shortreport

Regione Emilia-Romagna
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
osservatorio regionale per l'innovazione

n. 8

Technology

Implantable device for the treatment of drug-resistant hypertension.

Commercial technology name and producer's/supplier's name

Barostim *neo* System™, CVRx Inc., Minneapolis, Minnesota, USA.

Use

■ therapeutic

□ diagnostic

□ other: prognostic

Category

Medical device: implantable neurotransmitter.

Therapeutic/diagnostic field of application

Cardiovascular.

Target patients

– Patients with treatment-resistant arterial hypertension
– Patients with heart failure

This Short Report assesses the use of Barostim *neo*™ only in resistant hypertension.

Clinical condition

Resistant hypertension is defined as high blood pressure that remains above the goal of 140/90 mmHg despite the adoption of lifestyle changes and either a treatment with at least three antihypertensive agents (one of which is usually a diuretic) at best tolerated doses (Hoppe 2012, ESC-ESH 2013, Alberta Health Technologies Decision Process 2014) or a treatment with ≥4 antihypertensive agents of different classes irrespective of blood pressure (BP) values (AHA 2008). All drugs should be prescribed and taken at the optimal doses (ie, 50 percent or more of the maximum recommended anti-hypertensive dose) and any secondary causes (due to other diseases, primarily renal disease) must be ruled out (ESC-ESH 2013, Kaplan 2014). Actual treatment resistance should be confirmed by assessing the patients' real compliance to the prescribed treatments.
Resistant hypertension is associated with a high risk of cardiovascular and renal events (Fargard 2012, De La Sierra 2011, Daugherty 2012, Persell 2011).

Target Population

Accurate and reliable estimates of prevalence of resistant hypertension are not available (EunetHTA 2013). A recent systematic review and meta-analysis (Achelrod 2014) estimates that, among hypertensive patients treated with at least three antihypertensive medications, the prevalence of resistant hypertension is 13.72% (95%CI: 11,19%-16,24%) and 16.32% (CI95%: 10,68%-21,95%) pooled from 20 observational studies and 4 RCTs, respectively. Authors

The report

A brief presentation of a technology, providing sufficient information to decide whether to undertake a comprehensive assessment process.

The reported information derives from:

› the consultation of web materials supplied by the producer and of current national and/or regional registries
› the search of secondary studies on HTA databases and of primary studies, indexed on Medline.

! The report does not represent a definitive assessment of the technology.

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report that most studies were not able to rule-out pseudo-resistance due to white-coat effect, poor medication adherence, and suboptimal drug doses, thus true prevalence of resistant hypertension could be lower.
No published data for Italy and Emilia-Romagna region on resistant hypertension could be retrieved. Therefore, for the Emilia-Romagna region, the number of patients treated with at least three antihypertensive (one of which a diuretic) at optimal dose was estimated using administrative data from Emilia-Romagna's pharmaceutical database (AFT). For the year 2013 we selected patients on three or more anti-hypertensive drugs (beta-blockers, ACE inhibitors, diuretics, calcium-channel) one of which is a diuretic. The criteria used as a proxy of optimal dose were the proportion of days covered (PDC) equal to 1 for all four trimester of the year and MPR (Medication Possession Ratio)>=75% for the therapeutic strategy (Sattler 2013). The estimated number of patients with the above characteristics resulted to be 3,899. However, for reasons outlined before, this figure would represent a great overestimate of the number of patients with true resistant hypertension.
To provide a more reliable estimate, we applied to this population the meta-analytic results given by Achelrod 2014. The estimated number of patients with true resistant hypertension in Emilia-Romagna in 2013 would result to be between 535 (13.72% of patients treated with 3 or more drugs) and 636 (16.32% of patients treated with 3 or more drugs), i.e. around 0,10% and 0,12%, respectively, of overall hypertensive population (ASI 2014). Considering the contraindications to the procedure or the device, and the need to have true resistant hypertension confirmed by 24-h ambulatory blood pressure monitoring (ABPM) in highly specialised centres for the treatment of hypertension, a limited number of these patients would be eligible for Barostim *neo*™ implant.

Standard treatment/practice

Standard treatment is based primarily on drug treatment and lifestyle interventions. Most patients with resistant hypertension require the administration of more than three drugs. If the blood pressure remains high in spite of lifestyle correction and optimal drug therapy, additional diuretic therapy with low-dose spironolactone or higher-dose thiazide-like diuretic treatment may be considered (NICE 2011, ESC-ESH 2013).

Technology description

Barostim *neo* System™ is a second-generation system – an evolution of the first-generation device Rheos® (assessed in the Short Report n. 1) – for baroreflex activation therapy (BAT).
Baroreflex or baroreceptor reflex are terms used to describe the body's rapid response system for dealing with changes in the blood flow regulation system.
The human body has its own mechanisms for sensing changes in blood pressure and other blood flow changes. This natural system is made of a functional interaction between the brain and the walls of carotid arteries.
Pressure sensors, called baroreceptors, are found on the carotid artery and in the carotid sinus. These sensors measure and report blood flow to the brain, which compares it to the body's needs. BAT consists in stimulating carotid sinus baroreflex receptors that, through the sympathovagal system, activate the reduction of arterial resistance and stiffness and increase venous capacitance and renal natriuresis (Heuser 2010, Hoppe 2012). The Barostim *neo*™ system functions by activating baroreceptors in the wall of the carotid artery. The activation of baroreceptors may turn in a decrease in blood pressure.
The implant of Barostim *neo*™ system is carried out by an experienced and trained surgeon and it usually requires hospitalization and outpatient follow-up visits to a surgeon (number of visits is not specified) (Borisenko 2014).
The device is made of:

- a pulse generator which is battery-powered (expected life span: 2,8±1,4 years, Hoppe 2012) and provides unipolar stimulation without a sensing circuit; the pulse generator is implanted unilaterally (usually on the right side) in the pectoral region ipsilateral to the stimulated carotid sinus;
- a lead which consists of a single platinum-iridium disc coated with iridium oxide attached concentrically to a circular insulative backer and that is directly sutured to the carotid sinus, and
- a laptop computer-based programming system that allows clinic staff to adjust therapy settings, such as the frequency and amplitude of stimulation, using wireless communication when the patient attends hospital for follow-up appointments (NICE 2015).

The device can be turned off by clinic staff, if necessary (NICE 2015).
The miniaturized electrode and unilateral system design is positioned during a minimally invasive implant procedure (Hoppe 2012, Madershahian 2014) that requires general anaesthesia or conscious sedation and must be carried out by trained professionals, taking

approximately 100 minutes (Hoppe 2012, NICE 2015). No information on specific surgical requirements and emergency procedures in case of malfunction were retrieved.
Compared to the first generation device, the implant procedure of Barostim *neo*™ requires an unilateral (instead of bilateral) carotid sinus exposure, which can be performed via a smaller incision (2.5–5 cm), and the dissection of the internal (but not the external) carotid artery.
The device is usually activated about 2 weeks-1 month after implant (NICE 2015).

Main expected benefits

Through the activation of baroreflex system, Barostim *neo*™ system is expected to reduce blood pressure in patients with resistant hypertension (Borisenko 2014). The improved blood pressure control and achievement of blood pressure targets should lead to a reduction in doses/number of drugs and a reduction of cardiovascular risk (Franklin 2001) and renal events (Klag 1996, Hsu 2005). In order to better assess the therapeutic role of Barostim *neo* system™, an evidence profile for the technology was set up (Ballini 2010).
The evidence profile developed for Barostim *neo*™ is described in the following table:

Evidence profile of Barostim *neo*™ system		
Rationale		
Baroreflex activation therapy administered through the Barostim *neo*™ system, by reducing blood pressure through the activation of baroreceptros at level of carotid arteries, in patients with resistant hypertension should allow to achieve blood pressure control, reducing risk of cardiovascular and renal events, and possibly reducing drug dosage.		
Population	**Intervention**	**Comparator(s)**
Patients with resistant hypertension (ESC-ESH 2013, Kaplan 2014).	Barostim *neo*™ system	Best practice: treatment with appropriate lifestyle measures plus at least 3 anti-hypertensive drugs belonging to different classes at their optimal doses (ie, 50 percent or more of the maximum recommended anti-hypertensive dose) plus diuretic therapy with low-dose spironolactone or higher-dose thiazide-like diuretic treatment

Domain: safety			
Study designs: randomised controlled trials (RCTs), quasi-randomised controlled studies, non-randomised controlled trials			
Outcome level of importance 1	**Outcome level of importance 2**	**Outcome level of importance 3**	**Outcome level of importance 4**
Major procedure-related complications	Serious adverse events	Minor procedure-related complications	Non serius adverse events

Domain: efficacy
Study designs: randomised controlled trials (RCTs)

Clinical outcomes			
Outcome level of importance 1	**Outcome level of importance 2**	**Outcome level of importance 3**	**Outcome level of importance 4**
Overall mortality	Incidence of cardiovascular events	Incidence of renal events	QOL and/or pain

Surrogate outcomes	
Outcome level of importance 5	**Outcome level of importance 6**
Blood pressure reduction or achievement of blood pressure goal	Reduction of number / doses of anti-hypertensive drugs

AVAILABLE EVIDENCE

Literature research

The search for primary studies and systematic reviews was carried out in Pubmed, Embase and the Cochrane Library, restricting studies to humans and using key words that described the device (baroreflex, baroreceptors, pressoreceptor*, vagus nerve stimulation and synonymous) and the condition (hypertension, blood pressure) and was restricted to studies on humans. Literature search for HTA reports and/or horizon scanning was performed on HTA Agencies websites. Ongoing trials were searched in the main clinical trial registries (Clinical Trials.gov, ISRCTN Registry, EU CLINICAL Register, ICTRP – WHO, NIH clinical research studies, UK Clinical Research Network, EU Clinical Trials Register website, UK Clinical trials gateway).
All searches were performed in November 2014 and updated in July 2015 (details on bibliographic search strategy are available upon request).
Papers were included if addressed the use of Barostim *neo*™ system for resistant hypertension. Only systematic reviews, randomised controlled trials, non-randomised controlled studies (before-and-after studies, interrupted time series and controlled before-and-after studies) of at least 10 patients and only if published as full reports in peer-reviewed journals were included in the assessment.

Number and type of studies

The literature search retrieved 1,125 eligible records (1,030 records through the first literature search and 95 through the update carried out in July 2015). Among those, only four HTA reports (AETNA 2014, HealthPACT 2014, Topfer 2015, NICE 2015) and three non-randomised, before-and-after primary studies (Hoppe 2012, Hallbach 2015, Wallbach 2015) were eligible for inclusion and were assessed.

HTA reports
The four HTA report included were a report by HealthPACT (HealthPACT 2014), a Clinical Policy Bullettin by AETNA (AETNA 2014) – a U.S. health care insurance company –, an assessment by Canadian Agency for Drugs and Technologies in Health (Topfer 2015) and a preliminary Interventional procedure consultation document (IPCD) by NICE (NICE 2015).
All the documents consider implantable carotid sinus stimulators without major distinction between first (Rheos®) and second (Barostim *neo*™ system) generation device. AETNA and HealthPACT included only one study on Barostim neo™ system (Hoppe 2012), whilst the two most recent documents (Topfer 2015 and NICE 2015) included also Wallbach 2015.
All the included documents consider BAT as an experimental treatment and do not recommend their use in patients with resistant hypertension.
AETNA (AETNA 2014) considers implantable carotid sinus stimulators experimental and investigative for the treatment of hypertension and for all other indications (e.g., heart failure) because its effectiveness has not been established.
HealthPACT assessment (HealthPACT 2014) concludes that “currently there is a lack of clinical and cost-effectiveness evidence to support the use of the baroreflex stimulation to reduce hypertension. A large, prospective RCT on the Barostim *neo* device is due for completion in 2015, the results of which, if favourable, will be identified by horizon scanning activities. Therefore it is recommended that no further research on behalf of HealthPACT is warranted at this time.”
CADTH (Topfer 2015) concluded that “Based on early evidence from the Barostim *neo* trials and older evidence from the Rheos device trials, not all individuals with resistant hypertension will reach their target blood pressure reduction with BAT. Further evidence is needed on how to best identify individuals who will benefit from this procedure”.
Finally, the Interventional procedure consultation document (IPCD) by NICE (NICE 2015) sets provisional recommendations on baroreceptor stimulation devices. From a clinical point of view, NICE states that “current evidence on the safety and efficacy of implanting a baroreceptor stimulation device for resistant hypertension is inadequate. Therefore, this procedure should only be used in the context of research”.

Primary studies
Three studies were included (Hoppe 2012, Wallbach 2015, Hallbach 2015). All the included studies are sponsored case-series.
The Hoppe 2012 study was a prospective multi-centric case-series (7 European and 1 Canadian sites) and included 30 patients (16 females) with the following characteristics: mean age: 57 (SD ±12 years,) mean weight: 85 (SD±16 kg), mean systolic blood pressure (SBP) of 172 (SD±20) mmHg and mean diastolic blood pressure (DBP) of 100 (SD±14) mmHg (indicating that patients with DBP < 90 mmHg were also included).
Patients received a mean number of 6.1±2.7 drugs and 6 out of 30 were previously treated with renal denervation for resistant hypertension.

The objective of Hoppe 2012 was to evaluate safety and efficacy of the Barostim *neo*™ device in patients with resistant hypertension despite stable treatment. Resistant hypertension was defined by authors only in terms of SBP values. Specifically, resistant hypertension was defined as SBP≥ 140 mmHg despite prescription of at least 3 anti-hypertensive medications, including a diuretic (except for patients intolerant to diuretics) and on stable medication (defined as no more than a 100% increase or 50% decrease in any medication other than a diuretic during the 4 weeks before qualifying blood pressure measurements).
The Wallbach 2015 study was a single site prospective case series that included 25 patients (14 females) with mean body mass index (BMI) of 31.9 Kg/m^2 (SD ±6.5), mean age of 60.9 years (SD ±9.2), mean baseline values of SBP of 160.1 mmHg (SD ±26.9) and mean baseline values of DBP of 83.1 mmHg (SD ±16.6). Patients were treated with a mean of 6.6 (SD ±1.7) anti-hypertensive drugs and 9/25 had undergone previous renal denervation.
The objective of the study by Wallbach (Wallbach 2015) was to evaluate whether BAT has positive effects on central hemodynamics in patients with resistant hypertension (defined as BP values > 140/90 mmHg despite adherence to at least 3 optimally dosed anti-hypertensive medications of different classes, one of which is a diuretic).
The Hallbach 2015 study was a retrospective single site case series, that enrolled 17 patients (7/17 had been enrolled in a previously completed non-randomized trial - Hoppe 2012 -) with the following characteristics: 7/17 females, mean age: 54.8 years (SD ±14.1), BMI: 30.1 kg/m^2 (SD ±5.6), mean value of SBP of 179 mmHg (SD ±25) and mean value of DBP of 98 mmHg (SD ±18). Patients received a mean number of 6.1±1.5 drugs and 9/17 were previously treated with renal denervation for resistant hypertension. Also in this case, it is probable that some of included patients had DBP values < 90 mmHg.
The objective af Hallbach 2015 was to assess both the effect of deactivation and reactivation of the device on BP ("on/off effect") and the long-term effect of Barostim *neo*™ device on blood pressure in patients with resistant hypertension (defined as a blood pressure value ≥ 140/90mmHg despite anti-hypertensive therapy with 3 drugs from different classes including one diuretic, once excluded secondary causes of hypertension).

Results

Technical performance

The Hoppe 2012 study reported an average implant procedure time of 107±28 minutes, with time per procedure per centre diminishing through the trial duration due to the growing experience with the technique. No system failure was reported at 6 months and the pulse generator battery life was estimated in 2.8±1.4 years.
No data on technical performance was provided by Hallbach 2015 nor by Wallbach 2015.
To facilitate wound healing the device was activated two weeks after implant in Hoppe 2012 and Hallbach 2015, and four weeks after implant in Wallbach 2015.

Efficacy

Hoppe 2012 provided efficacy data at 6 months: patients experienced an average reduction of systolic pressure versus baseline of 26.0 mmHg (SD ±4.4; p<0.001) and an average reduction of diastolic blood pressure versus baseline of 12.4 mmHg (SD ±2.5; p<0.001). Similar reductions for both systolic and diastolic blood pressure were registered for the 6 patients who previously underwent renal denervation. Forty-three percent of patients reached the systolic blood pressure target of ≤ 140 mmHg; percentages of patients reaching target diastolic blood pressure and of those reaching both DBP and SBP targets were not provided.
Wallbach 2015 reported that the mean blood pressure decreased from 160/83 mmHg at baseline to 143/74 mmHg at 6 months follow-up (p<0.01). The peripheral mean arterial blood pressure was reduced from 109.9 mmHg to 97.3 mmHg (p<0.01).
Hallbach 2015 reported, after a mean of 15.1 months (SD ±8.7) since device activation, SBP and DBP values (baseline values) of 147±29 mmHg and 84+20 mmHg, respectively. After deactivation of the device, SBP increased at 158±38 (p=0,004 vs baseline) and DBP at 89±23 (p=0,04 vs baseline). Upon reactivation of the device, BP values returned similar to those registered before deactivation (SBP: 144±34, p=0,002 vs deactivation, DBP: 83±23, p=0,009 vs deactivation). Regarding long-term effects on BP, authors of Hallbach 2015 state that at the latest follow-up (16,5±7,7 months since device activation) a statistical significant reduction of both SBP and DBP was registered; however no further details or data were provided. At 12 months, 58% of patients reached the goal SBP below 140 mmHg.
All included studies evaluated impact on reduction of anti-hypertensive medications and reported a lack of effect. None of the included studies considered patient-important outcomes.

Safety

Only Hoppe 2012 reports data on safety. During the 30 days after the procedure, three patients (10%) experienced one minor system- and procedure-related complication each (device pocket

haematoma, self-inflicted wound complication, intermittent pain lateral of device system); complications were judged to be related to the procedure and not to the device and patients recovered with no residual effects. At 6 months, the primary safety endpoint of the trial (system- and procedure-related complications) was registered in one patient (3%) that experienced intermittent pain close to the device system.

Costs

The reported cost for full Barostim *neo*™ system is € 21,000 and the reported cost for battery is € 15,000 (Borisenko 2014). Because of the lifespan of the battery at optimal therapy settings (Hoppe 2012), the implanted generator requires surgical replacement every 3 years. Patients implanted with the device still need pharmacological treatment.
The only cost-effectiveness study retrieved (Borisenko 2014) was not included, as it did not use efficacy data of Barostim *neo*™, but those of the first generation device, Rheos®. Moreover the study's incremental cost-effectiveness ratio relates to German Health System's costs, making ICER results not transferable to the Italian system (Drummond 2005, Fattore 2009).

Presumed impact

Clinical

To date, due to limited evidence in terms of quality and quantity of the available studies, it is not possible to prove the presumed clinical impact consisting in a better control of blood pressure leading to, in the long run, a reduced morbidity (risk for cardiovascular and renal events) and mortality.

Economic

The use of the device would most probably produce an additional cost in the management of patients with resistant hypertension that are usually treated either by increasing the dose of already prescribed anti-hypertensive drugs or by adding other anti-hypertensive drugs. With regard to its budgetary impact, Barostim *neo*™ would probably be used as an add-on therapy, leading to additional health care resource expenditures for the cost of the device, the training of staff specialists, the surgical procedure and the required hospital stay, and follow-up visits.

Organizational

Specifically trained personnel would be required for the implant and the post-implant management of Barostim *neo*™. The implant of the device is an invasive procedure requiring surgery at level of carotid sinus, thus needing emergency and surgery services.

Ethical-social-legal

Presently no ethical or social issues have been considered relevant. Appropriate insurance coverage should be provided in case of system failure and/or removal.

Ongoing studies

The following registries of ongoing studies were searched (last access: 7 July 2015): Clinical Trials (www.clincaltrial.gov), ISRCTN (http://www.isrctn.com) and tha EU Clinical Trials Register (www.clinicaltrialsregister.eu). The following clinical trials were retrieved.

Study ID	Patients	Study design and comparison	Primary outcomes	Study deadline	Status
NCT01679132	Patients with uncontrolled hypertension, both genders, 21-80 years old (n=310)	RCT Neo Baroreflex Activation Therapy System (plus optimal medical management) VS (optimal) Medical Management	Primary Safety Objective [Time Frame: 30 days]: To demonstrate the safety of the Neo system by reporting all adverse events that are complications between implant and 30 days post-implant in the device arm. The incidence of adverse events will be categorized by relatedness. Primary Efficacy Objective [Time Frame: 6 months]: To demonstrate a significant reduction between the two treatment arms of protocol defined automated office cuff systolic blood pressure (SBP) from baseline to 6 months post-	July 2015	Currently recruiting participants

			activation.		
NCT01471834	Patients with uncontrolled hypertension, both genders, 21-80 years old (n=40)	Non-Randomized, single-arm (Baroreflex Activation Therapy using the Barostim Neo System)	Change from baseline in Systolic Blood Pressure at 6 months. [Time Frame: 6 months] [Designated as safety issue: No]	July 2015	Ongoing, but not recruiting participants
NCT02364310	Patients with resistant hypertension, both genders, 18-75 years old (n=128)	RCT (PROBE tria) (Baroreceptor stimulation with Barostim Neo TM vs best medical care)	12th month diurnal SBP (mmHg) measured on ABPM, adjusted on baseline SBP, also used to compute the incremental cost-effective ratio (to identify the extra cost of unilateral carotid barostimulation in BP reduction compared to usual care) [Time Frame: 12 months] [Designated as safety issue: Yes]	October 2018	Currently recruiting participants

Among the presently ongoing studies, one study (NCT01471834) seems to be very similar to the one published by Hoppe et al (Hoppe 2012) in terms of study design (non-randomised, single-arm study) and surrogate outcomes. The other ongoing study (NCT01679132) is a randomised study whose primary outcomes are short-term adverse events (at 30 days post-implant) and blood pressure reduction over a short period of time (6 months). The third study, the RCT PROBE, aims to assess both clinical and economic issues regarding the use of Barostim *neo*™ compared to usual care. In this case the follow-up is 12 months but modelling will assess cost-effectiveness with a lifetime-long approach.
In all the studies the primary outcome considers only reduction in systolic blood pressure and not in diastolic blood pressure.

Authorisation

The CVRx® Barostim *neo*™ system received a CE mark in 2013 (registration number: 253.104) for resistant hypertension. It is also CE marked for heart failure patients in Europe since 2014.
In the USA, Barostim *neo*™ is authorised by FDA as an investigational device and is regulated by United States law to investigational use.
In the Italian medical devices repertoire Barostim *neo*™ is registered as Neo Baroreflex Activation Therapy Systems with the following number: 501188.

Diffusion/diffusion prediction

In 2013, two Italian regions (namely Toscana and Lazio) implanted 2 and 1 Barostim *neo*™ system, respectively, for a total cost of approximately 70,000€.
In 2014 one Italian region, Toscana, implanted one Barostim *neo*™ system for a total cost of approximately 16,000€ (http://www.dati.salute.gov.it/dati/dettaglioDataset.jsp?menu=dati&idPag=71, access on 15th July 2015, and personal communication from general Directory of Health, Emilia-Romagna region).

Brief summary

Barostim *neo*™ is a second-generation implantable device that in 2013 received the CE mark for resistant hypertension, defined as blood pressure persistently ≥ 140/90 mm Hg despite administration of at least 3 anti-hypertensive drugs in adequate doses (including a diuretic), in absence of secondary cause of hypertension. The implant of the device is minimally invasive, takes approximately 100 minutes by trained surgeons, usually requires hospitalization and outpatient follow-up visits to a surgeon. No data on specific surgical requirements and emergency procedures in case of malfunction were retrieved. The device costs € 21,000; the reported cost for battery (estimated life: 2,8±1,4 years) is € 15,000.
In the Emilia-Romagna region, patients with drug-resistant hypertension are around 535-636. Considering the contraindications to the procedure or the device, and the need to have true resistant hypertension confirmed by 24-h ambulatory blood pressure monitoring (ABPM) in highly specialised centres for the treatment of hypertension, a limited number of these patients would be eligible for Barostim *neo*™ implant.
The literature search identified three primary non-randomised, before-and-after studies on a total of 72 patients. Evidence provided by the retrieved studies were assessed vis-a-vis the pre-defined Evidence Profile of the technology. No patient-important outcomes were evaluated. Results on the surrogate outcome report that the treatment decreased both systolic and diastolic blood pressure.
Included studies should be considered exploratory, as the lack of a comparison arm, short

duration of the trials and surrogate nature of the chosen endpoints are not considered sufficient to prove efficacy and safety of the device.
Moreover, given enrolled patients' baseline values of DBP and the lack of data on percentage of patients reaching the target blood pressure (i.e. < 140/90), there is concern that patients enrolled in these trials might have had isolated systolic hypertension only and that the device might not be useful to reach DBP targets.
This concern is further corroborated by the fact that the three ongoing studies presently registered in clinical trials' registries (two RCTs on 310 and 128 patients, respectively, and one non-randomised, before-and-after study on 40 patients, all on patients with uncontrolled hypertension) will evaluate, as primary efficacy endpoint, only the reduction of SBP.
In conclusion, 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.

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