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Baroreflex activation therapy for drug-resistant hypertension.

A single technology assessment

folkehelseinstituttet

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Executive summary

Background

The Barostim therapy device is an active implantable device which delivers electrical stimulation to the baroreceptors located on the carotid artery with the aim of lowering blood pressure in patients with resistant hypertension. This device for baroreflex activation therapy has been produced as a first generation system (Rheos system), and the currently available second generation system (Barostim Neo). The main difference between the two systems is that for the first generation system the electrical stimulation is applied via bilateral electrodes on the external surface of the carotid arteries, while for the second generation system this was done unilaterally.

Barostim Neo is currently the only commercially available baroreflex activation therapy delivery system.

As per the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) guidelines for arterial hypertension, hypertension is defined as resistant to treatment when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses fails to lower systolic-and diastolic blood pressure values to 140 and 90 mmHg, respectively.

The reported incidence of resistant hypertension varies from approximately 2% to 16% of a population with hypertension. Factors shown to influence the results includes white-coat effect (the elevation of blood pressure during the clinic visit in comparison with the patients' blood pressure at home), poor medication adherence and whether office or ambulatory measurements are used.

Objective

This single technology assessment was commissioned by the The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway. They wanted Norwegian Institute of Public Health to evaluate the efficacy, safety and health economic documentation for use of baroreflex activation therapy in patients with drug-resistant hypertension. We have evaluated the submitted documentation against available published documentation.

Methods

Efficacy and safety

We have evaluated the submitted PICO (Population, Intervention, Comparator and Outcomes), and performed our own systematic literature search. Two review authors identified literature, performed data extraction, and assessed the included trials for risk of bias and the overall quality of evidence for each endpoint using GRADE (Grading of Recommendations Assessment, Development, and Evaluation). Finally, we critically appraised the same points in the documentation submitted by the manufacturer.

Health economic methods

In the evaluation of the submitted cost-efffectiveness analysis and analysis of the budget impact from CVRx, Inc. we evaluated the submitted input data used to the cost-effectiveness model, the structure of the model and the calculations of the budget impact.

Evaluation of the documentation

Efficacy and safety

Most of the documentation, included the only randomized controlled trial, was from trials with the Rheos device. This bilateral delivery system is now unavailable.

We evaluated four multicenter trials, two for Rheos and two for Neo, including 448 patients (367 for Rheos and 81 for Neo) above 18 years with resistant hypertension.
The Rheos trials: A randomized controlled trial (The Rheos Pivotal Trial) (n=265 randomized), and the DEBuT-HT (Device Based Therapy in HypertensionTrial) with single-arm/”before and after” design (n=45). Both had published abstracts (n=322 and 18 respectively) with follow-up evidence up to six years again in a single-arm design.
The Neo trials: The Barostim Neo trial (n=30), and Wallbach 2016 (n=51), both single-arm//”before and after” design, both with 6 months follow-up.
Comparison of the efficacy and safety for the Rheos system versus the Neo system: One abstract describes a comparision of a cohort from a Neo trial with two matched cohorts from the Rheos pivotal trial.

The efficacy endpoints were changes in systolic-and diastolic blood pressure, heart rate and left ventricular mass index, and proportion of responders, either compared to a control group, or compared to a baseline value. Complications were procedure- and/or device-related serious adverse events measured for the total population. Pro-

cedural safety reports serious adverse events occurring within the 30 days of implant. Serious device-related adverse events were reported between 30 days post-implant and the month 12 visit.

Health economic documentation

The submitter performed a cost-effectiveness analysis for evaluating the cost-effectiveness of Baroreflex activation therapy for drug-resistant hypertension. They considered varation in outcomes and costs according to which treatment strategy a drug-resistant hypertension patient undergoes. A Markov cohort model was used to estimate the cost-effectiveness of the new technology compared to current practice, optimal medical therapy strategy, over a 60- year time horizon, for patients aged 54. The submitted model considered all patients who entered the Markov process, and covered the most important end-stage organ damage including myocardial infarction, stroke and transient ischemic attack, heart failure and end-stage renal disease.

In addition to presenting the results calculated by the sponsor, we performed three scenario analyses in which we adjusted various model parameters reflecting efficacy and health-related quality of life (utility values)in order to examine the effect of different assumptions on model outcomes.

We examined uncertainty in model parameters by performing one-way sensitivity analyses and presented the results as tornado diagrams.

Results

Efficacy

We have evaluated the evidence for the endpoints from the randomized controlled trial to have low risk of bias and moderate quality as assessed by GRADE. We evaluated the evidence for all endpoints from the publications with single-arm designs to have high risk of bias and very low quality, hence we have very little confidence in these results. This includes all the evidence from the Neo trials.

The randomized controlled trial failed to demonstrate statistically significant differences between the Rheos activated- and Rheos inactivated therapy (sham) between baseline and 6 months for the two predefined endpoints: 1) The mean decrease in systolic blood pressure in the intervention group was 7 mm Hg larger than in the control group (14.5 larger to 0.5 smaller). 2) The proportions of patients that achieved at least a 10 mm Hg drop in office systolic blood pressure from baseline to 6 months, were 54% versus 46% (p=0.97) in the intervention and the control group, respectively.

The evidence was influenced of when (pre-or post-implant) and how (office and ambulatory) blood pressure is measured.

Safety

The Rheos system had an event-free rate of serious adverse events, compared to prespecified objective performance criteria based on similar implantable devices, that was comparable ($p=1.00$) for procedural safety, and higher ($p<0.001$) for device- related safety. From the Neo trials there is too little evidence to conclude for safety (only 30 and 51 patients respectively in the two main trials). However, one may think that the safety for the unilateral device could be in the same order as the bilateral device. Long-term safety data beyond 12 months are missing.

Health economic results

The calculated incremental cost-effecivness ratio (ICER) based on the submitted economic model over a 60-year time horizon was NOK 509,016 per quality adjusted life year (QALY) gained for patients aged 54. We varied clinical effectiveness values for the reduction of systolic blood pressure in both treatment arms in order to test a different interpretation of trial results. In our first scenario, we captured changes in blood pressure based on the post-implant baseline measurement of office systolic blood pressure, measured at 6 months from the Rheos trial. The calculated ICER for this scenario analysis rose to NOK 796,761 per QALY gained. In a second scenario analysis we adjusted both the clinical effectiveness values (as in scenario 1) and the utility value related to the hypertensive state. The resulting ICER increased to NOK 896,898 per QALY gained. We also performed a third scenario analysis based on the post hoc analysis found in the Rheos trial, using pre-implant baseline measurements for the clinical effectiveness, and the adjusted utility value related to the hypertensive state (as in scenario 2). The calculated ICER increased to NOK 856,312 per QALY gained. All the scenario analyses showed a less cost-effective result than presented in the submission.

One-way sensitivity analysis showed that the results were most sensitive to changes in the age of the patient population, the costs related to the Barostim therapy (battery, system and replacement), and the 6-month probability of hypertensive crisis in the optimal medical therapy arm. The patient's age had the largest uncertainty and the ICER varied between NOK 517,286 and NOK 2,192,157.

The submitter estimated that the total added costs of implementing Barostim Neo system in Norway would be about NOK 24,000,000 for the first five years. Due to uncertainties associated with the yearly costs used in the calculation of budget impact by the submitter, we re-calculated the additional costs of introducing the technology in Norway. The results of our budget impact analysis showed that assuming 20 new patients each year, the total added expected cost would be about NOK 24,500,000 for the first five years after adoption of Barostim Neo system in Norway.

The cost of battery replacement (approximately half the cost of initial device and implantation) becomes relevant after six years.

Discussion

We have performed a single technology assessment of the use of Baroreflex activation therapy for drug-resistant hypertension. The submission came from CVRx, Inc. Our conclusion is that we disagree with the submitter's conclusion regarding efficacy and therefore also cost-effectiveness.

Efficacy and safety

Both the submitter and we have evaluated the same main trials and extracted the same main evidence from these. The reason for our disagreement lays in the analyses and the evaluation of the evidence.
The submitter chose to conclude (claim) from a pooled analysis based on evidence from trials with no control group, and not from available evidence with relative effect estimates from the randomized controlled part of the Rheos pivotal trial. The use of the evidence from the pooled analysis from trials with no control group, results in an overestimate of the efficacy evidence, with a following positive impact on the cost- effectiveness analysis.

Factors that influence on the results:
We have observed that office measurements give greater changes from baseline in systolic- and diastolic blood pressures than ambulatory measurements. Further, from the randomized controlled trial we observed that the use of pre-implant measurements as baseline values for systolic blood pressure gave larger reduction at 6 months, than if the baseline values were measured post-implant.

Further research
We believe a randomized controlled trial is needed. This is also suggested from our sister organizations in the United Kingdom and Canada (NICE and CADTH respectively). We suggest that the optimal study design would be a randomized controlled trial, with sufficient number of patients, comparing active Barostim Neo device with the best available pharmacological treatment using ambulatory measurements of blood pressure and pre-implant measurements as baseline. If the control group is a sham control (or if one want this as a third arm), it could possibly be necessary or interesting to use post-implant measurements in addition to pre-implant measurements. The follow-up should be at least one year.

Health economic

The submitter performed an economic evaluation by developing a decision tree combined with a Markov model. The model included all patients who entered the Markov process, and covered the most important end-stage organ damage including

myocardial infarction, stroke and transient ischemic attack (TIA), heart failure and end-stage renal disease.

Based on thorough review and input given by the clinical experts, we think that the health economic model captured the outcomes that are clinically relevant for the defined population and intervention.

However, there were some uncertain points to consider regarding the submission. We performed three scenario analyses, one scenario analysis where we revised only the clinical effectiveness values related to the reduction in systolic blood pressure and two scenario analyses where we revised and corrected both the clinical effectiveness values and the utility value related to the hypertensive state. In all scenario analyses the new technology combined with optimal treatment care became less cost-effective than the submitted cost-effectivness results.

Further, we investigated the impact of reducing the 60-year time horizon, which seemed too long for a population with an average age of 54, to a time horizon of 40-years. The shorter time horizon had little effect on the results. Finally, we adjusted the shares and dosages of the pharmacutical in both model arms to reflect actual practice in Norway. These adjustments had little impact on the results.

Conclusion

Efficacy and safety

Our data extraction from the available literature cannot support the claims from the submitter.
We found that there is insufficient evidence to demonstrate efficacy for both the Rheos system and the Barostim Neo™ system.

The safety for the Rheos system had an event-free rate, compared to pre-specified objective performance criteria based on similar implantable devices, that was comparable ($p=1.00$) for serious procedural safety, and higher ($p<0.001$) for serious device-related safety. One may think that the safety for the unilateral device could be in the same order as the bilateral device. Long-term safety data beyond 12 months are missing.

Cost-effectiveness

Based on ICER levels that have typically been considered cost-effective in Norway, the submitted economic analysis indicates that Barostim therapy could be cost-effective in patients with drug-resistant hypertension. However, after adjusting the model to account for important shortcomings in the submitted analysis, related to clinical effect and health-related quality of life, the ICER rises well above the level that has been considered cost-effective in Norway.

Scenario analyses indicate that the results are particularly sensitive to patient age and cost of the Barostim device (battery, system and replacement). Treatment could be cost-effective among a young population group or with a decrease in Barostim costs.

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Preface

What is a single technology assessment

A single technology assessment (STA) is one of the products in The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway. The system has a webside (https://nyemetoder.no/).

The Ordering Forum (Bestillerforum RHF) evaluates submitted suggestions and decides which methods they would like to have evaluated and the type of evaluation that is needed. In a single health technology assessment, methods are evaluated based on documentation submitted by a company owning the method or their representatives. A template is available to aid the submission of necessary information and documentation (https://nyemetoder.no/Documents/Administrativt%20%28brukes%20kun%20av%20sekretariatet%21%29/Template%20pharmaceuticals%20v3.pdf)

Norwegian Institute of Public Health receives and evaluates the submitted documentation, but is not the decision-making authority. The single technology assessment from Norwegian Institute of Public Health will be available at our website. The Decision Forum ("Beslutningsforum RHF"), consisting of the directors for the four Health regions in Norway, makes the decision whether to introduce new methods or not.

Objective

This single technology assessment was commissioned by the The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway. They wanted Norwegian Institute of Public Health to evaluate the efficacy, safety and health economic documentation for use of baroreflex activation therapy in patients with drug-resistant hypertension. We have evaluated the submitted documentation against available published documentation.

Logg

The Ordering Forum ("Bestillerforum RHF") reviewed the suggestion regarding use of Barostim® device, ID2015_011, in February 2015. On April 27. 2015 "Bestillerforum RHF" requested that the Norwegian Knowledge Center for the Health Services (now part of the Norwegian Institute of Public Health) perform a single technology assessment on its use as an implanted device for the management of drug-resistant hypertension (https://nyemetoder.no/metoder/baroreflaksstimulator)

February 2015: Publication of horizon scanning report on this device
27.04.2015: The Ordering Forum ("Bestillerforum RHF") commissioned a single technology assessment
February 2016-July 2016: dialogue and meeting with concerned company
02.08.2016: Valid submission acknowledged
17.02.2017: The Norwegian Institute of Public Health sent the single technology assessment to the Ordering Forum.
19.02.2017: End of 180 days evaluation period

Project group

The project group consisted of:
Project coordinator: Senior researcher Eva Pike
Health economist: Beate Charlotte Fagerlund
Senior researcher: Liv Giske
Health economist: Arna Desser
Research librarian: Ingrid Harboe

In addition, we have received help and feedback from the following persons:
Clinical expert: Reidar Bjørnerheim, MD, PhD, Head of Echocardiograpy unit, Oslo University Hospital.
Peer reeview: Arne Westheim, MD, PhD, Department of Cardiology, Oslo University Hospital.
Research librarian: Elisabet Hafstad, Norwegian Institute of Public Health.

Signe Agnes Flottorp	Ingvil Sæterdal	Eva Pike
Department director	*Head of unit*	*Project leader*

Background

Name of the device and the manufacturer who prepared the submission

Name of device: Barostim® device
Name of the manufacturer which submitted the application: CVRx, Inc., Minneapolis, USA.
The device has a first-and second generation system. The first generation, the Rheos system, is no longer commercially available. The second generation, the Barostim Neo™ system, is the only commercially available Baroreflex Activation Therapy (BAT) delivery system at present.

Present approval

Barostim® device is CE marked for the treatment of resistant hypertension. It is also CE marked for the treatment of New York Heart Association (NYHA) class III Heart Failure with reduced ejection fraction.
The Barostim Neo™ system was approved by FDA in December 2014 for for use in patients with resistant hypertension who have had bilateral implantation of the rheos® carotid sinus leads models 1010r, 1010l, 1014l, and 1014r (which have been discontinued and are obsolete) and were determined responders in the rheos® pivotal clinical study (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm430226.htm).

Description of the technology

In the healthy individual, increases in blood pressure activate stretch-sensitive baroreceptors in the carotid artery and the aortic wall. Counter-regulatory adjustments in sympathetic and parasympathetic activity lead to stabilization in blood pressure. Electric stimulation of baroreflex afferent nerves are interpreted by the brain as an increase in blood pressure with the consequence that sympathetic activity is lowered, whilst parasympathetic activity is raised, leading to an overall reduction in blood pressure.

The Barostim Therapy device is an active implantable device which delivers electrical stimulation to the baroreceptors located on the carotid artery with the aim of lowering blood pressure in patients with resistant hypertension. This device for baroreflex activation therapy has been produced as a first generation system (Rheos system), and the current available second generation system (Barostim Neo). The implanted portions of the Rheos and Neo systems consist of an implantable pulse generator (IPG) and leads. The electrical stimulation is applied via means of an electrode on the external surface of the carotid artery connected via a tunneled lead (sub-cutaneous and supra-clavicular) to the implantable pulse generator positioned in a sub-cutaneous pocket in the chest.
For the first generation system, the Rheos system, one implantable pulse generator and two carotid sinus leads were required (one per carotid sinus). In the case of the Neo system, the implantable pulse generator requirements remain the same but only one carotid sinus lead is required. Further, the leads used in the Neo system utilize smaller electrodes (Figure 1). A size comparison of the Rheos and Neo lead electrodes is shown in Figure 1.

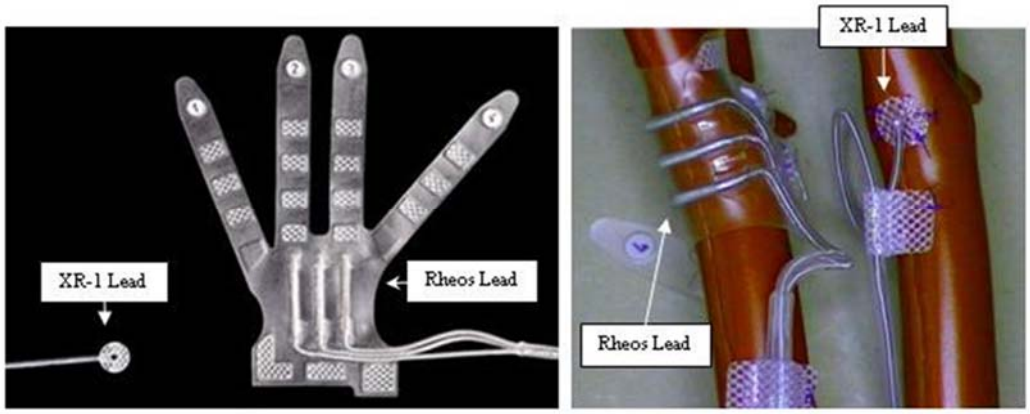


Figure 1. A size comparison of the Rheos and Neo lead electrodes

Description, incidence and present treatment for patients with resistant hypertension

Hypertension in general

Hypertension is a significant worldwide health problem that leads to some of the most common and debilitating diseases such as stroke, myocardial infarction, heart failure and end-stage renal disease. The European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) guidelines from 2013 definition of hypertension is a systolic blood pressure of >140 mm Hg and / or >90 mm Hg diastolic blood pressure (1).

Hypertension a leading cause of death worldwide and is estimated to cause 7.5 million deaths each year, which represents approximately 12.8% of all deaths (2). Globally, 51% of cerebrovascular disease and 45% of ischaemic heart disease are closely related to high blood pressure (3).

The prevalence of hypertension in the European countries is in average 44.2% (4), with rates between 26.7% for men and 20% for women (Belgium, MONICA study, 1985-1992) and 60.7% in men and 42.2% in women (Finland, FINMONICA, 1982). In Norway the estimated prevalence of hypertension is about 40% (5).

The present treatment is lifestyle changes and pharmacologic treatment.

Resistant hypertension

As per the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) guidelines for arterial hypertension, hypertension is defined as resistant to treatment when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses (but not necessarily including a mineralocorticoid receptor antagonist) fails to lower systolic-and diastolic blood pressure values to <140 mm Hg and 90 mmHg, respectively (1).

The reported incidence of resistant hypertension varies from approximately 2% to 16% of a population with hypertension (6), (7), (8), (9).
Factors shown to influence the results of blood pressure measurements include white-coat effect (the elevation of blood pressure during a clinic visit in comparison with the patients' blood pressure at home) (10), (1), poor medication adherence (11), (12) and whether office or ambulatory measurements are used (13), (14), (15). Office blood pressure is prone to "white coat influence", overestimation, and thus systematic biases (1), (10). Ambulatory measurements are considerably less influenced by these placebo/nocebo effects, and are considered to be the most valid method to measure blood pressure (16), (17), (18).
It has been reported that up to 40% of patients appearing to have resistant hypertension, actually had the "white coat effect" (10), and more than 50% of patients diagnosed as having resistant hypertension were in fact pseudo-resistant due to non-adherence to the prescribed medication (11).

The main research questions

Based on the original suggestion and the subsequent commission from The Ordering Forum ("Bestillerforum RHF"), the main research questions, as defined by the sub-

mitter, are shown in Table 1 below. The main research questions are organized according to the relevant PICO (P= Population, I= Intervention, C= Comparator, O=Outcomes (Endpoints).

Table 1. The main research questions in this single single technology assessment

Patient group:	Participants with an office baseline systolic blood pressure value of at least 140 mmHg systolic and/or a diastolic blood pressure values of at least 90 mmHg. Patients are not restricted by age, gender, baseline risk or any other co-morbid conditions.
Intervention:	Baroreflex activation therapy device Rheos or Barostim Neo or XR-1, manufactured by CVRx Inc.
Comparator:	Multi-drug treatment of hypertension
Outcomes:	Primary: • Change from baseline and/or peak office systolic- and diastolic blood pressure values compared with a control group or baseline at specified follow-up. Secondary: • Changes from baseline and/or peak ambulatory systolic- and diastolic blood pressure values are compared with a control group or baseline at specified follow-up. • Proportion of patients with a systolic- and diastolic blood pressure reduction of >10 mmHg, >20 mmHg or >30 mmHg is compared with a control group or baseline at specified follow-up. • Proportion of patients reaching a therapeutic goal (systolic blood pressure <140 mmHg) is compared with a control group or baseline at specified follow-up. • Proportion of patients reaching a therapeutic goal (systolic blood pressure <140 mmHg or <130 mmHg for diabetics and patients with renal diseases) is compared with a control group or baseline at specified follow-up. • Heart rate reduction is compared with a control group or baseline at specified follow-up. • Left ventricular mass index is compared with the baseline at specified follow-up. • Serious (death, life-threatening situation, in-patient hospitalization, prolongation of existing hospitalization or persistent or significant disability) procedure-related adverse events rate at 1-month follow-up. • Serious (death, life-threatening situation, in-patient hospitalization, prolongation of existing hospitalization, or persistent or significant disability) device-related adverse events rate at specified follow-up.

Comments from the Norwegian Institute of Public Health

The Barostim device has been produced as a first generation system (Rheos system), and a second generation system (Barostim Neo). The main difference between the two systems is that for the first generation system the electrical stimulation is applied via bilateral electrodes on the external surface of the carotid arteries, while for the second generation system this was done unilaterally.

Barostim Neo is currently the only commercially available Baroreflex Activation Therapy delivery system.

We have consulted with our clinical expert who agreed to the above PICO (Population, Intervention, Comparator and Outcomes). The expert, however, commented that it should be sufficient to include the Barostim Neo as the intervention.

We have, however, chosen to include both the first generation system (Rheos system), and the second generation system (Barostim Neo) in this single technology assessment. We did so because this was in agreement with the submitted PICO, most of the available evidence was with the Rheos system, and because a publication comparing the Rheos and the Neo system was available (19).

The Canadian Agency for Drugs and Technologies in Health (CADTH) (20), and the National Institute for Health and Clinical Excellence (NICE) (21), have published evaluations for Barostim in 2015. Both evaluations included evidence from both the Rheos and the Neo trials.

Clinical evaluation-Methods

In our evaluation of the submitted documentation from CVRx, Inc., we have assessed the PICO, the literature search, the included trials/publications and the conclusions.

We have done this by discussing the selected PICO with a clinical expert, and we have performed our own systematic literature search. Two review authors worked independently and in pairs and reviewed all citations generated by the search to identify potentially relevant publications based on title and/or abstract. Further we assessed whether these references should be included according to the inclusion criteria. One review author extracted data from the included references and another review author verified the data.

We assessed the included trials for possible risk of bias according to our Handbook (22). We assessed the overall quality of evidence for each endpoint using GRADE (Grading of Recommendations Assessment, Development, and Evaluation). We followed the guidelines provided by the GRADE working group (23) and categorized our confidence in the effect estimates into four levels: high, moderate, low and very low.

Finally, we critically appraised the same points in the documentation submitted by the manufacturer.

Clinical evaluation -Results

Literature searches and identification of relevant published literature

Literature searches

We performed our own searches to identify all trials and Health Technology Assessments (HTA's) evaluating the performance of the Barostim System within the bounds described in the PICO. We systematically searched for literature in the following databases 14 October 2016:

- Embase and MEDLINE via Ovid
- Cochrane Library: Cochrane Database of Systematic Reviews (CDSR)
  Cochrane Central Register of Controlled Trials (CENTRAL)
  Other Reviews (Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED)
- PubMed (2015-2016)

We searched for ongoing clinical trials in ClinicalTrials.gov and WHO ICTRP (International Clinical Registry Platform).
We also searched in relevant HTA organizations.

The research librarian Ingrid Harboe planned and executed all the searches. The complete search strategy can be seen in Appendix 1.

Critical appraisal of the submitter's literature searches

The submitter performed their searches on 22 December 2015, i.e. about a year before our searches. They did systematic literature searches in the same databases as we have done, except that they did not search in The Database of Abstracts of Reviews of Effects (DARE) or PubMed (2015-2016).

Identification of relevant published literature

We identified 31 publications and extracted data from 17, since some of the publications providing overlapping evidence. The flow chart for selection of literature is shown in figure 2. Appendix 3 shows details about the publications we extracted

data from, and the publications that had overlapping evidence. Of the 17 publications, there were four main trials in full text (14;15;24;25), including one randomized controlled trial (24), one fulltext with reanalysis of the population from the randomized controlled trial, but now in a non-randomized controlled design (26), six abstracts with follow-up or additional endpoints for the main trials (27-32), and five subgroup analyses (3 as full text and 2 as abstracts) of special populations from the main trials (33-37). Further, one abstract reanalyzed data from a Neo trial (the abstract does not tell which) in a comparision with two matched cohorts from the Rheos pivotal trial in order to compare the efficacy and safety for the two BAT generations (Rheos and Neo) (19).

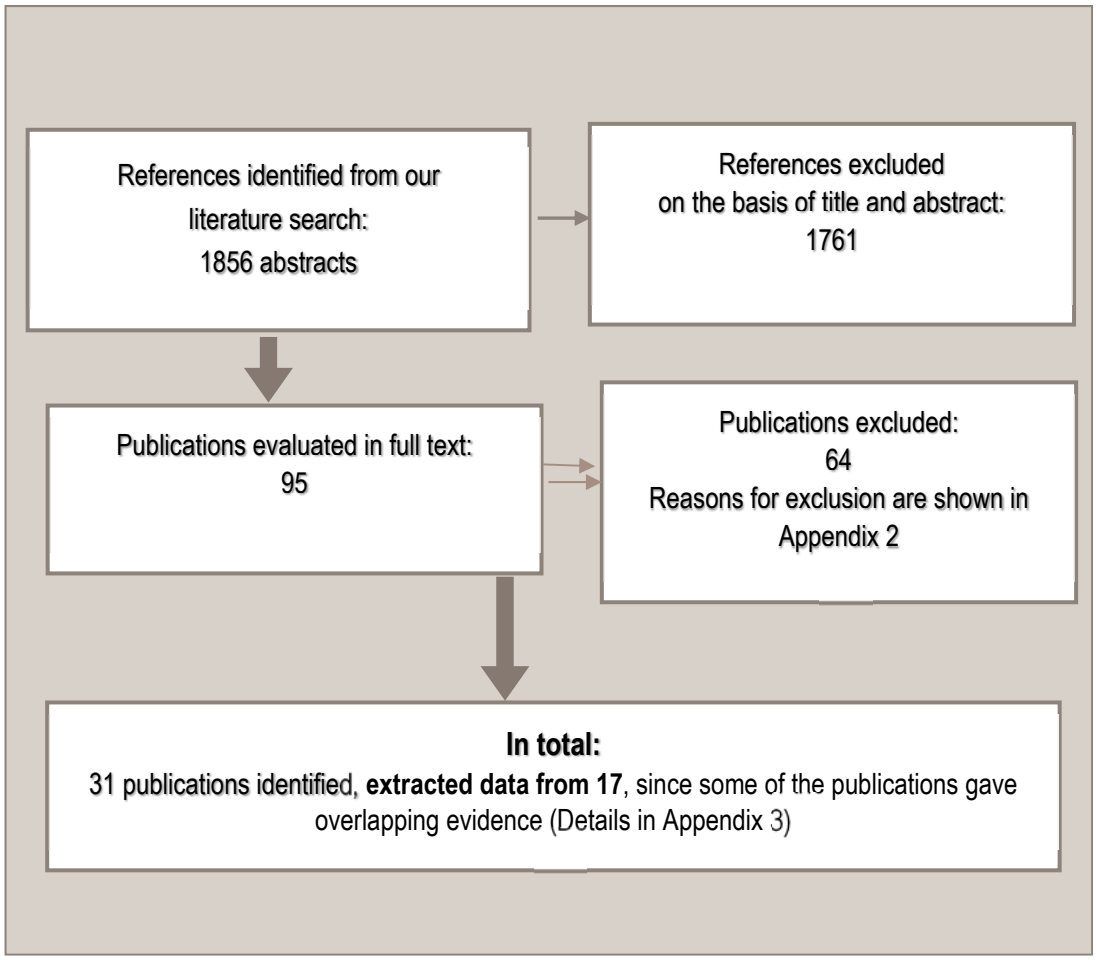


Figure 2. A flow chart of our selection of literature

Critical appraisal of the submitters' identification of literature

Appendix 4 gives a comparison of the publications that the submitter extracted data from versus the ones we extracted from.
Basically there were no differences. We both used the same four main trials, except for Wallbach where we used the 2016 publication (15), and the submitter used the publication published in 2015 (38). All the relevant evidence in the 2015 version

were found in the 2016 version. For the included publications with subgroup analyses, there were some differences between us and the submitter. None are important for the evaluation of the results. For the comparison of Rheos versus Neo, the submitter refers to unpublished data by Wachter 2015. We have included the published abstract by Wachter 2016 (19). For details see Appendix 4.

Identification of ongoing trials

We identified a total of 11 possibly ongoing trials, all 11 identified from ClinicalTrials.gov. No further trials identified from WHO ICTRP (International Clinical Trials Registry Platform) on 14 October 2016. These are listed in Appendix 5.

Critical appraisal of the submitters' identification of ongoing studies

They searched in ClinicalTrials.gov on February 8, 2016 using the search terms "Barostim", "BAT", "Baroreflex activation therapy", and "CVRx". Clinical trials that focused on treatment other than resistant hypertension were not included. They did not searched in WHO International Clinical Trials Registry Platform, however, we did not find any additional trials there.

The submitter identified two ongoing trials:

- Economic Evaluation of Baroreceptor STIMulation for the Treatment of Resistant HyperTensioN (ESTIM-rHTN) (NCT02364310). Estimated primary completion date is November 2018.

Our comments: We have also identied this.

- The Effect of Baroreflex Activation Therapy (BAT) on Blood Pressure and Symp athetic Function in Patients With Resistant Hypertension (The Nordic BAT Study) (The Nordic BAT) (NCT02572024) is currently recruiting participants. This randomized, double-blind, parallel-design clinical trial is to further examine the effect of Barostim Therapy compared to continuous pharmacotherapy on blood pressure, as well as arterial and cardiac function and structure using non-invasive high technology methodology, in a Nordic multicentre study. Estimated primary completion date is November 2020.

Our comments: We have aslo identified this. It is not clear neither from the submitters' comments nor from ClinicalTrials.gov if BAT here is Rheos or Neo.

The submitter identified two not active trials:

- Barostim Neo System in the Treatment of Resistant Hypertension (NCT01471834) is completed. The results are published, Hoppe et al 2012.

Our comments: We have aslo identified this. We have included Hoppe 2012 (as also the submitter did), however the Hoppe publication had no NCT number.

- CVRx Barostim Hypertension Pivotal Trial (NCT01679132) is a planned

prospective randomized controlled trial comparing patients receiving Barostim Neo system with patients receiving medical management. The trial is estimated to enroll 310 participants. The primary outcomes include the safety of the system at 30 days and efficacy (office systolic blood pressure) at six months. Secondary outcomes include office and ambulatory systolic blood pressure at 12 months, and safety outcomes such as incidence of hypertensive emergencies from activation to six months. This trial is yet to start due to lack of available funds.
Our comments: We have aslo identified this.

The submitter also informed that the long term results of the Rheos Pivotal Trial showing data to 6 years are soon to be published, plus an equivalence publication on Barostim first and second device generations.
Our comments: The 6 years results are published in an abstract, de Leeuw 2015 (28), and the equivalence trial is also now published, Wachter 2016 (19). We have included both.

Again, as informed by the submitter: There are two FDA-approved trials about to commence patient enrolment in the US; one for resistant hypertension, and one for heart failure.
Our comments: We have asked the submitter for more information about the trial for resistant hypertension. They answered: “Resistant Hypertension identifier is NCT01679132 but is not yet enrolling”.

Identification of relevant health technology assessments

We identified one bulletin published in May 2015 from Canadian Agency for Drugs and Technologies in Health (CADTH) (20), and an interventional procedure guidance published in October 2015 from National Institute for Health and Care Excellence (NICE)(21).

Further, from our own search we identified a technology brief update published in July 2014 from Australian Safety and Efficacy Register of New Interventional Procedures-Surgical (ASERNIP-S) (39). The last one we did not include, since we choose to use the two that were published later.
The Australian update, also included only two trials, Bakris 2012 and Hoppe 2012 (40), (25). Bakris 2012 (40) is excluded both by us and the submitter, since the data most probably are in de Leeuw 2015 that we included.

The submitter did not refer to any health technology assessments.

Description of included trials

Table 2a, 2b and 2c present an overview of the publications we extracted data from, for Rheos, Neo and the comparision of Rheos versus Neo. Appendix 3 provides descriptions of the trials, data extraction tables and risk of bias tables for these publications.

The trials for the first generation of the baroreflex activation therapy delivery system, the Rheos system were:

- *One randomized controlled trial, The Rheos Pivotal Trial (NCT00442286)* (24) with four additional publications (one full text and 3 abstracts) (26), (27), (33), (28).
- *One prospective non-randomized feasability study, single-arm design, the DEBuT-HT (Device Based Therapy in HypertensionTrial)(14)* with additional three publications (all abstracts) (29), (30), (34).

The trials for the second generation, the Neo system were:

- *The Barostim Neo trial (25), single-arm design,* with one additional publication (abstract) (31).
- *Other Neo trials, where the publication from Wallbach 2016 was the main publication* (15), with four additional publications (32), (35), (36), (37).

A publication comparing the Rheos system (the first generation) and the Barostim Neo system (the second generation):

- *One publication (abtract)* (19).

Table 2a. The Rheos publications that we extracted evidence from

Publication/ number of patients	Design	Endpoints (changes are between baseline and follow-up time)	Risk of bias
The Rheos pivotal trial, Bisognano 2011 (24) , (NCT00442286), fulltext (n=265)	RCT, placebo/sham controlled, double blinded, multicenter. Intervention: Active BAT for 12 months. Control: Inactive BAT for 6 months, followed by active BAT for the next 6 months. Measurements of BP: Office. Baseline measurements: Post-implant. Intention- to- treat.	At 6 months: Mean changes in SBP, proportion of responders, safety	Low

Alnima 2013, fulltext (26) (n=322)	Non-randomized, controlled. Reanalysis of all the patients who got the Rheos system implanted in the RCT. Measurements of BP: Office. Baseline measurements: Post-implant.	At 6 and 12 months: Mean changes in SBP, DBP and heart rate	High
Bisognano 2011, abstract (27) (n=46)	12 months follow- up of the RCT, now in a single-arm/"before and after" design. No control group. The baseline values were used as the "before values". Measurements of BP: Office. Baseline measurements: not reported.	At 12 months: LVMI	High
De Leeuw 2014, abstract (33) (n=82)	*A subpopulations of heart failure patients* A single-arm/"before and after" design. Measurements of BP: Not reported. Baseline measurements: Not reported.	At 1, 2, 3, 4 and 5 years: Mean changes in SBP and DBP. At 6 and 12 months at Mean changes in LVMI.	High
De Leeuw 2015, abstract (28) (n=322)	6 years follow-up of the RCT, in a single-arm/"before and after" design. Measurements of BP: Not reported. Baseline measurements: Not reported.	At 1, 2, 3,4, 5 and 6 years: Mean changes in SBP and DBP. Safety during 6 years	High
The DEBuT-HT, Scheffers 2010, fulltext (14) (n=45)	A prospective feasability trial. A single-arm/"before and after" design. No control group. The baseline values were used as the "before values." Measurements of BP: Both office and ambulatory. Baseline measurements: Post-implant	At 3 months, 1 and 2 years: Mean changes in SBP, DBP and heart rate (office and ambulatory) Safety during 2 years.	High
Kroon 2010, abstract (29) (n=18)	4 years follow-up of the DEBuT-HT. A single-arm/"before and after" design. Measurements of BP: Not reported. Baseline measurements: Pre-implant	At 3 and 4 years: Mean changes in SBP, DBP and heart rate. Safety during 4 years.	High
Bisognano 2011, abstract (30) (n=34)	Additional endpoint of the DEBuT-HT. A single-arm/"before and after" design. Measurements of BP: Office. Baseline measurements: Not reported.	At 3 and 12 months: Mean changes in LVMI	High
Bisognano 2009, abstract (34) (n=21)	*A subpopulations of heart failure patients* A single-arm/"before and after" design. Measurements of BP: Office. Baseline measurements: Not reported.	At 3 and 12 months: Mean changes in SBP, DBP and LVMI	High

RCT: randomized controlled trial. LVMI: Left ventricular mass index. BP: Blood pressure. SBP: Systolic blood pressure. DBP: Diastolic blood pressure.

Table 2b. The Neo publications that we extracted evidence from

Publication	Design/number of patients	Endpoints	Risk of bias
The Barostim Neo Trial, Hoppe 2012, fulltext (25) (n=30)	A single-arm/"before and after" design. No control group. The baseline values were used as the "before values." Measurements of BP: Office. Baseline measurements: Pre-implant	At 3 and 6 months: Mean changes in SBP. Proportion of responders. Safety during 6 months.	High
Brandt 2012, abstract (31) (n=30)	Initial data for the Barostim Neo Trial. A single-arm/"before and after" design. No control group. The baseline values were used as the "before values." Measurements of BP: Assumed office. Baseline measurements: Pre-implant	At 3 months: Mean changes in DBP.	High
Wallbach 2016, fulltext (15) (n=51)	Prospective, multicenter (4 centers) with a single-arm/"before and after" design. No control group. The baseline values were used as the "before values." Measurements of BP: Office and ambulatory Baseline measurements: Pre-implant	At 6 months: Mean changes in SBP, DBP (both office and ambulatory), and heart rate (office). Proportion of responders. Safety during 6 months.	High
Hickethier 2013, abstract (32) (n=7)	12 months follow-up of the Wallbach trial. A single-arm/"before and after" design. No control group. The baseline values were used as the "before values." Measurements of BP: Office. Baseline measurements: Pre-implant	At 12 months: Mean changes in SBPand DBP. Safety during 12 months.	High
Wallbach 2016, fulltext (35) (n=28)	*A subpopulations of patients with prior renal denervation* A single-arm/"before and after" design. No control group. The baseline values were used as the "before values." Measurements of BP: Office and ambulatory. Baseline measurements: Pre-implant .	At 6 months: Mean changes in SBP, DBP (both office and ambulatory) and heart rate (office). Proportion of responders. At 12 months: Mean changes in SBP, DBP (ambulatory), and proportion of responders. Safety during 6 months follow-up.	High
Wallbach 2014, fulltext (36) (n=23)	*A subpopulations of patients with chronic kidney disease*	At 6 months: Mean changes in SBP, DBP (both office and ambulatory) and heart rate (office)	High

	A single-arm/"before and after" design. No control group. The baseline values were used as the "before values." Measurements of BP: Office and ambulatory. Baseline measurements: Pre-implant		
Beige 2015, fulltext (37) (n=7)	*A subpopulations of patients with chronic kidney disease* A single-arm/"before and after" design. No control group. The baseline values were used as the "before values." Measurements of BP: Office and ambulatory. Baseline measurements: Pre-implant	At 6 and 12 months: Mean changes in SBP, DBP (both office and ambulatory) and heart rate (office). Safety over 12 months.	High

LVMI: Left ventricular mass index. BP: Blood pressure. SBP: Systolic blood pressure. DBP: Diastolic blood pressure.

Table 2c. A publication comparing efficacy and safety for Rheos versus Neo

Publication	Design	Endpoints	RoB
Wachter 2016, abstract, (19) (n=90)	A comparison of three cohorts: 1) A cohort of 30 patients from the randomized Rheos pivotale trial with 12 months of active BAT. 2) Another 30 patients from the randomized Rheos pivotale trial with 6 months inactive BAT followed by 6 months of active BAT. 3) 30 patients from a single-arm verification study with Neo. (Name of the study is not given).	At 6 months: SBP reduction for Neo versus sham control patients from the RCT. Over 12 months: Average SBP reduction for Neo patients. Proportion of patients reaching a systolic BP<140 mm Hg. (SBP reduction for Neo patients versus Rheos patients. This is only reported as graphs, no figures, cannot use).	High

SBP: Systolic blood pressure. RCT: randomized controlled trial.

General information about the trials

Design

Except for one randomized controlled trial (24) and one trial with a non-randomized controlled design (26), all the other trials had a single-arm/"before and after" design, with no control group. All the four main trials were multicenter trials (from 2 to 49 centers), performed in Europe and USA. A total of 448 patients were included in the trials, with 367 and 81 respectively for the Rheos and Neo trials. Of the

448 patients 322 came from the randomized Rheos trial. The studies were published from 2009-2016.
Five of the publications reported on subgroups of patients with a specific comorbidity, as heart failure (33), (34), patients with prior renal denervation (35), and patients with chronic kidney disease (36), (37).

For the publications with single-arm designs, the baseline values were used as the "before values". The time for the baseline measurements varied between the trials. Of the four main trials, the two Rheos trials used post-implant baseline measurements, whereas the two Neo trials used pre-implant values. In the randomized Rheos trial, they also included a post hoc analysis using pre-implant baseline values. For more information about time for baseline measurements see Appendix 6.

Population
All the trials included patients with resistant hypertension above 18 years, mostly middle-aged, the mean age was 53-57 years, and with about the same proportion of males and females. Inclusion criteria for resistant hypertension were systolic blood pressure ≥160/90 mm Hg despite receiving at least 3 antihypertensive medications, including a diuretic (for the Rheos trials) and resting systolic blood pressure (systolic blood pressure)≥140 mm Hg despite treatment with ≥3 antihypertensive medications, including a diuretic for the Neo trials.

Endpoints
The efficacy endpoints were changes in systolic-and diastolic blood pressure, proportion of responders, heart rate and left ventricular mass index (LVMI) either compared to a control group (24), (26), or as compared to a baseline value for the single-arm studies.
The two main studies for Rheos reported efficacy up to 6 months in the randomized controlled trial (24), and up to 2 years for the DEBuT-HT (14), and up to 6 and 4 years respectively in single-arm follow up studies (28), (29).
The two main Neo trials (25), (15) reported efficacy and safety for 6 months.
Complications were procedure- and/or device-related serious adverse events measured for the total population. Complications were reported in a 30 days period after implantation for procedure-related events, and up to 12 months for device-related events. In the randomized Rheos trial complications were reported up to 12 months, and for the patients in the single-arm Neo trials up to 6 months.

All the four main trials measured blood pressure as office measurements, two of the main trials (14), (15) measured blood pressure both with office and ambulatory measurements.

The measurements of blood pressure (both office and ambulatory) were well defined and quite similar between the trials. Office blood pressure was measured as the average of at least two readings in all trials, except for the randomized trial that had an average of five readings. For ambulatory measurements the numbers of measurements were described. For more information see Appendices 3 and 6.

Our confidence in the effect estimates

We evaluated the risk of bias for all the endpoints from the randomized controlled trial to be low, and for all the endpoints from the other trials to high.

We also used GRADE (23) to evaluate our confidence in the evidence for systolic blood pressure at 6 months from the randomized trial; systolic-and diastolic blood pressure, and heart rate at 6 months from the non-randomized controlled study (26); systolic blood pressure and safety from the publications with single-arm design. Our confidence were moderate for the results from the randomized controlled trial, low for the results from the controlled trial, low for safety from the uncontrolled part of the Rheos pivotal trial (24), and very low for the results from the publications with single-arm design. For more information see Table 3 below and Appendices 3 and 7.

Clinical results

All the endpoints defined in the inclusion criteria/PICO were reported on in the included publications. Changes in systolic-and diastolic blood pressure, and in heart rate were reported in all the four main trials (24), (14), (25), (15); proportion of responders in three of the main trials (24), (25), (15); changes in left ventricular mass index (LVMI) were only measured for Rheos in two trials (24), (30). Serious adverse events were measured as procedure-related and device-related events in all the four main trials.

We also present evidence from subgroup analysis of specific populations (specific comorbidities or previous treatment in addition to resistant hypertension). Two of these publications were subgroup analyses of patients with heart failure (33), (34), two publications with chronic kidney diseases (36), (37), and one publication with patients who had renal denervation at least five months before and still suffer from uncontrolled hypertension (35). See Appendix 3 for more information.

From the available evidence it can be seen that two important measurement methods influenced changes in blood pressure, namely whether the investigators used office or 24-hrs ambulatory measurements of blood pressure, and if the baseline value was measured pre- or post-implant. Therefore, we have included this information in our presentations of the evidence, both in the text below, in the Tables 2a, b and c below, and in the Appendices 3 (evidence presented by trials), 6 (evidence presented by the measurements methods for blood pressure (office or ambulatory, and if the

baseline value is measured pre- or post-implant)), and 8 (evidence presented by endpoints).

Evidence for systolic blood pressure (SBP)

For Rheos

The evidence came from: Three publications from the *Rheos Pivotal trial*: The randomized controlled trial (24) with 6 months evidence, one controlled non-randomized trial (26), and an abstracts with single-arm design giving follow-up evidence from 1-6 years (28). Two publications from the DEBuT-HT, the main trial (14), and an abstracts giving follow-up evidence from 1-4 years (29), both had single-arm designs.

We found:

From the Pivotal randomized trial (24) (n=265), *with office measurements of systolic blood pressure and post-implant baseline measurements:*

The pre-defined endpoint, comparison of Group A (active BAT for 6 months/intervention group) versus Group B (inactive BAT for 6 months/sham control group) for mean change between *post-implant baseline* and 6 months data for systolic blood pressure, failed to show a statistically significant difference betweenthe groups. The mean decrease in systolic blood pressure at 6 months in the intervention group was 7 mm Hg larger (14.5 larger to 0.5 smaller). This is the efficacy results that we used in our alternative cost-effectiveness analyses.

However, in a post hoc analysis, with office measurements and *pre-implant* baseline measurements, a greater difference between the groups was reported for the change in systolic blood pressure between pre-implant baseline and 6 months. The mean decrease in systolic blood pressure at 6 months in Group A was 26±30mm Hg versus 17±29 mm Hg in the control group, Group B (p=0.03). This means that the mean decrease in systolic blood pressure in the intervention group was 9 mm Hg larger (1.41 larger to 16.59 larger). We also used this results in our alternative cost-effectiveness analyses.

This demonstrate that the use of pre-implant baseline measurements gave greater mean changes in systolic blood pressure than with post-implant measurements.

We evaluated the quality of the evidence for these endpoints from the randomized controlled trial to be moderate (GRADE). The reasons for downgrading can be found in the footnotes in Table 3.

From the trial with controlled non-randomized design, with office measurements and post-implant baseline measurements:

The evidence came from: Alnima 2013 *(26)*, (n=322). The population are the same 322 patients who got the Rheos system inplanted in the randomized controlled trial. The difference is the inclusion of 57 patients that had not been randomized in the randomized controlled trial.

We found: The mean difference in systolic blood pressure between baseline and 6 months for Group 1 (6 months with active BAT, intervention group) (n=236) compared to Group 2 (6 months with inactive BAT, control group) (n=86) was from 169±27 mm Hg (baseline) to 151± 31 mm Hg for Group 1, and from 168± 24 mm Hg to 160± 26 for Group 2 (p=0.018). We see that the differences between the groups are similar to the results in the randomized controlled trial.

We evaluated the quality of the evidence for these endpoints from the non-randomized controlled trial to be low (GRADE). The reasons for downgrading can be found in the footnotes in Table 3.

From the trials with single-arm designs:
The mean changes reported from single-arm design trials are greater than those reported in the randomized controlled trial and in the controlled trial.
In the follow-up abstract from the Pivotal randomized controlled trial , measurements informations were not given, but probably office and pre-implant baseline measurements (28): Mean change in systolic blood pressure between baseline and 12 months (n=294) were -34.3±1.7 (p<0.001). About the same level of change for 2, 3, 4, 5 and 6 years.

The DEBuT-HT (14) *with office measurements and post-implant baseline measurements, fulltext, reported:* Mean changes in systolic blood pressure (mm Hg) between baseline and 3 (n=37) and 12 (n=26) months were -21±4 (p<0.001), and -30±6 (p<0.001) respectively. The values at 2 years were about similar as those at 1 year.
Further, the DEBuT-HT also reported changes in systolic blood pressure, measured with *ambulatory measurements*. This demonstrate that the use of office measurements gave larger mean changes in systolic blood pressure than the use of ambulatory measurements.
In the DEBuT-HT with ambulatory measurements and post-implant baseline measurements: Mean changes in systolic blood pressure between baseline and 3 (n=26) and 12 (n=15) months were -6±3 (p=0.102), and -13±3 (p<0.001) respectively. The mean change at 2 years, were here greater than at 12 months, -24±8 (p=0.017).
When comparing mean changes in office measurements of systolic blood pressure with to the ambulatory measurements, we see -21 versus -6 (at 3 months), -30 versus -13 (1 year), and -33 versus -24 (at 2 years) respectively.
From the DEBuT-HT publication with follow-up data up to 4 years (29): Only 18 patients included, the publication does not specify if office or ambulatory measurements were used. Due to the study design and few patients we have very little confidence in the results.

We evaluated the quality of the evidence for all endpoints for Rheos from the single-arm designs to be very low (GRADE). The reasons for downgrading can be found in the footnotes in Appendix 7.

For Neo

The evidence came from: Two main trials (25), (15), (n= 30, and n=51) both with single-arm designs, with office and pre-implant baseline measurements, reporting from 3 and 6 months; and a follow-up study with 12 months data (n=7) (32). Wallbach 2016 (15) also reported ambulatory mesurements (pre-implant baseline measurements).
We have chosen to disregard the 12 months data, since these reports were from only 7 patients.
We found:
From office measurements, with pre-implant baseline measurements:
The mean changes in systolic blood pressure between baseline and 3 and 6 months respectively were reported as -26.1±3.3 ($p<0.001$) and -26.0±4.4 ($p<0.001$) (n=30) (hoppe), and as mean values 171±24 (baseline) and 151±26 respectively (6 months), ($p<0.01$) (n=44) (15).
From ambulatory measurements, with pre-implant baseline measurements: Mean systolic blood pressure at baseline and 6 months were 148±17 and 140±23 ($p<0.01$) (15).

Again, (as in the results from Rheos) we see that the reported mean reductions in systolic blood pressure were larger with office measurements than with ambulatory measurements, about 26 mm Hg and about 8 mm Hg, respectively between baseline and 6 months.

We evaluated the quality of the evidence for all the endpoints for systolic blood pressure from the Neo trials to be very low (GRADE), implying that we are very uncertain about these results. The reasons for downgrading can be found in the footnotes in Appendix 7.

Evidence for diastolic blood pressure (DBP)

For Rheos

The evidence came from: Two publications from the Pivotal trial: One controlled non-randomized trial (26), and an abstracts with single-arm design giving follow-up evidence from 1-6 years (28). Two publications from the DEBuT-HT, the main trial (14), and an abstracts giving follow-up evidence from 1-4 years (29), both had single-arm designs.
We found:
From the non-randomized controlled trial, with office measurements and post-implant baseline measurements (26) (n=322):

A mean reduction in diastolic blood presseure from baseline to 6 months of 100±18 to 90±18 in the intervention group versus 100±14 to 95±15 in the control group, (p=0.018).

We evaluated the quality of the evidence for this endpoint to be low (GRADE). The reasons for downgrading can be found in the footnotes in Table 3.

From the publications with single-arm designs
The evidence came from: The follow-up publication from the Pivotal trial (28), this does not specify how blood pressure was measured, or when baseline measurements were done. We assume that it is office and pre-implant.
Two publications from the DEBuT-HT, the main trial (14), and the abstracts with follow-up evidence (29). Scheffers and coworkers measures diastolic blood pressure both in office and ambulatory, and the baseline measurements were taken post-implant. In the abstract with follow-up evidence (29), only 18 patients were included, and the publication does not specify if office or ambulatory measurements were used. Due to the study design and few patients we have very little confidence in the results from this publication.

The mean changes in diastolic blood pressure reported from single-arm design trials are greater than the changes reported in the controlled trial.

The publications reporting from the single-arm designs showed statistically significant reductions in diastolic blood pressure from baseline to all the measurements for 1, 2, 3, 4, 5 and 6 years respectively.
Both office and ambulatory measurements of diastolic blood pressure, both with a post-implant baseline, at 3 months, 1 and 2 years, were reported. Diastolic blood pressure reductions from baseline were larger with office measurements than with ambulatory measurements, both at 3 months, 1 and 2 years. The mean (±standard deviation) reductions at 1 year were -20 ±4 with office measurements (n=26) versus -8±2 with ambulatory measurements (n=15).

We evaluated the quality of the evidence for all endpoints from the single-arm designs to be very low (GRADE). The reasons for downgrading can be found in the footnotes in the Appendix 7.

For Neo
The evidence came from: One single-arm trial, reporting both office and ambulatory diastolic blood pressure values, and use pre-implant baseline measurements (n=51) (15).
We found: The reductions in mean diastolic blood pressure from baseline to 6 months were from and 91 ±18 to 82±17 ($p<0.01$) with office measurements (n=44), and 82 ±13 to 77±15 ($p<0.01$) with ambulatory measurements.

Again we see a larger reduction with the use of office measurements compared to ambulatory measurements.

We evaluated the quality of the evidence for these endpoints to be of very low (GRADE). The reasons for downgrading can be found in the footnotes in Appendix 7.

Evidence for proportion of responders

For Rheos

The evidence came from: The Pivotal trial, a randomized controlled trial with 6 months evidence, (n=265) (24).

We found: The proportion of patients that achieved at least a 10 mm Hg drop in office systolic blood pressure from baseline at month 0 (post-implant baseline) to months 6, failed to show statistically significant difference between Group A (active BAT in 6 months) and Group B (inactive BAT for 6 months/sham control). The proportion of patients who responded were 54 versus 46% (p=0.97) respectively. This was a predefined endpoint.

We evaluated the quality of the evidence for this endpoint to be of moderate quality (GRADE).

For Neo

The evidence came from: Two single-arm trials (25), (15), both with office measurements and pre-implant baseline measurements. Wallbach and coworkers (15) also measured ambulatory blood pressure.

We found:

The proportion of patients achieving systolic blood pressure≤140 mm Hg at 6 months, measured with office systolic blood pressure and pre-implant baseline was 43%, as compared to 0% at baseline (n=30) (25).

The proportion of patients who achieve at least a 10 mm Hg drop in office systolic blood pressure, and at least 5 mm Hg drop in ambulatory systolic blood pressure from baseline to 6 months: We found a higher proportion of responders when the systolic blood pressure were measured in office rather than with ambulatory measurements: 29/44 (66%) and 22/44 (55%) respectively (15).

We evaluated the quality of the evidence for these endpoints to be very low (GRADE).

Evidence for heart rate

For Rheos

The evidence came from: The non-randomized controlled trial (26) using the total population from the Pivotal trial, and two publications (14), (29) from the DEBuT-HT single-arm trial.

We found:

From the non-randomized controlled trial with office measurements and post-implant baseline measurements (26) (n=322): There was no statistically significant difference (p=0.096) between mean heart rate (beats per minute) in the intervention- and the control group at 6 months.

From the DEBuT-HT trials (with single-arm design):

Scheffers and coworkers 2010 (14) (n=45) reported both office and ambulatory measurements, both with post-implant baseline measurements.

Mean changes in heart rate (beats/minute) from baseline to 1 and 2 years respectively for office and ambulatory measurements were: -8±2 and -6±2 respectively at 1 year, and -11 ±4 and -11±34 respectively at 2 years. All were reported to have a statistical significant reduction from baseline. In the abstract with follow-up evidence (kroon), only 18 patients were included, and the publication does not specify if office or ambulatory measurements were used.

We evaluated the quality of the evidence for these endpoints to be very low (GRADE).

For Neo

The evidence came from: Two single-arm trials (25), (15) both with office measurements of heart rate, and with pre-implant baseline.

We found: Mean changes in heart rate (beats/minute) between baseline and 6 months were: -5.0±2.6 (p=0.07) (n=30) as reported by Hoppe and coworkers (25). A similar drop, from 72±12 at baseline to 69±11 (p=0.10) at 6 months, was reported by Wallbach and coworkers (15) (n=44).

We evaluated the quality of the evidence for these endpoints to be very low (GRADE).

Evidence for left ventricular mass index (LVMI)

For Rheos

The evidence came from: Two abstracts with single-arm designs (27), (30).

We found: The mean changes in left ventricular mass index (g/m²) from baseline to 1 year were -17.8±3 (p≤0.001) (n=46) (27), and -24.6±3.9 (p≤0.001) (n=21) (30) respectively.

We evaluated the quality of the evidence for these endpoints to be very low (GRADE).

For Neo

Left ventricular mass index endpoint was not reported for the Barostim Neo.

Evidence for serious adverse events (SAEs)

For Rheos:

The evidence came from:

The total randomized population in the Rheos pivotal trial (n=265) (24), and from 42 of the 45 patients in the DEBuT- HT (14) (the first three patients enrolled were excluded from safety and efficacy analyses per protocol). The safety evidence up to one year from the Rheos pivotal trial was compared to pre-specified objective performance criteria reported for similar implantable devices.

The safety evidence up to two years from the DEBuT- HT was not compared with other reported criteria.

The publications with the 6 and 4 years follow-up data respectively (28), (29) also reported safety. de Leeuw and coworkes (28) reported 28 deaths during 6 years, without saying anything about if these were device related, however, the also stated that "Long-term therapy safety was excellent with low rates of stroke, myocardial infarction and hypertensive urgency". Kroon and coworkes (29) reported "No unexpected system- or procedure- related serious adverse events." See Appendix 3 for more information.

We base our evaluation for safety on the evidence from the Rheos pivotal trial.

We found: For the total population in the randomized trial (n=265) it was reported a procedural safety with an event-free rate for serious adverse events of 74.8%, that was comparable to the pre-specified objective performance criterion of 82%, (p=1.00), and a device-related safety with an event-free rate for serious adverse events of 87.2, that exceeded the pre-specified objective performance criterion of 72%, (p<0.001).

We have evaluated the quality of the evidence for these endpoints from the Rheos pivotal trial to be low (GRADE) (Appendix 7).

Evidence for serious adverse events (SAEs)

For Neo

The evidence came from:

The two main trials for Neo (25), (15). From Hoppe and coworkers 2012 (25) safety evidence was reported from all the 30 included patients, and for Wallbach and coworkers 2016 (15) safety was reported from 44 of the included 51 patients (for more details see Appendix 3).

Twelve months safety data were reported from a follow-up publication (32) (n=7), and from the publication with the subgroup analysis of patients with chronich kidney disease (37) (n=7). We have choosen to disregard these 12 months data, since

both publications report from only from 7 patients. More detailed information is found in Appendix 3.

We found: A procedural safety with an event-free rate for serious adverse events of 90 (25) and 98% (15) respectively, and a device-related safety with an event-free rate for serious adverse events of 97% (25). Maximum follow up was 6 months for the device-related events.

We have evaluated the quality of the evidence for these endpoints to be very low (GRADE).
See Appendix 3 for more information.

Evidence from subgroup analyses from special populations

For Rheos

Evidence came from: One substudy (33) (n=82) from the Rheos pivotal trial, and one substudy (n=21) (34) from the DEBuT-HT, reported from from patients with resistant hypertension and heart failure. One of these, (34) specified that office measurements were used, but did not report time for baseline measurements, the other gave no information.
We found: Both publications reported significant reductions in systolic-and diastolic blood pressure. This was in agreement with the main trials.

For Neo

Evidence came from: Two substudies from Wallbach and coworkers 2016 (15): Wallbach 2016 (n=28) (35) reported from patients with resistant hypertension and prior renal denervation, Wallbach 2014 (n=23) (36) reported from patients with resistant hypertension and chronic kideney disease. Both were single-arm trials.
We have choosen to disregard the 12 months data for the patients with chronic kideney disease reported by Beige and coworkers (37), since they report from only 7 patients.
We found:
Mean changes in for systolic-and diastolic blood pressure between baseline and 6 months were measured in single-arm trials for patients with prior renal denervation (35), and for patients with chronic kideney disease (CKD) (36). Both trials used pre-implant baseline, and both reported both office and ambulatory measurements. In addition, 12 months ambulatory evidence for systolic blood pressure was reported for the patients with prior renal denervation. The reductions in both systolic-and diastolic blood pressure were in about the same order, or may be a bit lower in the special populations, than for the population in the main trial (15). Again we see larger reductions in mean systolic blood pressure when systolic blood pressure is measured with office rather than ambulatory measurements.

Changes in heart rate from baseline to 6 months (office measurements) were reported from both the the population with prior renal denervation (35), and the population with chronic kidney disease (36). None of them reported statistically significant reductions from baseline to 6 months, neither did the the main trial.

Proportion of responders (Responders were defined as patients with SBP reduction of ≥10 mm Hg in office or ≥5 mm Hg in ABPM, or both). Both office and ambulatory measurements at 6 and 12 month was reported from the substudy with prior renal denervation (35). The 6 months evidence from office measurements was similar to the evidence from the main trial, the ambulatory measurements gave a lower response rate than in the main study (48% and 55% respectively). Again we see larger response rates from the office measurements than from the ambulatory measurements.

Safety was reported from the substudy with prior renal denervation (35). No serious adverse events were reported.
We evaluated the quality of the evidence for these endpoints to be very low (GRADE).

Table 3 below, shows a summary of finding table from the randomized controlled trial and the non-randomized controlled trial.

Table 3: A summary of finding table for comparison of active baroreflex activation therapy (BAT) and inactive BAT for mean reductions in systolic-and diastolic blood pressure and heart rate between baseline and 6 months from the randomized controlled trial and the non-randomized controlled trial

Barostimulation compared to sham control (same device but with no stimulation) for drug-resistant hypertension

Patient or population: patients with drug-resistant hypertension
Intervention: Barostim
Comparison: A sham control with no stimulation

Outcomes	**Anticipated absolute effects*** (95% CI)		№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with no stimulation	**Risk with Barostim activated**		
Mean±SD changes in SBP (office), between *post-implant baseline* and 6 months (24)	The mean decrease in SBP, at 6 months, was 9 ± 29 mm Hg	The mean decrease in SBP at 6 months in the intervention group was **7 mm Hg larger (14.5 larger to 0.5 smaller)**	265 (1 RCT)	⊕⊕⊕◯ MODERATE [a,b]
Mean changes in SBP (office), between *pre-implant baseline* and 6 months (24)	The mean decrease in SBP, at 6 months, was 17 ± 29 mm Hg	The mean decrease in SBP at 6 months in the intervention group was **9 mm Hg larger (1.41 larger to 16.59 larger)**	265 (1 RCT)	⊕⊕⊕◯ MODERATE [a,b]
Mean SBP (office), at *post-implant baseline* and at 6 months (26)	The mean SBP at 6 months, was **160± 26** mm Hg	The mean SBP at 6 months in the intervention group was **9 mm Hg lower (2.23 lower to 15,72 lower)**	322 (1 non-randomized controlled trial)	⊕⊕◯◯ LOW [a b c]
Mean DBP (office), at *post-implant baseline* and at 6 months (26)	The mean DBP at 6 months, was **95± 15**mm Hg	The mean DBP at 6 months in the intervention group was **5 mm Hg lower (1.09 lower to 8.91 lower**	322 (1 non-randomized controlled trial)	⊕⊕◯◯ LOW [a b c]
Mean heart rate, 6 months from Month 0, (26)	The mean heart rate at 6 months, was 75±15**)** bpm	The mean heart rate at 6 months in the intervention group was **3 bpm lower (6.6 lower to 0.6 higher)**	322 (1 non-randomized controlled trial)	⊕⊕◯◯ LOW [a b c]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. high risk of bias, office BP and not ambulatory BP
b. just one study, but multicenter. Do not downgrade
c. the trial included additional non-randomized patients

SBP= systolic blood pressure. DBP= Diastolic blood pressure. SD= Standard deviation.

Summary of findings tables from the trials without a controlled group are shown in Appendix 7.

Comparison of the evidence from the first generation (Rheos) with the second generation (Neo) barostim activation therapy device

The evidence came from: Wachter 2016 (19). The evidence provided is from a comparison of three cohorts: two from the randomized controlled trial and one from an unidentified Neo trial.
We found: The evidence provided is changes from baseline to 12 months for the Neo patients only regarding systolic blood pressure and proportion of responders; and the comparisons between the Neo patients and the cohort of placebo patients (inactive BAT) from the Rheos pivotal trial. The only available evidence comparing Rheos and Neo is from the indirect comparison of the three cohorts. Based on this there is a graph presenting an indirect comparison between Rheos and Neo. This means that we have no direct comparison for the active Rheos device and the active Neo device that we can draw any conclusions from.

Critical appraisal of the submitters' evidence for efficacy and safety

We disagree with the submitters' interpretation of the evidence. We have the same data basis, but our interpretation of the data is, as described below, different.
The submitter claimed:

- "In the randomized controlled trial, Barostim Therapy compared with sham-control group, reduced level of SBP by 7 mm Hg (95% CI: -0.5 – 14.5 mm Hg) at six months".

Our comments: We found the same evidence, but we concluded that this pre-defined endpoint, the comparison of Group A versus Group B for mean change between post-implant baseline and 6 months data for systolic blood pressure, failed to

show a statistically significant difference between Group A (active BAT in 6 months) and Group B (inactive BAT for 6 months/placebo). The mean decrease in systolic blood pressure at 6 months in the intervention group was 7 mm Hg larger (14.5 larger to 0.5 smaller). The submitter reports the same results, without commenting on the lack of statistically significant differences between the groups.
Both we and the submitter have evaluated, by help of GRADE, the quality of systolic blood pressure at 6 months to be moderate.

- "In the pooled analysis of outcomes of three main studies (n=383) of first generation Barostim Therapy (DEBuT, Rheos Feasibility, and Rheos Pivotal Studies) Barostim Therapy was shown to statistically significantly improve outcomes compared with baseline up to 72 months of observation (with less observations available compared to baseline).
    - Reduction of the SBP level was 27.1 ± 1.74 mm Hg at six months, 32.6 ± 1.65 mm Hg at one year and 33.6 ± 4.37 mm Hg at six years (for all comparisons p<0.001). ..
    - Reduction of DBP level was 12.5 ± 0.92 mm Hg at six months, 15.2 ± 0.90 mm Hg at one year and 15.2 ± 0.90 mm Hg at six years (for all comparisons p<0.001)".

Our comments:
After a request to the submitter, we understand that the evidence from the Rheos pivotal trial, used in their pooled analysis, does not include a comparison between the intervention group (activated BAT) and the control group (inactivated BAT) for changes between baseline and at 6 months. In other words, no evidence from the controlled part of the Rheos pivotal trial is used in their analysis. The other trials, the with 6 years follow-up data (28) from the Rheos pivotal trial, and the two publications from the DEBuT-HT (information from the submitter) (14), (41), were trials with no control group. The pooled analysis from the submitter demonstrate a statistical significant reduction in both systolic-and diastolic blood pressure from baseline and up to 6 years.

We also concluded that the results from the single-arm trials showed statistically significant changes between baseline and the respective time points from 1-6 years. However, we have evaluated the risk of bias for all these endpoints to be high, and we have very little confidence in the results according to GRADE evaluations.

Therefore our main concern is that the submitter chose to conclude (claim) from a pooled analysis based on evidence from trials with no control group, and not from available evidence with relative effect estimates from the randomized controlled part of the Rheos pivotal trial.

A randomized controlled trial with a sufficient number of included patients is the gold standard to evaluate effect of interventions, and it is available for the present research questions.

The evidence from the randomized controlled Rheos trial showed no statistically difference between the intervention group (activated BAT) and the control group (inactivated BAT), for the pre-defined endpoint, mean changes in systolic blood pressure between baseline and at 6 months. Both the submitter and we evaluated the quality of the evidence for this endpoint to be moderate. The use of the evidence from the pooled analysis from trials with no control group, will results in an overestimate of the efficacy evidence, with a following positive impact on the cost- effectiveness analysis.

The submitter used their results from the pooled analysis in their cost-effectiveness analysis.

- "The post-hoc propensity matched cohort analysis comparing efficacy of second generation Barostim Therapy (Barostim Neo) vs first generation Barostim Therapy (Rheos device, active and sham-control arms) demonstrated that second generation device had no statistically significant changes in reduction of SBP and DBP at six ($p=0.46$ and $p=0.18$ respectively) and 12 ($p=0.71$ and $p=0.84$ respectively) months. Second generation device demonstrated statistically significant reduction of SBP (20.1 ± 7.3 mm Hg, $p=0.008$) and DBP (11.9±3.4 mm Hg, $p<0.001$) at six months vs sham-control arm in the Rheos trial"

Our comments: The only published documentation for the comparison between Rheos and Neo is to our knowledge, an abstract by Wachter and coworkers 2016 (19). The evidence provided is from a comparison of three cohorts: two from the randomized controlled trial and one from an unidentified Neo trial. The results from these indirect comparisons between Rheos and Neos are only reported in graphs. This means that we have no direct comparison for the active Rheos device and the active Neo device that we can draw any conclusions from.

- "Barostim Therapy is a safe technology with only minor peri-operative adverse events in a few patients. A 30-patient study of Hoppe et al. reported adverse events in three patients".

Our comments: In their summary of key findings, the submitter presents the safety for the Barostim Therapy by referring to the Barostim Neo trial (25).
Since there is sparse with documentation for the second-generation, and also that we evaluated the evidence for all the endpoints from the Neos trials to be of very low quality, we find it more reasonable to look at the safety evidence from the Rheos trials. We found that the evidence up to one year, tends to suggest that the Rheos system has about the same safety as similar implantable devices when it is assessed against

the pre-specified objective performance criteria. For the population in the randomized trial (n=265) it was reported a procedural safety with an event-free rate for serious adverse events of 74.8%, that is comparable to the pre-specified objective performance criterion of 82%, (p=1.00), and a device-related safety with an event-free rate for serious adverse events of 87.2, which exceeded the pre-specified objective performance criterion of 72%, (p<0.001). One may think, that the safety for the unilateral device is in the same order as the bilateral device. See Appendix 6 for more details. Evidence for safety only exists up to 12 months for Rheos and up to 6 months for Neo. Long-term data beyond 12 months are missing (except for 2 years data from 42 patients the DEBuT-HT).

Cost-effectiveness

General

CVRx, Inc. submitted a cost-effectiveness analysis of treating resistant hypertension using the Barostim Therapy device in combination with optimal medical therapy compared with optimal medical therapy alone, which is the current recommendation. The Barostim Therapy device is an active implantable pulse generator, which delivers electrical stimualtion to the baroreceptors located on the carotid artery.

The submitter referenced two published cost effectiveness analyses related to Barostim Therapy. The studies were conducted from US (42) and German (43) health care perspectives.

Table 4. Identified economic evaluations of Barostim Therapy in hypertension indication

Study	Model analysis	Population	Incr. QALY	Incr. costs	ICER	Comparison
Borisenko et al. 2014 (43) Germany	CUA	A single cohort of patients at high risk of end-organ damage was simulated. A cohort representative was a 50-year old smoking man with hyperlipidemia, and no history of CHD and atrial fibrillation, with SBP of 170 mm Hg, heart rate of 79 beats/min, BMI of 32.6 kg/m2, lung vital capacity of 2.5 l, cholesterol level of 9.06 mmol/l, HDL 1.32 mmol/l, no cardiomegaly or LVH	2.17	€16,891	€7,797 / QALY	Optimal drug therapy
Young et al. 2009 (42) USA	CUA	Asymptomatic 50-year old cohort with uncontrolled hypertension, despite poly-pharmacological management, and no history of CVD/stroke and initial SBP varying from 140 to 220 mm Hg	0.284	$18,278	$64,400/ QALY	Aliskiren

Explanations: CUA, Cost-utility analysis; CVD, Cardio vascular disease; SBP, systolic blood pressure; LVH, Left ventricular hypertrophy; BMI, Body mass index

Description of the identified economic analysis

Borisenko et al. 2014 (43) modeled the cost-effectiveness and long-term clinical performance of the Barostim Neo System compared to optimal medical therapy for treatment of resistant hypertension . The decision analytic model combined a decision tree and a Markov process. The clinical effectiveness of Barostim was based on results of a randomized, placebo-controlled Rheo trial and a follow-up substudy of the DEBuT-HT trial. Cost-effectiveness was modelled from a German societal perspective over a lifetime horizon. The estimated incremental cost-effectiveness ratio (ICER) for Barostim compared to optimal medical therapy was €7,797 / QALY.

Young et al. 2009 (42) investigated the cost-effectiveness of an implantable carotid body simulator (Rheos®) for treating resistant hypertension, and determined the range of starting systolic blood pressure (SBP) values for which the device remains cost-effective. Using a Markov model, they compared a 20 mmHg drop in SBP from an initial level of 180 with Rheos® to failed medical management in a hypothetical 50-year old cohort. They modeled direct costs (US$2,007), utilities and event rates for future myocardial infarction, stroke, heart failure and end-stage renal disease. Their calculated ICER was $64,400/QALY.

Patient population

The relevant population is patients with drug-resistant hypertension.

Based on the randomized clinical trial, Rheos RCT (24) and DEBuT study (using individual patient-level data, provided by the CVRx Inc.), the submitter assumed that patients entering the model were 54 years old, with an average systolic blood pressure of 169 mm Hg.

Choice of comparator

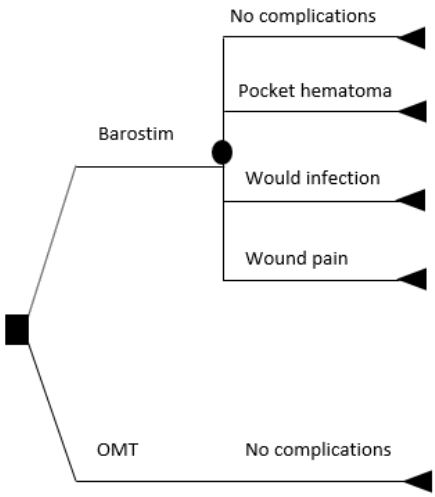
The submitter presented an analysis of Barostim therapy combined with optimal medical therapy compared to optimal medical therapy alone. The latter is the recommended treatment for patients with resistant hypertension.

Type of analysis and decision model

The submitted report used a model implemented in Excel that combined a decision tree and a Markov model to determine the intervention's cost-effectiveness as the incremental cost per QALY gained (ICER). The analysis was conducted from two perspectives: a Norwegian healthcare payer perspective and a Norwegian societal perspective.

The submitter reproduced the decision tree and Markov model from Borisenko et al. 2014 (43). The model measured absolute and incremental gains in life-years, quality-adjusted life-years, costs (from societal and healthcare perspectives), and incidence of end-stage organ damage events for both arms. The model assumed a baseline age of 54 years and baseline systolic blood pressure (SBP) of 169. The submitted model used a 60-year time horizon. Both costs and QALYs were discounted at an annual discount rate of 4%.

The decision tree structure included four branches for the Barostim Therapy arm (no complications, device pocket hematoma, wound complication and wound pain) and a single branch for the optimal medical therapy arm (OMT) (alive with hypertension) (Figure 3).



Figur 3 illustrates the structure of the decision tree and is reproduced from Borisenko et al. 2014

The submitted Markov model by Borisenko et al. 2014 (43) included all patients who entered the Markov process, and covered the most important end-stage organ

damage including myocardial infarction, stroke and transient ischemic attack (TIA), heart failure and end-stage renal disease (figure 4).

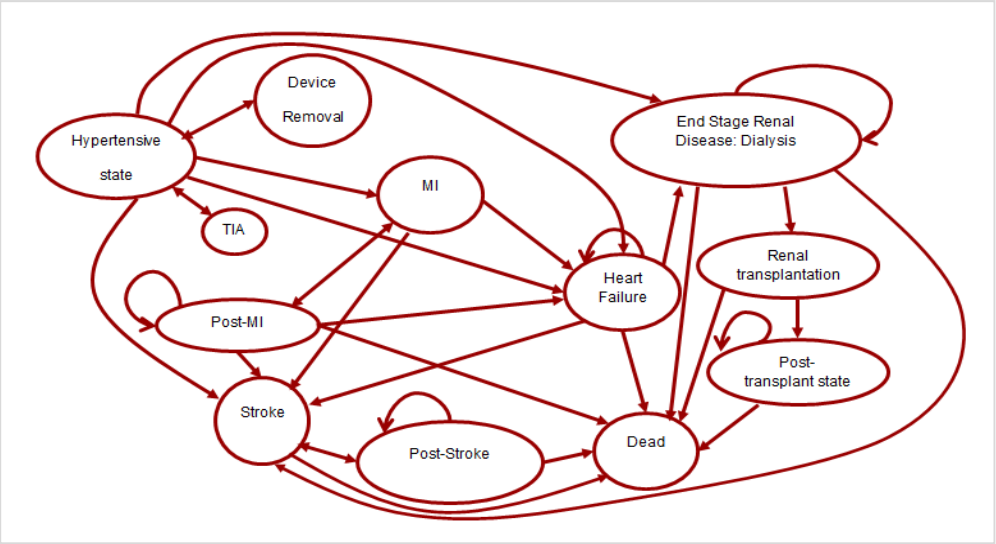


Figure 4. Structure of the Makov model reproduced from Borisenko et al. 2014

The submitter described the Markov model as follows:

During each cycle, patients in an initial hypertensive state could experience a non-fatal myocardial infarction, stroke or TIA, heart failure, end-stage renal disease or die from cardiovascular or other conditions. Patients could also experience a hypertensive crisis requiring hospitalization while being in a hypertensive state. Patients who experienced a non-fatal myocardial infarction could develop heart failure, stroke, survive or die from a non-cardiovascular condition. Survivors of a myocardial infarction could experience a recurrent fatal or non-fatal myocardial infarction, heart failure and stroke or remain in a post-myocardial infarction health state. Patients who experienced a non-fatal stroke could only proceed to a post-stroke health state or die from a non-cardiovascular condition. Survivors of stroke could experience a fatal or non-fatal recurrent stroke, die or remain in a post-stroke health state. Patients in a heart failure state could develop end-stage renal disease, stroke, die or remain in this state. End-stage renal disease was defined as kidney failure requiring renal replacement therapy with hemodialysis. Patients in an end-stage renal disease state could receive renal transplant, die or remain in the same state. Patients who underwent a renal transplantation could die or survive. Survivors of a renal transplantation could die or remain in a post-transplant health state.

Methods: Intervention and comparator

In the submitted analysis, Barostim combined with optimized drug treatment was compared with optimal medical therapy alone.

The pharmacological treatments, which consisted of more than five medications, included the full range of standard-of-care drugs with an emphasis on calcium channel blockers, renin angiotensin system inhibitors, and diuretic therapy. The exact list of medication groups were obtained from the Rheos RCT of Barostim Therapy: ACE inhibitors, Angiotensin II receptor blocker, Beta-blocker, Calcium channel blockers, Diuretics, Aldosterone antagonists, Vasodilators, Alpha-blockers and Central acting sympatholytic agents.

General comments on the submitted health economic analysis

The submitter adapted a cost-effectiveness model (43) to Norwegian conditions. Although the submitted analysis examined both a health care perspective and a societal perspective, our analysis focuses on the Norwegian health care perspective. A health care perspective is most appropriate when decision-making occurs with a fixed budget, as is the case for the Regional Health Authorities.

The submitted decision model considered one branch for the optimal medical treatment (no complications) and four possible branches for Barostim (no complications, pocket hematoma, wound infection and wound pain). The three adverse events illustrated in the Barostim arm are all mentioned in a study of the second generation (Neo) of Barostim Therapy (25). The Markov model contained 12 possible health states. Based on relevant literature, all these health states are common for patients having drug-resistant hypertension (2;3;44;45).

Our clinical expert thought it was reasonable to use the same patient population as found in the submission (Rheos Pivotal Trial (NCT00442286) (24)). For the comparator we used the control group found in Rheos Pivotal Trial ((NCT00442286) (24)). Patients in this control group were implanted with an inactivated Barostim device for six months.

The 60-year time horizon related to the model seemed too long based on the baseline age of 54 years. We adjusted the time horizon to shorter time horizons, which did not have a great impact on the results.

Our clinical expert reviewed the medications used in the relevant trials and reported that most of the medications, dosages and proportion of patients receiving specified

drugs seemed reasonable. While some of the medications differed from Norwegian practice, these minor corrections did not have a meaningful impact on the results.

Clinical and epidemiological data

The submitted model included incidence data for the following adverse events among patients with resistant hypertension: fatal cardiovascular events, mortality of non-cardiovascular disases, the non-fatal cardiovascular events (stroke, myocardial infarction, heart failure and transient ischemic attack), and end stage renal disease and renal replacement therapy.

The submitter used risk prediction models or epidemiological studies for the occurrence of the first adverse health event (myocardial infarction, stroke, heart failure or end-stage renal disease) to determine the input data. In the submission, disease-specific risks were used to model the increased mortality or transition to other negative health states when patients experienced an adverse event. The transformation of transition probabilities for different time horizons into monthly probabilities was performed using a standard approach (46).

In the submitted model, hypertension crisis was not modeled as a separate health state, but was only used for costing purposes. The probability of a hypertension crisis was based on values from the Rheos trial (24). This risk was assumed constant over the lifetime horizon. The base case value in the model for the six-month probability of hypertension crisis was 0.05 in Baroreflex Activation Therapy arm and 0.083 for 6-month probability of hypertension crisis in optimal medical treatment arm.

Efficacy

The clinical effectiveness of Barostim Therapy in the context of resistant hypertension was measured as the decrease in systolic blood pressure.

The submitted efficacy data for Barostim Therapy are based on studies of the first generation device (Rheos device) (24). An unpublished equivalence study of the Rheos and Barostim Neo devices confirmed that second generation efficacy was equivalent to first generation efficacy at 6 and 12 months (19). The submitter considered it appropriate to use efficacy data for the first generation device in the assessment of the cost-effectiveness of second generation of Barostim Therapy.

For the base-case analysis, the submitter derived the clinical efficacy of Barostim Therapy from a pooled analysis of outcomes using individual patient-level data from Rheos Pivotal RCT (24), Rheos Feasibility Study (47) and DeBuT study (14;48) with

a maximum six-year follow-up. In this pooled analysis, the impact of Barostim Therapy on systolic blood pressure was evaluated relative to baseline.

The submitter claimed that during the first cycle in the model, there was no decrease in systolic blood pressure in any of the arms. Beginning with the second cycle, patients in the Barostim Therapy arm experienced a decrease in systolic blood pressure. The basecase value of reduction in systolic blood pressure between 1st and 12th months in BAT arm compared to baseline was 27.1 mmHg (range 23.8 mmHg – 30.6 mmHg).

Data about impact of Barostim Therapy on the SBP from the latest observation (72nd month) were extrapolated over the patient lifetime. The submitter based this assumption on the stable impact of Barostim Therapy on SBP during all six years of observations. The reduction in SBP between 12th and 72nd months varied from 30.6 mmHg to 38.5 mmHg.

The submitter assumed that the blood pressure in the optimal medical management arm remained unchanged from the baseline. The submitter described this assumption as a conservative assumption, as placebo-controlled trial in a similar patient cohort showed a small increase (+1 mm Hg) in SBP in the optimal medical management treatment arm (49).

Safety

The submitted model contained only adverse events for the second generation Barostim device. The base case values of the parameters «probability of device pocket hematoma», «probability of wound complication» and «probability of wound pain» were all assigned a probability of 0.033. These values were based on the study of the second generation of Barostim Therapy (Neo) (25). The parameter «probability of Barostim Therapy explant during first year post-implant» was asigned the probability 0.019 based on a systematic review of all published Barostim Therapy studies (43).

Costs

The submitter identified resource use and cost data by searching in published Norwegian cost studies and administrative databases (50-60). When data were not available, they used expert opinion.

The cost of Barostim Therapy implantation procedure includes the cost of the procedure, the cost of treatment for complications and the cost of out-patient follow-up visits to a surgeon. The cost of Barostim Therapy was provided by CVRx Inc., the

manufacturer of the Barostim Therapy system. The procedure cost for implantation of Barostim Therapy was estimated using the bottom-up approach or micro-costing with following inputs: Hourly cost of operating room, length of hospital stay, cost of hospital stay per diem, hourly wage of cardiac surgeon, anesthesiologist and operative nurse and duration of implanting procedure. The micro-costing inputs are presented in the table 5.

Cost of operation room

The cost of the operating room was taken as an average of estimates extracted from two studies, both conducted in Norway in the setting of a cardiac surgery unit (58) and obstetrics unit (54), where the average estimation of the cost of operating room from these two studies where 16 127 NOK/hour. According to the CVRx Inc., typical duration of Barostim Therapy implantation procedure is one hour.

Cost of medical staff

An assumption was made that one cardiac surgeon, one anesthesiologist and one operating-room nurse are required to perform the implantation procedure. The mean salary per month of a physician was considered to be NOK 71,800 and the mean salary per month of a nurse was considered to be NOK 37,600, while the weekly working hours of a physician was expected to be 181 hours, and the weekly working hours of a nurse was expected to be 138 hours (59). Adjusted for social expenses and wage index (53) the hourly salary of a physician was calculated to be NOK 594 and the hourly salary of a specialist nurse was calculated to be NOK 408. The submitter calculated the hourly salary for medical staff to be approximately 1 600 NOK/hour.

Cost of hospital stay

Per diem cost of hospital stay was also obtained from the micro-costing study on dialysis treatment (59). The submitter adjusted the per diem cost to 2015 price, the estimate equalled to 10 632 NOK. According to the CVRx Inc., the typical duration of hospital stay for implantation of Barostim Therapy is two days, resulting in a cost of bed stay of 21 263 NOK.

Based on these calculations the cost of Barostim Therapy implantation procedure is estimated to be approximately 38,991 NOK (table 5). The cost of battery replacement procedure and explanting of device was assumed to be half the cost of the original implant procedure.

Table 5. Estimated cost of Barostim Therapy implantation and replacement procedures

Cost item	Cost
Operating room	16 127
Medical staff	1600
Hospital stay	21 263
Total	38 991

Costs in Norwegian Kroner

The expected battery life was six years. The cost of the battery replacement consisted of the Barostim Therapy battery cost and the cost of the procedure.

Cost of short-term complications

The submitter stated that the treatment of complications was costed using extra days of hospital stay. They assumed that the treatment of wound complications requires three additional hospital days, the treatment of pocket hematoma requires two additional days and device repositioning due to wound pain required one additional hospital day.

Cost of basic management of hypertension

The submitter assumed that the basic management of hypertension included pharmaceutical therapy and biannual visits to a general practitioner. They based their cost of out-patient medical services on the 2015–2016 Norwegian Medical Association Fee Schedule for General Practitioner/Specialist Consultations (52). Medication usage was taken from the Rheos study (24). Drug costs were calculated based on maximum pharmacy retail prices (AUP) from Norwegian Medicines Agency (51).

Cost of end-stage organ damage health states

The submitter obtained costs of end-stage organ damage health states from Norwegian sources (56;60;61), except for the cost of acute TIA treatment (DRG 15 "TIA og okklusjon av precerebrale arterie"), cost of renal transplantation (based on the DRG 302 "Nyretransplantasjon – Kirurgisk") and cost of hospitalization due to hypertensive crisis (DRG 134 "Hypertensjon – Medisinsk") (55). Cost data was based on representative population-based or administrative database studies.

Hypertensive crisis was not included as a health state in the model. The submitter assumed that each episode of hypertensive crisis required hospitalization.

Costs of post-myocardial infarction was time-dependent.

Health related quality of life

Health-related quality of life (HRQoL) utility values, based on scores from the generic EuroQol instrument (EQ-5D), were available for all but two health states. For the basic hypertensive state the utility value of 0.98 was based on a visual analogue scale (VAS) (ref). Because no published information was available for utility in the renal transplantation state, the submitter used a utility multiplier of 0.3. Table 6 provides utility values used in the submitted model.

Table 6. Utility values used in the submitted model

Health state	Quality of life weight	Range	Source
Hypertension	0.98	0.97-0.99	(62)
Acute myocardial infarction (AMI)	0.71	0.55 - 0.85	(63)
Post-Myocardial Infarct	0.83	0.8 - 0.86	(64)*
Acute stroke state	0.31	0.29 - 0.34	(65)
Transient ischemic attack (TIA)	0.75	0.67 - 0.82	(63)
Ischemic post-stroke state	0.8	0.77 - 0.83	(66)
Hemorrhagic post-stroke	0.7	0.67 - 0.73	
Heart failure	0.66	0.45 - 0.84	(63)
Hemodialysis	0.44	0.38 - 0.5	(67)
Multiplier for acute transplant	0.30	0.2 - 0.4	Assumption
Post-renal transplant	0.71	0.67 - 0.75	(67)

Except for Hypertension, all Quality of Life weights are based on EQ-5D utilities. Hypertension uses VAS utilities.

* Norwegian population

Based on the correction of the utility score related to the hypertension health state, we will perform a scenario analysis in the next section.

Our comments on the submitted parameters and input data

Comments on the submitted safety and clinical effectiveness

For data about adverse events connected to the implantation of the Barostim device, the submitter relied on a single study with only 30 patients and for three pre-specified complications (25). As a result there is large uncertainty connected to the 0,03 probability used in the model, but it is difficult to comment on whether this could have a significant impact on the results.

Because of the similar efficacy between the first generation of Barostim Therapy and the second generation of Barostim Therapy, and lack of reasonable input data based

on the single-arm studies, we based our analysis on the efficacy data found in Rheos Pivotal RCT (14;24;47;48). This trial consisted of two groups (Group A = Intervention group and Group B = Control group), where the intervention group experienced an immediate active Baroreflex Activation Therapy (BAT) from month 0 to month 12, and the control group experienced an inactive Baroreflex Activation Therapy for the first 6 months, followed by active Baroreflex Activation Therapy from month 6 to month 12. The randomized Rheos trial included both an analysis based on post-implant measurements, and a post hoc analysis using pre-implant baseline values (see Chapter "Clinical evaluation - Results" (see page 29).

In our main analysis, we captured changes in blood pressure based on the post-implant baseline measurement of office systolic blood pressure, measured at 6 months from the randomized Rheos trial. The intervention group showed a mean reduction of 16 ±29mm Hg in systolic blood pressure while the control group showed a mean reduction of 9 ±29 mm Hg. The mean difference in systolic blood pressure in the intervention group was 7 mm Hg larger (14.5 mm Hg larger to 0.5 mm Hg smaller) than in the control group. Based on the post-implant values, we assumed that Baroreflex Activation Therapy would reduce systolic blood pressure by 25 ± 32 mm Hg at 12 months and onwards. We also assumed that the intervention group would continue to have a 7 mm Hg larger reduction in systolic blood pressure than the control group, yielding a reduction in of systolic blood pressure of 18 mm Hg in the control group (inactive BAT for first 6 months, followed by active BAT for next 6 months)after one year (Table 7).

Table 7. Reduction in Systolic Blood Pressure (used in our model)

	Baroreflex Activation Therapy (SD)	**Optimal medical therapy (SD)**	**Mean difference (SD)**
Reduction in SBP 6 months, mm Hg	16 (± 29)	9 (± 29)	7 (±7.5)
Reduction in SBP 12 months and onwards, mm Hg	25 (±32)	18 (± 31)	7 (±7.5)

SBP, Systolic Blood Pressure; SD, Standard Deviation

We also performed a scenario analysis based on the post hoc analysis found in the Rheos trial, using pre-implant baseline measurements. This analysis reported a greater difference between the groups. The mean decrease in systolic blood pressure at 6 months in Group A was 26±30 versus 17±29 mm Hg in the control group, Group B (p=0.03), resulting in a mean decrease in systolic blood pressure in the intervention group was 9 mm Hg larger (16.59 larger to 1.41 larger) than in the control group. Results are presented in our comments in the «Cost-effectiveness results» section (see page 54 - 55).

Comments on the submitted costs

All submitted cost data are based on Norwegian sources or data provided by CVRx Inc. We quality checked the reported references, and verified the cost data with our clinical expert. All cost and resource use appear reasonable for the Norwegian context. Costs presented by the manufacturer, CVRx Inc, display the largest degree of uncertainty. The cost of the battery replacement procedure and of explanting a device were assumed to be half the cost of the original implant procedure. The cost of the Baroreflex Activation Therapy battery replacement procedure is given a range of NOK 9,746 – NOK 29,237, while the cost of full Baroreflex Activation Therapy implation procedure varies between NOK 19,496 – NOK 58,487. The cost of full Baroreflex Activation Therapy system is given a range of NOK 105,000 – NOK 315,000.

Comments on the health related quality of life utilities

In the submitted model, the hypertensive state was based on a VAS utility value. The use of a VAS-based utility value for the hypertension state when all other utility values were based on EQ5-D scores is likely to overstate utility gains in the model because VAS scores are known to be higher than EQ-5D scores in general (68). According to a study by Craig et al. 2009 (69) the mean difference between a HRQoL utility score based on VAS compared to a HRQoL utility score based on EQ-5D is about 0.11. Based on a report by Tran et al. 2012 (70) we found that a corresponding health state showed a utility score of approximatly 0.89. To determine the impact of using the VAS-based utility for hypertension, we conducted a scenario analysis (presented below) in which we substituted this lower EQ-5D utility score in the hypertensive health state for the 0.98 utility used in the submitted model. The other utility values matched with other sources we found.

Cost-effectiveness results

The submitter provided a base-case analysis over a time horizon of 60 years. Their analysis showed an increase in costs of NOK 617,005 of Barostim in combination with optimal medical care compared with optimal medical care. The increase in effect was 1.2 QALYs over 60 years, using Barostim compared with optimal medical care. Their calculated ICER was NOK 509,016 per QALY gained (Table 8).

Table 8 – Base-case results presented by the submitter

Intervention	Costs (NOK)	Incremental cost (NOK)	Effects (QALY)	Incremental effect (QALYs)	ICER (NOK/QALY)
BAT	1,071,443	617,004	14.6	1.2	509,016
OMT	454,439		13.4		

BAT, Baroreflex Activation Therapy; OMT, Optimal Medical Therapy; QALY, quality adjusted life years; NOK, Norwegian kroner; ICER, Incremental cost-effectiveness ratio. All costs in Norwegian kroner

Scenario analysis of revised efficacy values

To address our concerns about appropriate values for efficacy variables and HRQoL utilities for the hypertensive state, we conducted three scenario analyses. In the first scenario analysis, we changed the efficacy values related to the reduction in office systolic blood pressure at 6 months, and 12 months and onwards. The reduction in office systolic blood pressure was based on the post-implant measurements found in the Rheos trial (24). In the second scenario we revised the utility value for the hypertensive health state in addition to the changes from the first scenario. The third scenario analysis used efficacy values base on pre-implant measurements in conjunction with the revised utility values.

Table 9. Base-case results with revised clinical effectiveness values

Intervention	Costs (NOK)	Incremental cost (NOK)	Effects (QALY)	Incremental effect (QALYs)	ICER (NOK/QALY)
BAT	1,049,240	630,605	13.9	0.8	796,761
OMT	418,635		13.1		

BAT, Baroreflex Activation Therapy; OMT, Optimal Medical Therapy; QALY, quality adjusted life years; NOK, Norwegian kroner; ICER, Incremental cost-effectiveness ratio. All costs in Norwegian kroner

The first scenario analysis results in an ICER of NOK 796,761 per QALY gained, which is higher than the result in the submitted analysis, NOK 509,16 per QALY gained. (Table 9).

Table 10. Base-case results with corrected clinical effectiveness and utility values

Intervention	Costs (NOK)	Incremental cost (NOK)	Effects (QALY)	Incremental effect (QALYs)	ICER (NOK/QALY)
BAT	1,049,240	630,605	12.8	0.7	896,898
OMT	418,635		12.0		

BAT, Baroreflex Activation Therapy; OMT, Optimal Medical Therapy; QALY, quality adjusted life years; NOK, Norwegian kroner; ICER, Incremental cost-effectiveness ratio. All costs in Norwegian kroner

The second scenario analysis, which includes a lower utility value for the hypertensive state, yields an even higher ICER, NOK 896,898 per QALY gained (Table 10), than in the submitted results.

Further, we changed the reduction in the office systolic blood pressure from post-implant measurements to pre-implant measurement values, and kept the revised utility value for the hypertensive health state. This resulted in a somewhat lower ICER, NOK 856, 312 per QALY gained, than found in Table 10.

Sensitivity analysis

To explore the uncertainty of the different included parameters, we used one–way sensitivity analyses. Each parameter estimate was varied, individually, within reasonable bounds in order to investigate the impact on costs and QALYs. We have presented the results of the sensitivity analyses as tornado diagrams that show the variables which have a large potential impact on the ICER estimates (Figure 5).

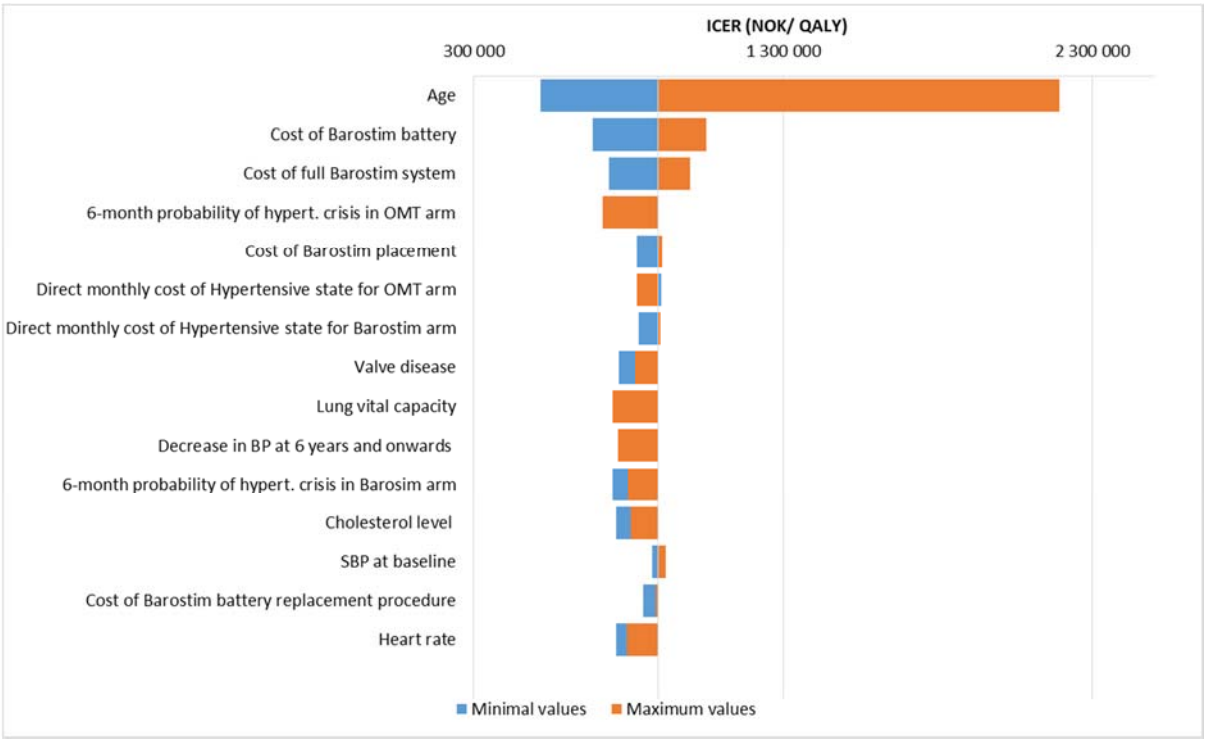


Figure 5. One-way sensitivity analysis (the top five variables in tornado diagram) Expected value: NOK/QALY 896,898

The results were most sensitive to changes in the age of the patient population; costs related to the Barostim battery, Barostim system and Barostim placement; and the 6-month probability of hypertensive crisis in the optimal medical therapy arm. Age had the largest uncertainty and the ICER varied between NOK 517,286 and NOK 2,192,157.

Budget impact analysis

The submitter calculated the budget impact, from a Norwegian health care perspective, of introducing Barostim Therapy as a second-line treatment in adult patients with resistant hypertension compared to optimal medical therapy. The budget impact was estimated as the net cost difference between a scenario in which Barostim Therapy is adopted for a full cohort of eligible patients relative to a scenario in which the device is not adopted. The budget impact was estimated over a 5-year time horizon. The submitter calculated three different budget impact scenarios. One scenario which excluded complications or mortality, a second scenario in which only mortality was included, and a third scenario in which both mortality and complications were included. We focused on the third scenario.

The submitter assumed that 20 new patients per year would become eligible for Barostim Therapy. Patients receiving Barostim Therapy will also receive optimal treatment care (pharmacological treatment, management of hypertensive crisis and

regular visits to GP) each year. Patients who do not undergo Barostim therapy will only receive optimal treatment care.

In both treatment strategies, a patient could experience a negative outcome (myocardial infarction or stroke, for example). The cost of treatment of this event was included in the budget impact analysis.

Table 11 shows the annual number and the cumulative number of patients treated by Baroreflex Activation Therapy if the new technology, Barostim Neo system, is adopted. If the new technology is not adopted all of these patients receive optimal medical therapy.

Table 11. Annual and cumulative number of patients

Number of patients if the new technology is adopted, NOK					
	Year 1	Year 2	Year 3	Year 4	Year 5
Annual number of patients	20	20	20	20	20
Cumulative number of patients	20	40	60	80	100

Table 12 shows the budget impact from the submitted evidence. The budget impact included the two scenarios: (1) Cost related to adoption of the Barostim Neo system and (2) Cost without adoption of the Barostim Neo system. The calculations showed the difference between the two scenarios in each of the five years of the analysis. The comparisons between the two scenarios showed a decrease in total added costs for each year. The sponsor estimated that the total added costs would be about NOK 24,000,000 for the first five years after adoption of Barostim Neo system in Norway.

Table 12. Budget impact (CVRx Inc.)*

Annual budget Impact	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
+ Cost if the New technology is adopted (NOK)	5,307,518	5,581,823	5,881,211	6,204,794	6,551,763
- Cost without adoption of the new technology, i.e. current situation (NOK)	313,356	663,493	1,049,464	1,472,318	1,932,049
Total added cost (NOK)	**4,994,162**	**4,918,330**	**4,831,747**	**4,732,476**	**4,619,714**

* Based on number of patients estimated in Table xx

Our comments

Our experts concurred with the assumption that a total of 20 new patients per year would become eligible for Barostim Therapy. We used our scenario analysis model in which both clinical effectiveness and utility values were adjusted to calculate the annual costs in our budget impact model (Table 13).

Table 13. Budget impact based on scenario analysis (revised annual costs)

Annual budget Impact	Year 1	Year 2	Year 3	Year 4	Year 5
+ Cost if the New technology is adopted (NOK)	5,318,567	5,604,756	5,917,953	6,259,362	6,628,938
- Cost without adoption of the new technology, i.e. current situation (NOK)	310,294	645,932	1,010,198	1,404,373	1,828,696
Total added cost (NOK)	**5,008,273**	**4,958,824**	**4,907,755**	**4,854,989**	**4,800,242**

Results, assuming 20 new patients per year, showed that the incremental cost of implementing Barostim Neo system in Norway will range from approximately NOK 5,000,000 in the first year to NOK 4,800,000 in the fifth during five-year time horizon (Table 13). The declining cost over time reflects the effect of 4% discount of future costs in conjunction with a growing number of patients. This gives a total added expected cost of approximately NOK 24,500,000 for the first five years after adoption of Barostim in Norway. It does not reflect the extra costs beginning at year six of replacing the Barostim battery.

Discussion

We have performed a single technology assessment of the use of Baroreflex activation therapy for drug-resistant hypertension.

The submission came from CVRx, Inc. We have reviewed the submission file and evaluated it towards the applied PICO (Population, Intervention, Comparator and Outcomes/endpoints), our own searches for literature, selection of studies, quality assessment of the included studies, data extraction, GRADE assessment of the quality of the evidence for the effect estimates of the endpoints, as well as health economic evaluations.

Our main objection is that we disagree with the submitter's conclusion regarding efficacy and therefore also cost-effectiveness.

Efficacy and safety

Our disagreement for efficacy is not due to the included trials. Both the submitter and we have evaluated the same main trials (With the exception of the Wallach 2016 trial (15). Ours were of a newer date and included the evidence from the Wallbach 2015 (38) that the submitter used). The reason for our disagreement lays in the analyses and the evaluation of the evidence.

Like the submitter, we have evaluated the evidence from the Rheos pivotal randomized trial by Bisognano 2011 (24) to have moderate quality according to GRADE. The randomized controlled trial failed to show a statistically significant differences between Group A (active Baroreflex Activation Therapy (BAT) and Group B (inactive BAT (placebo/sham) for the pre-defined endpoint mean change in systolic blood pressure between baseline and 6 months. The submitter reports the same results, without commenting on the lack of statistically significant differences between the groups.

The submitter chose to make their claims for the difference between the groups regarding mean changes for systolic-and diastolic blood pressure between pre-implant base line and timepoints up to 6 years from a pooled analysis of evidence from the following Rheos publications (information from the submitter): The Rheos pivotal

trials (24), (28), and two publications from the DEBuT-HT trial (14), (41). After a request to the submitter, we understand that the evidence from the Rheos pivotal trial, used in the pooled analysis, does not include a comparison and a relative effect estimate between the intervention group (activated BAT) and the control group (inactivated BAT) for changes between baseline and at 6 months. After 6 months, both groups have the device activated, this means that there is no longer a sham/inactive control present. In other words, no evidence from the controlled part of the Rheos pivotal trial is used in their analysis. The other trials, the follow-up publication with 6 years data (28) from the Rheos pivotal trial, and the two publications from DEBuT-HT (14), (41) were trials with no control group. The pooled analysis from the submitter showed a statistical significant reduction in both systolic-and diastolic blood pressure from baseline and up to 6 years.

We also concluded that the results from the single-arm trials gave statistically significant changes between baseline and the respective time points from 1-6 years. However, we have evaluated the risk of bias for all these endpoints to be high, and we have very little confidence in the effect estimate according to the GRADE evaluations.

Therefore our main concern is that the submitter chose to conclude (claim) from a pooled analysis based on evidence from trials with no control groups, and not from available evidence with relative effect estimates from the randomized controlled part of the Rheos pivotal trial. The use of the evidence from the pooled analysis from trials with no control group results in an overestimate of the efficacy evidence, with a following positive impact on the cost- effectiveness analysis.

A randomized controlled trial with a sufficient number of included patients is the gold standard to evaluate effect, and is available for the present research questions.

Further, the submitter claimed that the results indicate that the effectiveness of first- and second generation Barostim Therapy system is similar. The only published documentation for the comparison between Rheos and Neo is, to our knowledge, an abstract by Wachter and coworkers 2016 (19). From the available evidence, we have no direct comparison for the Rheos device and the Neo device from which we can draw any conclusions. The evidence provided by Wachter 2016 is from a comparison of three cohorts (two from the randomized controlled trial and one from an unidentified Neo trial), reporting the indirect evidence in graphs only. de Leeuw and coworkers 2015 (71) studied the effect of stimulating the baroreceptors bilaterally or unilaterally by using the Rheos device. They concluded that: “unilateral and in particular right-sided BAT has a more profound effect on blood pressure than bilateral or left-sided BAT”.

For safety, the submitter presents in their summary of key findings, the safety for the Barostim Therapy by referring to the Barostim Neo trial (25). Since there is sparse with documentation for the second-generation, and also that we evaluated the evidence for all the endpoints from the Neos trials to be of very low quality, we find it more reasonable to look at the safety evidence from the Rheos trials.
We found that the evidence up to one year, tends to suggest that the Rheos system has about the same safety as similar implantable devices when it is assessed against the pre-specified objective performance criteria. For the population in the randomized trial (n=265) it was reported a procedural safety with an event-free rate for serious adverse events of 74.8%, that is comparable to the pre-specified objective performance criterion of 82%, (p=1.00), and a device-related safety with an event-free rate for serious adverse events of 87.2, that exceeded the pre-specified objective performance criterion of 72%, (p<0.001). From the Neo trials there is too little evidence to conclude for safety (only 30 and 51 patients respectively in the two main trials). However, one may think, that the safety for the unilateral device is in the same order as the bilateral device. See Appendix 8 for more details. Evidence for safety only exists up to 12 months for Rheos and up to 6 months for Neo. Long-term data beyond 12 months are missing (except for 2 years safety data from 42 patients in the DE-BuT-HT).

Reports from our sister organizations, the National Institute for Health and Care Excellence (NICE) (21), and the Canadian Agency for Drug and Technologies in Health (CADTH) (20) support our conclusions. The interventional procedure guidance from NICE, October 2015, concluded that the current evidence on safety and efficacy for implanting a baroreceptor stimulation device for resistant hypertension is inadequate (they included both the randomized controlled trial for Rheos and the Barostim Neo trial). The bulletin of May 2015 from (CADTH) concluded- “that evidences from trials of the older Rheos system, and from a small trial of the Barostim Neo device indicates that some patients with resistant hypertension may benefit from this treatment”, and “Further evidence is needed on how best to identify individuals who will benefit from this procedure”.

Factors that may influence the results
In our assessment of the evidence for systolic- and diastolic blood pressure from the included trials, we have been aware of two important measurement methods that influence changes in blood pressure, namely whether the investigators use office or 24-hrs ambulatory measurements of blood pressure, and if the baseline value is measured pre- or post-implant. Factors influencing measurements of blood pressure includes the white-coat effect (10), (1), and whether office or ambulatory measurements are used (13), (14), (15). Office blood pressure is prone to “white coat influence”, overestimation, and thus systematic biases (10), (1). Ambulatory measurements are less influenced by these placebo/nocebo effects, and are considered to be the most valid method to measure blood pressure (16), (17), (18).

In the included trials we observed that office measurements of blood pressure give greater changes from baseline in systolic- and diastolic blood pressure than ambulatory measurements. This is shown both in a trial for Rheos with post-implant baseline measurements (-30±6 mm Hg, versus -13±3 mm Hg respectively for office and ambulatory systolic blood pressure at 1 year) (14), and in a trial for Neo with pre-implant baseline measurements (mean change about 20 mm Hg versus about 8 mm Hg respectively for office and ambulatory, at 6 months) (15).

Pre-implant baseline measurements also gave greater changes from baseline in systolic blood pressure than post-implant measurements. This is shown in the randomized controlled trial (24), reporting: Mean reductions in systolic blood pressure between baseline and 6 months were 26±30 mm Hg and 16±29 mm Hg in the intervention group, and 17±29 mm Hg and 9±29 mm Hg in the control group, respectively when used pre-implant or post-implant baseline. Whether this was due to placebo effects, or the effect of implantation of the device is not known. Nor do we know whether the same phenomenon would have happened for ambulatory measured blood pressure.

There are great variations between the trials in when and how they measure blood pressure. Of the four main trials, the two Rheos trials used post-implant baseline measurements, whereas the two Neo trials used pre-implant values. Office blood pressure measurements were used in all the trials, and two of the main trials also included ambulatory measurements (14), (15).

A summary of the main weaknesses of the available documentation

- Office measurements of blood pressure and not ambulatory
- Most of the documentation, including the only randomized controlled trial, were from trials with the Rheos device. This bilateral delivery system (first-generation), is now unavailable. Barostim Neo, the unilateral (second-generation) is the only currently commercially available Baroreflex Activation Therapy delivery system.
- For Barostim Neo there is too little evidence to conclude for efficacy (only 30 and 51 patients respectively in the two main trials).
- Long–term safety data, beyond 12 months, are missing.
- No consistency between the trials regarding time for baseline measurements (post-or pre-implant).

Further research

We believe a randomized controlled trial is needed. This is also actually stated by the authors' of the Barostim Neo Trial (25), describing the purpose of the trial as: "The purpose of this investigation was to measure the safety and efficacy profile of this new advancement (Neo) for BAT in resistant hypertensive patients over a 6-months

period, with the objective of verifying that it is suitable for demonstrating short-and long-term safety and efficacy in randomized, controlled trials". Such a randomized trial for Neo (NCT01471834) has been planned, but according to ClinTrials there are no results available (for more information see Appendix 5 Ongoing studies). The sponsor says in their submission that this trial is yet to start due to lack of available funds.
We suggest that the optimal study design would be a randomized controlled trial, with sufficient number of patients, comparing active Barostim Neo device with the best available pharmacological treatment using ambulatory measurements of blood pressure and pre-implant measurements as baseline. If the control group is a sham control (or if one want this as a third arm), it could possibly be necessary or interesting to use post-implant measurements in addition to pre-implant measurements. The follow-up should be at least one year.

Cost-effectiveness

The submitter conducted an economic evaluation using a four-branch decision tree combined with a Markov model. The model included all patients who entered the Markov process and covered the most important end-stage organ damage, including myocardial infarction, stroke and transient ischemic attack (TIA), heart failure and end-stage renal disease.

Based on thorough review and input given by the clinical experts, we believe that the health economic model captured the outcomes that are clinically relevant for the defined population and intervention.

The submitter provided a base-case analysis over a time horizon of 60 years. The submitter calculated a base-case incremental cost-effectiveness ratio for Barostim compared with optimal medical therapy of approximately NOK 509,000 per QALY gained.

There were, however, some weaknesses in the model that we felt should be addressed. The first was the choice of values for the reduction in systolic blood pressure; the second was the health-related quality of life (HRQoL) scores (utilities) used in the model.

In the submitted model, the reduction in systolic blood pressure to month 6 was specified as 27.1 mm Hg in Barostim arm and 0 mm Hg in the optimal medical therapy arm. The reduction in systolic blood pressure at month 12 and onwards was specified between 30 mm Hg and 38 mm Hg in Barostim arm and 0 mmHg in optimal medical therapy arm. Based on findings in the Rheos Pivotal trial (24), we adjusted these values and performed three different scenario analyses. The first and the second scenario analyses were based on post-implant measurements. In these

scenarios, we adjusted the clinical effectiveness values to reflect a reduction in systolic blood pressure at 6 months of 16 mm Hg in the Barostim arm and 9 mm Hg in the optimal medical therapy arm. At 12 months and onwards, we assumed that the mean difference in systolic blood pressure in the intervention group was 7 mm Hg larger (14.5 mm Hg larger to 0.5 mm Hg smaller) than in the control group. The third scenario analysis were based on pre-implant measurements. In this scenario, we adjusted the clinical effectiveness values to reflect a reduction in systolic blood pressure at 6 months of 26 mm Hg in the Barostim arm and 17 mm Hg in the optimal medical therapy arm. At 12 months and onwards, we assumed that a mean decrease in systolic blood pressure in the intervention group was 9 mm Hg larger (16.59 larger to 1.41 larger) than in the control group.

In the second and third scenario analyses, we also adjusted the utility parameter related to the hypertensive state. The submitter used health-related quality of life (HRQoL) scores based on EQ-5D utility values, except for the utility score related to the hypertensive state (0.98), which was measured by a visual analogue scale (VAS) (62). However, EQ-5D and VAS utilities are not directly comparable (68). Based on other references (69;70), we found that a corresponding health state showed a utility score of 0.89 based on EQ-5D. We performed two scenario analyses based on revised values for utility in the hypertensive state and for the reductions in systolic blood pressure in the different treatment arms.

In our scenario analyses the resulting ICERs were higher than the ICER in the submitted model, (NOK 509,016 per QALY gained), reflecting a less cost-effective result. In the first scenario analysis, based on the revised efficacy values (mean difference in systolic blood pressure of 7 mm Hg), the ICER was NOK 796,761 per QALY gained. In the second scenario analysis, based on revised efficacy (mean difference in systolic blood pressure of 7 mm Hg) and the revised utility value, the ICER was NOK 896,898 per QALY gained. The third scenario analysis based on revised efficiacy (mean difference in systolic blood pressure of 9 mm Hg) and revised utility value, the ICER was NOK 856,312 per QALY gained. We concluded that changes in the parameter values and assumptions had a sizable impact on the results.

We investigated the impact of reducing the 60-year time horizon, which seemed too long for a population with an average age of 57, to a time horizon of 40 years. The shorter time horizon had little effect on results. Finally, we adjusted the shares and dosages of the pharmacutical in both model arms to reflect actual practice in Norway. These adjustments had little impact on the results.

To examine the effects of uncertainty related to the values of several parameters, we conducted one-way sensitivity analyses. The results were most sensitive to changes in the age of the patient population, costs related to the Barostim therapy (battery,

system and replacement), and the 6-month probability of hypertensive crisis in the optimal medical therapy arm. Varying patient age had the greatest impact on the results, yielding ICERs ranging from NOK 517,286 to NOK 2,192,157.

The submitter estimated that the total added costs of implementing Barostim Neo system in Norway would be about NOK 24,000,000 for the first five years. Due to uncertainties associated with the yearly costs used in the calculation of budget impact by the submitter, we re-calculated the additional costs of introducing the technology in Norway. The results of our budget impact analysis showed that assuming 20 new patients each year, the total added expected cost would be about NOK 24,500,000 for the first five years after adoption of Barostim Neo system in Norway. It should be noted that the budget consequences of battery replacement, which the manufacuter reports as being approximately half as expensive as the initial implantation of the Barostim device, are not considered in the budget impact analysis because they begin after six years.

Conclusion

Efficacy and safety

Our data extraction from the available literature cannot support the claims from the submitter.
We found that there is insufficient evidence to demonstrate efficacy for both the Rheos system and the Barostim Neo™ system.

The safety for the Rheos system had an event-free rate, compared to pre-specified objective performance criteria based on similar implantable devices, that was comparable ($p=1.00$) for serious procedural safety, and higher ($p<0.001$) for serious device-related safety. One may think that the safety for the unilateral device could be in the same order as the bilateral device. Long-term safety data beyond 12 months are missing.

Cost-effectiveness

Based on ICER levels that have typically been considered cost-effective in Norway, the submitted economic analysis indicated that Barostim therapy could be cost-effective in patients with drug-resistant hypertension. However, after adjusting the model to account for two important shortcomings in the submitted analysis, related to clinical effect and health-related quality of life, the ICER rises well above the level that has been considered cost-effective in Norway.

Scenario analyses indicated that the results are particularly sensitive to patient age and the cost of the Barostim device (battery, system and replacement). Treatment

could be cost-effective among a young population group or with a decrease in Barostim costs.

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Appendix

Appendix 1. Norwegian Institute of Public Health's search strategies

Barostim - Literature search

Barostim - Hurtig metodevurdering

Databases: Embase and MEDLINE via Ovid, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Other Reviews (DARE), Economic Evaluations (NHS EED), PubMed (2015-2016),

Date: 2016.10.14

Other sources: ClinicalTrials.gov

WHO International Clinical Registry Platform

HTA organizations: We searched in Finnish data base Ohtanen for HTA reports, PROSPERO and CADTH (Canadian Agency for Drugs and Technologies in Health).

Limit: 2005-2016

Results: 1856 from databases

19 + 21 ongoing trials (ClinicalTriasl.gov and WHO ICTRP)

Search strategies

Databases: Embase 1974 to 2016 October 14

Epub Ahead of Print, In-Process & Other Non-Indexed Citations,

Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Results: 2075

1	Hypertension/	720279
2	resistant hypertension/ use oemezd	3445
3	Pressoreceptors/	15001
4	carotid sinus pressoreceptor/ use oemezd	714
5	exp *Carotid Arteries/ [inklud. Carotid Sinus/]	59930

6	*common carotid artery/ or *carotid artery/ or *left common carotid artery/ or *right common carotid artery/ use oemezd	42761
7	hypertensi*.tw.	888978
8	(pressoreceptor* or baroreceptor*).tw.	16065
9	(carotid adj1 (arteries* or artery or sinus)).tw.	145013
10	or/1-9	1282487
11	cvrx.af.	195
12	Rheos.af.	178
13	Baroreflex/ and therap*.tw.	1431
14	pressoreceptor reflex/ and therap*.tw. use oemezd	1104
15	Electric stimulation therapy/	18740
16	electrotherapy/ use oemezd	153
17	Electrodes,Implanted/	18987
18	(baroreflex adj2 (therap* or treat* or stimulat*)).tw.	610
19	(barostim* or ((baroreceptor* or pressoreceptor*) adj2 stimulat*)).tw.	1412
20	(electric* adj2 (therap* or treat* or stimulat*)).tw.	126867
21	(implant* adj2 (electrode* or device* or monitor*)).tw.	44309
22	or/11-21	195626
23	10 and 22	7470
24	(comment or editorial or letter or news).pt.	3176659
25	23 not 24 [fjerner comment, editorial osv]	7409
26	limit 25 to yr="2005 -Current"	2990
27	26 use oemezd	2020
28	Animals/	7546102
29	Humans/	27861963
30	28 not (28 and 29)	5515150

31	26 not 30 use ppez [uten dyrestudier]	2674
32	31 use ppez	654
33	27 or 32	2674
34	remove duplicates from 33	2075
35	34 use oemezd	1895
36	34 use ppez	180

Database: Cochrane Library
Date Run: 14/10/16 11:47:43.403
Results: 290 hits:
Cochrane Reviews (2), Trials (CENTRAL) (282), Technology Assessments (3), Economic Evaluations (NHS EED) (3)

Search strategy

ID	Search	Hits
#1	MeSH descriptor: [Hypertension] this term only	14849
#2	MeSH descriptor: [Pressoreceptors] this term only	168
#3	MeSH descriptor: [Carotid Arteries] this term only	674
#4	MeSH descriptor: [Carotid Sinus] this term only	45
#5	hypertensi*:ti,ab	33878
#6	(pressoreceptor* or baroreceptor*):ti,ab	312
#7	(carotid near/1 (arteries or artery or sinus)):ti,ab	2167
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7	38243
#9	cvrx:ti,ab	1
#10	Rheos:ti,ab	9
#11	MeSH descriptor: [Baroreflex] this term only	375
#12	#11 and (therap* or treat*):ti,ab	119
#13	MeSH descriptor: [Electric Stimulation Therapy] this term only	1778
#14	MeSH descriptor: [Electrodes, Implanted] this term only	396
#15	(baroreflex near/2 (therap* or treat* or stimulat)):ti,ab,kw	40
#16	(barostim* or ((baroreceptor* or pressoreceptor*) near/2 stimulat*)):ti,ab,kw	44
#17	(electric* near/2 (therap* or treat* or stimulat*)):ti,ab,kw	6990
#18	(implant* near/2 (electrode* or device* or monitor*)):ti,ab,kw	1326
#19	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18	8498
#20	#8 and #19	290

Database: PubMed
Date: 2016.10.14
Results: 81
Search (((((((Hypertension[MeSH Terms]) OR Pressoreceptors[MeSH Terms]) OR Carotid Arteries[MeSH Terms]) OR Carotid Sinus[MeSH Terms])) AND ((((Baroreflex therap*[Title/Abstract]) OR Electric stimulation therapy[MeSH Terms]) OR Electrodes,Implanted[MeSH Terms]) OR ((barostim*[Title/Abstract] OR baroreceptor* stimulat*[Title/Abstract] OR pressoreceptor* stimulat*[Title/Abstract])))) AND ("2015/01/01"[Date - Publication] : "3000"[Date - Publication]))

Database: Clinicaltrials.gov
Date: 2016.10.14
Search: Barostim
Search: "Baroreflex activation therapy"
Search: CVRx
Results: 19 records

Database: WHO ICTRP
Search: barostim OR baroreflex activation therapy OR cvrx
Results: 21 records

Appendix 2. Excluded trials from our search, and the reasons for the exclusions

Abe N, Bisognano JD. Non-pharmacological interventions for patients with resistant hypertension. Interventional Cardiology (London) 2012;7(2):93-96.
Reason for exclusion: Review, no further information.

Abeer Abdelhameed A. Effect of electrical stimulation on selected left ventricular parameters among hypertensive over-weight middle aged men. European Journal of Preventive Cardiology2014. p. S40.
Reason for exclusion: Inappropiate intervention.

Alnima T. Hw 03-4 Carotid Baroreflex Activation Therapy. J Hypertens 2016;34 Suppl 1:e538.
Reason for exclusion: Review, no further information.

Alnima T, de Leeuw PW, Kroon AA. Baroreflex activation therapy for the treatment of drug-resistant hypertension: new developments. Cardiol Res Pract 2012; 2012:587194.
Reason for exclusion:

Alnima T, De Leeuw PW, Kroon AA. Baropacing as a new option for treatment of resistant hypertension. Eur J Pharmacol 2015;Part A. 763:23-27.
Reason for exclusion: Review, no further information.

Alnima T, De Leeuw PW, Tan F, Kroon AA. Renal responses to long-term carotid

baroreflex activation in patients with drug-resistant hypertension. J Hypertens 2012;Conference:24th Meeting of the International Society of Hypertension. Sydney, NSW Australia. Conference Start: 20120930. Conference End: 20121004. Conference Publication: (var.pagings). 20120930 (pp e20120912-e20120913).
Reason for exclusion:

Alnima T, Goedhart EJBM, Seelen R, Van Der Grinten CPM, De Leeuw PW, Kroon AA. Baroreflex Activation Therapy Lowers Arterial Pressure Without Apparent Stimulation of the Carotid Bodies. Hypertension 2015;65(6):1217-1222.
Reason for exclusion:

Alnima T, Scheffers I, De Leeuw PW, Winkens B, Jongen-Vancraybex H, Tordoir JHM, et al. Sustained acute voltage-dependent blood pressure decrease with prolonged carotid baroreflex activation in therapy-resistant hypertension. J Hypertens 2012;30(8):1665-1670.
Reason for exclusion:

Alnima T, Schutten M, de Leeuw PW, Kroon AA. 8b.09: Right-Sided Dominance of Carotid Baroreceptor Reflexes in Patients with Resistant Hypertension. J Hypertens 2015;33 Suppl 1:e109.
Reason for exclusion:

Aronow HD, Li J, Parikh SA. Where and when Device Therapy May Be Useful in the Management of Drug-Resistant Hypertension. Curr Cardiol Rep 2014;16(11).
Reason for exclusion: Review, no further information.

Aursulesei V. Resistant hypertension: the role of interventional therapy. Rev Med Chir Soc Med Nat Iasi 2013;117(1):127-136.
Reason for exclusion: Review, no further information.

Australian Safety and Efficacy Register of New Interventional Procedures - Surgical. Implantable carotid sinus baroreflex device for the treatment of drug-resistant hy pertension (Structured abstract). Health Technology Assessment Database: Austral ian Safety and Efficacy Register of New Interventional Procedures -Surgical ASERNIP-S); 2014.
Reason for exclusion: HTA with no new information, we use the ones from NICE and CADTH, both from 2015.

Azizi M. [New invasive therapies for management of resistant hypertension]. Biol Aujourdhui 2014;208(3):211-216.
Reason for exclusion: Review, no further information.

Beige J, Hennig G, Wachter R. Barorezector activation (BAT) for resistant hypertens ion. [German]. Nieren- und Hochdruckkrankheiten 2012;41(11):464-471.
Reason for exclusion: Review, no further information.

Briasoulis A, Bakris G. The future of interventional management of hypertension: Threats and opportunities. Curr Vasc Pharmacol 2014;12(1):69-76.
Reason for exclusion: Review, no further information.

Chavanon ML, Bergau PF, Wallbach M, Wachter R, Koziolek MJ, Herrmann-Lingen C. Baroreflex activation therapy: Do you need to suffer to improve your car

diovascular risk profile? Psychosom Med 2016;78 (3):A145-A146.
Reason for exclusion: Abstract, inappropriate intervention

Davidson AC, Bisognano JD. Interventional approaches for resistant hypertension. Curr Opin Nephrol Hypertens 2012;21(5):475-480.
Reason for exclusion: Review, no further information.

De Ferrari G. Cardiac-neuromodulation: Neural based approaches for management of heart failure. Autonomic Neuroscience: Basic and Clinical 2015;192:51.
Reason for exclusion: Not an effect trial**.**

De Leeuw PW, Alnima T, Lovett E, Sica D, Bisognano J, Haller H, et al. Bilateral or unilateral stimulation for baroreflex activation therapy. Hypertension 2015;65(1):187-192.
Reason for exclusion: Not our focus; diagnostic methods.

Doumas M, Faselis C, Tsioufis C, Papademetriou V. Carotid baroreceptor activation for the treatment of resistant hypertension and heart failure. Curr Hypertens Rep 2012;14(3):238-246.
Reason for exclusion: Review, no further information.

Doumas M, Papademetriou V, Douma S, Faselis C, Tsioufis K, Gkaliagkousi E, et al. Benefits from treatment and control of patients with resistant hypertension. Int J Hypertens 2010;2011:318549.
Reason for exclusion: Review, no further information.

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Reason for exclusion: Review, no further information.

Grassi G, Mancia G. New therapeutic approaches for resistant hypertension. Journal of Nephrology 2012;25(3):276-281.
Reason for exclusion: Review, no further information.

Halbach M, Fritz T, Madershahian N, Pfister R, Reuter H. Baroreflex activation therapy: A novel interventional approach to treat heart failure with reduced ejection fraction. [German]. Herz 2015;40(7):959-965.
Reason for exclusion: Review, no further information.

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Reason for exclusion: Acute experimental tests. The objectives of the study were acute changes in SBP and DBP after deactivation and reactivation of the BAT device (Neo).

Hering D, Schultz C, Schlaich MP. Device Therapies for Resistant Hypertension. Clin Ther 2016;38(10):2152-2158.
Reason for exclusion: Review, no further information.

Heusser K, Brinkmann J, Menne J, Kaufeld J, Linnenweber-Held S, Beige J, et al. Acute effect of unilateral unipolar electrical carotid sinus stimulation in patients with treatment-resistant arterial hypertension. Hypertension Conference: American Heart Association's Council on Hypertension 2015;66(no pagination).
Reason for exclusion: Acute experimental tests.

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Reason for exclusion: Acute experimental tests.

Heusser K, Tank J, Brinkmann J, Menne J, Kaufeld J, Linnenweber-Held S, et al. Acute Response to Unilateral Unipolar Electrical Carotid Sinus Stimulation in Patients with Resistant Arterial Hypertension. Hypertension 2016;67(3):585-591.
Reason for exclusion: Acute experimental tests.

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Reason for exclusion: Acute experimental tests.

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Reason for exclusion: Acute experimental tests.

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Reason for exclusion: Acute experimental tests.

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Reason for exclusion: Acute experimental tests.

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Reason for exclusion: Review, no further information.

Illig KA, Levy M, Sanchez L, Trachiotis GD, Shanley C, Irwin E, et al. An implantable carotid sinus stimulator for drug-resistant hypertension: Surgical technique and short-term outcome from the multicenter phase II Rheos feasibility trial. J Vasc Surg 2006;44(6):1213-1218.
Reason for exclusion: Not our focus: Details of surgical implantation and early postoperative results.

Joshi N, Taylor J, Bisognano JD. Implantable device therapy for the treatment of resistant hypertension. J Cardiovasc Transl Res 2009;2(2):150-153.
Reason for exclusion: Review, no further information.

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Reason for exclusion: Inappropiate outcome.

Kroon A, Sica D, Bisognano J, Nadim M, Sanchez L, Bakris G. Confirmation of sustainability of hemodynamic response to baroreflex activation therapy in patients with resistant hypertension. Eur Heart J2011. p. 501.
Reason for exclusion: Compare evidence from trials that we already have in cluded.

Kroon A, Sica D, Bisognano J, Nadim M, Sanchez L, Bakris G. Individualized programming demonstrates feasibility of unilateral approach to delivery of baroreflex activation therapy. Eur Heart J 2011;Conference:European Society of Cardiology, ESC Congress 2011. Paris France. Conference Start: 20110827. Conference End: 20110831. Conference Publication: (var.pagings). 20110832 (pp 20110645).
Reason for exclusion: Not our focus. Compare different programming of the Rheos device.
Krum H, Schlaich M, Sobotka P, Scheffers I, Kroon AA, De Leeuw PW. Novel procedure- and device-based strategies in the management of systemic hypertension. Eur Heart J 2011;32(5):537-544.
Reason for exclusion: Review, no further information.

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Reason for exclusion: Review, no further information.

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Reason for exclusion: Review, no further information.

Lantelme P, Harbaoui B, Courand PY. Resistant hypertension and carotid baroreceptors stimulation. [French]. Presse Med 2015;44(7-8):730-736.
Reason for exclusion: Review, no further information.

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Reason for exclusion: Review, German, no reference list.

Linnenweber-Held S, Haller H, Menne J. Innovative treatment options in resistant arterial hypertension. [German]. Journal fur Hypertonie 2012;16(1):20-25.
Reason for exclusion: Review, no further information.

Lobo MD, Paton JFR. The use of devices to treat hypertension. Eur Heart J 2016;37(12):927-929.
Reason for exclusion: Not an efficacy trial.

Lobodzinski SS. An implantable device for the treatment of drug resistant hypertension. Cardiol J 2010;17(1):100-103.
Reason for exclusion: Review, no further information.

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Reason for exclusion: Review, no further information.

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Reason for exclusion: Review, no further information.

Navaneethan SD, Lohmeier TE, Bisognano JD. Baroreflex stimulation: A novel treatment option for resistant hypertension. J Am Soc Hypertens 2009;3(1):69-74.
Reason for exclusion: Review, no further information.

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Reason for exclusion: Review, no further information.

Ng MM, Sica DA, Frishman WH. Rheos: An implantable carotid sinus stimulation device for the nonpharmacologic treatment of resistant hypertension. Cardiol Rev 2011;19(2):52-57.
Reason for exclusion: Review, no further information.

Ott C. Interventional procedures for treatment-resistant hypertension. [German]. Diabetologe 2015;11(5):400-406.
Reason for exclusion: Review, no further information.

Paivanas N, Bisognano JD, Gassler JP. Carotid Baroreceptor Stimulation and Arteriovenous Shunts for Resistant Hypertension. Methodist Debakey Cardiovasc J 2015;11(4):223-227.
Reason for exclusion: Review, no further information.

Rossignol P. Carotid barostimulation in the treatment of resistant hypertension. [French]. Nephrologie et Therapeutique 2016;12:S133-S134.
Reason for exclusion: Review, no further information.

Ryan DJ, Nick S, Colette SM, Roseanne K. Carotid sinus syndrome, should we pace? A multicentre, randomised control trial (Safepace 2). Heart (British Cardiac Society)2010. p. 347-351.
Reason for exclusion: Inappropiate population and intervention

Santini M, Di Fusco SA, Santini A, Magris B, Pignalberi C, Aquilani S, et al. Prevalence and predictor factors of severe venous obstruction after cardiovascular electronic device implantation. Europace 2016;18(8):1220-1226.
Reason for exclusion: Inappropiate intervention.

Scheffers IJM, Kroon AA, Tordoir JHM, de Leeuw PW. Rheos Baroreflex Hypertension TherapyTM System to treat resistant hypertension. Expert Rev Med Devices 2008;5(1):33-39.
Reason for exclusion: Inappropiate population and intervention

Schrader J, Luders S. Therapy-resistant hypertension. [German]. Internist 2015;56(2):195-202.
Reason for exclusion: Review, no further information.

Stivanello E, Giovannini T, Negro A, Pirini G, Ballini L. Implantable device for the treatment of drug-resistant hypertension (Structured abstract). Health Technology Assessment Database: Agenzia sanitaria e sociale regionale, Regione Emilia-Romagna; 2009.
Reason for exclusion: Review, no further information.

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Reason for exclusion: Inappropiate population, intervention and outcome.

Todoran TM, Zile MR. Neuromodulation device therapy for treatment of hypertensive heart disease. Circ J 2013;77(6):1351-1363.
Reason for exclusion: Review, no further information.

Tordoir JHM, Scheffers I, Schmidli J, Savolainen H, Liebeskind U, Hansky B, et al. An Implantable Carotid Sinus Baroreflex Activating System: Surgical Technique and Short-Term Outcome from a Multi-Center Feasibility Trial for the Treatment of Resistant Hypertension. Eur J Vasc Endovasc Surg 2007;33(4):414-421.
Reason for exclusion: Describes surgical techniques and acute tests.
Zhang J, Zhou S, Xu G. Carotid baroreceptor stimulation: A potential solution for resistant hypertension. Interventional Neurology 2014;2(3):118-122.
Reason for exclusion: Inappropiate population and intervention

Appendix 3. Trial description, data extraction and Risk of Bias tables for the included trials

In the following tables we used these abbreviations:

AEs: Adverse events

ABPM: Ambulatory blood pressure measurements

BAT: Baroreflex activation therapy

BP: Blood pressure

CI: Confidential interval

CKD: Chronic kidney disease

DBP: Diastolic blood pressure

RCT: Randomized controlled trial

SAEs: Serious adverse events

SBP: Systolic blood pressure

SD: Standard deviation

SE: Standard error

Baroreflex activation therapy trials with the Rheos system device

1. All publications from the Rheos Pivotal Trial (NCT00442286):

Trials:

1) Bisognano JD, Bakris G, Nadim MK, Sanchez L, Kroon AA, Schafer J, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled Rheos pivotal trial. J Am Coll Cardiol2011. p. 765-773.
Comments: A multicenter, randomized controlled trial (RCT). **This is the main trial: The Rheos pivotal trial.** We extract data from this trial.

The publications 2-10 are all with patients from the pivotal trial, but in a design that is no longer randomized:

2) Alnima T, Leeuw PW, Tan FE, Kroon AA. Renal responses to long-term carotid baroreflex activation therapy in patients with drug-resistant hypertension. Hypertension (Dallas, Tex : 1979)2013. p. 1334-1339
Comments: We extract data for SBP, DBP and heart rate at 6 and 12 months from this publication.

3) Bisognano JD, Bakris GL, Nadim MK, Sanchez LA, Sica DA. Baroreflex hypertension therapy improves cardiac structure and function in resistant hypertension: Results from the pivotal trial of the Rheos system. J Am Coll Cardiol 2011;Conference:60th Annual Scientific Session of the American College of Cardiology and i62 Summit: Innovation in Intervention, ACC.11. New Orleans, LA United States. Conference Start: 20110402. Conference End: 20110405. Conference Publication: (var.pagings). 20110457 (20110414 SUPPL. 20110401) (pp E20110491).
Comments: We extract data for LVMI from this publication.

4) de Leeuw P, Bakris G, Haller H, Nadim M, Karunaratne H, Lovett E, et al. Baroreflex activation therapy improves status of resistant hypertension patients with heart failure. Eur Heart J 2014;35:843.
Comments: We extract data for SBP and DBP baseline and at 1, 2, 3, 4 and 5 years; and LVMI at baseline and at 6 and 12 months from this publication.The population is resistant hypertension patients with heart failure.

5) de Leeuw PW, Bakris GL, Nadim MK, Haller H, Lovett EG, Bisognano JD. 8b.06: Baroreflex Activation Therapy Consistently Maintains Blood Pressure Reduction in a Large Resistant Hypertension Cohort for at Least 6 Years. J Hypertens 2015;33 Suppl 1:e108.
Comments: We extract data for SBP and DBP for baseline and, 1, 2, 3, 4, 5 and 6 years from this publication.

6) Bakris GL, Nadim MK, Haller H, Lovett EG, Schafer JE, Bisognano JD. Baroreflex activation therapy provides durable benefit in patients with resistant hypertension: results of long-term follow-up in the Rheos Pivotal Trial. Journal of the American Society of Hypertension : 2012. p. 152-158.
Comments: We do not extract data from this publication, since results from the same patients are extracted from the publication of De Leeuw 2015, which we extract data from. Further, Bakris 2012 classify the patients into specific subgroups, that are not to our focus.

7) Sicat DA, Bakris G, Bisognano J, Nadim M, Sanchez L. A phase III trial of baroreflex activation therapy for resistant hypertension: Trial design and baseline characteristics in the Rheos Pivotal Trial. J Clin Hypertens2010. p. A114.
Comments: We do not extract data from this publication. Only baseline values, we use Bisognano 2011.

8) Bakris G, Bisognano J, Nadim M, Sanchez L, Sica D. Achievement of blood pressure goal in patients with resistant hypertension treated with baroreflex activation therapy. J Hypertens2010. p. e282.

Comments: We do not extract data from this publication. These data are included in Alnima 2013.

9) Bakris GL, Nadim MK, Haller H, Lovett E, Schafer JE, Bisognano J. Baroreflex activation therapy provides durable benefit in patients with resistant hypertension: Long-term follow-up results from the Rheos pivotal trial. J Am Coll Cardiol2012. p. E1730.

Comments: We do not extract data from this publication. These data are included in de Leeuw 2015.

10) Bakris G, Nadim M, Haller H, Lovett E, Bisognano J. Baroreflex activation therapy safely reduces blood pressure for at least five years in a large resistant hypertension cohort. J Am Soc Hypertens 2014;1):e9.

Comments: We do not extract data from this publication. These data are included in de Leeuw 2015.

Trial description of the primary study: The randomized Rheos Pivotal Trial (NCT00442286)

Trial: *Bisognano 2011* (24), full text publication

Design:
Double-blind, randomized placebo-controlled multicenter trial performed in USA and Europe. Parallell design. 49 centers – included between march 2007 and november 2009.
265 patients randomized 2:1 and included in the intention to treat analyses.
Group A: n= 181 immidiate active BAT from month 0 to month 12,
Group B: n=84 deferred (delayed) BAT (inactive BAT for the first 6 month, followed by active BAT for the next 6 months).
Data reported at baseline and at 6 and 12 months.
Baseline values were measured:
Post-implant, i.e. 1 month post- implant (Month 0).
They also included a post hoc analysis utilizing change from pre-implant rather than from month 0.

The Rheos system device was implanted in 322 patients one months ahead of the randomisation (randomisation =month 0). The device was activated 1 month post-implant= month 0.
Patients and investigators remained blinded to treatment until after the 12- month visit.
Efficacy analyses were conducted according to the principles of intention to treat, with unblinded and withdrawn patients treated as failures.

Population: *Enrollment criterion*: resistant hypertension defined as at least 1 out-patient, in-office, systolic blood pressure (SBP) ≥ 160 mm Hg with diastolic BP ≥ 80 mm Hg taken per protocol utilizing a standardized device. This measurement was obtained following at least 1 month of maximally tolerated therapy with at least 3 appropriate antihypertensive medications, including a diuretic. An ambulatory SBP ≥135 for a 24-h average, obtained via a standardised protocol and assessed at a core laboratory, and an absence of clinically significant orthostatic BP changes were additional enrollment criteria. *Exclusion criteria*: not reported explicitly – but the main reasen for ineligibility were due to office SBP or ambulatory SBP below inclusion criteria, the presence of carotid stenosis, being an inappropriate surgical candidate, or not exhibiting an acute testing response during surgery.

Number of subject with the device implanted: 322
Number randomized: 265, randomized 2:1 to:
Group A: n=181 (immidiate BAT/active BAT from months 0 to month 12) and
Group B: n=84 (inactive BAT for the first 6 month, followed by active BAT for the next 6 months).
(Patients with the device implanted that were not randomized: 57 (55 went into an open label group (each enrollment center was allowed to implant up to 2 nonrandomized (open-label) patients prior to en-rolling patients in the randomized portion of the trial) and 2 patients that had had the Rheos device explanted before randomisation).

Intervention/comparators: 322 included, 265 randomized:

Treatment group: Group A: n=181, immidate active BAT from month 0 to month 12.

Control group: Group B: n=84, BAT deferred (inactive) for the first 6 month, followed by active BAT for the next 6 months.

Investigators were not prevented to change medication during the course of the trial.

Endpoints:

Efficacy, only office measurements:

Primary, pre-defined:

- Compare Group A versus Group B for proportion of patients that achieve at least a 10 mm Hg drop in SBP at month 6 compared with Month 0 (Acute efficacy/acute responder).

Secondary, pre-defined:

- Compare Group A versus Group B for mean change in SBP at Month 6 compared with Month 0.

Additionaly efficacy analyses, not pre-defined:

1. An ancillary analysis was percentage of patients, in Group A and B respectively, attaining SBP ≤140 mm Hg at 6 and 12 months. This have results only as graphs, no figures except for the p-value.

A post hoc analysis utilizing change from *pre-implant rather than from Month 0:*
At 6 and 12 months: Changes from pre-implant baseline for SBP (office).
At 12 months: Proportion of patients with at least 10 mm Hg drop from pre-implant baseline.

Safety:

Primary, pre-defined:

- *Procedural safety*: Compare the serious procedure- or system-related adverse event–free rate for events occurring within 30 days of implant to a pre-specified objective performance criterion of 82% based on historical literature on implantable cardioverter-defibrillators and pacemakers.
- BAT safety: Compare Group A versus Group B therapy-related adverse event–free rates for serious adverse events occurring between 30 days post-implant (Month 0) and the Month 6 visit. Therapy-related adverse events included events attributable to therapy to treat resistant hypertension, including but not limited to serious adverse drug reactions, hypotension, bradycardia, hypertensive crisis requiring hospitalization, and extraneous stimulation.
- *Device safety:* Compare the event-free rate for all major hypertension-related and serious device-related adverse events occurring between 30 days post-implant (Month 0) and the Month 12 visit, to a pre-specified objective performance criterion of 72% based on similar implantable devices such as defibrillators and resynchronization devices. Hypertension-related adverse events include fatal and nonfatal myocardial infarction, heart failure requiring hospitalization, fatal and nonfatal stroke, and renal failure requiring dialysis.

Change in out-patient office BP was calculated using the average of the 5 measurements from the standardised automated device measurements (BpTRU) at each visit and month 0 (month 0 is defined as the BP obtained at the randomization visit 1-month post-implant). The measurements were taken with the investigator not in the room.

All adverse events were reviewed and submitted for adjunction to an independent adverse events committee. Serious adverse events included death, life-threatening events, hospitalization or prolongationof a hospitalization, permanent functional or structural damage, or other medical events.

Follow-up: The average follow-up was 21±8 months.
Numbers lost to follow-up: One subject, in Group A, was determined to be lost to follow-up prior to the 12-month visit.

Funding source: The trial was funded by CVRx, Inc.

Data extraction from the RCT:

Bisognano 2011 (24)

Endpoints	**Intervention Group A** n=181	**Control Group B** n=84	p value
SBP (office), mean (SD) decrease at 6 months: *with post-implant baseline* *with pre-implant baseline*	 16±29 26±30	 9±29 17±29	 0.08 0.03
SBP (office), mean (SD) decrease at 12 months (**Immediate versus deferred BAT** (with 12 months BAT in Group A and 6 months BAT in Group B): *with post-implant baseline* *with pre-implant baseline*	 25±32 35±28	 25±31 33±30	 Not given 0.57
SBP≤140 mm Hg at 6 months, additional efficacy analyses: percentage of patients, *with post-implant baseline*	figure	figure	p=0.005
SBP≤140 mm Hg at 12 months, additional efficacy analyses: percentage of patients, *with post-implant baseline*	figure	figure	p=0.70
Acute responder: Proportion of patients that achieve at least a 10 mm Hg drop in SBP at month 6 compared with month 0, *with post-implant baseline*	54%	46%	p=0.97
Proportion with sustained efficacy at 12 months in responders from Group A at 6 months, *with post-implant baseline*	88%		p<0.001

SAFETY:		
Serious procedure-or system-related event–free rate (%)	74.8%	
Number (%) of serious procedure-or system-related events	68 (25.5%)	
Surgical complications	13 (4.8)	
Nerve injury with residual deficit	13 (4.8)	
Transient nerve injury	12 (4.4)	
Respiratory complications	7 (2.6)	
Wound complications	7 (2.6)	
Device, event–free rate (%), between month 0 and month 12	87.2%, p<0.001	
Number (%) of serious device-related and major hypertension-related AEs , between month 0 and month 12	34 (12.8%)	
Hypertension related stroke	6 (2.3)	
BAT, therapy-related event-free rate (%)	Group B: 89.3%	Group A: 91.7%, p<0.001

Number (%) of serious therapy-related AEs (BAT safety)	Not given	
1. Hypertensive crisis	Group B: 7 (8.3%)	Group A: 9 (5.0%)
Deaths, during the 12 months	4, none were related to either the procedure or the device	

Risk of Bias for the RCT:

Bisognano 2011 (24)

Entry/Domain	Judgement	Description
Random sequence generation?	low	The procedure not reported
Allocation concealment?	low	The proceure not reported
Blinding of participants and personnel?	low	Report that all blinded in 12 months
Blinding of outcome assessments?	low	Report that all blinded in 12 months
Incomplete outcome data?	low	Pre-defined and reported on
Selective reporting?	low	
Other sources of bias?	low	
Conclusions	Low risk of bias for all endpoints up to 6 months, for 12 months data high risk of bias (no longer a control group)	

Trial description of the controlled, non-randomized publication

(with patients from the pivotal study)

Trial: Alnima 2013 (26). Full text publication.
Design: This publication reports from a **controlled, but no longer randomized design** for some of the patients from the pivotal study. The difference between the pivotal trial and this publication is that Group 1 also includde the 55 patients from the non-randomized, open label group (each enrollment center was allowed to implant up to 2 nonrandomized (open-label) patients prior to enrolling patients in the randomized portion of the trial); and Group 2 also included the 2 patients that had the Rheos device explanted before randomisation. Baseline values were measured: Post-implant, i.e. 1 month post- implant (Month 0).
Population: *Group 1*=Group A in the pivotal study +55 patients (not randomized), n=236 *Group 2*= Group B in the pivotal study +the 2 patients with the device explanted before randomisation, n=86.
Intervention/Comparator: *Intervention: Group 1*= 236 patients with BAT activated from month 0 to month 12. *Comparator: Group 2*= 86 patients with BAT inactive for first 6 months, followed by active BAT for the next 6 months.
Endpoints: SBP, DBP and heart rate at month 0, 6 and 12 monts for both groups. Only office values. We only reports for the difference between 0 and 6 months, since at 12 months, we do no longer have a real control group.
Follow-up: 12 months
Funding source: The trial was funded by CVRx, Inc.

Data extraction from the controlled, non-randomized publication

Alnima 2013 (26)

Endpoints	**Intervention Group 1** *n=236: 181 + 55*	**Control Group 2** *n=86: 84 +2*	P value
SBP (office), **mean (SD)** month 0 month 6	 169 (27) 151 (31)	 168 (24) 160 (26)	 0.788 0.018
DBP (office), **mean (SD)** month 0 month 6	 100 (18) 90 (18)	 100 (14) 95 (15)	 0.731 0.032
Heart rate (office)**, mean (SD)** month 0 month 6	 79 (14) 72 (14)	 79 (17) 75 (15)	 0.959 0.096

Risk of Bias from the controlled, non-randomized publication

Alnima 2013 (26)

Entry/Domain	**Judgement**	**Description**
Random sequence generation?	High	Included patients that were not randomized, ie a nonrandomized population
Allocation concealment?	High	See above
Blinding of participants and personnel?	High	Includes open label patients
Blinding of outcome assessments?	High	
Incomplete outcome data?	unclear	BP predefined, heart rate not pre-defined
Selective reporting?	low	
Other sources of bias?	low	
Conclusions	High risk of bias for all endpoints	

Trial description of single-arm publications

Trials: Bisognano 2011 (27). Abstract. de Leeuw 2015 (28).Abstract. de Leeuw 2014 (33). Abstract. Resistant hypertension patients *with heart failure.*
Design: For all the three abstracts, the design was single-arm/ "before and after trial". No control group. They used the baseline values as the "before values". *Bisognano 2011*: 46 patients from 10 centers from the pivotal study. Echo data were analyzed at a blinded core lab. Changes at follow-up (12 months) vs activation were analyzed with paired t-tests. *De Leeuw 2015:* 322 patients, i.e.all patients with the Rheos System implanted in the RCT. These were followed in a single-arm for 6 years. Measurements of SBP and DBP taken every year. *De Leeuw 2014:* A retrospective single-arm design. 82 resistant hypertension patients with *heart failure* identified from the pivotal RCT. It was not reported when the baseline values were measured (but probably pre-implant for de Leeuw) .
Population: *Bisognano 2011*: n=46, sub-population of the pivotal RCT. All had 12 months with activated BAT. *De Leeuw 2015:* n=322, i.e.all subjecst with the Rheos System implanted in the RCT. *De Leeuw 2014:* n=82 resistant hypertension patients *with heart failure* (preserved-ejection fraction) retrospectively identified from the pivotal RCT population.
Intervention/Comparators: All single-arms: *Bisognano 2011*: Intervention: 12 months with activated BAT. *De Leeuw 2015:* Intervention: Six years with activated BAT *Leeuw 2014*: Intervention: Five years with activated BAT
Endpoints: *Bisognano 2011*: We extract: LVMI (Left Ventricular Mass Index) (g/m^2) at 12 months versus activation. We do not extract: Office SBP and DBP since we here use data from the pivotal RCT. *De Leeuw 2015* (n=322): Changes in SBP and DBP values between baseline and at 1, 2, 3, 4, 5 and 6 years respectively. Long-term (6 years?) safety. N=322 at baseline and n=34 at 6 years. *De Leeuw 2014* (n=82) : Changes in SBP and DBP values between baseline and at 1, 2, 3, 4 and 5 years respectively; and changes in LVMI between baseline and at 6 and 12 months in resistant hypertension patients *with heart failure.* These publications do not tell if there were office or ambulatorty measurements, we assume office, since substudy of Bisognano 2011.
Follow-up: Bisognano 2011: 12 months De Leeuw 2015 (n=322): six years De Leeuw 2014 (n=82): one year, *subgroup HF*
Funding source: The trial was funded by CVRx, Inc.

Data extraction from single-arm publications

Endpoints, mean (SD) or mean (SE), publication	**Baseline** (not specified if pre-or post-implant) **mean (SD)**	1 year Δ mean (SE)	2 years Δ mean (SE)	3 years Δ mean (SE)	4 years Δ mean (SE)	5 years Δ mean (SE)	6 years Δ mean (SE)
SBP (assume office) de Leeuw 2015	n=322 178.1 (±22.6)	n=294 -34.3 (±1.7)**	n=255 -31.9 (±2.0)**	n=238 -34.3 (±2.2**)	n=214 -31.6 (±2.1)**	n=114 -37.6 (±2.8)**	n=34 -33.0 (±5.6)**
• **SBP** (assume office) de Leeuw 2014 *Heart failure*	n=82 178.9 (±24.6)	n=82 -36.1 (±2.9)**	n=61 -30.7 (±4.4)**	n=67 -37.3 (±4.2)**	n=53 -36.8 (±4.6)**	n=9 -30.3 (±5.4)**	
DBP de Leeuw 2015 (assume office)	n=322 103.1 (±15.4)	n=294 -15.5 (±1.0)**	n=255 -15.2 (±1.1)**	n=238 -17 (±1.2)**	n=214 -15.9 (±1.2)**	n=114 -20.1 (±1.6)**	n=-34 -15.1 (±3.1)**
• DBP (assume office) de Leeuw 2014 *Heart failure*	n=82 99.7 (±17.0)	n=82 -16.3 ± (1.7)**	n=61 -14.2 (±1.9)**	n=67 -18.3 (±2.3)**	n=53 -17.7 (±2.4)**	n=9 -13.3 (±3.8)**	
Left ventricular mass index (g/m²) Bisognano 2011 abstract	n=46 117.7 (±4.3)	n=46 -17.8 (±3.0)**					
• **Left ventricular mass index (g/m²)** de Leeuw 2014 *Heart failure*	n=14 127.6 (±41.1)	n=14 -13.5 (±6.6),n.s.					
Safety							
de Leeuw 2015	28 deaths, the publication reports up to 6 years. "Original trial enrollment consisted of 322 patients. Of those 182 presently remain active, while 140 are inactive due to withdrawal from the study (1122) or death (28)." "Long-term therapy safety was excellent with low rates of stroke, myocardial infarction and hypertensive urgency".						

Risk of bias for the single-arm publications

Entry/Domain	**Judgement**	**Description**
Random sequence generation?	high	no randomisation - all - single-arm
Allocation concealment?	high	
Blinding of participants and personnel?	high	
Blinding of outcome assessments?	high	
Incomplete outcome data?	low	

Selective reporting?	high	
Other sources of bias?		
Conclusions	High risk of bias for all endpoints	

2. All publications from the (Rheos Feasability study) DEBuT-HT

Trials:

1) **Scheffers IJM**, Kroon AA, Schmidli J, Jordan J, Tordoir JJM, Mohaupt MG, et al. Novel baroreflex activation therapy in resistant hypertension: Results of a European multi-center feasibility study. J Am Coll Cardiol 2010;56(15):1254-1258.

Comments: A multicenter, prospective, nonrandomized feasibility trial. This is the main trial: The DEBuT-HT (Device Based Therapy in HypertensionTrial).
We extract 3 months, 1 and 2 years changes from baseline for SBP, DBP and heart rate from this publication.

The publications 2-4 are specific cohorts of patients from the main trial (DEBuT-HT):

2) Kroon A, Schmidli J, Scheffers I, Tordoir J, Mohaupt M, Allemann Y, et al. Sustained blood pressure reduction by baroreflex activation therapy with a chronically implanted system: 4-year data of Rheos debut-HT study in patients with resistant hypertension. J Hypertens 2010;Conference:20th European Meeting on Hypertension of the European Society of Hypertension, ESH. Oslo Norway. Conference Start: 20100618. Conference End: 20100621. Sponsor: Boehringer Ingelheim, Daiichi-Sankyo, NOVARTIS, SERVIER, RECORDATI . Conference Publication: (var.pagings). 20100628 (pp e20100441).

Comments: We extract 3 and 4 years changes from baseline for SBP, DBP and heart rate from this publication.

3) Bisognano JD, Kaufman CL, Bach DS, Lovett EG, De Leeuw P. Improved cardiac structure and function with chronic treatment using an implantable device in resistant hypertension: Results from European and United States trials of the Rheos system. J Am Coll Cardiol 2011;57(17):1787-1788.

Comments: We extract 3 and 12 months changes from baseline for LVMI from this trial publication.

4) Bisognano JD, De Leeuw P, Bach DS, Lovett EG, Kaufman CL. Improved functional capacity and cardiovascular structure after baroreflex activation therapyTM in resistant hypertension patients with symptomatic heart failure: Results from european and united states trials of the Rheos system. J Card Fail 2009;Conference:13th Annual Scientific Meeting of the Heart Failure Society of America, HFSA. Boston, MA United States. Conference Start: 20090913. Conference End: 20090916. Conference Publication: (var.pagings). 20090915 (20090916 SUPPL. 20090911) (pp S20090963).

Comments: This is a subgroup of patients from DEBuT-HT: *Resistant hypertension patients with symptomaptic heart failure.* We extract 3 and 12 months changes from baseline for SBP, DBP and LVMI from this publication.

The publications 5-11 are publications from the DEBuT-HT that we do not extrat data from (the reasons are given under Comments):

5) Bisognano JD, De Leeuw PW, Bach DS, Kaufman CL, Lovett EG. Improved cardiac structure and diastolic flow velocities in early-stage heart failure with chronic treatment using an implantable device: Results from European and United States trials of the Rheos system. J Am Coll Card 2009;Conference:American College of Cardiology 58th Annual Scientific Session and i52 Summit: Innovation in Intervention. Orlando, FL United States. Conference Start: 20090329.

Conference End: 20090331. Conference Publication: (var.pagings). 20090353 (20090310) (pp A20090188).

Comments: We do not extract data from this publication. These data are included in Bisognano 2011.

6) Bisognano JD, De Leeuw PW, Bach DS, Lovett EG, Kaufman CL. Baroreflex hypertension therapy improves cardiac structure and arterial compliance in resistant hypertension: Results from European and United States trials of the Rheos system. J Clin Hypertens 2009;Conference:24th Annual Scientific Meeting and Exposition of the American Society of Hypertension, ASH. San Francisco, CA United States. Conference Start: 20090506. Conference End: 20090509. Conference Publication: (var.pagings). 20090511 (20090504 SUPPL. 20090501) (pp A20090511).

Comments: We do not extract data from this publication. These data are included in Bisognano 2011.

7) Kroon AA, Bisognano JD, Bach DS, Kaufman CL, De Leeuw PW. Baroreflex activation therapy improves functional capacity and reduces left ventricular mass index: Results from european and united states trials of the Rheos system. J Hypertens 2010;Conference:20th European Meeting on Hypertension of the European Society of Hypertension, ESH. Oslo Norway. Conference Start: 20100618. Conference End: 20100621. Sponsor: Boehringer Ingelheim, Daiichi-Sankyo, NOVARTIS, SERVIER, RECORDATI . Conference Publication: (var.pagings). 20100628 (pp e20100278).

Comments: We do not extract data from this publication. These data are included in Bisognano 2011.

8) Georgakopoulos D, Kroon A, Bach DS, Kaufman CL, Abraham WT, Little WC, et al. Improved ventricular-arterial elastance following chronic treatment using the Rheos system implantable device in resistant hypertension. J Card Fail 2010;Conference:14th Annual Scientific Meeting Heart Failure Society of America. San Diego, CA United States. Conference Start: 20100912. Conference End: 20100915. Conference Publication: (var.pagings). 20100916 (20100918 SUPPL. 20100911) (pp S20100927).

Comments: We do not extract data from this publication. These data are included in Bisognano 2011.

9) Georgakopoulos D, Kroon A, Bach DS, Kaufman CL, Abraham WT, Little WC, et al. Improved left ventricular end-systolic myocardial wall stress following chronic baroreflex activationwith the Rheossystem in resistant hypertension. J Card Fail 2010;Conference:14th Annual Scientific Meeting Heart Failure Society of America. San Diego, CA United States. Conference Start: 20100912. Conference End: 20100915. Conference Publication: (var.pagings). 20100916 (20100918 SUPPL. 20100911) (pp S20100925).

Comments: We do not extract data from this publication. These data are included in Bisognano 2011.

10) Wustmann K, Kucera JP, Scheffers I, Mohaupt M, Kroon AA, De Leeuw PW, et al. Effects of chronic baroreceptor stimulation on the autonomic cardiovascular regulation in patients with drug-resistant arterial hypertension. Hypertension 2009;54(3):530-536.

Comments: We do not extract data from this publication. These data are included in in Scheffers 2010.

11) Scheffers I, Schmidli J, Kroon A, Toirdoir J, Mohaupt M, Allemann Y, et al. Functional safety in resistant hypertensive patients with baroreflex activation therapy. J Hypertens 2010;Conference:20th European Meeting on Hypertension of the European Society of Hypertension, ESH. Oslo Norway. Conference Start: 20100618. Conference End: 20100621. Sponsor: Boehringer Ingelheim, Daiichi-Sankyo, NOVARTIS, SERVIER, RECORDATI . Conference Publication: (var.pagings). 20100628 (pp e20100540). *Comments: We do not extract data from this publication.* These data are included in Scheffers 2010

Data description from the DEBuT-HT

Trials:
Scheffers 2010 (14). Full text publication. The main trial.
Kroon 2010 (29). Abstract
Bisognano 2011 (30).Research Correspondance
Bisognano 2009 (34). Abstract. Patients with resistant hypertension *and symptomaptic heart failure..*

Design:
Scheffers 2010: Multicenter (9 centers), prospective nonrandomized feasability study performed in Europe. The design was single-arm/ "before and after trial". No control group. They used the baseline values as the "before values".
The results at 3 months, 1 year and 2 years were reported as changes from baseline. The device was activated 1 month after implant, which is the study baseline time point.
Patients included between March 2004 and November 2007.
Inclusion criteria: > 21 years, BP ≥160/90 mm Hg despite receiving at least 3 anti hypertensive agents, including a diuretic.
Exclusion criteria included baroreflex failure, significant orthostatic hypotension, cardiac arrhythmias, chronic atrialfibrillation, clinically significant cardiac valvular disease or hypotension secondary to a treatable cause, carotid atherosclerosis with >50% stenosis determined by ultrasoundography, prior implant or radiation in the carotid sinus region, currently implanted electrical medical devices, dialysis, and pregnancy or contemplating pregnancy.
Kroon 2010: A substudy of 18 patients from 4 European centers from the 45 *patients enrolled in the DEBuT-HT. This publication reports changes in SBP, DBP and heart rate between pre-implant values* and 1, 2, 3 and 4 years respectively.
Bisognano 2011: A substudy with 35 patients from 8 centers from the the DEBuT-HT. Main focus were to measure echocardiograms. They also reported changes in SBP, DBP, heart rate and LVMI between baseline and 3 and 12 months respectively. The time for baseline measurements were not specified.
Bisognano 2009: A substudy with 21 patients with resistant hypertension *and symptomaptic heart failure* from the the DEBuT-HT. The publication reported changes in SBP, DBP, heart rate and LVMI beteen baseline and 3 and 12 months respectively for this patient group with heart failure. The time for baseline measurements were not specified.

Population:
Scheffers 2010: n=45 patients with resistant hypertension
Kroon 2010: substudy of Scheffers 2010 with 4 years follow-up: n=18
Bisognano 2011: substudy of Scheffers 2010: n=34 with additional end points
Bisognano 2009: substudy of of Scheffers 2010 patients with heart failure: n=21

Interventions/comparators:
No control, the results after activated BAT for a spesific time is compared with the baseline values.
Scheffers 2010: I: Active BAT with the Rheos system for 2 years.
Baseline values: Post-implant (1 month after), before activation of the BAT.
Medication were kept constant for 2 months before entry and during the first 3 months of therapy. All information on antihypertensiva, including dosage was recorded.
Kroon 2010: I: Active BAT with the Rheos system for 4 years. Baseline values: Before activation of the BAT, here the baseline values were taken pre-implant.
Bisognano 2011: I: Active BAT with the Rheos system for 12 months. Baseline values: Before activation, but do not tell if pre- or post-implant..
Bisognano 2009: (*Patients with resistant hypertension and symptomaptic heart failure)*: I: Active BAT with the Rheos system in 2 years. Baseline values: Before activation, but do not tell if pre- or post-implant.

Endpoints:
Scheffers 2010:
Efficacy: Changes in SBP, DBP and HR (office and ambulatory) between baseline and 3 months, 1 year and 2 years respectively.
Office BP measurements were taken with a validated electronic device, and readings were repeated when 2 consecutive measurements varied by >5mm. The recorded BP was the mean of the 2 last readings.

In addition ambulatory BP measurements were performed with at least 40 measurements during 24 h using a validated device. *Safety:* Procedure-or device-related SAE. Death, life-threatening situations, inpatient hospitalization, prolongation of existing hospitalization, or persistant or significant disability were classified as serious adverse events (SAEs) An independent committee adjudicated adverse events to determine the severity and relationship to the procedure or device. *Kroon 2010:* We extract changes in SBP, DBP and HR (assume office, not specified) between baseline (pre-implant values) and 3 and 4 years respectively. Safety during 4 years. The other data we have extracted from Scheffers 2010. *Bisognano 2011:* We extract changes in LVMI between baseline and 3 and 12 months respectively. The other data we have extracted from Scheffers 2010. *Bisognano 2009:* We extract changes in SBP and DBP (office) and LVMI between baseline baseline and 3 and 12 months respectively for these subgroup of patients with *symptomaptic heart failure*
Follow-up and Drop outs: *Scheffers 2010* (n=45): 2 years (at 2 years n=17) *Kroon 2010* substudy (n=18): 4 years *Bisognano 2011* substudy (n=34): 1 year (at 1 year n=21) *Bisognano 2009* substudy, heart failure patients (n=21 for SBP and DBP; n=9 for LVMI): 1 year (at 1 year: same number of patients)
Funding source: The trial was funded by CVRx, Inc.

Data extraction from the DEBuT-HT

Endpoints (Publication)	**Baseline** mean (SD)	Δ3 months mean change (SE)	Δ 1 year mean change (SE)	Δ2 years mean change (SE)	Δ 3 years mean change (SE)	Δ 4 years mean change (SE)
Office **SBP** **DBP** **HR** (Scheffers 2010)	n=45 179 (29) 105 (22) 80 (13) Basline: Post-implant	n=37 -21 (4)** -12 (2)** -8 (2)**	n=26 -30 (6)** -20 (4)** -8 (2)**	n=17 -33 (8)** -22 (6)** -11 (4)**		
Do not specify if office or ambulatory, assume office, since substudy) • SBP • DBP • HR *(Kroon 2010)*	n=18, 193 (36) 111 (20) 74 (13) Basline: Pre-implant	Not reported	n=18 -38 (7)** -22 (4)** -4 (2) n.s.	n=18 -36 (7)** -18 (5)** -5 (3) n.s.	n=18 -40 (9)** -21 (6)** -1 (3) n.s.	n=18 -53 (9)** -30 (6)** -5 (2)*
Office, mean ±SD • SBP • DBP *(Bisognano 2009) Heart failure patients*	n=21 165 (27) 99 (22) Basline time: not reported	n=21 -16 (19)** -10 (12)*	n=21 -15 (29)* -11 (19)**			

Ambulatory **SBP** **DBP** **HR** (Scheffers 2010)	Not reported	n=26 -6 (3) n.s. -4 (2)* -5 (2)**	n=15 -13 (3)** -8 (2)** -6 (2)*	n=8 -24 (8)* -13 (5)* -11 (34)**		
LVMI (g/m²) *(Bisognano 2011)*	n=34 138.9 (6.0) Basline time: not reported	n=34 -18.0 (2.7)**	n=21 -24.6 (3.9)**			
• LVMI (g/m²) (*Bisognano 2009)* *Heart failure*	n=9 121.4 (19.8) Basline time: not reported	n=9 -9.8 (11.8)*	n=9 -22.2 (21.7)*			
Safety						
Procedure related SAE (*Scheffers 2010)*	n=7/42 **n=1 fatale event** n=3 had the device explanted before activation due to infection n=3, perioperative stroke, tongue paresis most likely due to intraoperative injury, and moderat pulmonary edema.					
Device related SAE *Scheffers 2010)*	n=1/42 (Movement of the implantable pulse generator, resulting in the need for further surgery to reposition the implantable pulse generator, which resolved the problem).					
System-or procedure-related SAE During a period of 4 years (1042 patient months) *(Kroon 2010)*	"No unexpected system- or procedure- related serious adverse events"					
*p<0.05; **≤0.01						

Risk of Bias for the from the DEBuT-HT

Scheffers 2010 (14)

Entry/Domain	Judgement	Description
Random sequence generation?	high	single-arm
Allocation concealment?	high	single-arm
Blinding of participants and personnel?	high	Assume no blinding
Blinding of outcome assessments?	high	Assume no blinding
Incomplete outcome data?	High	Start with 37 patients , after 1 year 26, and after 2 years 17
Selective reporting?	Low	
Other sources of bias?		
Conclusions	high risk of bias for all endpoints	

Since the other publications (Kroon 2010, Bisognano 2011 and Bisognano 2009) are substudies of Scheffers, it follows that the endpoints in these studies also are evaluated to have high risk of bias.

Baroreflex activation therapy trials with the Neo device

1. Publications from the Barostim Neo trial

Trial description*:*

Trials: 1) *Hoppe* UC, Brandt MC, Wachter R, Beige J, Rump LC, Kroon AA, et al. Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: Results from the Barostim Neo trial. J Am Soc Hypertens 2012;6(4):270-276. *Comments:* **This is the main trial: The Barostim Neo trial.** From this trial we extract: 3 and 6 months data for changes in SBP and heart rate. AEs for the 6 months period.Further SBP, DBP and heart rate at 6 months from a subgroup of patients with prior renal nerve ablation. 2) *Brandt* MC, Wachter R, Beige J, Haller H, Hoppe U, Lovett E, et al. Minimally-invasive syste for baroreflex activation therapy chronically reduces blood pressure: Initial results from the barostim Neo trial. J Am Coll Cardiol 2012;Conference:61th Annual Scientific Session of the American College of Cardiology and i62 Summit: Innovation in Intervention, ACC.12. Chicago, IL United States. Conference Start: 20120324. Conference End: 20120327. Conference Publication: (var.pagings). 20120359 (20120313 SUPPL. 20120321) (pp E20121784). *Comments:* We extract data for DBP at 3 months from this trial.
Design: Non-randomized, single-arm, open-label, "before and after trial" multicenters trial conducted at six centerss in the European Union and one centers in Canada. No control group. They used the baseline values as the "before values". The patients were enrolled from January 2012 to Januar 2015. The baseline measurements were done pre-implant. The purpose of this investigation was to measure the safety and efficacy profile of this new advancement (Neo) for BAT in resistant hypertensive patients over a 6-months period, with the objective of verifying that it is suitable for demonstrating short-and long-term safety and efficacy in randomized, controlled trials.
Population: *Hoppe 2012:* 30 patients with resistant hypertension, defined as resting systolic blood pressure (SBP)≥140 mm Hg despite treatment with ≥3antihypertensive medications, including a diuretic. Male and female, above 18 years, generally middle-aged (mean 57±12 years), obesed. Major exclusion criteria included hypertension secondary to an identifiable and treatable cause other than sleep apnea, known or suspected baroreflex failure or autonomic neuropathy, and myocardial infarction, unstable angina, syncope, or cerebral vascular accident within 3 months before implant. Main comorbidities were history of diabetes (23%), history of renal nerve ablation (20% and history of chronic kidney disease (10%). Six of the patients had prior renal nerve ablation. *Brandt 2012:* The same 30 patients.
Intervention/comparator: 30 patients got the Barostim *Neo*™ system implanted and initiated 2 weeks after implant. *Control group:* No control group. They used the baseline values as the "before values". Qualifying BP baseline measurements required two consecutive measurements at least 24 hours apart within 14 days before implant. Stable medical therapy was required for ≥4 weeks before establishing pretreatment baseline by averaging two SBP readings taken≥24 hours apart. Physicians were encouraged to maintain patients on a consistent medical regimen through the course of the study, although changes were permitted when dictated by a documented medical need.
Endpoints: *Hoppe 2012: Efficacy:* *Pre-defined:* Reduction in office cuff systolic BP through 6 months of BAT relative to baseline BP.

Others, not pre-defined: At 3 months: SBP, DBP. At 6 months: DBP, heart rate and the percentage of patients achieving systolic BP≤140 mm Hg. From a subset of patients with prior renal nerve ablation: Changes beteen baseline and 6 months in SBP, DBP and heart rate. *Safety: Pre-defined*: All system-and procedure-related complications through the 6-monhs visit. *Brandt 2012:* Initial results for changes between baseline and 3 months for DBP The reduction in BP was defined as the difference between the average of the *2 pre-implant values* minus the value recorded at the 6-month follow-up visit, or the first visit after if the 6-months visit was missed. Complication rates were computed as the number of system-and procedure-related complications divided by the duration of follow-up through 6 months for patients in the trial.
Follow-up: *Hoppe 2012:* 29 patients completed their month 6 visit, one patient missed this visit, and used the next visit (month 9) (by protocol). *Brandt 2012:* 3 months
Funding source: CVRx, Inc..

Data extraction:

Endpoints	**Baseline values** (pre-implant) Data reported as mean ±SD	**Intervention: Barostim Neo** **Changes** (mean ± SE) for BP and heart rate
Blood pressure, office **SBP**, (N=30) *3 months* (Hoppe 2012)	171.7±20.2	-26.1±3.3 (P<0.001)
6 months (N=30) (Hoppe 2012)	171.7±20.2	-26.0±4.4 (P<0.001)
6 months (*subset of patients with prior renal denervation*, (n=6) (Hoppe 2012)	178.7±18.7	-22.3±9.8, (P not reported)
DBP, office *3 months,* (N=30) (Hoppe 2012)	99.5 ±13.9	Not reported (only from graph)
3 months, (N=30) (Brandt 2012)	99.5 ±13.6	-12.5±2.1 (P<0.05)
6 months, (N=30) (Hoppe 2012)	99.5 ±13.9	Not reported (only from graph)
6 months (subset of patients with prior renal denervation,(n=6) (Hoppe 2012)	106.3±13.2	-11.3±8.1(P not reported)
The percentage of patients achieving systolic BP≤140 mm Hg (Hoppe 2012) at *6 months*	0%	+43%

Heart rate beats/minute (mean ±SD) *6 months,* (N=30) (Hoppe 2012) *6 months (subset of patients with prior renal denervation,* (n=6) (Hoppe 2012)	 75.0 ±12.1 86 ±12	 - 5.0±2.6 (P=0.07) - 5.3±7.7 (P not reported)
System or procedure-related complications (Hoppe 2012) During the perioperative period of 30 days after surgery (Procedure-re-lated) Long- term events >180 days after the perioperative period (Device related) Death	3 complications: Device pocket hematoma, self-inflicted wound complication and internittent pain lateral of device system. Patients free from Events: 90%. Intermittent pain near the device system. Patients free from Events: 97%. None reported All the complications were procedure–related, none were system-related. All recovered, with no residual effects.	

Risk of Bias:

Hoppe 2012 (25). Full text publication (n=30) with results at 3 and 6 months for changes in SBP, heart rate, and AEs. Further SBP, DBP and heart rate at 6 months from 6 of the patients with prior renal nerve ablation.

Brandt 2012 (31). Abstract (n=30) with *initial* results 3 months for SBP and DBP changes.

Entry/Domain	Judgement	Description
Random sequence generation?	High	Not randomized
Allocation concealment?	High	High
Blinding of participants and personnel?	High	No blinding. May have effect on the participants
Blinding of outcome assessments? Blood pressure Heart rate Complications	 Low Low Uncertain	We do not think that BP and heart rate will be influenced by the lack of blinding of the investigators.
Incomplete outcome data? Blood pressure Heart rate Complications	 Low Low Low	All patients were included in the analyses

Selective reporting? *All patients:* SBP DBP Heart rate Complications *Subset of patients with prior renal nerve ablation* SBP DBP Heart rate	 Low Uncertain Uncertain Low Uncertain Uncertain Uncertain	 SBP and complications were pre-specified, and reported on for all patients. DBP and heart rate were not predefined, but reported on for all patients. None of the endpoints were pre-defined. All patients (n=6) in the subset were reported on
Other sources of bias?	High	The main results (n=30), and the results from the subset group (n=6) both included a low number of patients (events). Several of the authors have received grant from CVRx, Inc. (the manufacturer of Barostim Neo)
Conclusions	High risk of bias for all the end points	

2. Publications from other Neo trials (than the Barostim Neo trial)

Trial descriptions:

Trials:

1) Wallbach M, Lehnig LY, Schroer C, Luders S, Bohning E, Muller GA, et al. Effects of baroreflex activation therapy on ambulatory blood pressure in patients with resistant hypertension. Hypertension 2016;67(4):701-709.
Comments: **This is the main trial.** We extract changes in SBP, DBP and proportion of responders between baseline and 6 months data (all both office and ambulatory measurements); changes in heart rate (office) between baseline and 6 months data. Safety over the 6 months from this trial.

The other publications listed below (2-7) are, we believe, substudies of this one:

2) Hickethier T, Halbach M, Madershahian N, Brandt MC, Hoppe UC, Velden R, et al. Chronic baroreflex activation persistently lowers blood pressure in resistant hypertension: Single-center experience with the barostim Neo system. Eur Heart J 2013;34:824.
Comments: We extract data for changes in office SBP and DBP between baseline and 12 months.

3) Wallbach M, Halbach M, Reuter H, Passauer J, Luders S, Bohning E, et al. Baroreflex activation therapy in patients with prior renal denervation. J Hypertens 2016;34(8):1630-1638.
Comments: In this subgroup of patients with prior renal denervation we extract data for changes between baseline and 6 months data for SBP, DBP, responders (all office and ambulatory) and heart rate (office measurements). Safety during the 6 months follow-up. Changes between baseline and 12 months data for ambulatory SBP and DBP, and responders (office and ambulatory measurements).

4) Wallbach M, Lehnig LY, Schroer C, Hasenfuss G, Muller GA, Wachter R, et al. Impact of baroreflex activation therapy on renal function - A pilot study. Am J Nephrol 2014;40(4):371-380.
Comments: In this subgroup of patients with chronic kidney disease we extract data for changes in SBP and DBP (both office and ambulatory measurements), and heart rate (office measurements) between baseline and 6 months.

5) Beige J, Koziolek MJ, Hennig G, Hamza A, Wendt R, Muller GA, et al. Baroreflex activation therapy in patients with end-stage renal failure: Proof of concept. J Hypertens 2015;33(11):2344-2349.

Comments: In this subgroup of patients with chronic kidney disease (CKD stage ≥5) we extract data for changes in SBP and DBP (office and ambulatory), and heart rate (office) between baseline and 12 months data. Safety over 14.5 patient-years.

6) Wallbach M, Lehnig LY, Helms HJ, Schroer C, Muller GA, Wachter R, et al. Long-term effects of baroreflex activation therapy on glucose metabolism. Acta Diabetol 2015;52(5):829-835.

Comments: We do not extract data from this study. These data are included in the main study.

7) Wallbach M, Lehnig LY, Schroer C, Helms HJ, Luders S, Patschan D, et al. Effects of baroreflex activation therapy on arterial stiffness and centersl hemodynamics in patients with resistant hypertension. J Hypertens 2015;33(1):181-186.

Comments: We do not extract data from this study. These data are included in the main study.

Design: Prospective, multicenter (4 centerss) single-arm/ "before and after trial" conducted in Germany. No control group. They used the baseline values as the "before values". The baseline measurements were done pre-implant.
The patients were enrolled from January 2012 to January 2015.

Population:
Wallbach 2016, the main trial: 51 patients with therapy-resistant hypertension, defined as resting systolic blood pressure (SBP)≥140 mm Hg in general or ≥130 mm Hg for patients with chronic kidney disease and proteinuria despite maximal tolerated and optimized therapy with ≥3 antihypertensive medications, including a diuretic. Male and female ≥ above 18 years (mean 57±12 years). Exclusion criteria were pregnancy,untreated secondary cause for hypertension, acute myocardial infarction, unstable angina, stroke, or transitory ischemic attack within the previous 6 months; stenosis of the carotid artery >70%. Main comorbidities were hyperlipoproteinemia (75%), adipositas stage ≥1 (BI≥30 kg/m2) (68 %), history of smoking (63%), microalbuminuria/acroalbuinuria (56%), diabetes mellitus (36%), CKD≥CKD stage 3 (36%)obstructive sleep apnea (32%) and coronary heart disease (27%).
All patients involved in the study were already treated for hypertension for at least 1 year. Baseline medication was unchanged for at least 3 months before implantation of the device. Antihypertensive medication was allowed to be reduced after specific criteria.
Hickethier 2013: 7 patients, one center.
Publications of specific subgroups:
Wallbach 2016: 28 patients from four centers. Male and female above 18 years with resistant hypertension and BP still above national and international target, *despite prior renal denervation* at least 5 months before, polypharmacy strategies as well as life-style interventions and optimal therapy for secondary reasons were included. Main comorbidities were CKD (≥CKD stage 1) (79%), history of smoking (58%) and diabetes mellitus (43%).
Wallbach 2014: 23 patients from one center. Male and female above 18 years with therapy-resistant hypertension and *CKD* (≥64% of the patients had CKD-stage III or above). Present comorbidities at baseline included: history of smoking (74%), hyperlipoproteinemia (78%), coronary heart disease (30%) and diabetes mellitus (30%).
Beige 2015: 7 patients from two centers. Male and female above 18 years with resistant hypertension and *CKD* stage 5D. The patients were treated with BAT if they had resistant hypertension along with SBP 160mm Hg or higher on nondialysis day despite use of at least three antihypertensive drugs including a diuretic, life-style behaviors and optimal therapy for secondary reasons.

Intervention/comparator:
Treatment group: The Barostim *Neo*™ system implanted and initiated 4 weeks after implantation.
Control group: No control group. They used the baseline values as the "before values".

Endpoints:
Efficacy:
Wallbach 2016, the main trial: At 6 months:
Changes in systolic and diastolic BP both with ambulatory and office measures, change in heart rate, proportion of responders and safety. Changes were measured between baseline (before the implant of the device and at 6 months after activating the device).
Hickethier 2013: At 12 months: Changes from baseline in office SBP and DBP. Safety.

Wallbach 2016. Patients with resistant hypertension and *prior renal denervation:* At 6 months: Changes from baseline in SBP, DBP, and proportion of responders (all office and ambulatory measurements); heart rate (office measurements). Safety during the 6 months follow-up. At 12 months: Changes from baseline in ambulatory SBP and DBP, and proportion of responders. *Wallbach 2014.* Patients with resistant hypertension and *chronic kidney disease (CKD stage ≥3):* At 6 months: Changes in SBP and DBP (both office and ambulatory measurements), and heart rate (office). *Beige 2015:* Patients with resistant hypertension and *chronic kidney disease (CKD stage ≥5):* 6 and 12 months: Changes from baseline in SBP and DBP (both office and ambulatory), and heart rate (office). Safety over the 12 months period. Office baseline BP: The average of two readings (3 minute interval), taken pre-implant. 24-hour ambulatory BP: Readings every 15 minutes in daytime and every 30 minutes at nighttime. Ambulatory BP readings were averaged for 24 hours. Responders to BAT were defined as: Patients with SBP reduction of ≥10 mm Hg in office or ≥5 mm Hg in ambulatory BP, or both.
Follow-up: *Wallbach 2016, the main trial:* 6 months. *Hickethier 2013: 12 months* *Wallbach 2016; patients with prior renal denervation:*12 months *Wallbach 2014; CKD patients:* 6 months *Beige 2015; CKD patients:* 6 and 12 months **Drop out:** *Wallbach 2016, the main trial:* Of the 51 patients included, 44 patients completed the 6 months, and were the basis for the analysis. Seven patients were excluded from analyzes because of missing or insufficient follow-up ABPM data (1 patient died because of a pneumonic sepsis and 6 patients refused ambulatory measurements). *Hickethier 2013:* None *Wallbach 2016; patients with prior renal denervation:* Of 28 enrolled patients 5 and 11 patients dropped out of the ambulatory measurents at 6 and 12 months respectively. *Wallbach 2014; CKD patients:* Of 23 enrolled patients, one dropped out from the ambulatory measurents. *Beige 2015; CKD patients:* Of 7 enrolled patients, 1 died because of pneumonia sepsis, this is the same patient as in the main study. 6 patients were included in the analyses. Ambulatory measurents at month 12 were for 5 patients (1 dropped out).
Funding source: From the partcipants departments. Some of the authors have however received grants from CVRx, Inc.

Data extraction:

Endpoints	**Baseline values (average of two measurements)**	**Intervention: Barostim Neo** **Changes:** (mean ± SD) for BP and heart rate
Blood Pressure (mm Hg**)** (mean ±SD) **Ambulatory measurements:** **Systolic BP** 6 months Wallbach 2016 (15) (n=51)	148±17 (n=44)	140±23 (P<0.01) (n=44)

6 months, *patients with prior renal denervation* (35)	162±21 (n=28)	-2±19 (n=23) (P=0.60)
6 months, *patients with CKD* (36)	142.3±16.4 (n=23)	136.0±23.74; Change: -5.7± 15.4 (P=0.08) (n=22)
12 months*, patients with prior renal denervation* (35)	162±21 (n=28)	-14±23 (P=0.02), (n=17)
12 months, patients with CKD (37)	167±30 (n=7)	137±24 (P=0.17) (n=5)
Diastolic BP		
6 months (15)	82±13 (n=44)	77±15 (P<0.01) (n=44)
6 months, *patients with prior renal denervation* (35)	90±17 (n=28)	-1 (SD not given) (P=0.69) (n=23)
6 months, *patients with CKD* (36)	79.6±11.7 (n=23)	74.8±16.4 (P=0.09) (n=22)
12 months, *patients with prior renal denervation* (35)	90±17 (n=28)	-6 (SD not given) (P=0.07) (n=17)
12 months, patients with CKD (37)	94±24 (n=6)	76±19 (P=0.10) (n=5)
Office measurements: Systolic BP		
6 months, Hickethier 2013 (15)	171±24 (n=44)	151±26 (P<0.01) (n=44)
6 months, *patients with prior renal denervation* (35)	182±28 (n=28)	163±27; Change: -18±28 (P<0.01) (n=28)
6 months, *patients with CKD* (36)	161.0±31.9 (n=23)	144.0±32.3 (P<0.01) (n=23)
12 months Hickethier 2013 (32)	183.4±28.3 (n=7)	157.1±55.5 (P=0.12) (n=7)
12 months, *patients with CKD* (37)	194±28 (n=6)	137±16 (P<0.01) (n=6)
Diastolic BP		
6 months (15)	91±18 (n=44)	82±17 (P<0.01) (n=44)
6 months, *patients with prior renal denervation* (35)	96±22 (n=28)	92±25; Change: -5±15 (P=0.11) (n=28)

6 months, *patients with CKD* (36)	87.4±15.2 (n=23)	77.7±17.1 (P<0.01) (n=23)
12 months, Hickethier 2013 (32)	97.4±19.1 (n=7)	84.0±30.5 (P=0.11) (n=7)
12 months, *patients with CKD* (37)	97±19 (n=6)	73±17 (P=0.01) (n=6)
Correlation analyses between BP changes in office measure-ments and ABPM	A significant correlation for systolic (r=0.413; P<0.01) and diastolic (r=0.321; P=0.03) values	
Therapy responders (Propotion of patients (%)). **Office measurents** 6 months (15)	29/44 (66%)	
6 months, *patients with prior renal denervation* (35)	19/28 (68%)	
12 months, *patients with prior renal dener-vation* (35)	20/26 (77%)	
Ambulatory Measurements 6 months (15)	24/44 (55%)	
6 months, *patients with prior renal denervation* (35)	11/23 (48%)	
12 months, *patients with prior renal dener-vation* (35)	11/17 (65%)	
Heart rate *Office measurements* beats/minute (mean ±SD) 6 months (15)	72 ±12 (n=44)	69±11 (n=44) (P=0.10)
6 months, *patients with prior renal denervation* (35)	78 ±18 (n=28)	74±13 (n=28) (P=0.28)
6 months, *patients with CKD* (36)	73.0 ±12.7 (n=23)	68.4±10.8 (P=0.06) (n=23)
12 months, *patients with CKD* (37)	69±11 (n=6)	67±15 (n=6)

Device or procedure-related complications **SAEs** **Major adverse neurological and cardiovascular events (number of events (%))**	
6 months (15)	1 event/44 patients (contralateral stroke (2%)). Event free rate: 98% as major adverse device-and procedure-related .
6 months, *patients with prior renal denervation* (35)	None (n=28)
12 months: Hicketier 2013 (32) (n=7)	During the 12 months of follow-up: 1 SAE, a device pocket haematoma. This resolved completely All major neurological and cardiovascular events and complications resolved completely and explantation of the device was necessary in none of the patients.
Beige 2015, *patients with CKD* (37) (n=7)	None
Device-related complications 6 months (15)	2/44 (5%) (1 patients because movement of the implantable pulse generator, resulting in a need for reposition, another patient, revision surgery was necessary because of a strong tendency to for keloids)
6 months, *patients with prior renal denervation* (35)	None
Death 6 months Wallbach 2016 (15)	1/55 died because of a pneumonic sepsis
Beige 2015 *patients with CKD* (37)	(1/7 died because of a pneumonic sepsis (not procedure related). This is the same patient as reportet in Wallbach 2016.

Risk of Bias:

Wallbach 2016 (15) Full text publication (n=51) reports 6 months data for office and ambulatory SBP and DBP, proportion of responders (office and ambulatory), heart rate and safety. This is the main study.

Entry/Domain	Judgement	Description
Random sequence generation?	High	Not randomized
Allocation concealment?	High	High

Blinding of participants and personnel?	High	No blinding. May have effect on the participants
Blinding of outcome assessments? Blood pressure Heart rate Complications	 Low Low Uncertain	We do not think that BP and heart rate will be influenced by the lack of blinding of the investigators
Incomplete outcome data? Blood pressure Heart rate Complications	 Uncertain Uncertain Uncertain	Seven patients dropped out, i.e. only 44 of 51 patients included in the analyses.
Selective reporting? Blood pressure Heart rate Complications	 Low Uncertain Uncertain	The endpoint BP was pre-specified, and reported on. Pulse rate and safety were not pre-defined.
Other sources of bias?	Low	Several of the authors have received grant from CVRx, Inc. (the manufacturer of Barostim Neo)
Conclusions	High risk of bias for all the end points	

Since we evaluated the main study Wallbach 2016 (Effects of..) to have high risk of bias for all the end points, it follows that this will also be the case for the endpoints in the other included publications (Hickethier 2013 ();Wallbach 2016 (Baroreflex activation..with prior renal); Wallbach 2014 (); Beige 2015 ().

A publications that compare Barostim Rheos and Barostim Neo

Trial description:

Trial: Wachter R, Halbach M, Bakris G, Bisognano J, Haller H, Beige J, et al. [Op.7d.01] Safety and Blood Pressure Effects of Second Versus First-Generation System for Administering Baroreflex Activation Therapy. J Hypertens 2016;34 Suppl 2:e94.
The aim: To compare safety and blood pressure (BP) reductions obtained with first- and second generation systems for administering baroreflex activation therapy (BAT) in patients with resistant hypertension, as well as to verify that BP reductions with active BAT are distinguishable from placebo. *Design:* A comparison of three cohorts: *Second generation*: 30 patients from a single-arm verification study. Name of the study is not given. *First generation, immediate BAT:* A cohort of 30 patients from the randomized Rheos pivotale trial with 12 months of active BAT. *First generation, delayed BAT*: Another 30 patients from the randomized Rheos pivotale trial with 6 months inactive BAT followed by 6 months of active BAT. The first generation cohorts were generated by propensity-matching demographic characteristics to the second generation cohort. The randomization period in the Rheos pivotal trial stops at 6 months.

Population: 90 patients in three cohorts with 30 patients in each. The 30 patients from the second generation study, i.e.Neo, came from an unidentified trial. The two cohorts, with 30 patients each, from the first generation (Rheos) came from the Rheos pivotal trial.
Intervention/comparators: They compare: 6 and 12 months data for: The patients on Neo, the patients on Rheos (immediate BAT) and the patients on delayed BAT (Rheos), i.e. 6 months with inactive BAT (sham control), followed by 6 months with active BAT. The randomization period in the Rheos pivotal trial stops at 6 months.
Endpoints: Over 12 months: Average SBP reduction for second generation patients. Proportion of patients reaching a systolic BP<140 mm Hg. SBP reduction for second generation versus immediate (active) BAT from first generation (Rheos). This is only reported as graphs, no figures, cannot use At 6 months: SBP reduction for second generation versus sham control (delayed BAT from first generation).
Follow- **up: 6 and 12 months**
Funding source: The manufactur (CVRx) is one of the authors.

Data extraction: Wachter 2016 (19)

Endpoints	**First generation: Sham control** (Inactive BAT for first 6 months)	**First generation: Rheos (Immediate (active) BAT)**	**Second generation: Neo** **Changes:** (mean ± SE) for BP
Systolic BP (mm Hg**)** (mean ±SE), Average reduction for second generation patients *through 12 months*			25 ± 3 (p < 0.001)
Additional SBP reduction relative to sham control, *6 months*			20 ± 7 mm Hg (p = 0.008)
Proportion of the second generation patients reaching a systolic BP < 140 mm Hg *through 12 months*			47%
SBP *At 12 months*	Comparable results for first generation, Rheos (Immediate (active) BAT and second generation Neo. No figures given, only a graph.		
Safety	Safety of the second generation system was superior in terms of procedure time, complications and pulse generator lifetime. No more details given		

Risk of Bias: Wachter 2016 (19)

Entry/Domain	**Judgement**	**Description**

Random sequence generation?	High	Not randomized. Compare three cohorts, two of these came from a randomized trial, but in Wachter the patients are no longer randomized
Allocation concealment?	High	High
Blinding of participants and personnel?	High	At least one of the cohorts (second generation) is not blinded. May have effect on the participants
Blinding of outcome assessments? Blood pressure Complications	 Low Uncertain	 We do not think that BP and heart rate will be influenced by the lack of blinding of the investigators
Incomplete outcome data? Blood pressure Complications	 Low Low	Three cohorts with 30 patients each are compared.
Selective reporting? Blood pressure Complications	 Low Uncertain	The endpoint BP was pre-specified and reported on. Safety was pre-specified as such, but lack further details.
Other sources of bias?	Low	Several of the authors have received grant from CVRx (the manufacturer of Barostim Neo)
Conclusions	High risk of bias for all the end points	

Appendix 4. Comparisons of the publications evaluated by the submitter and by us

References	Evaluated by submitter	Evaluated by us	Comments
The Rheos pivotal trial, Bisognano 2011 (24), (NCT00442286), fulltext (n=265)	yes	yes	**Main trial**
Alnima 2013, fulltext (26) (n=322)	no	yes	The submitter gaves this explanation for their exclusion: "BAT therapy effects on renal responses". We choose to include since the publication also reported systolic- and diastolic blood pressure and heart rate at 6 and 12 months.

Bisognano 2011, abstract (27) (n=46)	yes	yes	
de Leeuw 2014, abstract (33) (n=82)	yes	yes	
de Leeuw 2015, abstract (28) (n=322)	yes	yes	
De Leeuw 2015b (71)	yes	no	We have excluded: Not our focus; diagnostic methods.
Bakris 2010 (72)	yes	no	We did not extract data from this, since these data are included in Alnima 2013.
The DEBuT-HT, Scheffers 2010, fulltext (14) (n=45)	yes	yes	**Main trial**
Kroon 2010, abstract (29) (n=18)	no	yes	The submitter gaves this explanation for their exclusion: "There is a high risk of reporting outcomes for the same patient group as in the study of Scheffers 2009, which was included into the review".
Bisognano 2011, abstract (30) (n=34)	yes	yes	
Bisognano 2009, abstract (34) (n=21)	no	yes	The submitter has not listed this trial as either included nor excluded. This is a subgroup analysis of the patients from the DEBuT-HT. The subgroup is patients with resistant hyoertension and symptomatic heart failure.
Bisognano 2006 (47)	yes	no	We found this from manual search in one of the reviews. We have excluded this, since this is interim results from the DEBuT-HT. If we had included, we would have included 10 of the same patients as in the DEBuT-HT.
Study of pooled results from DEBuT-HT, unpublished	yes	no	unpublished
Scheffers 2009 (73)	yes	no	This report 3-years data, we used Kroon 2010 with 4 years data

The Barostim Neo Trial, Hoppe 2012, fulltext (25) (n=30)	yes	yes	**Main trial**
Brandt 2012, abstract (31) (n=30)	no	yes	The submitter gaves this explanation for their exclusion:" There is a high risk of reporting outcomes for the same patient group as in the study of Hoppe 2012, which was included in the review". We included since we extracted data for diastolic blood pressure at three months from this trial (as we did not have from Hoppe 2012).
Wallbach 2015 (38)	yes	no	We use the 2016, that included data from the 2015
Wallbach 2016, fulltext (15) (n=51)	no	yes	**Main trial** The submitter has not listed this trial as either included nor excluded. (They use Wallbach 2015 see above)
Hickethier 2013, abstract (32) (n=7)	No	yes	The submitter gaves this explanation for their exclusion:" There is a high risk of reporting outcomes for the same patient group as in the study of Halbach 2015 , which was included into the review". We have exluded Halbach 2015 since the objectives of the study were acute changes in SBP and DBP after deactivation and reactivation of the BAT device (Neo).
Wallbach 2016, fulltext (35) (n=28)	no	yes	The submitter has not listed this trial as either included nor excluded. This is a subgroup analysis of the patients from the Wallbach 2016 main trial.The subgroup is patients

			with prior renal denervation.
Wallbach 2014, fulltext (36) (n=23)	no	yes	The submitter gaves this explanation for their exclusion:" BAT therapy effect on renal responses". We included and extracted data for changes in systolic- and diastolic blood pressure (both office and ambulatory, heart rate (office) at 6 months. Safety up to 6 months. 12 months data for changes in ambulatory systolic- and diastolic blood pressure.
Beige 2015, fulltext (37) (n=7)	yes	yes	
Halbach 2015 (74)	yes	no	We exclude, acute tests
Comparison of Rheos vs Neo			
Wachter 2015, unpublished	yes	no	We have not evaluated, since unpublished
Wachter 2016 (19)	no	yes	The submitter evaluated the unpublished results from 2015

Appendix 5. Ongoing trial of possible interest

From ClinTrials.gov

Recruitment status/last verified	Main ID	Public title	Date of registration	Comments
Not yet recruiting, no results available/August 2016	NCT02880631	BAROSTIM THERAPY™ In Resistant Hypertension	August 15, 2016	
Active, not recruiting, no results available/September 2016	NCT01679132	CVRx Barostim Hypertension Pivotal Trial	August 31, 21012	This is the planned RCT with Neo.
Active, not recruiting, no results	NCT01471834	Barostim Neo System in the Treatment of Resistant Hypertension	November 9, 2011	According to the submission, this is published, Hoppe et al

available/December 2015				2012. We have included this.
Recruiting, no results available/August 2015	NCT02364310	Economic Evaluation of Baroreceptor STIMulation for the Treatment of Resistant HyperTensioN	February 2, 2015	
Recruiting, no results available/August 2016	NCT02572024	The Effect of Baroreflex Activation Therapy (BAT) on Blood Pressure and Sympathetic Function in Patients With Resistant Hypertension (The Nordic BAT Study)	October 7, 2015	
Recruiting, no results available/August 2014	NCT02210923	Effect Baroreflex Activation Therapy on the Carotid Body	August 4, 2014	
Completed, no results available/October 2011	NCT 00710294	Device Based Therapy in Hypertension Extension Trial	July 2, 2008	
Recruiting, no results available/September 2013	NCT01355510	Effects of Electrical Baroreflex Stimulation on Sympathetic Activity, Renal Hemodynamics, and Insulin Sensitivity	May 16, 2011	
Completed/ no results available/September 2016	NCT01077180	Rheos Feasibility Trial	February 25, 2010	
Completed/ no results available/October 2011	NCT 00710190	Device Based Therapy in Hypertension Trial	July 1, 2008	
Completed/ no results available/July 2016	NCT00442286	Rheos® Pivotal Trial	February 27, 2007	Same NCT number as the included RCT. We have asked the submitter for information, they answer: "The study was formally closed when the FDA gave HDE approval for us to commercially sell the second generation BAROSTIM NEO (Legacy) devices to

				replace the batteries of those patients who were enrolled in this trial. The 6 year results that are currently under review for publication, the abstract of de Leeuw 2015 will most likely be the final publication on this dataset". This is de Leeuw 2015, 6 years follow-up from the Rheos pivotal trial.

From WHO ICTRP: No additional trials identified (in addition to these already identified in ClinTrials.gov).

Appendix 6 The evidence presented by the measurements methods for blood pressure

Endpoints, mean (SD) or mean (SE), publication	**Pre-implant Baseline mean (SD)**	**Post-implant Baseline mean (SD)**	6 months, mean (SD) or mean difference (SE)	1 year mean (SD) or mean difference (SE)	2 years mean difference (SE)
SBP					
Rheos					
Pivotal					
Office, Group A Bisognano 2011 (24)		n=181 169±26	-16±SD29	-25±SD32	
Office, Group B Bisognano 2011		n=84 168±24	-9±SD29	-25±SD31	
mean difference Group A and B			*7 (95% CI: -0.50 to 14.50)*		
Office, Group A Bisognano 2011	n=181 pre-implant*		-26±SD30	-35±SD28	
Office, Group B Bisognano 2011	n=84 pre-implant*		-17±SD29	-33±SD30	
mean difference Group A and B			*9 (95% CI: 1.41 to 16.49)*		

Office, Single-arm de Leeuw 2015 (28)	n=322 178.1±22.6			n=294 -34.3±1.7	n=255 -31.9±2.0
DEBUt-HT					
Office Scheffers 2010 (14)		n=45 179±29 n=26 180±31 n=17 188 ±132		n=26 -30±6	n=17 -33±8
Ambulatory Scheffers 2010				n=15 -13±3	n=8 -24±8
Neo					
STUDY 1					
Office Hoppe 2012 (25)	n=30 171.7±20.2		n=30 -26.0±4.4 (P<0.001)		
STUDY 2					
Office Wallbach 2016 (15)	n=44 171±24		n=44 151±SD26		
Ambulatory Wallbach 2016	n=44 148±17		n=44 140±SD23		
DBP					
Rheos					
Pivotal					
Office, Group 1 Alnima 2013 (26)		n=236 100±18	n=236 90±SD18	n=236 87±SD18	
Office, Group 2 Alnima 2013		n=86 100±14	n=86 95±SD15	n=86 87±SD15	
Office, single-arm de Leeuw 2015 (28)	n=322 103.1±15.4			n=294 -15.5±1.0	n=255 -15.2±1.1
DEBUt-HT					
Office Scheffers 2010 (14)		n=45 105±22 n=26 108±24 n=17 114±23		n=26 -20±4	n=17 -22±6
Ambulatory Scheffers 2010				n=15 -8± 2	n=8 -13±5
Neo					
STUDY 1					

Hoppe 2012 (25)	n=30 99.5 ±13.9				
STUDY 2					
Office Wallbach 2016 (15)	91±18 (n=44)		82±SD17 (P<0.01) (n=44)		
Ambulatory Wallbach 2016	82±13 (n=44)		77±SD15 (P<0.01) (n=44)		
HEART RATE					
Rheos Pivotal					
Pivotal					
Office, Group 1 Alnima 2013 (26)		n=236 79±14	n=236 72±SD14	n=236 71±SD14	
Office, Group 2 Alnima 2013		n=86 79±17	n=86 75±SD15	n=86 72±SD15	
DEBUt-HT					
Office Scheffers 2010 (14)		n=45 80±13 n=26 80±15 n=17 81±11		n=26 -8±2	n=17 -11±4
Ambulatory Scheffers 2010				n=15 -6±2	n=8 -11±34
Neo					
STUDY 1					
Office Hoppe 2012 (25)	n=30 75.0 ±12.1		n=30 - 5.0±2.6 (p=0.07)		
STUDY 2					
Office Wallbach 2016 (15)	72 ±12 (n=44)		69±SD11 (n=44)		
Ambulatory Wallbach 2016					
Left ventricular mass index (g/m²)					
Rheos					
Pivotal					
de Leeuw 2014	n=82 127.6±41.1			n=82 -13.5±6.6	

Heart failure (33)					
DEBUt-HT					
Bisognano 2011 (30)	n=34 138.9±6.0		3 mnd, n=34 -18.0±2.7)	n=21 -24.6±3.9	
NEO					
not reported					

Appendix 7 Summary of Finding Tables from trials without a control group

Office and ambulatory systolic blood pressure (SBP) after Barostimulation in trials without control groups

Patient or population: Patients with drug-resistant hypertension
Intervention: Barostim activated
Comparison: no comparison/use baseline as "before value"

Outcomes	**Anticipated absolute effects** mean ± SD/SE or mean difference SD/SE	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
Rheos				
SBP office, 1 year, Pivotal and DEBuT-HT (28), (14)	The decrease in *office* SBP was between -34.3 ±1.7 and -30 ±6 mm Hg	n=294 +26 (2 single-arm trials)	⨁◯◯◯ VERY LOW [a] [b]	Abstract: n=294, Fulltext n=26
SBP *ambulatory*, 1 year from Pre-implant, DEBuT-HT (14)	The decrease in *ambulatory* SBP was -13± SE 3 mm Hg	n=26 (1 singel arm trial)	⨁◯◯◯ VERY LOW [a] [c]	Fulltext n=26
SBP *office*, 2 years from Pre-implant, Pivotal and DEBuT-HT (28), (14)	The decrease in *office* SBP was between -31.9±SE 2 and -33± SE 8 mm Hg	n=255+17 (2 single-arm trials)	⨁◯◯◯ VERY LOW [a] [b]	Abstract, n=255, Fulltext:, n=17
SBP *ambulatory*, 2 years. from Pre-implant, DEBuT-HT (14)	The decrease in *ambulatory* SBP was -24 ±SE 8 mm Hg	n=8 (1 single-arm trial)	⨁◯◯◯ VERY LOW [a] [c]	Fulltext: n=8
SBP *office*, 6 years from Pre-implant, Pivotal (28)	The decrease in *office* SBP was -33 ±SE 5.6 mm Hg	n=34 (1 single-arm trial)	⨁◯◯◯ VERY LOW [a] [b c]	Abstract
Neo				
SBP *office*, 6 months from Pre-implant (25), (15)	The decrease in *office* SBP was -26±4,4 mm Hg (Hoppe 2012) or from 171 ±SD24 to 151 ± SD26 mm Hg (Wallbach)	n=30+44 (2 sinlge arm trials)	⨁◯◯◯ VERY LOW [a] [c]	Fulltext= n=30 and 44
SBP *ambulatory*, 6 months from Pre-implant (15)	The decrease in *ambulatory* SBP was from 148 ±SD17 to 140 ±23 mm Hg	n=44 (1 single-arm trial)	⨁◯◯◯ VERY LOW [a] [c]	Fulltext
Observational studies start at Low quality				

Office and ambulatory systolic blood pressure (SBP) after Barostimulation in trials without control groups

Patient or population: Patients with drug-resistant hypertension
Intervention: Barostim activated
Comparison: no comparison/use baseline as "before value"

Outcomes	**Anticipated absolute effects** mean ± SD/SE or mean difference SD/SE	№ of participants (studies)	Quality of the evidence (GRADE)	Comments

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. high risk of bias, office BP and not ambulatory BP
b. publication type: abstract
c. few patients
d.

We evaluated that also the quality of the evidence from all the other endpoints from the single- arm trials will be very low

Safety for the total population in the Rheos pivotal trial

Patient or population: Patients with drug-resistant hypertension
Intervention: Barostim activated
Comparison:Pre-specified objective performance criteria based on similar implantable devices

Outcomes	**Compare total population in Rheos pivotal with results from similar implanted devices**	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
Rheos				
Safety Rheos pivotal trial (24), 1 year	The Rheos system had an event-free rate of serious adverse events, compared to pre-specified objective performance criteria based on similar implantable devices, that was comparable (p=1.00) for procedural safety, and higher (p<0.001) for device- related safety.	n=265 (as single-arm)	⊕⊕◯◯ LOW	Fulltext n=265

Observational studies start at Low quality

Safety for the total population in the Rheos pivotal trial				
Patient or population: Patients with drug-resistant hypertension **Intervention**: Barostim activated **Comparison**:Pre-specified objective performance criteria based on similar implantable devices				
Outcomes	**Compare total population in Rheos pivotal with results from similar implanted devices**	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
GRADE Working Group grades of evidence **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect				

Appendix 8. The evidence presented by endpoints

The evidence for systolic blood pressure (SBP)

Trial/Type of BAT system	**Control or Baseline mean (SD)**	3 months Δ mean (SE)	6 months Δ mean (SE)	1 year Δ mean (SE)	2 years Δ mean (SE)	3 years Δ mean (SE)	4 years Δ mean (SE)	5 years Δ mean (SE)	6 years Δ mean (SE)
Rheos **The Rheos pivotal RCT** (24) office measurements *Post-implant baseline* *Pre-implant baseline*	n=181 9±29 17±29	Not reported	n=84 16±29 26±30*	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Alnima 2013 (26) controlled, non-randomized, office measurements, post-implant baseline	Group 1: n=236 Group 2: n=86 Group 1: 169 ±27 Group 2: 168±24	Not reported	151±31* 160±26	143±29 143±28	Not reported	Not reported	Not reported	Not reported	Not reported
de Leeuw 2015 (28) most probably office, propably pre-implant	n=322 178.1±22.6	Not reported	Not reported	n=294 -34.3 ±1.7*	n=255 -31.9 ±2.0*	n=238 -34.3 ±2.2*	n=214 -31.6 ±2.1*	n=114 -37.6 ±2.8*	n=34 -33.0 ±5.6*
de Leeuw 2014 (33) *heart failure*, most probably office,	n=82 178.9 ±24.6	Not reported	Not reported	n=82 -36.1 ±2.9*	n=61 -30.7±4.4*	n=67 -37.3 ±4.2*	n=53 -36.8 ±4.6*	n=9 -30.3 ±5.4*	Not reported

propably pre-implant									
The DE-BuT-HT (14) post-implant baseline *Office* *Ambulatory*	n=45 179 ±29 Not re-ported	n=37 -21 ± 4* n=26 -6 ±3	Not reported	n=26 -30 ±6* n=15 -13 ±3*	n=17 -33± 8* n=8 -24±8*	Not re-ported	Not re-ported	Not re-ported	Not re-ported
Kroon 2010 (29)do not tell if office or ambula-tory, pre-im-plant base-line	n=18, 193 (36)		Not reported	n=18 -38 (7)*	n=18 -36 (7)*	n=18 -40 (9)*	n=18 -53 (9)*	Not re-ported	Not re-ported
Bisognano 2009 (34) *heart failure,* office, time for baseline not reported	n=21 165 (27)	n=21 -16 (19)*	Not reported	n=21 -15 (SD±29)*	Not re-ported	Not re-ported	Not re-ported	Not re-ported	Not re-ported
<u>Neo</u> **The Barostim Neo trial** (25) office, pre-implant baseline	n=30 171.7±20.2	n=30 -26.1±3.3*	n=30 -26.0±4.4*	Not re-ported	Not re-ported	Not re-ported	Not re-ported	Not re-ported	Not re-ported
Wallbach 2016 **(15)**, pre-implant baseline, n=51 *Office* *Ambulatory*	n=44 171±24 n=44 148±17	Not re-ported	n=44 151±26* n=44 140±23*	Not re-ported	Not re-ported	Not re-ported	Not re-ported	Not re-ported	Not re-ported
Hickethier 2013 (32),pre-implant, *office*	n=7 183.4±28.3	Not re-ported	Not reported	n=7 157.1±55.5	Not re-ported	Not re-ported	Not re-ported	Not re-ported	Not re-ported
Wallbach 2016 (35) *Prior renal denervation,* pre-implant baseline *Office* *Ambulatory*	n=28 182±28 n=28 162±21	Not re-ported	n=28 163±27; Change: -18±28* n=23 -2±19	Not re-ported n=17 -14 ±23*	Not re-ported	Not re-ported	Not re-ported	Not re-ported	Not re-ported
Wallbach 2014 (36) *Chronic*		Not re-ported		Not re-ported	Not re-ported	Not re-ported	Not re-ported	Not re-ported	Not re-ported

kidney disease, pre-implant baseline *Office* *Ambulatory*	n=23 161.0±31.9 n=23 142.3±16.4		n=23 144.0±32.3* n=22 136.0±23.74; Change: -5.7 ± 15.4						
Beige 2015 (37) *Chronic kidney disease* pre-implant baseline *Office* *Ambulatory*	n=6 194±28 n=7 167±30	Not reported	Not reported	n=6 137±16* n=5 137±24	Not reported	Not reported	Not reported	Not reported	Not reported

*p<0.05

The evidence for diastolic blood pressure (DBP)

Trial/Type of BAT system	**Baseline** (not specified if pre- or post-implant) **mean (SD)**	3 months Δ mean (SE)	6 months Δ mean (SE)	1 year Δ mean (SE)	2 years Δ mean (SE)	3 years Δ mean (SE)	4 years Δ mean (SE)	5 years Δ mean (SE)	6 years Δ mean (SE)
Rheos: Alnima 2013 (26), controlled, non-randomized, office measurements, post-implant baseline	Group 1: n=236 Group 2: n=86 Group 1: 100 ±18 Group 2: 100±14	Not reported	90±18* 95±18	87±18 87±15	Not reported	Not reported	Not reported	Not reported	Not reported
de Leeuw 2015 (28), most probably office, propably pre-implant	n=322 103.1±15.4	Not reported	Not reported	n=294 -15.5 ±1.0*	n=255 -15.2 ±1.1*	n=238 -17 ±1.2*	n=214 -15.9 ±1.2*	n=114 -20.1 ±1.6*	n=34 -15.1 ±3.1*
de Leeuw 2014 (33) *heart failure,* most probably office, propably pre-implant	n=82 99.7 ±17.0	Not reported	Not reported	n=82 -16.3 ± 1.7*	n=61 -14.2 ±1.9*	n=67 -18.3 ±2.3*	n=53 -17.7 ±2.4*	n=9 -13.3 ±3.8*	
The DEBuT-HT (14), post-implant baseline Office Ambulatory	 n=45 105 ±22 Not reported	 n=37 -12 ± 2* n=26 -4 ±2*	Not reported	 n=26 -20 ±4* n=15 -8±2*	 n=17 -22±6* n=8 -13±5*	Not reported	Not reported	Not reported	Not reported

Kroon 2010 (29), do not tell if office or ambulatory, pre-implant baseline	n=18, 111 (20)	Not reported	Not reported	n=18, -22 (4)*	n=18, -18 (5)*	n=18, -21 (6)*	n=18, -30 (6)*	Not reported	Not reported
Bisognano 2009 (34) *heart failure*, office, time for baseline not reported	n=21 99 (22)	n=21 -10 (12)*	Not reported	n=21 -11 (19)*	Not reported	Not reported	Not reported	Not reported	Not reported
Neo Brandt 2012 *(31)*, office, pre-implant baseline	n=30 99.5 ±13.6	n=30 -12.5 ±2.1*	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Wallach 2016 (15), pre-implant baseline *Office* *Ambulatory*	n=44 91±18 n=44 82±13	Not reported	n=44 82±17* n=44 77±15*	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Hickethier 2013 (32), pre-implant (n=7) *Office*	n=7 97.4±19.1	Not reported	Not reported	n=7 84.0±30.5	Not reported	Not reported	Not reported	Not reported	Not reported
Wallbach 2016 (35) *Prior renal denervation*, pre-implant baseline, *Office* *Ambulatory*	n=28 96±22 n=28 90±17	Not reported	n=28 92±25; Change: -5±15 n=23 -1 (SD not given)	n=17 -6 (SD not given)	Not reported	Not reported	Not reported	Not reported	Not reported
Wallbach 2014 (36) *Chronic kidney disease,* pre-implant baseline, *Office* *Ambulatory*	n=23 87.4±15.2 n=23 79.6±11.7	Not reported	n=23 77.7±17.1* n=22 74.8±16.4	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Beige 2015 (37) *Chronic kidney disease,* pre-implant baseline, *Office*	n=6 97±19	Not reported	Not reported	n=6 73±17*	Not reported	Not reported	Not reported	Not reported	Not reported

Ambulatory	n=6 94±24			n=5 76±19					

*p<0.05

The evidence for responders

Trial/Type of BAT system	**Baseline** (not specified if pre- or post-implant) **mean (SD)**	3 months Δ mean (SE)	6 months Δ mean (SE)	1 year Δ mean (SE)	2 years Δ mean (SE)	3 years Δ mean (SE)	4 years Δ mean (SE)	5 years Δ mean (SE)	6 years Δ mean (SE)
Rheos **The Rheos pivotal RCT** (24),Proportion of patients that achieve at least a 10 mm Hg drop in SBP at month 6 compared with month 0, *with post-implant baseline, Office*	Group B: n=84 46%	Not reported	Group A: n=181 54%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Neo **The Barostim Neo trial** (25), office, pre-implant baseline. The percentage of patients achieving systolic BP≤140 mm Hg	n=30 0%	Not reported	n=30 +43%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Wallach 2016 (15), pre-implant baseline: The percentage of patients achieving reduction in ambulatory SBP≥5 mm Hg; or reduction in office SBP≥10 mm Hg. *Office* *Ambulatory*		Not reported	29/44 (66%) 29/44 (55%)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Wallbach 2016 (35) *Prior renal denervation*, pre-implant baseline, *Office*		Not reported	19/28 (68%)	20/26 (77%)	Not reported	Not reported	Not reported	Not reported	Not reported

Ambulatory			11/23 (48%)	11/17 (65%)					

*p<0.05

The evidence for heart rate

Trial/Type of BAT system	**Baseline** (not specified if pre-or post-implant) **mean (SD)**	3 months Δ mean (SE)	6 months Δ mean (SE)	1 year Δ mean (SE)	2 years Δ mean (SE)	3 years Δ mean (SE)	4 years Δ mean (SE)	5 years Δ mean (SE)	6 years Δ mean (SE)
Rheos Alnima 2013 (26), controlled, non-randomized, office measurements, post-implant baseline	Group 1: n=236 Group 2: n=86 Group 1: 79±14 Group 2: 79±17	Not reported	72±14 75±15	71±14 72±15	Not reported	Not reported	Not reported	Not reported	Not reported
The DEBuT-HT (14), post-implant baseline *Office* *Ambulatory*	n=45 80 ±13 Not reported	n=37 -8 ± 2* n=26 -5 ±2*	Not reported	n=26 -8±2* n=15 -6±2*	n=17 -11±4* n=8 -11±34*	Not reported	Not reported	Not reported	Not reported
Kroon 2010 (29), do not tell if office or ambulatory, pre-implant baseline	n=18, 74 (13)	Not reported	Not reported	n=18, -4 (2)	n=18, -5 (3)	n=18, -1 (3)	n=18, -5 (2)*	Not reported	Not reported
Neo **The Barostim Neo trial** (25), office, pre-implant baseline	n=30 75.0 ±12.1	Not reported	n=30 - 5.0 ±2.6	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Wallach 2016 (15), pre-implant baseline, *Office*	n=44 72 ±12	Not reported	n=44 69±11	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Wallbach 2016 (35) *Prior renal denervation,* pre-implant baseline, *Office*	n=28 78 ±18	Not reported	n=28 74±13	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Wallbach 2014 (36) *Chronic kidney disease*, pre-implant baseline, *Office*	n=23 73.0 ±12.7	Not reported	n=23 68.4±10.8	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Beige 2015 *(37) Chronic kidney disease*, (n=7) pre-implant baseline, *Office*	n=6 69±11	Not reported	Not reported	n=6 67±15	Not reported	Not reported	Not reported	Not reported	Not reported

*p<0.05

The evidence for left ventricular mass index (LVMI)

Trial/Type of BAT system	**Baseline** (not specified if pre- or post-implant) **mean (SD)**	3 months Δ mean (SE)	6 months Δ mean (SE)	1 year Δ mean (SE)	2 years Δ mean (SE)	3 years Δ mean (SE)	4 years Δ mean (SE)	5 years Δ mean (SE)	6 years Δ mean (SE)
Rheos Bisognano 2011 (24), single-arm, office measurements time for baseline not reported.	n=46 117.7 ±4.3	n=46 -17.8 ±3.0*	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
de Leeuw 2014 (33) *heart failure,* most probably office, propably pre-implant	n=14 127.6 ±41.1	n=14 -13.5 ±6.6	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
2 substudies to the DEBuT-HT: Bisognano 2011 (30), office, time for baseline not reported	n=34 138.9 (6.0)	n=34 -18.0 (2.7)*	Not reported	n=21 -24.6 (3.9)*	Not reported	Not reported	Not reported	Not reported	Not reported
Bisognano 2009 (34) heart failure, office, time for baseline not reported	n=9 121.4 (19.8) Basline time: not reported	n=9 -9.8 (11.8)*	Not reported	n=9 -22.2 (21.7)*	Not reported	Not reported	Not reported	Not reported	Not reported

*p<0.05

The evidence for serious adverse events (SAEs)

Type of SAEs	**Evidence from the Rheos publications**	**Evidence from the Neo publications**
Serious procedure-or system-related event–free rate (%)	*Bisognano 2011* (24): 74.8%, as compared to a pre-specified objective performance criteria of 82% based on historical literature on implantable cardioverter-defibrillators and pacemakers. P=1.00	*Hoppe 2012* (25): 90%, during the 30 days post surgery. *Wallbach 2016* (15): 98% as procedure -and device related major adverse events free rate.
Number (%) of serious procedure-or system-related events	*Bisognano 2011* (24): 68 (25.5%) (13 surgical complications, 13 nerve injury with residual deficit, 12 transient nerve	*Hoppe 2012* (25): During the 30 days after surgery: 3 complications: Device pocket hematoma, self-inflicted wound

	injury, 7 respiratory complications, 7 wound complications). Scheffers (14): n=7/42 (3 had the device explanted before activation due to infection, 3 perioperative stroke, tongue paresis most likely due to intraoperative injury, and moderat pulmonary edema, 1 fatal).	complication and internittent pain lateral of device system. All the complications were procedure–related, none were system-related. All recovered, with no residual effects. Wallbach 2016 (15):1 event/44 (contralateral stroke (2%)). *Hickethier 2013* (32): During the 12 months of follow-up: 1 SAE, a device pocket haematoma. This resolved completely. All major neurological and cardiovas-cular events and complications re-solved completely and explantation of the device was necessary in none of the patients.
Device, event–free rate (%), between month 0 and month 12	*Bisognano 2011* (24): 87.2%, as compared to a pre-specified objective performance criteria of 72% based on similar implantable devices such as defibrillators and resynchronization devices. p<0.001.	*Hoppe 2012* (25): Long-term (180 days): 97%
Number (%) of serious device-related and major hypertension-related AEs , between month 0 and month 12	*Bisognano 2011* (24): 34 (12.8%). Scheffers 2010 (14): n=1/42 (Movement of the implantable pulse generator, resulting in the need for further surgery to reposition the implantable pulse generator, which resolved the prob-lem).	*Wallbach 2016* (15): During 6 months: 2/44 (5%) (1 patients because movement of the implantable pulse generator, resulting in a need for reposition, another patient, revision surgery was necessary because of a strong tendency to for keloids).
Deaths	*Bisognano 2011* (24): During 12 months: 4, none were related to ei-therthe procedure or the device. *De Leeuw 2015* (28): 28 deaths (6 years). *Scheffers 2010* (14): 1 death	*Hoppe 2012* (25): None *Wallbach 2016* (15):1/55 died because of a pneumonic sepsis

Appendix 9 – The submitted sources of the incidence of the negative events in the cost-effectiveness model

Adverse event	Findings and sources
Fatal cardio-vascular events	Fatal cardiovascular events were determined by the SCORE project data (75;76). Data were modelled for low-risk popula-tions (77).

Normal mortality	Normal mortality was estimated using Norwegian life tables for 2012 by subtracting mortality for cardiovascular conditions (50). Age- and gender-specific proportions of cardiovascular mortality in overall mortality were obtained from the Norwegian causes of death statistics using following ICD code: I00-I99 (Diseases of the circulatory system) (50). Cardiovascular mortality was substracted, as it was determined indepenently, using Framingham erquations (50).
End stage renal disease and renal replacement therapy	End stage renal disease secondary to systolic blood pressure was determined using data from a large cohort study (78). Time- and age-dependent mortality risks were used for end-stage renal disease (79). Time-dependent mortality risk was used for post-transplant health states (80).
Stroke*	Stroke data were sourced from the regional stroke register from Innhered, Norway (81;82). Both age- and gender-specific incidence of stroke were sourced. The proportion of non-fatal strokes among males and females was informed by Wolf et al. 1992 (83). The relative risk of dying after stroke compared to healthy subjects is based on the probability of death in van Wijk et al. 2005 (84). Relative risk of death from stroke being on dialysis was derived from Seliger et al. 2003 (85). Probability of stroke shortly after myocardial infarction and during 6 months onwards was based on data from recognized international GRACE registry (86). Monthly probabilities of stroke after heart failure were taken from the relevant meta-analysis (87). Probability of recurrent stroke was obtained from the results of the Prevention Regimen for Effectively Avoiding Second Strokes (PROGRESS) trial (88). Probabilities of acute mortality for recurrent stroke were also obtained from the literature (89).
Myocardial infarction*	The relative risk of mortality in the post-MI state was informed by the results of 16-year follow-up of the Primary Prevention Study (Goteborg, Sweden) (90). The relative risk of recurrent myocardial infarction was based on the substudy DANAMI-2 (91). Probabilities of acute mortality for recurrent myocardial infarction were also obtained from DANAMI-2 trial (92).

Heart Failure*	The relative risk of death in patients with heart failure was informed by the Prevention of Heart Failure in Patients in the Heart Outcomes Prevention Evaluation (HOPE) Study (93). The probability of heart failure after myocardial infarction was taken from retrospective study of Velagaleti et al. 2008 (94).
Hypertension crisis	Probability of a hypertension crisis was guided by the Rheos RCT (24). This risk was assumed constant over lifetime horizon. Hypertension crisis was not implemented as a health state in the model, and was only used for costing purposes.

**The risks of a non-fatal cardiovascular event (myocardial infarction, stroke, transient ischemic attack and heart failure) were based on Framingham equations (44;95-97)*

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