were aware of the morbidity and mortality associated with their condition.

If RDN had been a drug treatment, two initial trials of 260 patients would not have sufficed to allow the drug to be released for general use outside the rigorous controls of an RCT.
So should medical devices be treated any differently from drugs? In the field of renal denervation there are now seven CE-marked devices, but many more at various stages of development. Should each of these undergo the rigour of a randomised controlled trial with a sham procedure? And then should these trials be repeated for newer generations of each device? In an ideal world: perhaps. However, RCTs are expensive to conduct and are often slow to achieve results. In addition, there is a real risk of stifling the innovation which drives the development of new, beneficial technologies and significantly raising the cost of treatment. Both effects may not ultimately be in patients' best interests.

A middle ground is required and indeed the Proposal for a Regulation on Medical Devices which has been adopted by the European Commission on 26 September 2012 will address the scientific evidence required for market authorisation. New procedures using new devices should be introduced in a controlled manner allowing evaluation at every step. National procedure registries may go some way to ensuring this responsible uptake with reimbursement only for properly selected patients with appropriate follow-up, and a time limit for review of results before a decision is made whether to commission a procedure.

In contrast to the EMEA/FDA systems, which may well have halted the development of renal denervation technology too early, the current regulatory model for medical devices in Europe allows for further exploration of a concept that may still hold some value and a technology that may show some promise for other indications. We believe the current regulatory environment in Europe strikes a careful balance between patient safety and technological innovation, leaving the responsibility for adopting new technology with the individual doctor. European doctors, therefore, play a much larger role in adopting new technology and have a significant responsibility for patient safety when using new devices. The lessons learned by the widespread adoption of RDN technology before proof of efficacy are salutary and ideally dictate the adoption of new technology within clinical trials or registries until efficacy is proven.

Conclusion

Patients with resistant hypertension account for between 5-10% of all patients with hypertension. They are a very high-risk group and RDN has the potential to result in a marked reduction in cardiovascular morbidity and mortality. RDN appears consistently safe across all trials albeit with limited short-term follow-up. The main controversy is with regard to efficacy and here the trials have produced mixed and conflicting results. Enthusiasm has inevitably been dented and there has beenw a large reduction in the use of RDN globally. However there are lessons to be learnt in the trial methodology for RDN and this group strongly supports further high-quality research, ideally conducted in high-volume specialist centres. Until we have results from the new sham-controlled trials in patients with severe and mild/moderate hypertension, our guidance is that RDN may be considered and performed by experienced interventionists in hypertension centres. Patients should be selected by multidisciplinary team discussion which includes a hypertension expert and interventionist experienced in renal artery intervention and denervation. Participation in clinical trials and registries is strongly recommended.

List of tables

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