Baroreceptor activation therapy for treatment-resistant hypertension

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

Decision Support Document No. 113
ISSN online: 1998-0469

Baroreceptor activation therapy for treatment-resistant hypertension

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, March 2018

Project Team

Project leader: Dr.in med. Katharina Hawlik, MSc

Authors: 1. Dr.in med. Katharina Hawlik, MSc
2. Dr. phil. Roman Winkler, MSc

Project Support

Systematic literature search: Tarquin Mittermayr, BA, MA

Internal Review: Dr.in rer. soc.oec. Ingrid Zechmeister-Koss

External Review: Priv.-Doz. OA. Dr. Thomas Weber, Präsident Österr. Gesellschaft für Hypertensiologie, Kardiologische Abteilung, Klinikum Wels – Grieskirchen

Correspondence

Katharina Hawlik, Katharina.hawlik@hta.lbg.ac.at

This report should be referenced as follows:

Hawlik K, Winkler R, Baroreceptor-activation therapy for treatment-resistant hypertension. Decision Support Document No. 113; 2018. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the LBI-HTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the LBI-HTA.

The HTA Core Model®, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. The following version of the Model was used: [HTA Core Model Version 4.2]. Use of the HTA Core Model does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

CONTENT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Wien
http://hta.lbg.ac.at/page/imprint

Responsible for content:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at"

Decision Support Document No.: 113

ISSN-online: 1998-0469

Content

List of Figures

List of tables

List of abbreviations

AE ..... adverse event
AHA ..... American Heart Association
AMBP ..... ambulatory blood pressure measurement
BAT ..... Baroreceptor activation therapy
BD ..... Blutdruck
BP ..... blood pressure
Chir ..... chirurgisch
CKD ..... chronic kidney disease
DBP ..... diastolic blood pressure
ESH ..... European Society of Hypertension
ESC ..... European Society of Cardiology
HF ..... heart failure
IPG ..... implantable pulse generator
ITT ..... intension to treat
IV ..... Intervention
KG ..... Kontrollgruppe
mmHG ..... millimetre of mercury, manometric unit of pressure
NW ..... Nebenwirkungen
RCT ..... randomised controlled trial
RDN ..... renal denervation
RoB ..... Risk of bias
SAE ..... serious adverse event
SBP ..... systolic blood pressure
SR ..... systematic review
TRH ..... treatment-resistant hypertension
US ..... Ultraschall

Executive Summary

Introduction

Health Problem

Treatment-resistant hypertension (TRH) is defined as blood pressure (BP) that remains above goal despite adhering to the maximally tolerated doses of three antihypertensive drugs with complementary mechanism of action, and including one diuretic agent. Hypertension, especially if not controlled, is a leading cause of cardiovascular and renal diseases and it increases the risk for stroke, coronary artery disease, arrhythmias, and heart-, and renal failure. Hypertension is usually asymptomatic, and treatment adherence is one major obstacle to the successful control of BP.

TRH: BP above 140/90mmHg despite 3 or more anti-hypertensive medicines

Other causes for uncontrolled hypertension need to be ruled out, in order to correctly diagnose a patient with TRH. The most common underlying reasons for uncontrolled hypertension are poor adherence to anti-hypertensive treatment, inaccurate or suboptimal therapy or BP measurements, and pseudo-elevated BP due to white-coat effect. Furthermore, secondary causes of hypertension, such as primary aldosteronism and renal artery stenosis, should be considered. The adequate diagnostic approach includes 24-hours ambulatory blood pressure measurements (AMBP) to rule out white-coat hypertension. First-line therapy of TRH includes lifestyle modifications, such as diet and exercise and a combination of anti-hypertensive medicines, such as an ACE-inhibitor, a calcium channel blocker and a diuretic.

other causes for uncontrolled hypertension need to be excluded: Pseudo-resistant hypertension, secondary hypertension, white-coat hypertension

The actual prevalence of TRH is unknown and controversially discussed. A wide variability exists in the reported prevalence ranging from 2% to 30% of hypertensive patients [3], depending on the population examined [4]. In a recent Austrian cross-sectional multicentre study on 4,303 patients with hypertension, BP remained uncontrolled in more than 50% of patients (defined as <140/90 mmHg office BP).

unknown prevalence : ranging from 2%-30% of patients with diagnosed hypertension

Description of technology

Baroreceptor activation therapy (BAT) is a treatment option proposed for patients with TRH. The BAT aims to reduce BP by electrically stimulating the carotid baroreflex, which acts on the sympathetic and parasympathetic nervous system. The Barostim neo™, a second-generation device for BAT, is currently the only available CE-marketed device that activates the baroreceptor reflex by electric impulses. The first generation device Rheos® system is not marketed anymore and has been entirely replaced by the second generation.

BAT: reduction of BP by electric stimulation of baroreceptors

2 devices: Barostim neo™ and Rheos® system, the latter not marketed anymore

The two generations of devices feature major differences: the Barostim neo™ consists of a smaller electrode, and a smaller pulse generator with a longer battery life, the electrode is placed unilaterally on only one carotid sinus, and thus the surgical procedure is simpler and shorter, requiring less recovery time. Due to these substantial differences, pooling of efficacy and safety data of both devices would not be sensible.

major differences between the 2 generation-devices

Other technologies exist targeting the baroreceptors (MobiusHD®) or the sympathetic system to lower BP (renal denervation), however, effectiveness and safety of these procedures have not yet been established.

other emerging technologies

Methods

sytematic review in 4 databases, and hand search

The aim of this report was to assess effectiveness and safety of the BAT to decrease BP and reduce the number of cardiovascular events as compared to standard therapy. A systematic literature search was performed in December 2017 in four databases (Cochrane Library, Centre for Research and Dissemination, Embase, Medline), complemented by a hand search in the reference list of relevant studies. In addition, clinical trials databases were searched to identify non-published results and ongoing studies. Overall, 416 citations were identified, of which 63 were assessed for full text review, and finally seven were selected for the qualitative synthesis.

416 publikations, 63 for fulltext analysis, 7 selected for review

risk of bias and quality of evidence assed with tools

The IHE-20-checklist was used in order to assess the risk of bias (RoB) for case series, the Cochrane RoB tool was applied to check the RoB of RCTs. The quality of the body of evidence was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation).

exclusion of retrospective study design, case series < 20

Studies with retrospective study design, and case series with less than 20 patients enrolled were excluded.

Results

Available evidence

Barostim neo™: 3 case series (N=106), 1 cross-sectional study (N=16)

For the second-generation device, the Barostim neo™, three case series with a total of 106 patients were identified [5-7], and one randomised, controlled crossover trial on 16 patients [8]. The latter assessed the effects of treatment withdrawal of BAT within an 8-week period, but did not include outcomes related to device safety.

RCT on Rheos® system (N=265)

We identified one comparative study, which compared BAT with a sham procedure: an RCT on the first generation device on 265 patients [9].

evidence from Rheos® system not considered for recommendation

For the first generation device, two additional studies were included, one long-term open label follow up on the RCT [10], and one case series on 45 patients [11]. Evidence from the first generation device was not considered relevant for the recommendation, as the device is no longer available on the market and differs substantially from the second-generation device.

Clinical effectiveness

clinical effectiveness:

For the second-generation device, no evidence was available comparing BAT to the sham procedure, or BAT to standard therapy.

no studies comparing BAT to standard therapy, BAT to sham procedure only for Rheos® system: no significant BP differences after 6 months follow-up

One case series on the second generation device (n=44) measured a decrease of BP by means of 24-hours AMBP. They reported an average decrease in SBP by 8 mmHg. A reduction of at least 5 mmHg was not achieved in 20 of 44 patients (45%) [5].

The RCT on the first generation device reported no significant difference in systolic BP (SBP) within the two groups after a follow-up period of 6 months (54% in the interventional group, to 46% in the sham group, p> 0.005, office BP measurement) [9].

no evidence on reduction of cardiovascular events

No evidence was available comparing the number of cardiovascular events in patients receiving BAT versus standard therapy.

From the available evidence, no conclusion on the clinical effectiveness of BAT can be drawn, and the quality of evidence was considered very low.

Safety

No studies comparing safety of BAT to standard therapy were available.

no studies comparing BAT to standard therapy

The only comparative data to evaluate safety was derived from the RCT on the first generation device, the Rheos pivotal trial [12], which reported 68 procedural complications (13 surgical complications, 13 nerve injuries with residual effect, 12 temporary nerve injuries, 7 respiratory complications, 7 wound complications). Furthermore, 34 device-related adverse events were reported, of which six were hypertension-related strokes. Five of the 265 patients had their device removed during the 12 months follow up time. Within the six years follow-up, de Leeuw et al. 2017 reported 335 serious adverse events (SAEs) occurring in 111 patients, of which 26 SAEs (23%) were directly related to the procedure or BAT system [10].

Rheos pivotal trial: 68 procedural complications, 34 device-related-adverse events

For the second generation device, safety outcomes were reported by two case series for a total patient population of 74 patients [7]. In total, 23 procedural AE (surgical complications, device pocket haematoma, pain near the device site, wound healing complication) and three SAEs were reported (one hypertension-related stroke, one movement of the IPG, one serious wound healing defect). Within the six months follow-up, none of the second-generation devices needed to be explanted.

Barostim neo™: less adverse events, no device explanations

The quality of evidence is very low.

Upcoming evidence

Three ongoing RCTs on the BAT were identified:

ongoing studies

- The Barostim neo™ Pivotal Trial (n=310), a non-blinded RCT comparing BAT to standard management, has a completion date of September 2017, results are still pending.
- The Nordic BAT Study (n=100) is a double-blinded RCT comparing BAT to the sham procedure. Its primary completing date is November 2020.
- The ESTIM-rHTN trial (n=128), a randomised medico-economic study that assesses economic efficacy of BAT compared to standard therapy. This is the first evaluation of BAT compared to standard therapy, which includes a comparison of the number of CV events, yet as secondary outcome measure.

In addition to the indication of TRH, BAT is currently evaluated as therapeutic option in patients with heart failure (NYHA Class III). The pivotal trial of Barostim Therapy for Heart Failure (BeAT-HF) enrolled 800 participants and aims at FDA approval (estimated completion date 2021).

ongoing study assessing BAT as treatment for heart failure

Reimbursement

BAT is currently not included in the Austrian benefit catalogue.

not included in Austrian benefit catalogue

Estimated treatment costs for the implantation are at 3,500 Euros, the Barostim neo™ system costs 21,000 Euros, and the battery costs are 15,000 Euros if replacement is needed [13].

Conclusion

no sufficient evidence to conclude on effectiveness or safety of BAT

Substantial evidence proving the efficacy and safety of BAT is limited. For the second-generation device, no controlled studies are available to date that compared BAT to sham procedure or BAT to standard management (information confirmed by manufacturers), despite being the only BAT device available on the market.

low quality of evidence due to small sample sizes, lacking blinding, and control group

The small patient population, lacking control groups and blinding, and the paucity of studies on the second-generation device contribute to an overall very low quality of evidence, for both efficacy and safety-related outcomes. All of the studies were either directly funded by the manufacturer, or first authors received study grants or consultancy fees. No independently conducted study could be identified. Importantly, the most crucial outcome of a reduction in the number of cardiovascular events as compared to standard therapy was not assessed by any of the studies.

therapy adherence not assessed by most studies

A major obstacle to control hypertension is poor adherence to hypertensive therapy. Therapy adherence is seldomly assessed during the cause of a clinical trial, and if, mostly by means of patient-reported questionnaires rather than urine analysis or other objective measures. An increase or decrease in therapy adherence during the trials could thus be a major confounder of the trial results.

future studies shall assess BP reduction based on AMBP measurements, monitor therapy adherence, and assess differences in the number of cardiovascular events

BAT has not conclusively provided robust evidence for its benefit and safety. By contrast, the only comparative data on the first generation device was not able to establish a meaningful benefit for patients. Future clinical trials should assess BP reduction based on AMBP measurements, and include monitoring of therapy adherence. More importantly, apart from a reduction in BP emerging technologies on TRH need to prove if they provide a benefit in the long-term reduction of CV events.

Recommendation

inclusion currently not recommended

BAT is currently not recommended for inclusion in the Austrian benefit catalogue due to insufficient evidence.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Therapieresistenter Bluthochdruck (TRH) ist definiert als Blutdruck (BD), der über dem Zielwert von 140/90 mmHg bleibt, trotz Einhaltung der maximal tolerierten Dosen von drei blutdrucksenkenden Medikamenten mit komplementärem Wirkungsmechanismus inklusive eines Diuretikums. Bluthochdruck, insbesondere unkontrollierter Bluthochdruck, ist eine der Hauptursachen für Herz-Kreislauf- und Nierenerkrankungen und erhöht das Risiko für Schlaganfälle, koronare Herzkrankheiten, Herzrhythmusstörungen sowie Herz- und Nierenversagen. Bluthochdruck ist in der Regel asymptomatisch. Therapieadhärenz spielt deshalb eine entscheidende Rolle für den Therapieerfolg.

Definition therapieresistente Hypertonie (TRH)

Für die Diagnose TRH müssen zunächst andere Ursachen für unkontrollierte Hypertonie ausgeschlossen werden: Pseudoresistente Hypertonie und Weißkittelhypertonie zählen zu den häufigsten Ursachen für unkontrollierten Bluthochdruck. Mangelnde Therapieadhärenz, eine suboptimale Therapie, oder ungenaue Blutdruckmessungen sind oft ursächlich für die sogenannte Pseudoresistenz. Des Weiteren sollten sekundäre Ursachen für Bluthochdruck erwogen werden, wie primärer Aldosteronismus und Nierenarterienstenose. Der diagnostische Ansatz umfasst eine 24-stündige ambulante Blutdruckmessung (AMBP), um Weißkittelhypertonie auszuschließen. Die First-Line-Therapie der TRH besteht in einer Lebensstilmodifikation, z. B. Diät, sowie einer Kombinationstherapie mehrerer blutdrucksenkender Medikamente (anfänglich zumeist einem ACE-Hemmer, einem Kalziumkanalblocker und einem Diuretikum).

Diagnose: Ausschluss anderer Ursachen, 24-h Blutdruckmessung

Die Prävalenz von TRH ist nicht bekannt, und liegt, abhängig von der untersuchten Population [3], zwischen 2 % und 30 % der hypertensiven PatientInnen [4]. In einer rezenten multizentrischen Querschnittsstudie an 4.303 österreichischen HypertonikerInnen blieb der Blutdruck bei mehr als 50 % der PatientInnen unkontrolliert (definiert als <140/90 mmHg).

Prävalenz nicht bekannt: von 2 %-30 % der PatientInnen mit diagnostizierter Hypertonie

Beschreibung der Technologie

Die Barorezeptortherapie (BAT) ist eine alternative Behandlungsoption für PatientInnen mit TRH. Durch Aktivierung des Baroreflexes mittels elektrischer Impulse zielt BAT darauf ab den Blutdruck zu reduzieren. Durch die Stimulation der Barorezeptoren soll eine Aktivierung des Parasympathikus und Deaktivierung des Sympathikus erreicht werden, was in weiterer Folge eine Senkung des Blutdrucks bewirkt. Derzeit ist nur ein Produkt der zweiten Generation der BAT-Produkte zugelassen, der Barostim neo™. Das Rheos®-System, das Produkt der ersten Generation, ist nicht mehr erhältlich und wurde gänzlich durch die neue Generation ersetzt.

BAT: Stimulation der Barorezeptoren zur Senkung des BD

zwei Produkte: Barostim neo™ und Rheos®-System

Das Vorgänger und Folgeprodukt unterschieden sich wesentlich in ihrem Aufbau, und dem Implantationsprozedere: der Barostim neo™ besteht aus einer kleineren Elektrode, einem kleineren Pulsgenerator mit einer längeren Batterielebensdauer. Die Elektrode wird einseitig auf nur einem Karotissinus platziert und somit ist der chirurgische Eingriff einfacher und kürzer, und erfordert kürzere Rehabilitation. Aufgrund dieser wesentlichen Unterschiede wurden Wirksamkeits- und Sicherheitsdaten beider Produkte getrennt bewertet.

Rheos®-System: derzeit nicht mehr verfügbar, und mit Barostim neo™ ersetzt

andere Technologien zur Behandlung der TRH derzeit in klinischen Studien

Weitere Technologien, die auf die Barorezeptoren (MobiusHD®) oder das Sympathikus-System zur Senkung des Blutdrucks (renale Denervation) abzielen, werden derzeit innerhalb von Studien untersucht, ihre Wirksamkeit und Sicherheit ist jedoch noch nicht erwiesen.

Methoden

systematische Literatursuche und Handsuche in 4 Datenbanken

Bias-Risiko mit IHE Checkliste und Cochrane RoB tool

Ziel dieses Berichts war es, die Wirksamkeit und Sicherheit der BAT zur Senkung des Blutdrucks und zur Verringerung der Anzahl kardiovaskulärer Ereignisse im Vergleich zur Standardtherapie zu bewerten. Eine systematische Literaturrecherche wurde im Dezember 2017 in vier Datenbanken (Cochrane Library, Zentrum für Forschung und Dissemination, Embase, Medline) durchgeführt, ergänzt durch eine Handsuche in der Referenzliste relevanter Studien. Darüber hinaus wurden Datenbanken für klinische Studien durchsucht, um nicht-veröffentlichte Ergebnisse und laufende Studien zu identifizieren. Insgesamt wurden 416 Zitate identifiziert, von denen 63 Volltexte analysiert und schließlich sieben für die qualitative Synthese ausgewählt wurden.

Qualität der Evidenz mit GRADE

Das Bias-Risiko (RoB) auf Studienebene wurde für Fallserien mit der IHE-20-Checkliste bewertet, für randomisierten kontrollierten Studien mit dem Cochrane RoB-Tool. Die Qualität der Evidenz wurde mit GRADE bewertet.

Studien mit retrospektivem Studiendesign und Fallserien mit weniger als 20 eingeschlossenen PatientInnen wurden ausgeschlossen.

Ergebnisse

Verfügbare Evidenz

insgesamt 4 Studien zu Barostim neo™: 106 PatientInnen in 3 Fallserien, 16 PatientInnen in Cross-over Studie

Für das Produkt der zweiten Generation, Barostim neo™, wurden drei Fallserien mit insgesamt 106 PatientInnen und eine randomisierte, kontrollierte Cross-Over-Studie an 16 PatientInnen identifiziert. Letztere bewertete die Auswirkungen eines Therapieabbruchs bei der Behandlung mit BAT in einem Zeitraum von 8 Wochen.

Insgesamt konnte eine Vergleichsstudie identifiziert werden die BAT mit einem Scheinverfahren vergleicht: das Rheos pivotal trial an 265 PatientInnen.

3 Studien zum Vorgängermodell Rheos® system – jedoch keine GRADE-Bewertung/ Empfehlungen

Für das Rheos® system wurden zusätzlich zwei weitere Studien eingeschlossen, eine langfristige Open-Label-Follow-up des RCT und eine Fallserie mit 45 PatientInnen. Wirksamkeits- und Sicherheitsdaten dieses Produktes wurden für die Empfehlung als nicht relevant angesehen, da es nicht mehr erhältlich ist, zur Gänze mit dem Barostim neo™ ausgetauscht wurde und sich zu diesem wesentlich unterscheidet.

Klinische Wirksamkeit

Barostim neo™: keine Vergleichsstudien zur Standard- oder Scheintherapie

Für Barostim neo™ lagen keine Vergleichsstudien vor, um die Wirksamkeit von BAT im Vergleich zu einem Scheinverfahren oder zur Standardtherapie zu beurteilen.

eine Fallserie zur Senkung des 24h BD: durchschnittlich 8 mmHg

Eine Fallserie (n=44) zum Barostim neo™ berichtete eine Verringerung des 24-Stunden Blutdrucks, mit einer durchschnittlichen Abnahme des systolischen Blutdrucks um 8 mmHg. Eine Reduktion von mindestens 5 mmHg wurde bei 20 von 44 PatientInnen (45 %) nicht erreicht [5]. Die verbleibenden beiden Fallserien berichten diesen Endpunkt nicht und es erfolgte eine Messung der Blutdruckreduktion mittels Office-Blutdruckmessungen.

Das RCT zum Erstprodukt Rheos® system zeigte keinen signifikanten Unterschied in den systolischen Blutdruckwerten zwischen der Interventions- und der Scheingruppe nach einer Beobachtungszeit von sechs Monaten (54 % in der Interventionsgruppe, 46 % in der Scheingruppe, p>0,005, Office-Blutdruckmessung).

RCT zu Rheos® system: keine signifikanten Unterschiede zw Interventions- und Kontrollgruppe

Es liegen keine Studienergebnisse zur Reduktion der Anzahl an kardiovaskulären Ereignissen im Vergleich zur Standardtherapie vor.

keine Studie berichtet zu kardiovaskuläre Ereignissen

Aus der verfügbaren Evidenz lassen sich keine Schlussfolgerungen zur klinischen Wirksamkeit der BAT ableiten. Die Qualität der Evidenz wurde als sehr gering ermessen.

Qualität der Evidenz sehr niedrig

Sicherheit

Die einzigen Vergleichsdaten zur Bewertung der Sicherheit stammten aus der RCT der Erstgeneration, der Rheos-Zulassungsstudie [6], die über 68 operative Komplikationen berichteten (13 chirurgische Komplikationen, 13 bleibende Nervenverletzungen, 12 temporäre Nervenverletzungen, 7 respiratorische Komplikationen, 7 Wundkomplikationen). Darüber hinaus wurden 34 Produktassoziierte unerwünschte Ereignisse berichtet, von denen sechs Bluthochdruckbedingte Schlaganfälle waren. Bei fünf der 265 PatientInnen wurde das Implantat während der 12-monatigen Nachbeobachtungszeit entfernt. In der Langzeit-Beobachtungsstudie wurden nach sechs Jahren 335 schwere unerwünschte Ereignisse bei 111 Patienten erhoben, von denen 26 (23 %) direkt mit dem Verfahren oder BAT-System in Zusammenhang standen.

Vergleichsdaten zur Sicherheit aus Rheos RCT: 68 operative Komplikationen, 34 unerwünschte NW

6 Jahres-Follow-up: 335 schwere NW in 111 PatientInnen, davon 26 BAT-bezogene schwere NW

Zwei Fallserien berichten Endpunkte zur Bewertung der Sicherheit von Barostim neo™ für eine Gesamtpopulation von 74 PatientInnen. Insgesamt wurden 23 unerwünschte Nebenwirkungen (chirurgische Komplikationen, Hämatom, Schmerzen, Wundheilungskomplikationen) und drei schwere unerwünschte Nebenwirkungen (Bluthochdruck bedingter Schlaganfall, Bewegung des IPG, schwerer Wundheilungsdefekt) berichtet. Innerhalb der Nachuntersuchung von sechs Monaten musste keines der Geräte der zweiten Generation explantiert werden. Die Qualität der Evidenz wurde als sehr gering erachtet.

2 Fallserien berichten bzgl. Barostim neo™ zum Endpunkt Sicherheit (74 PatientInnen)

Laufende Studien

Derzeit laufen drei randomisierte, kontrollierte Studien zum BAT-Verfahren:

laufende Studien

- Barostim neo™ Zulassungsstudie (n=310), ein nicht-verblindetes RCT, welches BAT mit der Standardtherapie vergleicht. Fertigstellung sollte im September 2017 stattfinden, die Ergebnisse stehen derzeit noch aus.
- Nordic BAT Study (n=100), ein doppelt-verblindetes RCT, das BAT zur Scheinprozedur vergleicht. Die Fertigstellung ist für November 2020 angedacht.
- ESTIM-rHTN Trial (n=128), eine randomisierte-ökonomische Studie, die neben Wirksamkeit und Sicherheit auch Kosteneffizienz der BAT untersucht. BAT wird hierbei mit der Standardtherapie verglichen. Diese Studie beinhaltet erstmalig den Endpunkt "Reduktion in der Anzahl an kardiovaskulären Events", allerdings als sekundären Endpunkt.

Neben der Indikation TRH wird die BAT derzeit als Therapieoption bei PatientInnen mit Herzinsuffizienz (NYHA-Klasse III) evaluiert. Die Zulassungsstudie zur BAT bei Herzinsuffizienz (BeAT-HF) umfasst 800 TeilnehmerInnen und zielt auf eine FDA-Zulassung ab (geschätzte Fertigstellung 2021).

Trial zu BAT bei Herzinsuffizienz – Ergebnisse für 2021 erwartet

Kostenerstattung

bislang keine Erstattung von BAT in Österreich

BAT ist derzeit nicht im österreichischen Leistungskatalog enthalten.

geschätzte Kosten des Produkts: 21.000 Euro

Geschätzte Behandlungskosten für die Implantation liegen bei 3.500 Euro, das Barostim neo™-System kostet 21.000 Euro und die Batteriekosten betragen 15.000 Euro, wenn ein Ersatz erforderlich ist [13].

Fazit

Conclusio: unzureichende Evidenz bzgl. Wirksamkeit und Sicherheit von BAT bei TRH

Die derzeitige Evidenz ist nicht ausreichend, um die Wirksamkeit und Sicherheit der BAT nachzuweisen. Obwohl Barostim neo™ das derzeit einzig verfügbare BAT-Produkt ist, gibt es für das Produkt bis dato keine Ergebnisse kontrollierter Studien, in denen BAT mit einem Scheinverfahren oder BAT mit Standardtherapie verglichen wurden.

insgesamt geringe Studienqualität bzgl. Barostim neo™

Studien mit Firmensponsoring

Die kleine Studienpopulation ohne Kontrollgruppen, fehlende Verblindungen sowie die wenigen Studien zum Produkt der zweiten Generation tragen zu einer insgesamt sehr niedrigen Qualität der Evidenz bei. Alle Studien wurden entweder direkt vom Hersteller finanziert oder mehrere AutorInnen erhielten Beratungsgebühren. Eine unabhängig durchgeführte Studie konnte nicht identifiziert werden. Besonders hervorzuheben ist, dass der wichtigste Endpunkt (Verringerung der Anzahl an kardiovaskulären Ereignissen im Vergleich zur Standardtherapie) in keiner der Studien betrachtet wurde.

keine Angaben zu Anzahl an kardiovaskulären Ereignissen bei BAT im Vergleich zu Standardtherapie

Bedarf an Studien mit Erhebung von Therapieadhärenz und Langzeitergebnisse bzgl. kardiovaskulärer Ereignisse erforderlich

Fehlende Therapieadhärenz stellt eines der Hauptprobleme bei der Blutdruckkontrolle dar, wird jedoch in klinischen Studien selten gemessen, und wenn dann nur in Form von Fragebögen, anstelle von Urinanalysen oder anderen objektiven Messungen. Eine Erhöhung oder Verringerung der Therapieadhärenz während der Studien könnte daher zu einer wesentlichen Verzerrung der Studienergebnisse beitragen. Zukünftige klinische Studien sollten eine Evaluierung der Therapieadhärenz einschließen und die Blutdruckreduktion basierend auf 24-Studen Blutdruckmessungen beurteilen. Abgesehen von einer Blutdrucksenkung, sollten neue Technologien zur Therapie der TRH einen Nutzen in Bezug auf eine langfristige Reduzierung der kardiovaskulären Ereignisse und damit der Mortalität und Morbidität aufweisen können.

Empfehlung

unzureichende Evidenz, daher Aufnahme nicht empfohlen; neuerliche Evaluation in 3 Jahren

Auf Basis der vorliegenden Evidenz wird die Aufnahme in den Leistungskatalog derzeit nicht empfohlen. Die vorhandene Evidenz zur Wirksamkeit und Sicherheit wurde als nicht ausreichend angesehen. Eine Re-Evaluierung wird empfohlen, wenn aussagekräftige und kontrollierte Langzeitdaten zur Verfügung stehen, ehestens 2020.

1 Scope

1.1 PICO question

Is baroreceptor activation therapy in patients with treatment-resistant hypertension a more effective and safe alternative to decrease blood pressure and reduce the number of cardiovascular events in comparison to standard therapy with medication?

PIKO-Frage

1.2 Inclusion criteria

Inclusion criteria for relevant studies are summarized in Table 1-1.

Einschlusskriterien für relevante Studien

Table 1-1: Inclusion criteria

Population	Patients with **treatment-resistant hypertension**: systolic blood pressure >140mmHG despite drug- therapy with three or more antihypertensive medications, including one diuretic agent, in the maximal indicated doses and after diagnostic exclusion of secondary hypertension (ICD I15) ICD-10 Code: I10 essential (primary) hypertension MeSH terms: hypertension (C14.907.489) Synonyms: high blood pressure; (atrial) (benign) (essential) (malignant) (primary) (systemic) hypertension; treatment-resistant, therapy-resistant, resistant hypertension
Intervention	Baroreceptor activation by implantation of a baroreceptor stimulation device to lower blood pressure by stimulating the carotid baroreflex; Synonyms: baroreflex activation therapy, baroreceptor stimulation therapy, carotid baroreceptor stimulation MeSH terms: baroreflex (G09.330.380.057, G11.561.731.063) Devices: Barostim neo™; Rheos® system/ Rheos® device Companies: CVRx, Inc. Minneapolis
Control	placebo/ sham procedure (by activating device at different time points); guideline-oriented therapy
Outcomes	
Efficacy	❁ sustained (>1 year) systolic blood pressure reduction by more than 10 mmHg over 24 hours (critical) ❁ decrease in cardiovascular events (death from cardiovascular causes, non-fatal myocardial infarction, acute coronary syndrome not resulting in a myocardial infarction, non-fatal stroke, non-fatal acute decompensated heart failure) (critical) ❁ QoL (Patient-reported QoL (important) ❁ Hospitalisation rate (important) ❁ reduction of antihypertensive medication to reduce blood pressure to <140 mmHg (important)
Safety	❁ device-related serious adverse events (SAE): stroke, transient ischemic attack, systemic embolization, infection, arterial damage, pain, nerve damage, hypotension, hypertensive crisis, injury of baroreceptors, cardiac arrhythmias, worsening of kidney disease (critical) ❁ procedure related SAE: nerve damage, pain of glossopharyngeal nerve, surgical or anaesthetic complications (critical)

Study design	
Efficacy	Randomised controlled trials (RCT) Prospective non-randomised controlled trials (NRCT) Before-after studies Prospective observational studies: cohort studies, case- control studies (N>20)
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case-series, registries (N>20)

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What is baroreceptor activation therapy (BAT)?
A0020	For which indications has BAT received marketing authorisation or CE marking?
B0002	What is the claimed benefit of BAT in relation to the comparators?
B0003	What is the phase of development and implementation of BAT and the comparator(s)?
B0004	Who administers BAT and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use BAT?
B0009	What supplies are needed to use BAT?
A0021	What is the reimbursement status of BAT?

Health problem and Current Use	
Element ID	**Research question**
A0002	What is the condition in the scope of this assessment?
A0003	What are the known risk factors of treatment resistant hypertension (TRH)?
A0004	What is the natural course of TRH?
A0005	What is the burden of disease for the patients with TRH?
A0006	What are the consequences of TRH for the society?
A0024	How is TRH currently diagnosed according to published guidelines and in practice?
A0025	How is TRH currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is TRH utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of BAT on mortality?
D0003	What is the effect BAT on the mortality due to causes other than the target disease?
D0005	How does BAT affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does BAT affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of BAT on patients' body functions?
D0016	How does the use of BAT affect activities of daily living?
D0012	What is the effect of BAT on generic health-related quality of life?
D0013	What is the effect of BAT on disease-specific quality of life?
D0017	Was the use of BAT worthwhile?

Safety	
Element ID	Research question
C0008	How safe is BAT in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying BAT?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed by the use of BAT?
C0007	Is BAT and comparator(s) associated with user-dependent harms?

2.2 Sources

Quellen: systematische Suche, Handsuche, Informationen der Hersteller und des einreichenden Krankenhauses

Description of the technology

- Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturers
- Questionnaire completed by the submitting hospitals

Health problem and Current Use

- Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturers
- Questionnaire completed by the submitting hospitals

For the domains clinical effectiveness and safety a systematic literature search and hand search was conducted, and described in detail in 2.3.

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 06.12.2017 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

The systematic search was limited to the years 2008 to 2017, and to articles published in English or German. After deduplication, overall 414 citations were included. The specific search strategy employed can be found in the Appendix.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 03.01.2018 resulting in 31 potential relevant hits.

One manufacturer of the most common product (Barostim neo™) submitted 15 publications, yet these citations were already included in the systematic search.

insgesamt 414 Publikationen identifiziert

Two additional publications were found by handsearch.

2.4 Flowchart of study selection

Literaturauswahl

Overall 414 hits were identified. The references were screened by two independent researchers (KH, RW) and in case of disagreement, a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

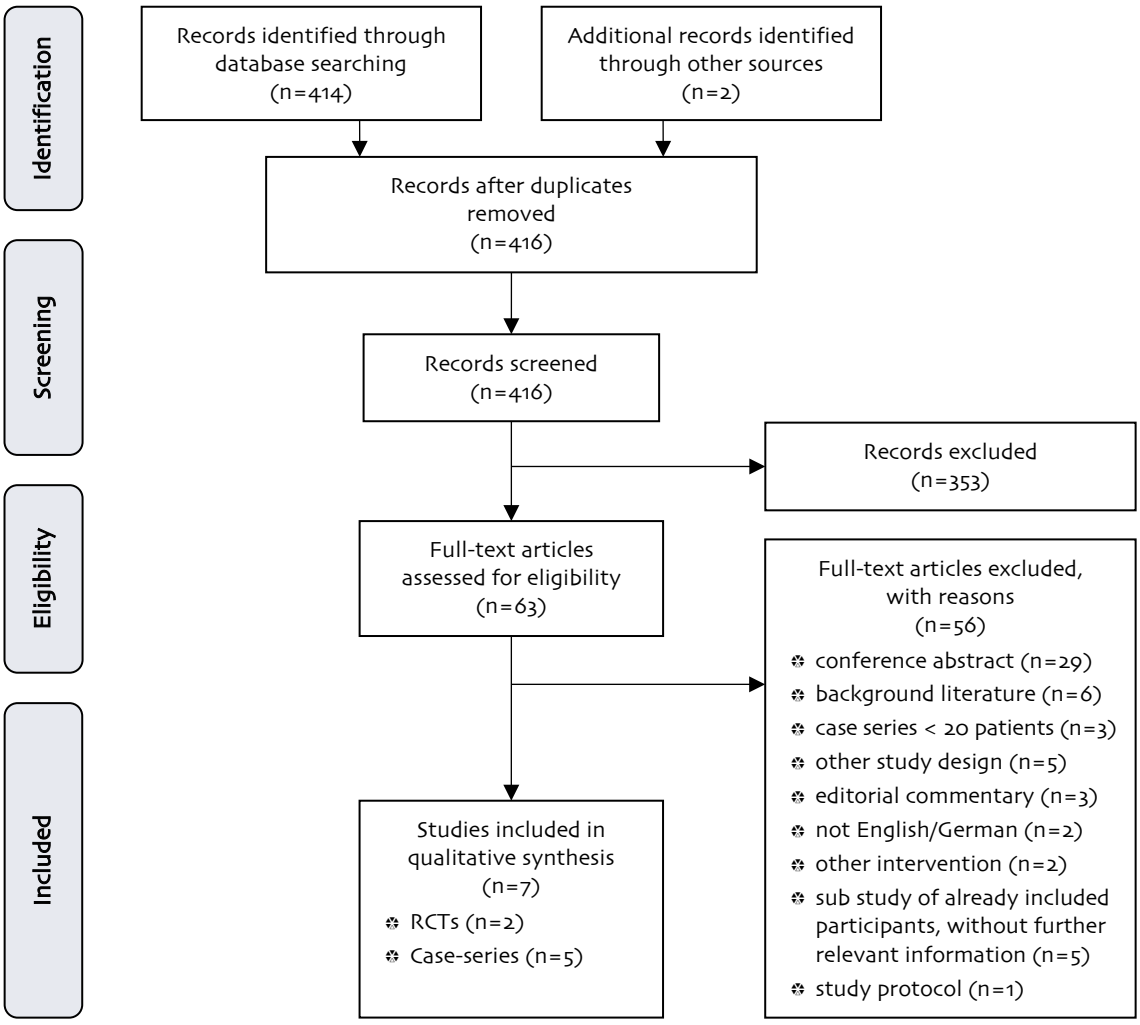

Figure 2-1: Flowchart of study selection (PRISMA Flow Diagram)

1 rezenter SR zu BAT, jedoch Ausschluss aufgrund methodischer Mängel

Within the systematic search, we also identified one systematic review (SR) on BAT [14], however, due to methodological limitations of the review and conflict of interest, we decided not to include the review as a whole, but rather compare if the included studies would also meet the inclusion criteria for this review. This was not the case; no additional studies were included.

3 HTAs zu BAT

Furthermore, three health-technology assessments were identified, stemming from the UK (NICE) [15], Canada (CADETH) [16], and Australia (Asernip) [17]. We compared these reports with our findings, and searched references for additional studies and background information on BAT.

2.5 Analysis

Datenextraktion aus Studien

We retrieved data from the selected studies and systematically extracted those into the data-extraction-tables (see Table A-1 and Table A-2). No further data processing (e.g. indirect comparison) was applied.

Qualitätsbeurteilung der Studien mit Cochrane RoB und IHE Checkliste

Two independent researchers (KH, RW) systematically assessed the quality of evidence and risk of bias (RoB) using the Cochrane Risk of Bias tool for RCTs [18] and the IHE Risk of Bias checklist for case series [19]. The risk of bias analysis for each individual study can be found in the Appendix (Table A-3 and Table A-4).

2.6 Synthesis

qualitative Synthese der Evidenz

Due to the heterogeneity of studies, study design, and the paucity of data no meta-analysis was calculated. Hence, a qualitative synthesis of efficacy and safety data was performed. The questions were answered in plain text format.

Zusammenfassung der Ergebnisse mit GRADE

In addition, a GRADE evidence table and a GRADE summary of findings table were created in order to synthesize data on each selected outcome category across studies (Table A-7and Table A-5).

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What is Baroreceptor Activation Therapy (BAT) and its comparators?

Baroreceptor activation therapy (BAT) is a treatment option proposed for patients with treatment-resistant hypertension (TRH).

Einsatz von BAT bei therapieresistentem Bluthochdruck (TRH)

Baroreceptors are a mechanosensitive sensory nerve ending in the walls of the carotid sinuses and the aortic arch that measure and respond to a rise and fall in the arterial BP [20]. As response to increasing BP, the baroreceptors send afferent impulses to the central nervous system that reflectively decrease sympathetic activity and increase parasympathetic activity, leading to a reduction of BP. Conversely, if BP falls the receptors cease their stimulation. This reflex mechanism of the body to respond to high or low BP is called carotid baroreflex.

Barorezeptor-Reflex: Barorezeptoren aktivieren das zentrale Nervensystem bei Anstieg oder Absinken des Blutdrucks (BD)

By inducing the baroreflex, BAT activates the carotid baroreceptors with electric impulses. The stimulation leads to a decrease of sympathetic activity, a relaxation of the blood vessels (vasodilatation), decrease of the heart rate and ultimately a reduction of BP [20]. Figure 3-1 shows the anatomic location of the baroreceptors and working mechanism behind BAT [2].

BAT stimuliert mittels elektrischen Impulsen die Barorezeptoren in der Karotis, Ziel ist hierbei eine BD-Senkung

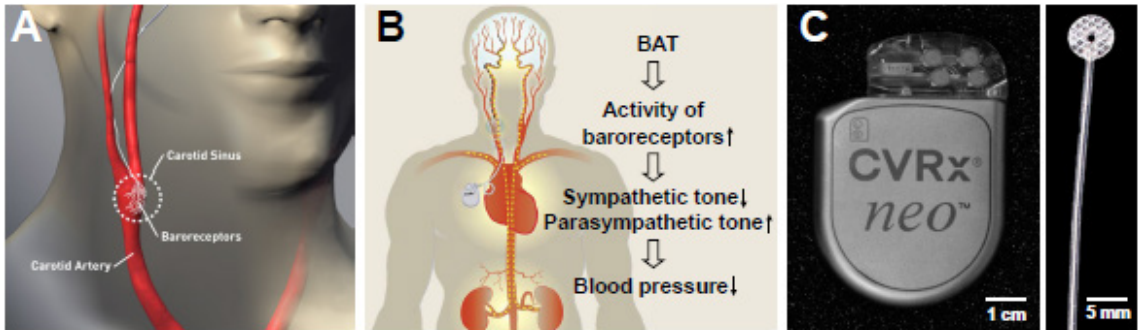

Figure 3-1: Baroreceptor activation therapy (A = anatomic location of the baroreceptors at the carotid sinus; B = BAT operating-principle; C = BAROSTIM NEO™ device), adapted from [2]

The stimulation is performed by a neurostimulator device, which consists of a pulse generator (left side of picture C) that is connected to a 2mm sized electrode (right side of picture C). The implantable pulse generator (IPG) is similar to a pacemaker and implanted under the skin below the collarbone. The carotid sinus lead connected to the IPG is tunnelled under the skin, and the electrode is sutured to the carotid sinus. A wireless programmer system exists to activate and deactivate the device externally and to customize the stimulation intensity by changing the frequency and the amplitude of the stimulation.

Stimulation erfolgt mittels Impulsgenerator der mit einer 2 mm großen Elektrode verbunden ist; Ein- und Ausschalten sowie das Anpassen der Stimulationsfrequenz erfolgt über ein externes Programmiersystem

Marketed products and comparators

Barostim neo™: (derzeit) einzig verfügbare BAT-Technologie

The Barostim neo™ by CVRx. Inc is currently the only marketed device that activates the baroreceptor reflex by electric impulses.

However, other procedures and devices similarly target the sympathetic activity in order to lower the BP:

andere Technologien: 1.MobiusHD®: Stent ähnliches Implantat im Karotissinus, das zu einer Amplifikation des Baroreflexes führt, ohne elektrische Stimulation;

derzeit in klinischen Studien untersucht bzgl. Wirksamkeit und Sicherheit

The MobiusHD® by Vascular Dynamics aims at endovascular baroreflex amplification by use of a stent-like device that increases wall strain in the carotid sinus. The baroreceptors sense the strain as an increase of pressure and respond by inhibiting sympathetic outflow. The procedure provides a passive amplification of the baroreflex without the need for electric stimulation, and, as the self-expanding device is implanted through the femoral artery by a guidewire similarly as a carotid stent, is suggested to be a less invasive procedure [21]. However, data on efficacy and safety are very limited so far, and we only identified one study on this procedure in the systematic search. Several CALM studies (Controlling and Lowering Blood Pressure with the MobiusHD®) currently investigate the efficacy and safety profile. The initial first-in-human open-label study on 30 patients with TRH showed a significant reduction in BP at an acceptable safety profile [21], however, these data need to be confirmed by controlled studies and RCTs. The CALM-II study, a multicenter, prospective sham-controlled RCT in Europe and the US was initiated in 2017 (Table A-7).

2. renale Denervation zeigte sich bei TRH als nicht überlegene Technologie – große internationale Studie wurde eingestellt

Another procedure targeting sympathetic activity, yet in the renal arteries is catheter-based radiofrequency ablation of renal sympathetic nerves, also called renal denervation (RDN). A recent double-blind RCT, Symplicity HTN 3, with 535 participants with TRH could not prove the benefit of this technique [22]. A recent sham controlled RCT on 80 patients confirmed the biological proof-of principle to lower BP in absence of anti-hypertensive medicines, however, was not compared to standard treatment, and did not include patient-relevant outcomes on changes in mortality or morbidity [23]. Following the results of the first trial and subsequent studies, a larger ongoing international trial was halted prematurely [24].

Komperatoren lt. Leitlinien bzw. Scheinkontrollen (Sham)

All of these device-based strategies to lower BP in patients with TRH can be regarded as experimental, as substantial evidence proving efficacy and safety are lacking to date. Furthermore, none of these techniques is reimbursed and included in the Austrian benefit catalogue. Thus, guideline oriented therapy (as described in A0025), as well as sham-controlled procedure were chosen as comparators to assess effectiveness in this report.

B0002 – What is the claimed benefit of BAT in relation to the comparators?

Erwarteter Nutzen: BD-Senkung durch BAT als erwarteter nach erfolglosen medikamentösen Therapien

The claimed benefit of BAT is the ability to lower BP despite failure of >3 pharmacological therapies. BAT was described to be the only procedure to target both sympathetic and parasympathetic limbs of the autonomic nervous system [25]. However, it is possible that novel techniques such as the MobiusHD® would also influence parasympathetic activity, as both interventions target the baroreceptor reflex. Furthermore, adherence was suggested to be improved and potentially lead to a reduction of dosages or anti-hypertensive medicines prescribed [25]. Concurrently, heart rate is decreased and beneficial effects in patients with heart failure have been described and are currently investigated.

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers BAT and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use BAT?

B0009 – What supplies are needed to use BAT?

Barostim neo™ umfasst Karotissinuselektrode, IPG, Programmiersystem

Barostim neo™ consists of the IPG, the carotid sinus lead, implant adapter, implant tool, and the program system [26].

BAT-Implantation als minimal-invasive Intervention

The implementation of BAT requires a surgical procedure and takes place in a hospital setting. The patient receives general anaesthesia or conscious sedation for the procedure. A surgeon, trained to perform the procedure as well as an experienced anaesthetist are needed.

chir. Eingriff mit Spitalsaufenthaltsdauer von circa 3 Tagen

The surgical procedure consists of three phases: exposure of the carotid sinus, carotid sinus mapping and positioning of the electrode and implanting the IPG under the skin. In order to identify the optimal location for placing the electrode, a mapping of the carotid sinus and system testing is performed during the procedure. Subsequently, the electrode is sutured to the vessel, and the IPG under the skin near the clavicle. After surgery, patients remain in hospital for approximately three days, if no complications occur (a maximum of four days and a minimum of two days) (information provided by submitting hospital).

US-Untersuchung zur präoperativen Diagnostik

Prior to surgery, preoperative duplex ultrasonography should confirm the absence of complex arterial anatomy and verify absence of any stenosis greater than 50% of the carotid arteries, as well as the absence of any ulcerative plaques [26].

BAT-Aktivierung ca. 1 Monat nach Eingriff

The device is usually activated one month after the implantation in an ambulatory setting.

Regulatory & reimbursement status

B0003 – What is the phase of development and implementation of BAT?

Barostim neo™: 2. BAT-Generation-CE-Marks zur Behandlung von TRH (2011) und Herzinsuffizienz (2014)

The Barostim neo™device is the second generation of baroreceptor stimulators by CVRx. The first clinical trial on the second generation device was published in 2012 [7]. The device received market-authorization in Europe (CE-mark) for the treatment of resistant hypertension in 2011 and for the treatment of reduced ejection heart failure in 2014 (information provided by the manufacturer).

kein Einsatz mehr des Vorgängermodells Rheos® system, Austausch aller Geräte, Grund: kurze Batteriedauer (1,5-2 Jahre); Elektroden an beiden Halsseiten

The predecessor device is the Rheos® system, which received CE mark in 2007. This device is not marked anymore. The first feasibility trial was performed in 2006; a randomised controlled trial (RCT) was completed in 2011. The reason for market withdrawal was the end-of-battery life, which was very short with one-and-a-half to a maximum of two years [10]. To date, all Rheos® devices have been replaced with the new generation device (information provided by manufacturer in personal correspondence). In contrast to the second generation, the Rheos® system consisted of two bilateral leads to both the left and right carotid sinus and a bigger IGP.

Barostim neo™ Elektrode nur bei einem Karotissinus, kleinerer IPG, Eingriff weniger invasiv; Batteriedauer mit 5-6 Jahre angenommen

The Barostim neo™ is fairly different to the first generation, with only one stimulating electrode to one carotid sinus. The device has a smaller IGP, can be implanted with a smaller surgical incision (<5cm) and is thus less invasive and requires less recovery time, since surgical incision is needed on only one side of the neck [27]. Furthermore, the battery life is said to be increased to five to six years (information provided by manufacturer in personal correspondence). These changes are claimed to improve the safety profile of the second generation device, reduce procedural time and patient discomfort, without changes in performance of BP reduction.

A0020 – For which indications has BAT received marketing authorisation or CE marking?

seit 2014 auch CE-Mark für Behandlung von Herzinsuffizienz – Evidenzlage: Studien laufen, daher verfrüht für HTA-Bericht

In addition to resistant hypertension, Barostim neo™ has received CE marking for the treatment of reduced ejection heart failure in 2014. For the latter indication, preliminary evidence exists from two ongoing clinical trials (NCT-01471860; NCT01720160). Both trials are not completed yet, but initial evidence from a first interim analysis after six months of treatment is available [28, 29]. Due to the early stage of evidence development, we deemed an assessment of this second indication premature.

in USA laufende klinische Evaluation zu BAT für beide Indikationen

In the United States, BAT is under clinical evaluation for both indications but has not received market-authorisation. FDA granted 'Humanitarian Device Exemption' to the participants of the Rheos Pivotal trial that showed sustained BP reduction, allowing CVRx.Inc. to sell the second generation device to those patients as replacement of the Rheos® system [30].

A0021 – What is the reimbursement status of BAT?

bislang keine Erstattung von BAT in Österreich

BAT is currently not included in the Austrian benefit catalogue, thus hospitals performing BAT would have to cover treatment costs for their patients.

geschätzte Kosten des Produkts: 21,000 Euro

A cost-effectiveness analysis for the European healthcare settings in 2014 described treatment costs for the implantation with 3,500 Euro [13]. The Barostim neo™ system itself costs 21,000 Euro, and the battery costs 15,000 Euro if replacement is needed. The replacement procedure for the battery was approximated with 2,000 Euro. Since no substantial changes in the therapeutic approach can be expected, apart from a claimed change in anti-hypertensive medications, these costs can be regarded as additional costs to the current treatment costs of TRH.

4 Health Problem and Current Use

Overview of the disease or health condition

A0002 – What is the disease or health condition in the scope of this assessment?

The scope of this assessment was treatment-resistant hypertension (TRH). Hypertension is as defined as resistant if three antihypertensive medications do not achieve control of blood pressure (BP). Patients with persistent hypertension are at high risk to have cardiovascular events (CV) or subsequent renal failure.

TRH: keine BD-Senkung trotz antihypertensiver Medikation – Risiko für kardiovaskuläre und renale Ereignisse

Definition of TRH:

Resistant hypertension is defined as BP that remains above goal despite adhering to the maximally tolerated doses of three antihypertensive drugs with complementary mechanism of action, including one diuretic according to the American College of Cardiology (ACC) and American Heart Association (AHA) consensus guidelines from 2017 [1]. This recent definition is in line with the previous 2013 definition by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) [4].

Definitionen von TRH lt. kardiologischen Fachverbänden in USA und Europa

The definition of the goal BP differs in the two guidelines since the 2017 ACC/AHA guidelines defined a new goal BP as below 130 mmHg systolic and 80 mmHg diastolic. The ESH/ESC guidelines, among other guidelines, define goal BP as below 140 mmHg systolic and 90 mmHg diastolic [4]. The new ACC/AHA definition of goal BP came as response to the results of the SPRINT trial showing significantly reduced mortality rates, and number of CV in the intensive treatment group with a BP below 130 mmHg [1, 31]. However, since certain patient populations were excluded in the study, such as diabetics, patients younger than 50 years of age, patients with a prior stroke, and those with heart failure, some guidelines, and the Austrian Society for Hypertension only recommend the new goal BP for patients with similar characteristics as the SPRINT study population [32, 33].

Unterschiede in Leitlinien bzgl. cut-off Werte des Ziel-BDs

Patients with TRH can have both a high systolic and a high diastolic BP, but an isolated elevation of the systolic blood pressure (SBP) is common, in particular in older patients. Isolated systolic TRH is more difficult to manage, as often underlying conditions such as stiff aorta make systolic BP control harder to achieve, and intensification of therapy may result in too low diastolic BP [34].

erhöhter systolischer BD v. a. bei älteren TRH-PatientInnen

Importantly, resistant hypertension is not synonymous with uncontrolled hypertension. Several other causes of uncontrolled hypertension exist including secondary causes for hypertension and pseudo-resistance due to non-adherence and inadequate treatment regimens (see differential diagnosis).

TRH ist kein Synonym für eine unkontrollierte Hypertonie

A0003 – What are the known risk factors for treatment-resistant hypertension (TRH)?

Predicting patient characteristics and risk factors to develop TRH are a high baseline BP (particularly SBP), older age, obesity, African-American race, chronic kidney disease (CKD) and diabetes mellitus [34].

TRH-Risikofakoren, z. B. erhöhter Baseline-BD, Alter, Adipositas etc.

Potentially reversible factors that could cause or contribute to TRH include suboptimal therapy, lifestyle and diet, medications that can raise the BP, and secondary causes of hypertension [34].

potentiell reversible Gründe für TRH

A0004 What is the natural course of TRH?

TRH erfordert permanente Medikation zur Risikominimierung

There is no ultimate cure for hypertension and TRH, and patients need long-lasting, chronic therapy to lower the BP and concurrently the risk for CV events. Age and comorbidities could worsen TRH, especially if BP is not controlled by medication or therapy.

erhöhte Prävalenz von Organschäden bei TRH-PatientInnen

Hypertension, especially if not controlled, is a leading cause of cardiovascular and renal diseases and it increases the risk for stroke, coronary artery disease, arrhythmias, and heart-, and renal failure. Patients with TRH are characterised by an increased prevalence of target organ-damage [35].

Current clinical management of the disease or health condition

A0024 – How is TRH currently diagnosed according to published guidelines and in practice?

Berücksichtigung von Differenzialdiagnosen, wie z. B. ...

In order to diagnose patients with suspected TRH other causes of uncontrolled hypertension need to be ruled out. The following differential diagnoses need to be considered [34]:

... pseudo-resistente Hypertonie, die u. a. folgende Ursachen hat ...

- **Pseudo-resistant hypertension:**
  Patients with pseudo-resistant hypertension have poorly controlled hypertension that appears to be resistant but is actually attributable to other factors.

  The five most common reasons for pseudo-resistance are:

  ... fehlerhafte BD-Messungen, mangelhafte Befolgung von Lifestyle- und Diätmaßnahmen, Non-Adhärenz bzgl. Medikamenteneinnahme ...

  - Inaccurate BP measurements (for instance by use of an inadequate cuff size)
  - Poor adherence to lifestyle and dietary measures to lower BP
  - Poor adherence to antihypertensive therapy:
    Poor therapy adherence is a major cause of uncontrolled hypertension. Several studies estimated the percentage of non-adherent hypertonic patients to be between 35-80% [36-38], whereby fewer medications were detected than prescribed in patients urinary or blood samples. The highest prevalence of partial and total non-adherence was found among patients with inadequate BP control [36, 38].

  ... suboptimale Medikation ...

  - Suboptimal antihypertensive therapy:
    From the medical side, suboptimal therapy is also a common cause of uncontrolled hypertension, due to lacking administration of more effective drugs, suboptimal doses, or inadequate combinations of antihypertensive medicines [34].

  ... „Weisskitteleffekt" ...

  - White coat hypertension ('isolated clinic/office hypertension') refers to patients who have BP readings above 130/80 mmHg when measured in the doctor's office, but normal BP when measured in non-office readings or in 24-hours ambulatory blood pressure measurements (AMBP) [34]. One indicator for white coat hypertension is high office BP without signs of target organ damage, and symptoms of hypotension, such as fatigue, dizziness, related to overtreatment with antihypertensive medication [35].

sekundäre Hypertoniegründe, wie z. B. renale Arterienstenose, chron. Nierenerkrankung etc.

- **secondary causes of hypertension:**
  Patients with resistant hypertension are more likely to suffer from underlying secondary causes for hypertension than the general hypertensive population. In a study on renal denervation for the treatment of TRH, almost 50% of the 1,416 patients with TRH needed to be excluded due to secondary causes of hypertension [39]. The most com-

mon causes of secondary hypertension include primary aldosteronism, renal artery stenosis, CKD, and obstructive sleep apnea. Less common causes are pheochromocytoma, Cushing's syndrome, and aortic coarctation [1, 4, 34].

diagnostische Evaluation und Behandlungspfade bei TRH

The adequate diagnostic approach for suspected TRH requires detailed information on the patient's history, including lifestyle characteristics and diet, a detailed physical examination and laboratory test to identify risk factors and exclude secondary causes of TRH [4]. Laboratory test should include measurement of serum electrolytes, glucose, and creatinine as well as a urinalysis with estimation of proteinuria.

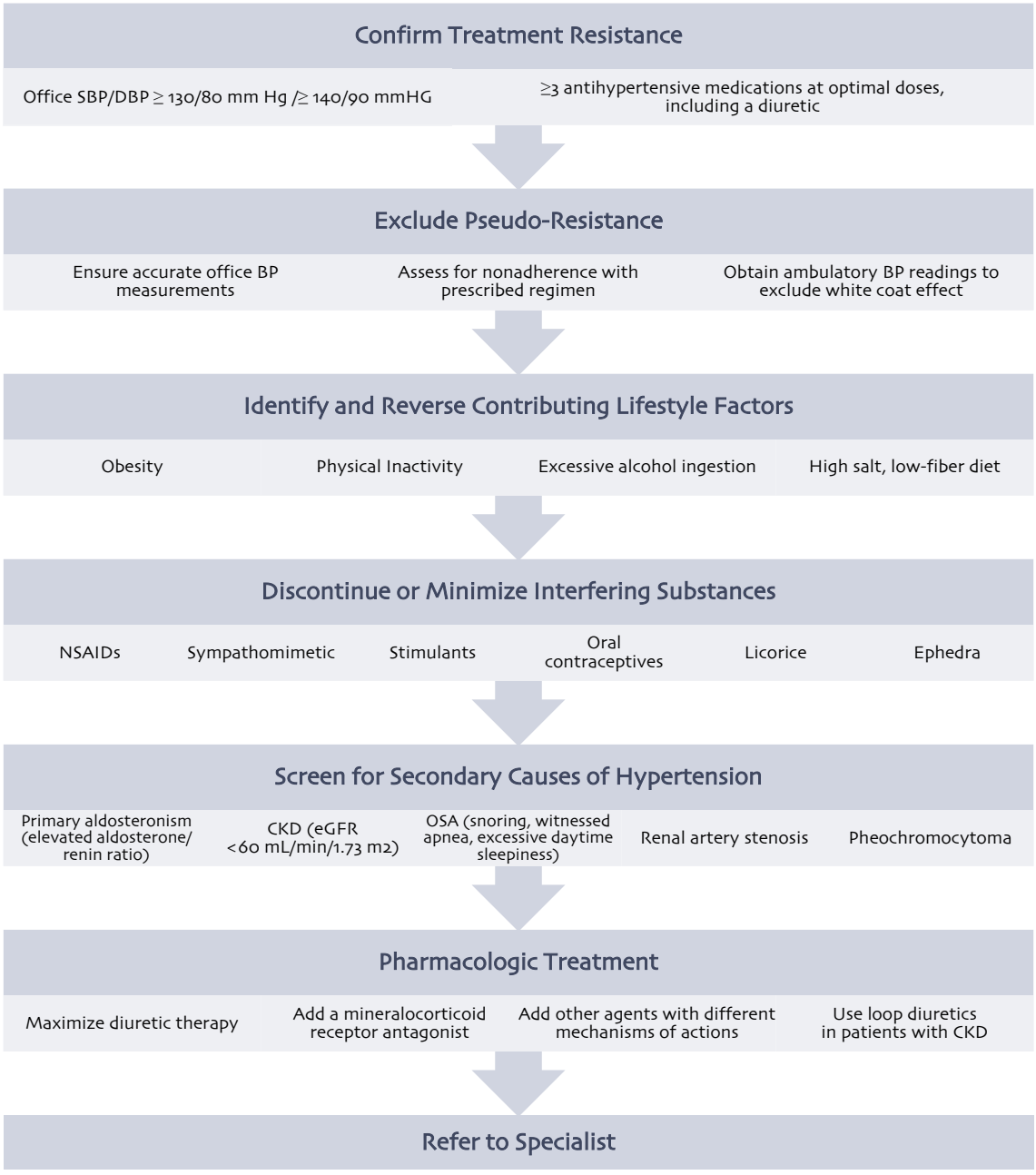

Figure 4-1: Diagnostic evaluation and treatment for resistant hypertension [1]

24-Stunden BD-Monitoring als integraler Teil in der TRH-Diagnostik

The definition of TRH as BP above 130/80mmHg [1] or 140/90 mmHg [4] despite three or more antihypertensive medicines is based on office BP measures. Given the high number of white-coat hypertension in suspected TRH patients, 24-hours AMBP is recommended as integral part of the diagnosis of TRH [4, 35]. Furthermore, secondary causes of hypertension need to be considered. An absence of the night-time drop of BP ('dipping') or increase of BP during night ('reverse dipping') provide clues for the presence of secondary hypertension and can be seen in the 24-hour AMBP measurements [35]. The diagnostic and management algorithm for patients with suspected TRH based on the 2017 ACC/AHA guidelines is presented in Figure 4-1.

A0025 – How TRH currently managed according to published guidelines and in practice?

TRH-Behandlung: Kombination aus ...

A combination of non-pharmacologic and pharmacologic approaches is recommended for the treatment of TRH [4].

nicht-medikamentösen Maßnahmen, wie z. B. salzarmer Kost, Gewichtsreduktion ...

Non-pharmacologic therapy includes the identification and subsequent treatment of potentially reversible and lifestyle related factors that contribute to TRH [24]. Initially, medications that raise BP need to be discontinued and lifestyle related factors modified. A low-salt diet, weight loss in overweight patients and moderation of alcohol intake are essential components of TRH treatment. Involving the patient in monitoring their BP at home and increasing awareness of the risk factor may help to improve control of BP.

... sowie medikamentöse Kombinationstherapie

The pharmacologic treatment of resistant hypertension involves combinations of three or more drugs. The preferred three-drug regimen consists of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), a long-acting calcium channel blocker such as amlodipine, and a long-acting thiazide diuretic, preferably chlorthalidone [4]. If hypertension persists, the ESH/ESC guidelines recommend the use of mineralocorticoid receptor antagonists such as spironolactone or eplerenone, the alpha-1-blocker doxazosin and a further increase of diuretic doses. If renal function is impaired, the switch to a loop diuretic replacing thiazides or chlorthalidone is suggested. Monitoring of serum potassium levels for both hypokalemia and hyperkalemia are necessary if are mineralocorticoids used [4, 24].

europäische Leitlinien-Empfehlungen

Überweisung an SpezialistIn bei persistierendem Bluthochdruck

As described above, secondary causes need to be considered. If a secondary cause is suspected or if BP remains high despite six months of treatment intensification, referral to a hypertension specialist is recommended [24].

Leitlinien schlagen Erwägung von BAT vor, wenn Medikation nicht zu gewünschten Effekten führt

allerdings deutliche Einschränkungen

If multiple-drug treatment at the maximum tolerated dosage remains ineffective, the ESH/ESC 2013 guidelines suggest taking other invasive approaches such as BAT into consideration (class IIb, Level C[1]). While the utility of renal denervation has not been established in a large, blinded RCT (Symplicity-HTN-3), the results for BAT are still pending. It is recommended that these experimental procedures remain in the hands of experienced specialists and are restricted to hypertension centres. Furthermore, the recommendation is limited to patients at high risk, with >160 mmHg SBP or >110 mmHg DBP and where actual resistance has been confirmed by ABPM [4].

[1] Class of recommendation, Level of evidence

Effects of the disease or health condition on the individual and society

A0005 – What is the burden of disease for patients with TRH?

A0006 – What are the consequences of TRH for the society?

TRH verläuft zumeist asymptomatisch

As with hypertension, TRH is usually asymptomatic. The patients would therefore often not realize having an elevated BP, and would not complain about symptoms.

erhöhte Krankheitslast bei TRH u. a. durch Chronizität und Risiken für kardiovaskuläre Ereignisse

The chronicity of the condition and the significance as a risk factor for CV events makes most of the burden for patients, and society. Due to the lack of symptoms, compliance and adherence to the antihypertensive medicines is a major factor when treating hypertension and TRH.

Since hypertension is a major risk factor for CV, the societal burden comes with the number of CV and/or renal events, and related treatment costs.

Target population

A0007 – What is the target population in this assessment?

A0023 – How many people belong to the target population?

A0011 – How much are the technologies utilised?

BAT-Zielgruppe sind TRH-PatientInnen

The target population of this assessment are patients diagnosed with TRH as defined above, after exclusion of secondary causes of uncontrolled hypertension and pseudo-resistance.

Kontraindikationen

BAT is contraindicated in patients with baroreflex failure or autonomic neuropathy, uncontrolled, symptomatic bradyarrhythmias, carotid atherosclerosis greater than 50% or ulcerative plaques in the carotid artery [26].

Prävalenzschätzungen bei TRH zw. 2 % und 30 %

The actual prevalence of TRH is not known and controversially discussed. A wide variability exists in the reported prevalence ranging from 2% to 30% of hypertensive patients [3], depending on the population examined [4].

TRH-Prävalenzdaten aus USA

Using population-based data from the National Health and Nutrition Examination Survey from 2003 to 2008 in the US Persell et al. reported a prevalence of 8.9% among individuals with hypertension (defined as a BP ≥140 mmHg systolic or ≥90 mmHg diastolic), and 12.8 % among patients treated with antihypertensive medication [40]. A Spanish patient register of 68,000 patients showed a similar prevalence of 12.2%; however, after AMBP, one third of these patients were diagnosed as having white-coat resistance [41]. The prevalence and incidence rate was substantially lower in a retrospective analysis in two US states by Daugherty et., showing that among 205,750 patients with newly diagnosed hypertension, 1.9% developed TRH with a median of 1.5 years from initial treatment start [3].

Anstieg an TRH-PatientInnen für kommende Jahre erwartet

According to an analysis by Egan et al. the number of TRH patients is likely to rise in the coming years [42]. They showed a difference in prevalence rates of 15.9% in 1998-2004 and 28% in 2005-2008 (data was derived from the National Health and Nutrition Examination Survey and included 13,375 patients). An increased awareness and improved screening could, however, also explain the rise in the numbers of TRH patients.

nicht alle PatientInnen mit Bluthochdruck erfüllen Kriterien einer TRH

One reason for the wide range in prevalence rate is that not all patients with uncontrolled hypertension would meet the defined requirements for TRH, and poor adherence or inadequate treatment regimens are often the underlying factors for uncontrolled hypertension. Furthermore, not all epidemiologic studies include detailed information on medication dosing and treatment adherence [43]. An evaluation of the prevalence of truly resistant hypertension among 140 patients with uncontrolled hypertension showed that only 45% would meet the definition of TRH [44]. Moreover, an estimated 37-44% of patients with uncontrolled hypertension have white-coat hypertension [41].

Prävalenz von Bluthochdruck in Ö bei 25 % (Männer) bzw. 17 % (Frauen) – >50% nicht kontrollierter BP; Zahl an TRH-PatientInnen ist nicht verfügbar

In 2015, the prevalence of hypertension in Austria was estimated at 25.2 % among men and 16.8% among women [45]. In a recent Austrian cross-sectional multicentre study on 4303 patients with hypertension, only 40% of patients achieved BP control (defined as <140/90 mmHg office BP), despite a high degree of awareness (93% of study participants answered to be aware of the condition and associated risk factors) [46]. The number of patients with true TRH in Austria is not known.

5 Clinical effectiveness

5.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

kritische Endpunkte: BD-Senkung über 1 Jahr von mehr als 10 mmHg (24-Studen Messung) und Rückgang von kardiovaskulären Ereignissen

- decrease in cardiovascular events (CV) (death or morbidity from cardiovascular causes: non-fatal myocardial infarction, acute coronary syndrome, non-fatal stroke, non-fatal acute decompensated heart failure) (critical)
  - decrease in mortality due to CV events compared to standard therapy
  - decrease in morbidity due to CV events compared to standard therapy
- sustained BP (>1 year) reduction by more than 10 mmHg, measured by 24 hours AMBP (critical). While BP reduction is usually regarded as surrogate parameter, we deemed it crucial to assess the effectiveness of BAT, as the primary goal of this therapy is BP reduction.

Furthermore, the following outcomes were considered relevant to answer the research questions:

relevante Endpunkte: Lebensqualität, Hospitalisierungsrate und reduzierte Medikation

- Hospitalisation rate
- reduction of antihypertensive medication (number of anti-hypertensive medicines) to reduce BP to <140 mmHg
- Quality of life (QoL)

5.2 Included studies

In total, seven references to six studies were selected for data extraction, of which one was a randomised controlled trial, one a randomised cross-over trial, and five studies were case series, of which one was the long-term follow-up of an included study. The case series did not include a comparison group, yet, had a before-after design, comparing baseline values with results after at least 6 months of BAT therapy. Due to the limited amount of available evidence, case studies with a minimum number of 20 cases and a prospective, before-after design were thus also considered to also answer efficacy-related research questions.

7 Studien eingeschlossen: 1 RCT, 1 randomisierte Cross-over Studie und 5 Fallserien (ohne Kontrollgruppen)

Other than the follow-up study on long-term BAT effects, we did not include studies where duplication of data was suspected, due to similar sampling periods, study centres, and patient characteristics. Furthermore, we excluded conference abstracts and posters.

Ausschlusskriterien

All studies were either sponsored by the device manufacturer or several authors received consultancy fees from the manufacturer.

Herstellersponsoren bei allen eingeschlossenen Studien

Rheos® system

3 Studien zum Vorgängermodell Rheos® system – jedoch keine GRADE-Bewertung/ Empfehlungen

Three studies assessed effectiveness and safety of the first generation devices, the Rheos® system, which is not marketed anymore, and where devices have been entirely replaced with the second generation device, the Barostim neo™. For completeness, we extracted these data and describe them in the results questions were relevant, however, did not consider them for the GRADE summary of findings and the subsequent recommendation, as this product is not available anymore.

1 RCT und 2 Fallserien zu Rheos® system

The three studies on the Rheos® system were one RCT, and two case series, of which one was the long-term follow up of patients included in the Rheos trials (DEBut-HT, Rheos pivotal trial, Rheos feasibility study). The two original studies included a total of 310 patients, 265 within the Rheos trial and 45 within the case series. The follow-up study analysed data from 383 patients, of which 143 completed 5-year follow-up and 48 completed 6-year follow-up. Data from these patients were also included in the two original trials. The studies were similar as regard to inclusion and exclusion criteria, mean age (53 years), number of anti-hypertensive medicines (on average 5), and percentage of female participants (around 40%). The studies had a follow up of one year (RCT), two years (case-series), and the follow-up study 6 years.

Barostim neo™

4 Studien zu Barostim neo™ eingeschlossen

We identified four studies on the Barostim neo™, of which none had a control group that did not receive the intervention.

1 Studie mit Cross-over Design mit 16 PatientInnen (je 8 PatientInnen in BAT-on bzw. BAT-off Gruppe)

One study had a randomised, controlled cross-over study-design, whereby both groups had received the intervention BAT with the Barostim neo™ one year prior to the study, and withdrawal of BAT therapy was assessed [8]. The study randomised 16 patients that had previously received BAT with the Barostim neo™ for the duration of one year into a BAT-on and a BAT-off group. After four weeks, the groups switched from the off-phase to an on-phase and vice versa. Patients included in Beige et al. were previously also included in the case series by Hoppe et al. 2011 and Wallbach et al. 2016 [5, 7].

insgesamt 106 PatientInnen in den 3 Fallserien mit einem Durchschnittsalter von 57 Jahren

The three remaining case series on the second generation device included a total of 106 patients, ranging from 30 to 51 participants [5-7]. The inclusion and exclusion criteria were similarly in between studies. The mean age of the patients receiving BAT with Barostim neo™ was slightly higher than for the trials on the Rheos® system, with a mean age of about 57 years. The mean anti-hypertensive medicines at baseline were also higher than in the Rheos® study population with an average of 6 medicines. Three studies reported an average BMI above 30, one study did not report on this patient characteristic [5].

in 3 Studien lag BMI der PatientInnen > 30

Diabetes und chron. Nierenleiden als primäre Komorbiditäten

In each of the four studies on Barostim neo™ at least 20% of study participants had a history of renal denervation (in total 33 of 122). Relevant comorbidities of the study population were diabetes (30% of study participants) and CKD > stage III (28%); but the proportion of these comorbidities was similar across studies. One study did not report on these patient characteristics [8].

3 von 4 Barostim neo™ Studien hatten 6-Monate follow-up

All studies on the Barostim neo™ had a follow-up of 6 months, apart from the withdrawal study by Beige et al. 2017, which followed patients for eight weeks only.

Table 5-1 provides an overview of the included studies regarding the device, the study design, number of participants and lengths of follow-up. Detailed study characteristics and results of included studies are displayed in the Appendix Table A-1 and Table A-2 and in the evidence profile in Table A-6.

Table 5-1: Overview of included studies on Baroreceptor Activation Therapy

Study	Bisognano, 2011	Scheffers, 2010	de Leeuw, 2017	Hoppe, 2012	Wallbach, 2015	Wallbach, 2016	Beige, 2017
Devices	Rheos® system	Rheos® system	Rheos® system	Barostim neo™	Barostim neo™	Barostim neo™	Barostim neo™
Design	RCT	Prospective case series	Open-label follow-up	Prospective case series	Prospective case series	Prospective case series	Cross-over study
Number of participants	265	54	383*	30	25	51	16**
Lengths of follow-up	1 yr	2 yrs	6 yrs	6 months	6 months	6 months	6 months
Conflict of interest	authors received consultancy fee and research grants form CVRx						

* *patients were also included in Bisognano, 2011 and Scheffers, 2010*

** *patients were also included in Hoppe et al, 2011; Wallbach et al. 2016*

5.3 Results

Mortality

D0001 – What is the expected beneficial effect of BAT on mortality?

D0003 – What is the effect of BAT on the mortality due to causes other than TRH?

Whether BAT has a beneficial effect on mortality has not been established in the studies.

keine Ergebnisse zu positiven Effekten von BAT auf Mortalität

The RCT on the Rheos® system reported a total number of 7 deaths in the whole patient population, of which 4 occurred during the initial 12 months follow-up, and additional three in long-term follow-up [12]. The causes of death were three intracerebral haemorrhages, two cardio-pulmonary arrests and one ruptured aortic aneurysm, and one drug overdose. In the long-term follow up on the Rheos® system, de Leeuw et al reported 28 deaths over a time span of six years. Whether some of these deaths were related to the therapy, or whether on the contrary BAT prevented further deaths as a result of long-term hypertension, cannot be evaluated, due to a lacking control group of TRH-patients that did not receive the intervention.

RCT zu Rheos® System berichtet 7 Todesfälle – davon 4 innerhalb des ersten 12 Monate follow-ups

im Langzeit follow-up 28 Todesfälle über 6 Jahre

In the four studies on the Barostim neo™, no cases of death related to hypertension or the device occurred [5-8].

keine Todesfälle in den 4 Barostim neo™ Studien

Morbidity

D0005 – How does BAT affect symptoms and findings (severity, frequency) of TRH?

Reduction in the number of cardiovascular events

No studies assessed a difference in the number of CV events between TRH patients that received BAT, and patients with conventional standard therapy.

keine Studie berichtet kardiovaskuläre Ereignisse

Reduction of blood pressure

24-hours ambulatory blood pressure

In total, three of seven studies reported data on 24-hours AMBP: two observational before-after case series, and one interventional, randomised cross-over withdrawal study.

3 von 7 Studien berichten zu 24-Std. BD-Werten

1 Fallserie zu Rheos® system verzeichnete BD-Senkung bei Fallzahl von 15 PatientInnen

For the first generation device, the case series by Scheffers et al., 2010 presented data from 15 patients at 12 months of BAT. They reported a significant change in systolic AMBP by -13 mmHg (SD ±3), and diastolic AMBP by -8 (SD ±2) (n=15; p <0.001) [11].

1 Fallserie zu Barostim neo™ verzeichnete BD-Senkung – Sample 44 PatientInnen bei 6 Monate follow-up

For the second generation device, the case series by Wallbach et al. 2016 reported data form 44 patients at 6 months of BAT. SBP changed by 8 mmHg (from 148 mmHg ±17 to 140 mmHg ±23, p <0.01), and DBP by 5 mmHg (from 82 ±13 to 77 ±15 mmHg, p> 0.01). In 24 of 44 patients (55%) AMBP dropped by more than 5 mmHg.

1 randomisierte Cross-over Studie zu Barostim neo™ – Sample 16 PatientInnen;

erhöhte 24-h BD-Werte in der Off-Gruppe

Beige et al. 2017 reported changes in AMBP in a randomised cross-over withdrawal study [8]. They randomised a total of 16 patients that had previously received BAT with the Barostim neo™ for the duration of one year into a BAT-on and a BAT-off group. After four weeks, the groups switched from the off-phase to an on-phase and vice versa. They hypothesised an increase in BP in the BAT-off groups that was similar to the initial BP drop when the device was first implanted, and subsequently, a BP drop when BAT is re-activated. A significant increase of AMBP by 10 mmHg systolic and 8 mmHg diastolic (±4/±3, p=0.007/0.002) during the BAT-off phase compared to the BAT-on phase was found. However, the BP change did not reach a similar magnitude to the initial BP drop after implantation of the device.

Office blood pressure

1 RCT zu BD Senkung anhand Office-messungen: nach 6 Monaten keine signifikanten Gruppenunterschiede

One comparative study provided data on changes in office BP: the RCT Rheos pivotal trial (n=265) [12]. Participants were randomised at a 2:1 ratio, whereby group A (n=181) received immediate activation of the Rheos® device, while group B (n=84) received delayed activation after 6 months. Mean change in systolic BP at 6 months was not significantly different between the intervention group and the control group (16 ± 29 mmHg to 9 ±29mmHg; p=0.08).

2 Fallserien zu Barostim neo™ mit Follow-up Daten zu je 6 Monaten

For the second generation device, mean changes in office BP were available from two case series (n=44, n=30), at 6 months follow-up, but no comparative studies were available. The mean change in systolic BP ranged from – 20 ± 8 to -26 ± 4 mmHg [5, 7].

BD-Anstieg in Cross-over Studie nach 4 Wochen

The crossover withdrawal study by Beige et al. 2017 reported an increase of BP by 10 mmHg after a four-week period of deactivating BAT therapy; however, it did not reach the same magnitude as the initial BP drop at time of implantation.

Percentage of patients < 140 mmHg

2 von 7 Studien berichten zu PatientInnen (in %) mit BD-Werten < 140 mmHg

This outcome was reported by two studies:

- In the Rheos pivotal trial 42% of patients from the intervention group and 24% of patients from the control group achieved a BP reduction to < 140 mmHg after 6 months (p=0.005). After one year, when BAT was activated in both groups, this number increased to 50% of all patients [9].
- Data for the second generation device was available from one case series by Hoppe et al. 2011 (n=30), showing that 43% of patients achieved a BP reduction below 140 mmHg at 6 months of BAT [7].

Antihypertensive medication

The RCT on the Rheos® system did not report on changes in the number of antihypertensive medicines.

In two case-series on the second generation device, no significant changes in the number of prescribed antihypertensive medicines were found [6, 7]. Wallbach et al. 2016 found a reduction from 6.5 (±1.5) to 6.0 (±1.8) medicines (n=51, p=0.03) [5].

Veränderungen von BD-senkender Medikation im RCT zu Rheos® system unbekannt; 2 Fallserien zu Barostim neo™ zeigen keine Veränderungen

Hospitalisation rate

There was no data available for this outcome.

keine Angaben verfügbar

D0006 – How does BAT affect progression (or recurrence) of TRH?

Long-term open-label follow-up on data of the first generation device showed sustained response of BAT at 5 years follow-up with a mean reduction of SBP by 30 mmHg and DBP 10 mmHg (n=143; no confidence intervals or standard deviations were reported) [10].

Effektkontinuität bei Rheos® system vorhanden

There was no comparative data on patients that received standard therapy. There was no data available that compared disease progression in terms of occurrence of CV events.

keine Vergleichsdaten zu Standardtherapie

Function

D0011 – What is the effect of BAT on patients' body functions?

Apart from a reduction of BP, which is described in D005, BAT is currently evaluated for its effects on heart failure.

laufende Evaluierung zu BAT bei Herzinsuffizienz

The studies did not report on further effects on patients body function.

D0016 – How does the use of BAT affect activities of daily living?

None of the identified studies addressed this question.

keine Angaben bzgl. Einfluss von BAT auf Alltagsleben verfügbar

Health-related quality of life

D0012 – What is the effect of BAT on generic health-related quality of life?

D0013 – What is the effect of BAT on disease-specific quality of life?

No evidence was found on health or disease-specific quality of life.

keine Angaben zu LQ verfügbar

Patient satisfaction

D0017 – Was the use of BAT worthwhile?

No evidence was found on patient satisfaction with BAT.

keine Angaben zu PatientInnenzufriedenheit verfügbar

6 Safety

6.1 Outcomes

kritische Endpunkte bzgl. Sicherheit:

schwere verfahrensspezifische NW (z. B. chirurgische Komplikation) und

schwere IV-bezogene NW (z. B. plötzliche Bradykardie)

The following outcomes were defined as *crucial* to derive a recommendation:

- *Serious procedure-related adverse events (AE):* defined as adverse events that occurred within the first 30 days of implantation, such as surgical complications, nerve injury, wound complications, pain of glossopharyngeal nerve, surgical or anaesthetic complications.
- *Serious adverse events (SAE):* defined as events that occurred after the initial 30 days until the final follow-up. Hypertension or device-related AE were considered, as the causality and differentiation are not plausible for most events (i.e sudden bradycardia could stem from a high stimulation with BAT, be related to the disease or underlying comorbidities, or to drug treatment). The system reference guide provides a list of possible adverse events during BAT, such as myocardial infarction, stroke, transient ischemic attack, systemic embolization, infection, arterial damage, pain, nerve damage, hypotension, hypertensive crisis, injury of baroreceptors, cardiac arrhythmias, worsening of kidney disease, the dislocation or the pulse generator or other reasons resulting in the need for re-operation.

EC-Guidelines zu Definitionen von schweren NW und Komplikationen bei Medizinprodukten

In accordance with the European Commission guidelines for medical devices on SAE reporting, the following definition was applied[2]:

SAE is an adverse event that led

1. to death,
2. to a serious deterioration in health of the subject that either resulted in a life-threatening illness or injury,
3. a permanent impairment of a body structure or a body function,
4. in-patient hospitalisation or prolongation of existing hospitalisation,
5. medical or surgical intervention to prevent life-threatening illness or injury.

6.2 Included Studies

keine zusätzlichen Studien für Sicherheit identifiziert

To evaluate safety of BAT, no additional studies were identified that met the inclusion criteria. Included studies and characteristics are described in 5.2. Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-6.

[2] http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_3_en.pdf

6.3 Results

Patient safety

C0008 – How safe is BAT in comparison to standard therapy?

keine Vergleiche bzgl. Sicherheit BAT mit Standardtherapie vorhanden

No studies comparing BAT to standard therapy were available.

Vergleichsdaten nur aus RCT zu Sham-Prozedur für Rheos® system verfügbar

The only comparative data to evaluate safety was derived from the RCT on the first generation device, the Rheos pivotal trial [12]. Bisognano et al. 2011 reported 68 procedural complications, of which 13 patients experienced surgical complications, 13 had nerve injuries with residual effect, 12 patients had temporary nerve injuries, seven patients had respiratory complications and seven patients wound complications. Furthermore, they reported 34 device-related adverse events, of which six were hypertension-related strokes, reasons for the remaining 28 adverse events were not provided. The Rheos pivotal trial missed its primary safety outcome on procedural safety, targeting an event-free rate of more than 82%, as only 74.8% of patients were event-free, and 25% experienced adverse events. For device safety, 87.2% of patients were event-free, which exceeded the target criterion of >72%. Five of the 265 patients had their device removed during the 12 months follow up time.

335 schwere NW in 111 PatientInnen, davon 26 BAT-bezogene schwere NW

Within the six years follow-up, de Leeuw et al. 2017 reported 335 SAEs occurring in 111 patients. 26 SAEs (23%) were directly related to the procedure or BAT system. Five SAE were related to the IPG and four events to the carotid sinus lead, such as migration of the device or lead, tension, and haematoma. 12 patients experienced a total of 13 CV events, six hypertensive crises, five cases of hypotension, one case of bradycardia. One patient suffered a hypertension-related stroke with residual effects, other complications resolved without residual effects.

2 Fallserien berichten bzgl. Barostim neo™ zum Endpunkt Sicherheit (74 PatientInnen)

For the second generation device, safety outcomes were reported by two case-series for a total patient population of 74 patients. Hoppe et al. 2012 (n=30) described three procedural AE, all of which were resolved: device pocket haematoma, pain near the device site, and wound healing complication. Furthermore, one patient reported pain near the device system beyond 30 days. Wallbach et al. 2016 (n=44) described 20 procedure-related AEs and three SAEs. The reported procedure-related adverse events were surgical complications, wound healing problems, postoperative haematomas, and pain near the surgical wound. Wallbach et al. 2016 reported two cases were revision of surgery was necessary, one due to movement of the IPG and one due to wound healing defects. Furthermore, one patient experienced a hypertension-related stroke.

keine Explantationen bei Barostim neo™

Within the 6 months follow-up, none of the second generation devices needed to be explanted. A detailed listing of adverse events is provided in Table A-2.

C0002 – Are the harms related to dosage or frequency of applying BAT?

C0004 – How does the frequency or severity of harms change over time or in different settings?

keine Angaben zu Stärke bzw. Häufigkeit von NW verfügbar

None of the studies that met the inclusion criteria described harms related to dosage or frequency.

C0005 – What are the susceptible patient groups that are more likely to be harmed by the use of BAT?

No evidence was found in susceptible patients groups more likely to be harmed by BAT.

keine Angaben bzgl. speziell gefährdeter PatientInnen

C0007 – Is BAT associated with user-dependent harms?

The implantation requires surgical skills, and experience to place the electrode in the correct place. As afore-described, 23 SAE were related to surgical and procedural complications. Furthermore, the frequency and amplitude of BAT stimulation need to be set correctly by trained personnel in order to ensure adequate stimulation that does not result in hypotension, bradycardia or other adverse events.

BAT-Implantation erfordert chir. Kompetenz und Erfahrung, ebenso ExpertInnen für BAT-Betrieb und -Ablauf

7 Quality of evidence

RoB mittels IHE-Checkliste

RoB for individual studies was assessed with the IHE checklist (case series) [47] and with the Cochrane RoB tool for RCTs [18]. Results of the RoB assessment are presented in Table A-3 and Table A-4.

hoher RoB in 1 von 2 kontrollierten Studienund in 2 von 5 Fallserien

Regarding the two controlled studies, one was graded with high RoB, due to lacking statistical reporting of relevant comparators, a short follow-up and partial reporting of patient characteristics. Two of the five case series were assessed with high RoB, due to partial or none reporting of AE, and loss to follow-up. The remaining three studies were considered to have low RoB.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme for each endpoint individually [48]. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group.

4 GRADE-Kategorien bzgl. Stärke der Qualität

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = 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** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-6.

prinzipiell schwache Evidenz bzgl. Wirksamkeit und Sicherheit zu BAT

Overall, the strength of evidence for the effectiveness and safety of BAT is very low. For the comparison of BAT to standard therapy, no evidence was available.

Table 7-1: Summary of findings table of BAT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard therapy (or BAT-off)	Risk with Barostim Activation Therapy				
Reduction of systolic 24-hour AMBP (Reduction of AMBP)		The mean reduction of systolic 24-hour AMBP in the intervention group was 8 mmHg lower (2 lower to 14 lower)	-	44 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	No comparison group was available.
Reduction of office SBP		The mean reduction of office SBP in the intervention group was 23 mmHg lower (0 to 0)	-	74 (2 observational studies)	⨁◯◯◯ VERY LOW [a,b]	No comparison group was available. Confidence Intervals were not reported
Mortality (reduction in the number of lethal CV events)	**not reported**	-	-	-	-	The number of lethal CV events in comparison to standard management was not reported by any of the studies
Morbidity (reduction in the number of CV events)	**not reported**	-	-	-	-	The number of CV events in comparison to standard management was not reported by any of the studies
Procedure-related serious adverse events	24 events in 74 patients			74 (2 observational studies)	⨁◯◯◯ VERY LOW [a,b]	Safety outcomes were only considered for the second generation device
Device-related serious adverse events	4 events in 74 patients			74 (2 observational studies)	⨁◯◯◯ VERY LOW [a,b]	Safety outcomes were only considered for the second generation device

[a] *not blinded, no adjusted for confounding*

[b] *small sample size, wide confidence intervals*

[c] *First generation device, different operating mechanism and safety profile; not in clinical use anymore*

Abbreviations: *AMBP = ambulatory blood pressure, CI = confidence interval, CV = cardio-vascular, SBP = systolic blood pressure*

8 Discussion

The stimulation of the baroreceptors to provoke a decrease in blood pressure (BP) fostered new interest in and high hopes for the treatment of resistant hypertension (TRH). However, substantial evidence proving the efficacy and safety of BAT remains limited. While BAT devices have been introduced to the European market already in 2007 when the Rheos® system (the first generation device) received its CE mark, the available evidence is scarce and the quality of evidence is very low.

Stimulation der Barorezeptoren bei TRH durch BAT – jedoch eingeschränkte Evidenzlage

For the purpose of this review, we identified seven studies on BAT that met our predefined inclusion criteria (Table 1-1): Three studies on the first generation device, the Rheos® system, and four studies on the second generation device, the Barostim neo™. The two generations of devices are fairly different: the Barostim neo™ features a smaller electrode requiring a smaller incision, and a smaller pulse generator with a longer battery life. Since the electrode is placed unilaterally on only one carotid sinus, the surgical procedure is simpler and shorter, requiring less recovery time [20]. Due to these substantial modifications and differences between the two generations of devices, the available evidence for each device needed to be evaluated separately, and a pooling of efficacy and safety data would not be sensible. Importantly, the Rheos® system is not available on the market anymore, and implanted devices have been entirely replaced with the second generation device at the end of battery life.

7 Studien eingeschlossen; 3 von 7 Studien zu Rheos® system (Gerät erster Generation) und 4 von 7 zu Barostim neo™ (aktuell verwendetes Gerät); getrennte Studienbewertungen; Geräteunterschiede bzgl. Implantation, techn. Ausstattung und Batterielaufzeit

For the Rheos® system, we could identify one double-blind RCT on 265 patients [9], one uncontrolled trial on 45 patients (not blinded, not randomised) [11], and one open-label follow-up pooling patients from these trials in a six-year follow-up [10]. The Rheos Pivotal trial was the only controlled study that compared active BAT to non-active BAT (sham). However, the controlled period was short with only six months, thereafter the devices in the control group were turned on and the study continued as an open-label follow-up. For the primary endpoint of an SBP reduction by more than 10 mmHg after six months no significant difference was observed within the two groups (54% in the interventional group, to 46% in the sham group, p> 0.005, office BP). In the long-term open-label follow-up of the Rheos® patients, a sustained BP reduction in office BP by 35/18 mmHg was documented, and apparently, no signs of the formerly expected adaptation of the reflex were noted [10].

1 RCT, 2 Fallserien zu Rheos® system;

nur eine kontrollierte Studie zu BAT (Rheos® system) mit 6 Monate Follow-up; keine signifikante Senkung des systolischen BDs

BD-Senkung in unkontrollierter Studie im 6 Jahres Follow-up

For the second generation device, no controlled studies are available to date that compared BAT to sham procedure or BAT to standard management (information confirmed by manufacturers). We identified three case series with a patient population ranging from 33 to 51 patients, and one randomised-controlled cross-over withdrawal trial on 16 patients [8]. The latter assessed whether a withdrawal of therapy in terms of a deactivation of already implanted BAT devices would lead to a substantial increase of BP, comparable to the initial BP drop at the time of implantation [8]. To note, patients included in this trial were also included in the case series. While Beige et al. 2017 could indeed show a BP increase both in AMBP and office BP during the BAT-off phases, the increase did not show the same magnitude as the initial BP drop at the time of implantation, and thus, the primary endpoint was missed [8]. These findings open questions whether the initial BP drop might be related to the surgical intervention itself, or if other underlying reasons exists that would explain the more pronounced decrease in BP at the time of implantation. Due to the small case count of only 16 patients, no conclusive evidence could be derived from this trial.

keine kontrollierten Studien zu Barostim neo™ verfügbar; 3 Fallserien identifiziert;

insgesamt keine robusten Ergebnisse bzgl. BD-Senkung

sehr kleine Fallzahl an PatientInnen

nur 1 von 3 Studien zu Barostim neo™ mit 24 Std. BD-Messung

jedoch nur moderate BD-Senkung feststellbar

The evidence from three observational case series reported an average office SBP decrease ranging from -20 to -26 mmHg. The observed BP reductions are of comparable magnitude to those reported in the Rheos trial [12]. Importantly, only one study measured a decrease of BP by means of AMBP, while the other studies applied in office BP measurements. The reported decrease in AMBP was, however, relatively modest, with an average decrease in SBP by 8 mmHg. A reduction of at least 5 mmHg was not achieved in 20 of 44 patients (45%) [5].

TRH-Leitlinien empfehlen 24 Std. BD-Messung statt Ordinationsmessungen aus Gründen der Messgenauigkeit; nur 2 von 7 Studien mit 24 Std. BD-Messungen (je 1 zu Rheos® system und Barostim neo™)

Several guidelines on TRH have recommended the use of AMBP measurements rather than office BP measurements, since the latter is less reproducible and relate to a greater extent on the situational evoking of BP elevation, for instance, due to white coat hypertension [1, 4, 49]. Studies indicated that AMBP provides a better prognostic value compared to office BP [50]. Furthermore, office BP measurements are more prone to mistakes in the measurement technique, such as improper patient positioning, wrong cuff size, poor timing of measurements, and equipment-related errors [43]. Yet, for the whole body of evidence on BAT only two studies reported changes of BP by means of AMBP measurements, one on the first (n=45) and one on the second generation device (n=44) [5, 11].

keine Konklusion bzgl. BAT und Reduktion von BD-Medikation möglich

BAT was suggested to reduce the number of needed anti-hypertensive medications. However, the evidence of a change in the number of anti-hypertensive medications was very heterogeneous without a clear pattern of an increase or a decrease.

5 % mit schweren NW und 25 % der PatientInnen mit verfahrensspezifisc hen NW im Rheos® system Trial; Batteriewechsel war bei Rheos® system nach 1,5 bis 2 Jahren notwendig und auch mit hohen Kosten verbunden

Regarding the safety of BAT, comparative evidence was only available from the Rheos pivotal trial for the initial 6 months [9]. The implantation of the first generation device was associated with a number of SAE, whereby nearly 5% of patients experience nerve injuries with residual effects. The Rheos pivotal trial missed its primary safety endpoint on procedural safety, as one-fourth of the patients experienced AE related to the surgical procedure. In the long-term follow-up de Leeuw et al.2017 reported 335 SAE occurring in 111 patients [10]. Patients needed to undergo surgical revision and battery replacement after one and a half to two years of treatment. Consequently, every patient that remained on treatment for more than two years needed to undergo battery replacement. Apart from the discomfort for the patients to undergo surgical revision, the battery exchange also comes with large expenses: A cost-effectiveness study from the European context documented battery costs at 15,000 Euro; procedural costs for the replacement were approximated with 2,056 Euro [13].

weniger (schwere) NW beim Nachfolgegerät Barostim neo™ – keine direkten Vergleichsdaten mit Rheos® system; Bedarf an kontrollierten Studien zu Barostim neo™ für Bewertung von Sicherheit

In contrast to the first generation device, less procedure-related AE and SAE were reported for the second generation. The most commonly reported AEs for the Barostim neo™ device were temporary nerve injuries, wound healing complications, haematoma, and pain at the site of the device. Regarding SAE, Wallbach et al. 2016 reported one case of hypertension-related stroke [5]. Since the total patient population on the second generation device is much smaller than for the first generation and comparative evidence is missing, true differences can only be established by larger, controlled and ideally blinded studies. While the safety of the device is claimed to be markedly improved in the new generation device, these claims need to be substantiated by controlled studies to prove an actual safety benefit in comparison to standard therapy and sham procedure.

insgesamt geringe Studienqualität bzgl. Barostim neo™

Studien mit Firmensponsoring

keine Angaben zu Anzahl an kardiovaskulären Ereignissen bei BAT im Vergleich zu Standardtherapie

The small patient population, lacking control groups and blinding, and the paucity of studies on the second generation device contribute to an overall very low quality of evidence, both for efficacy and safety-related outcomes. Although it is currently the only marked product, no comparative evidence on the second generation device is available. All of the studies were either directly funded by the manufacturer, or first authors received study grants or consultancy fees. No independently conducted study could be identified. Reporting of safety outcomes was not consistent, and at time lacked details on the adverse events. Importantly, the most crucial outcome of a reduction in the number of cardiovascular events as compared to standard therapy was not assessed by any of the studies. This lack of reporting on this crucial outcome and the lacking comparison to standard management is also the major factor limiting the applicability of the results to the clinical context. Details on the applicability of the body of evidence can be found in Table A-6.

renale Denervation als weitere experimentelle Intervention bei der Behandlung von TRH – nur geringer Nutzen für TRH-PatientInnen in Studien nachweisbar;

Rheos RCT: kritische Endpunkte verfehlt, daher nicht in US zugelassen

Looking at other emerging technologies for the treatment of TRH, another intervention also targeting sympathetic activity is renal denervation, which similarly to BAT held great promises and received vast attention in recent years [27]. However, through the publication of the first RCT results on renal denervation the limited benefit for patients became evident [22]. Similarly, the Rheos Pivotal Trial as first RCT on BAT failed to establish clear benefits on efficacy and safety, as it missed two out of five primary outcomes. On basis of these mixed results, the FDA did not approve the device to treat TRH, but only allowed an open-label extension study under an investigational device exemption. Under this exemption, the new generation device is currently evaluated within the Barostim neo™ Pivotal Trial. Results were initially planned to be published by 2015 and later postponed to September 2017; yet to date, the results of this trial are still pending.

MobiusHD®-Gerät zur Stimulation von Barorezeptoren mittels Stents – nur vorläufige Ergebnisse verfügbar

Another emerging technology targeting the baroreceptors and the baroreceptor reflex is a stent-like device, the MobiusHD® aiming at amplifying the BAT response by increasing wall strain in the carotid sinus. Initial results have been published in the previous year for 30 patients [21], and controlled trials are currently on the way.

laufende Evaluation von Barostim neo™ bei Herzinsuffizienz

In addition to the indication TRH, the Barostim neo™ is concurrently evaluated for its efficacy and safety in the treatment of heart failure. Initial six months results from the ongoing trials have already been published, yet evidence for this indication is yet too limited to draw conclusions on benefits or harms [28], thus, an assessment of this indication was considered premature.

BAT bei TRH auch umstritten aufgrund diagnostischer Abgrenzung der echten Therapieresistenz; unklar welche PatientInnen von BAT profitieren

BAT for the treatment of TRH remains a controversially discussed therapy, not only due to the lacking data on efficacy and safety but also due to difficulties to delineate TRH to other causes of uncontrolled hypertension, such as secondary causes, and pseudo-resistance [51]. Likewise, the actual prevalence of TRH is highly disputed [4]. Consequently, establishing which patient population could actually benefit from the intervention remains undefined. To overcome the diagnostic barriers, AMBP measurements received a prominent placement in the diagnosis algorithm, yet it is unclear how often it is applied outside of clinical trials in daily practice. (see also applicability table Table A-6).

Therapieadhärenz als wesentliche Prämisse bei Behandlung von Bluthochdruck – kaum direkte Erhebungen in Studien

fehlende Einschätzungen zu Therapieadhärenz können Fokus von BAT-Zielgruppen verfälschen

Furthermore, a major obstacle to control hypertension is poor adherence to hypertensive therapy. Therapy adherence is seldomly assessed during the cause of a clinical trial, and if, mostly by means of patient-reported questionnaires rather than urine analysis or other objective measures. An increase or decrease in therapy adherence during the trials could thus be a major confounder of the trial results. Therapy adherence is expected to be improved when patients receive an interventional procedure, yet, the opposite was suggested in a recent study on renal denervation, indicating a decreased adherence after the intervention [52]. Furthermore, the lacking assessment of therapy adherence could lead to inclusion of patients with pseudo-resistant hypertension rather than true TRH, who would not necessarily benefit from the treatment. Future clinical studies should thus require proven therapeutic adherence as inclusion criteria.

Conclusio: unzureichende Evidenz bzgl. Wirksamkeit und Sicherheit von BAT bei TRH; Bedarf an Studien mit Erhebung von Therapieadhärenz und Langzeitergebnisse bzgl. kardiovaskulärer Ereignisse erforderlich

In conclusion, despite the strong physiological rationale of the baroreflex activation, BAT has not conclusively provided robust evidence for its benefit and safety. By contrast, the only comparative data on the first generation device was not able to establish a meaningful benefit for patients. For the new generation device, evidence does not suffice to conclude on effectiveness or safety. Future clinical trials should assess BP reduction based on AMBP measurements, and include monitoring of therapy adherence. More importantly, apart from a reduction in BP emerging technologies on TRH need to prove if they provide a benefit in the long-term reduction of CV events.

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence is not sufficient to prove, that the assessed technology BAT is more effective than, and as safe as the standard management for TRH. No comparative studies on the effects of BAT compared to standard therapy were available. Furthermore, comparative evidence on the only marketed device Barostim neo™ is still lacking. RCTs and controlled studies on the second generation device could allow assessment of actual efficacy and safety for patients, if patient-relevant outcomes, such as a decrease in the number of CV events, is assessed.

unzureichende Evidenz bzgl. Überlegenheit von BAT gegenüber Standardtherapie bei TRH

The re-evaluation is recommended in 2020, if evidence from RCTs has become available.

neuerliche Evaluation in 3 Jahren empfohlen

Ongoing research

The Barostim neo™ Pivotal Trial, a non-blinded RCT comparing BAT to standard management was said to be published in 2015 and postponed to September 2017. However, the results of this RCT on 310 patients are still pending.

noch ausständiger RCT mit 310 PatientInnen zu Barostim neo™

As the first trial not funded by the manufacturers, an RCT conducted by several universities in Norway and Sweden has been initiated in 2015. The Nordic BAT Study includes 100 patients with TRH, is double blinded and compares BAT to the sham procedure. Its primary completing date is November 2020. Furthermore, the ESTIM-rHTN trial, a randomised medico-economic study assesses economic efficacy of BAT compared to standard therapy in 128 patients with TRH. This is the first evaluation of BAT compared to standard therapy, and includes a comparison of the number of CV events, yet as secondary outcome measure.

weiterer laufender RCT in Skandinavien – Ergebnisse für 2020 erwartet

ökonom. Evaluation laufend

In addition to the indication of TRH, BAT is currently evaluated as therapeutic option in patients with heart failure (NYHA Class III). This pivotal trial on Barostim Therapy for Heart Failure (BeAT-HF) enrolled 800 participants and aims at FDA approval (estimated completion date 2021).

Trial zu BAT bei Herzinsuffizienz – Ergebnisse für 2021 erwartet

MobiusHD® (BAT Stimulation auf Stents-Basis) in laufenden CALM Studien untersucht

A second procedure targeting the baroreceptors for the treatment of TRH, the MobiusHD®, is also currently investigated within the CALM studies. The CALM-Start, an RCT including 110 patients has an estimated study completion date in December 2019.

Details on these ongoing RCTs on BAT can be found in Table A-7.

10 References

[1] Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017. Epub 2017/11/15.

[2] Halbach M, Grothaus D, Hoffmann F, Madershahian N, Kuhr K, Baldus S, et al. Reduced rate and duration of hypertension-related hospitalization after treatment with baroreflex activation therapy. J Hypertens. 2017;35((Halbach M.; Grothaus D.; Hoffmann F.; Baldus S.; Reuter H.) University of Cologne, Department of Internal Medicine III, Cologne, Germany):e215-e6.

[3] Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, et al. Incidence and Prognosis of Resistant Hypertension in Hypertensive Patients. Circulation. 2012;125(13):1635-42.

[4] Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31(7):1281-357. Epub 2013/07/03.

[5] Wallbach M, Lehnig L-Y, 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):701-9.

[6] Wallbach M, Lehnig L-Y, Schroer C, Helms H-J, Luders S, Patschan D, et al. Effects of baroreflex activation therapy on arterial stiffness and central hemodynamics in patients with resistant hypertension. J Hypertens. 2015;33(1):181-6.

[7] Hoppe UC, Brandt M-C, 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):270-6.

[8] Beige J, Jentzsch T, Wendt R, Hennig G, Koziolek M, Wallbach M. Blood pressure after blinded, randomized withdrawal, and resumption of baroreceptor-activating therapy. J Hypertens. 2017;35(7):1496-501.

[9] 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;57(14):E491.

[10] de Leeuw PW, Bisognano JD, Bakris GL, Nadim MK, Haller H, Kroon AA, et al. Sustained Reduction of Blood Pressure With Baroreceptor Activation Therapy: Results of the 6-Year Open Follow-Up. Hypertension. 2017;69(5):836-43.

[11] 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):1254-8.

[12] 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 Cardiol. 2011;58(7):765-73.

[13] Borisenko O, Beige J, Lovett EG, Hoppe UC, Bjessmo S. Cost-effectiveness of Barostim therapy for the treatment of resistant hypertension in European settings. J Hypertens. 2014;32(3):681-92.

[14] Wallbach M, Koziolek MJ. Baroreceptors in the carotid and hypertension-systematic review and meta-analysis of the effects of baroreflex activation therapy on blood pressure. Nephrol Dial Transplant. 2017.

[15] NICE. Implanting a baroreceptor stimulation device for resistant hypertension. National Institute for Health and Care Excellence, 2015.

[16] Topfer L. Baroreflex Activation Therapy for Treatment-Resistant Hypertension: the Barostim neo. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2015.

[17] Australian Safety Efficacy Register of New Interventional Procedures – Surgical. Implantable carotid sinus baroreflex device for the treatment of drug-resistant hypertension. Australia: Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S); 2014.

[18] Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343.

[19] Guo B, Moga C, Harstall C, Schopflocher D. A principal component analysis is conducted for a case series quality appraisal checklist. Journal of clinical epidemiology. 2016;69:199-207 e2. Epub 2015/08/27.

[20] Victor RG. Carotid baroreflex activation therapy for resistant hypertension. Nat Rev Cardiol. 2015;12(8):451-63.

[21] Spiering W, Williams B, Van der Heyden J, van Kleef M, Lo R, Versmissen J, et al. Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle clinical study. Lancet. 2017.

[22] Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. The New England journal of medicine. 2014;370(15):1393-401. Epub 2014/04/01.

[23] Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. The Lancet. 2017;390(10108):2160-70.

[24] Calhoun DA, Townsend RT. Treatment of resistant hypertension. Waltham, MA: UpToDate Inc.; 2017 [cited 01/2018]; Available from: https://www.uptodate.com/contents/treatment-of-resistant-hypertension?search=resistenter%20bluthochdruck&usage_type=default&source=search_result&selectedTitle=2~113&display_rank=2.

[25] CVRx. Barostim Therapy. United States: CVRx; 2017 [cited 01/2018]; Available from: http://barostimtherapy.com/en/healthcare-professional/hypertension-management-view.

[26] CVRx I. Barostimneo® Hypertension- System Reference Guide. 2015 [cited 01/2018]; Available from: http://www.barostimtherapy.com/sites/default/files/inline-images/1473863073-SxXiDFRccd-900088-001J_Neo_%20HTN_ReferenceGuide_Clinical_US.pdf.

[27] Erne P, Sudano I, Resink TJ, Luscher TF. Interventional therapy for hypertension: Back on track again? Crit Rev Clin Lab Sci. 2017;54(1):18-25.

[28] Zile MR, Abraham WT, Weaver FA, Butter C, Ducharme A, Halbach M, et al. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction: safety and efficacy in patients with and without cardiac resynchronization therapy. Eur J Heart Fail. 2015;17(10):1066-74.

[29] Abraham WT, Zile MR, Weaver FA, Butter C, Ducharme A, Halbach M, et al. Baroreflex Activation Therapy for the Treatment of Heart Failure With a Reduced Ejection Fraction. JACC: Heart Failure. 2015;3(6):487-96.

[30] FDA. Humanitarian Device Exemption (HDE). US Food and Drug Administration; 2014 [cited 01/2018]; Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H130007.

[31] Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. The New England journal of medicine. 2015;373(22):2103-16. Epub 2015/11/10.

[32] Weber T, Horn S, Slany J, Watschinger B, Wenzel R, Zweiker R. Die SPRINT-Studie (Systolic Blood Pressure Intervention Trial)–Müssen wir jetzt die Guidelines umschreiben? Journal für Hypertonie-Austrian Journal of Hypertension. 2016;20(1):16-20.

[33] Mann JF, Hilgers KF. What is goal blood pressure in the treatment of hypertension?: Waltham, MA: UpToDate Inc.; 2017 [cited 01/2017]; Available from: https://www.uptodate.com/contents/what-is-goal-blood-pressure-in-the-treatment-of-hypertension.

[34] Calhoun DA, Raymond RT. Definition, risk factors, and evaluation of resistant hypertension. Waltham, MA: UpToDate Inc. ; 2017 [cited 01/2017]; Available from: https://www.uptodate.com/contents/definition-risk-factors-and-evaluation-of-resistant-hypertension?source=see_link#H3.

[35] Rimoldi SF, Messerli FH, Bangalore S, Scherrer U. Resistant hypertension: what the cardiologist needs to know. Eur Heart J. 2015;36(40):2686-95.

[36] de Jager RL, de Beus E, Beeftink MM, Sanders MF, Vonken EJ, Voskuil M, et al. Impact of Medication Adherence on the Effect of Renal Denervation: The SYMPATHY Trial. Hypertension. 2017;69(4):678-84. Epub 2017/03/08.

[37] Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens. 2013;31(4):766-74. Epub 2013/01/23.

[38] Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart. 2014;100(11):855-61. Epub 2014/04/04.

[39] Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. Lancet. 2015;385(9981):1957-65. Epub 2015/01/30.

[40] Persell SD. Prevalence of Resistant Hypertension in the United States, 2003–2008. Hypertension. 2011;57(6):1076-80.

[41] de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, et al. Clinical Features of 8295 Patients With Resistant Hypertension Classified on the Basis of Ambulatory Blood Pressure Monitoring. Hypertension. 2011;57(5):898-902.

[42] Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation. 2011:CIRCULATIONAHA. 111.030189.

[43] Braam B, Taler SJ, Rahman M, Fillaus JA, Greco BA, Forman JP, et al. Recognition and Management of Resistant Hypertension. Clin J Am Soc Nephrol. 2017;12(3):524-35.

[44] Grigoryan L, Pavlik VN, Hyman DJ. Characteristics, drug combinations and dosages of primary care patients with uncontrolled ambulatory blood pressure and high medication adherence. J Am Soc Hypertens. 2013;7(6):471-6. Epub 2013/07/31.

[45] Zhou B, Bentham J, Di Cesare M, Bixby H, Danaei G, Cowan MJ, et al. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. The Lancet. 2016;389(10064):37-55.

[46] Rohla M, Haberfeld H, Tscharre M, Huber K, Weiss TW. Awareness, treatment, and control of hypertension in Austria: a multicentre cross-sectional study. J Hypertens. 2016;34(7):1432-40.

[47] Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014 [cited 01/2018]; Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about.

[48] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction –GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-94.

[49] Ewen S, Bohm M, Mahfoud F. Long-Term Follow-Up of Baroreflex Activation Therapy in Resistant Hypertension: Another Piece of the Puzzle? Hypertension. 2017;69(5):782-4.

[50] Mancia G, Verdecchia P. Clinical Value of Ambulatory Blood Pressure. Evidence and Limits. 2015;116(6):1034-45.

[51] Taddei S, Bruno RM. Resistant hypertension: A real entity requiring special treatment? European Cardiology Review. 2016;11(1).

[52] Ewen S, Meyer MR, Cremers B, Laufs U, Helfer AG, Linz D, et al. Blood pressure reductions following catheter-based renal denervation are not related to improvements in adherence to antihypertensive drugs measured by urine/plasma toxicological analysis. Clinical Research in Cardiology. 2015;104(12):1097-105.

[53] Ludwig Boltzmann Institut für Health Technology Assessment (LBI-HTA). Internes Manual Abläufe und Methoden Vienna: LBI-HTA; 2006 [cited 2017]; Available from: http://hta.lbg.ac.at/uploads/tableTool/UllCmsPage/gallery/InternesManual_2.Aufl..pdf.

[54] EUnetHTA Joint Action 2. Internal validity of non-randomised studies (NRS) on interventions. 2015.

[55] EUnetHTA Joint Action 2 WP. Levels of evidence: Internal validity of randomized controlled trials. 2015.

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Baroreceptor activation therapy: Results from randomised, controlled trials

Author, year	Bisognano, 2011 [12]	Beige, 2017 [8]
Country	USA	Germany
Sponsor	CVRx Inc	CVRx Inc
Intervention/Product	Rheos® system (CVRx)	Barostim neo™device (CVRx)
Comparator	device ON vs OFF	device ON vs OFF
Study design	double-blind randomised controlled trial	double-blind, randomised cross-over trial
Trial Number/Name	NCT00442286, Rheos Pivotal Trial	Barostim neo™withdrawal study
Number of pts	265 randomised(plus 55 patients open label, 2 patients explant)	16
Allocation	randomisation in 2:1 ratio: Group A (n=181) activation one month after implant; Group B (n=84) delayed activation (at seven months post-implant)	randomisation in BAT-On and BAT-Off group, groups changed after 4 weeks
Population	patients with TRH defined as office cuff SBP ≥ 160 mmHg DBP ≥80 mmHg as well as a 24-hour ambulatory SBP ≥ 135 mmHg despite at least one month of maximally tolerated therapy with at least three antihypertensive medications, of which at least one must be a diuretic	patients with implanted BAT between 2010 and 2014; preimplant condition was TRH (office SBP>140mmHg or 130 mmHg if CKD, despite maximally tolerated therapy with at least three antihypertensive medications, of which at least one must be a diuretic
Inclusion criteria	✿ ≥21 years <80 years ✿ have been assessed with bilateral carotid bifurcations that are easily interrogated by carotid duplex ultrasound and are below the level of the mandible. ✿ must have completed the drug compliance questionnaire and have been judged to be compliant with medications. ✿ for subjects with prior bariatric surgery: ≥1 year post-surgery, at a stable weight. ✿ not pregnant ✿ must be an appropriate or reasonable surgical candidate. ✿ have signed a CVRx approved informed consent form for participation in this study	✿ ≥18 years ✿ exclusion of secondary causes of hypertension ✿ exclusion of pseudo-resistance by ambulatory BPM ✿ drug adherence was evaluated by directly observed therapy and/or urine medication analysis ✿ not pregnant ✿ no change in antihypertensive treatment for at least 4 weeks

Author, year	Bisognano, 2011 [12]	Beige, 2017 [8]
Exclusion criteria	✿ hypertension secondary to an identifiable and treatable cause other than sleep apnea ✿ prior surgery, radiation, or endovascular stent placement in either carotid sinus region ✿ known or suspected baroreflex failure or autonomic neuropathy ✿ arm circumference greater than 46 cm and/or body mass index of greater than 45; ✿ currently taking an imidazoline receptor agonist ✿ unable or unwilling to fulfil the protocol medication compliance and follow-up requirements. ✿ active infection within the last month. ✿ enrolled in another concurrent clinical trial, without prior approval of CVRx ✿ comorbidities: significant cardiac bradyarrhythmias; chronic atrial fibrillation; significant orthostatic hypotension; organ or hematologic transplant; myocardial infarction, unstable angina, syncope, or cerebral vascular accident within the past 3 months; carotid atherosclerosis producing a 50% or greater reduction in linear diameter (determined by ultrasound or angiographic evaluation as determined within 6 months of enrollment in the trial); ulcerative plaques in the carotid artery as determined by ultrasound or angiographic evaluation; severe CKD as defined by:Currently undergoing dialysis or dialysis is planned within 3 months of the implant date;eGFR of ≤30 ml/min/1.73m²; clinically significant cardiac structural valvular disease; clinically significant reactive airway disease, chronic obstructive pulmonary disease, and/or primary pulmonary hypertension; uncontrolled comorbid medical condition that would adversely affect participation in the trial; clinically significant psychological illness that would prohibit the subject's ability to meet the protocol requirements; co-morbid condition that reduces life expectancy to less than one year	✿ untreated secondary hypertension ✿ carotid artery stenosis > 70% ✿ SBP < 120 mmHg ✿ major cardiovascular events within previous 6 months: acute myocardial infarction, unstable angina, stroke, transitory ischemic attack
Age of patients (yrs)	53.7 ±10.5 (n=181) vs 52.4 ±9.8	53.5±16.1 (n=8) BAT off-on ITT vs 59.1 ±13 BAT on-off ITT
Sex (% female)	65 (36%) vs. 38 (45%)	7 (87%) vs 6 (66%)
Follow-up (months)	mean: 21 ±8 months; 463 person-years of follow-up	8 weeks
Loss to follow-up, n (%)	17 (9) vs 6 (7)	4 (25)
Primary outcome measures	✿ acute efficacy: % of patients with > 10mmHg reduction in office cuff SBP [Time Frame: 6 months post-activation] superiority margin of 20%. ✿ sustained efficacy: % of group A (Rheos® Device On) patients who maintain a 10 mmHg drop in SBP at 12 mo post-activation; response at 12 mo is at least 50% of the response at 6 mo post-activation. ✿ BAT safety: therapy-related Adverse Event-free rate ✿ device safety: major hypertension-related and Serious Device-related Adverse Event-free rate ✿ procedural safety: Serious procedure- or system-related Adverse Event-free rate	✿ systolic automated office BP should increase by more than 35 mmHg (SD 25 mmHg) when BAT is turned off for 4 weeks
Mean BP medications	5.2 vs 5.2	4.7 vs 5.67
BP mmHg at baseline (office BP)	systolic: 169 ±26 vs 168 ±24 diastolic: 101 ±17 vs 100 ±14	(after previous BAT implantation) systolic: BAT off-on 135± 14 vs BAT on-off 142 ±44 diastolic: 75 ±12 vs 90 ±22

Author, year	Bisognano, 2011 [12]	Beige, 2017 [8]
Outcomes		
Efficacy		
Acute efficacy (proprotion of subjects with >10mmHg drop, 20% superiority margin)	at 6 mo: 54% vs 46% p=0.97	no patient had increase >35 mmHg after BAT off
Sustained efficacy (>10mmHg drop at 12 months, at least 50% of 6 months reduction)	88% at 6 months (p<0.001)	-
Mean change in office SBP	at 6 months:16 ±29 mmHg vs 9 ±29 mmHg (p=0.08)	at 4 weeks: BAT off vs BAT on 10 mmHg
Mean change in 24-h ambulatory BP	-	at 4 weeks: ABP BAT off vs BAT systolic by 10 ±4 and diastolic 8 ±3
% of patients SBP <140 mmHg	at 6 months: A: 40% vs B 22% (p=0.005) at 12 months: A: 52% vs B: 51% (p=0.7)	-
Quality of life	-	-
Number of CV events	-	
Number of anti-hypertensive medicines	-	none
Saftey		
Mortality	at 12 months: 4	-
Number of SAE n, (%)	**Procedural: 68 (25.5)** surgical complications 13 (4.8) Nerve injury with residual deficit 13 (4.8) Transient nerve injury 12 (4.4)	-
	Device: 34 (12.8) Hypertension-related stroke 6 (2.3)	-
Number of BAT AE	Hypertensive crisis: A 9 (5) vs 7 (8.3)	-
Procedure-related AE in %	30 days: event free rate of 74.8% , p=1.0	-
BAT AE in %	therapy-related event free rate of 91.7% vs 89.3% (p<0.001)	-
Device safety in %	event-free rate of 87.2% (p<0.001)	-
Device explantation	2	-

Abbreviations: *AE = adverse event, BAT = baroreceptor activation therapy, BP = blood pressure, CKD = chronic kidney disease, CV = cardio-vascular, ITT = intension to treat, SAE = severe adverse event, SBP = systolic blood pressure, SD = standard deviation, TRH = treatment-resistant hypertension, yrs = years*

Table A-2: Baroreceptor activation therapy Results from observational studies

Author, year	Scheffers, 2010 [11]	de Leeuw, 2017 [10]	Hoppe, 2012 [7]	Wallbach, 2016 [5]	Wallbach, 2015 [6]
Country	Multi-Center (Netherlands, Switzerland, Germany, Latvia, Poland)	The Netherlands	Austria	Germany	Germany
Sponsor	CVRx	CVRx	CVRx	Grant support (authors received grant support from CVRx)	CVRx
Trial Name	DEBuT-HT	Rheos Feasibility trial, DEBuT-HT Trial, Rheos Pivotal trial	Barostim neo™trial	-	-
Intervention/Product	Rheos® system CVRx	Rheos® system CVRx	Barostim neo™ CVRx	Barostim neo™ CVRx	Barostim neo™ CVRx
Comparator	Before-after	Before-after	Before-after	Before-after	Before-after
Study design	Multi-centre, prospective, single arm, open-label	Open-label follow-up of [11, 12]	Single-arm, open-label study	Prospective observational study	Prospective observational study (pre-specified subanalysis)
Number of pts	45 (42 analysed)	383	30	51 (44 analysed)	30 (25 analysed)
Inclusion criteria	BP ≥160/90 mmHg despite ≥ 3 antihypertensive agents including diuretic; compliant with medications; >21 years of age;	Not described (described in original studies)	Patients with resistant HTN (SBP ≥140 mm Hg) despite being prescribed at least 3 anti-hypertensive medications including a diuretic and on stable medication (defined as no more than a 100% increase or 50% decrease in any one medication other than a diuretic during 4 weeks before qualifying BP measurements); compliant with medications;	Office SBP ≥140 mm Hg, despite at least 3 antihyper-tensive medications including a diuretic; age ≥ 18 years; all patients involved in this study were treated for HTN for at least 1 year	Patients fulfilling diagnosis of resistant hypertension with BP ≥140/90 mm Hg and optimal therapy for secondary reasons were included.
Exclusion criteria	✪ Baroreflex failure or significant orthostatic hypotension ✪ Cardiac bradyarrhythmias or chronic atrial fibrillation ✪ carotid atherosclerosis determined by ultrasound or angiographic evaluation with a stenosis of greater than 50%. ✪ prior surgery or radiation in either carotid sinus region ✪ implanted electrical medical devices such as cardiac pacing, defibrillation or neurologic stimulation systems. ✪ pregnancy ✪ dialysis	Not described (described in original studies)	HTN 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.	✪ Pregnancy ✪ untreated secondary cause of HTN ✪ acute myocardial infarction ✪ unstable angina ✪ stroke, or transitory ischemic attack within the previous 6 months	✪ White-coat hypertension was excluded by 24-h ambulatory BP monitoring (ABPM).

Author, year	Scheffers, 2010 [11]	de Leeuw, 2017 [10]	Hoppe, 2012 [7]	Wallbach, 2016 [5]	Wallbach, 2015 [6]
Exclusion criteria *(continuation)*	✿ hypertension secondary to a treatable cause ✿ clinically significant cardiac valvular disease ✿ unable to comply with protocol requirements ✿ unlikely to survive the protocol follow-up period ✿ enrolled in another concurrent clinical trial			✿ Anatomic exclusion criterion was stenosis of the carotid artery >70% (routinely assessed in all patients by ultrasound and duplex sonography using North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria).	
Age of patients (yrs)	54 ±9	53 ±10	57 ±12	57 ±12	61 ±9
sex (% female)	19 (42)	153 (40)	16 (53)	23 (52)	14 (56)
Follow-up (months)	3 months, 1 year, 2 years	3 months - 6 years	3 months, 6 months	At 6 months	At 6 months
Loss to follow-up, n (%)	8 (17) 26 subjects completed 1 year; 17 completed 2 year follow-up	142 (37) 34 (8) within the 1st year	0 (0)	7 (14) 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 ABPM)	5 (17) were excluded from the analysis: 2 patients with atrial fibrillation as well as another 3 patients (1 patient died due to pneumonic sepsis, 1 patient failed follow-up visit and in one patient quality index was < 80 %).
primary outcome measures	✿ Safety by evaluating all AE and procedure related AE rate ✿ 10 mmHg decrease from baseline (= 1-month office BP) in SBP after three months of incrementally optimized therapy	✿ Office SBP; ✿ safety, AE	✿ Office SBP; ✿ all system- and procedure-related complications	✿ Change in systolic 24-hour BP;	✿ Change in carotid-to-femoral PWV (PWVcf), central BP, PP, and Aix
BP medications (mean, SD)	5 (3-9)	5 (3-12)	6.1 ± 2.7	6.5 ± 1.5	6.6 ± 1.7
BP mmHg at baseline (office BP)	SBP:179 ±29 DBP: 105±22	SBP: 179 ±24 DBP: 103 ±16	SBP:172 ±20 DBP: 100±14	SBP:171 ±24 DBP: 91 ± 18	SBP:160 ± 27 DBP: 83 ± 17
Outcomes					
Efficacy					
Mean change in office BP	**12 months** (n=26): **SBP** -21 ±6 (p<0.001) **DBP** -20 ±4 (p<0.001) **24 months** (n=17): **SBP** -33 ±8 (p=0.001) **DBP** -22 ±6 (p=0.002)	**12 months** (n=335) **SBP**: ~-32; **DBP** ~-12 **24 months** (n=299) **SBP:** ~-30; **DBP** ~-12 **3 years** (n=278) **SBP**:~-32; **DBP**~-12 **6 years** (n=48) **SBP** ~-33; **DBP**~-13	6 months (n=30) SBP: -26 ± 4 (p<0.01)	6 months (n=44) SBP: -20 ± (28 – 12) (p<0.01); DBP: -9 ± (-13 – 4) (p<0.01)	Mean not calculated 6 months (n=25) SBP: 143 ± 27; DBP: 97 ± 18 (p<0.01)

Author, year	Scheffers, 2010 [11]	de Leeuw, 2017 [10]	Hoppe, 2012 [7]	Wallbach, 2016 [5]	Wallbach, 2015 [6]
Mean change in 24-h ambulatory BP	**12 months** (n=15): **SBP** -13 ±3 (p<0.001) **DBP** -8 ±2 (p<0.001) **24 months** (n=8): **SBP** -24 ±8 (p=0.017); **DBP** -13 ±5 (p=0.049)	-	- (Lack of ambulatory BP measurement considered as a study limitation)	Mean not calculated Baseline: SBP: 148 ± 17; DBP: 82 ± 13 (p<0.01) At 6 months: SBP: 140 ± 23; DBP: 77 ± 15 (p<0.01)	-
% of patients SBP <140 mmHG	-	-	43 at 6 months	-	-
Quality of life	-	-	-	-	-
Number of CV events	-	-	-	-	-
Number of antihypertensive medicines	No significant changes	27% (n=129) from median of 6 to 3 34% (n=129) no change 39% (n=149) increase from median of 5 to 7	No significant changes	Antihypertensives could be reduced significantly to 6.0 ± 1.8 (p=0.03)	No significant changes
Saftey					
Mortality	Angioneurotic oedema (n=1), 6 days post-operative	-	-	-	-
SAE n, (%)	8 (20)	335 (246) (n=136) relatable to procedure/ device/BAT: 26 (19)	-	Contralateral stroke 1 (2)	-
Procedure related AE SAE, n, (%)	7 (16) angioneurotic edema (n=1) explantations due to infection (n=3) perioperative stroke (n=1) tongue paresis (injury of hypoglossal nerve) (n=1) pulmonary edema (n=1)	16 (12) CV events (n=13) other (n=3)	Perioperative events: 3 (10) Device pocket hematoma (n=1) Self-inflicted wound complication (n=1) Intermittent pain lateral of device system (n=1)	20 (45) minor procedure-related complication (n=10). disturbance of wound healing (n=5) a postoperative hematoma (n=4) a hematoma of the vocal cord seemed transiently after device implantation (n=1)	-
Device related AE SAE, n, (%)	1 (2) movement of IPG, re-operation	9 (6) related to IPG (n=5) lead-related (damage/ migration/tension/ haematoma) (n=4)	Long-term event: 1 (3) Intermittent pain near the device system (n=1)	2 (5) movement/ pain of the IPG (resulting in the need for reposition) (n=2)	-
Device explantations n, (%)	3 (6)	15 (11)	0 (0)	0 (0)	-

Abbreviations: *AE = adverse event, BAT = baroreceptor activation therapy, BP = blood pressure, CKD = chronic kidney disease, CV = cardio-vascular, ITT = intension to treat, SAE = severe adverse event, SBP = systolic blood pressure, SD = standard deviation, TRH = treatment-resistant hypertension, yrs = years)*

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement, a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [53] and in the Guidelines of EUnetHTA [54, 55].

Table A-3: Risk of bias – study level (randomised studies), evaluated with Cochrane Risk of Bias tool, 2011 [18]

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Incomplete outcome data	Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician				
NCT00442286, Rheos Pivotal Trial	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	low
Beige et al, 2017	Unclear	Yes	Yes	Yes	No1	No1	No2	High

[1] *statistically relevant comparisons not reported; the study fails to report on safety-related outcomes and adverse events;* [2] *had unexplained baseline imbalances*

Table A-4: Risk of bias – study level (case series), IHE checklist [47]

Study reference/ID	Scheffers, 2010 [11]	de Leeuw, 2017 [10]	Hoppe, 2012 [7]	Wallbach, 2016 [5]	Wallbach, 2015 [6]
Study objective					
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	No	Yes	Yes	Yes
Study design					
2. Was the study conducted prospectively?	Yes	No	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	Yes	Yes	Yes	Unclear	Unclear
4. Were patients recruited consecutively?	Unclear	Unclear	Unclear	Unclear	Unclear
Study population					
5. Where the characteristics of the participants included in the study described?	Yes	No	Yes	Yes	Yes
6. Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	No	Yes	Yes	Partial
7. Did participants enter the study at a similar point in the disease?	Yes	Unclear	Unclear	Unclear	Unclear
Intervention and co-intervention					
8. Was the intervention clearly described?	Yes	No	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	No	Yes	Yes	Partial
Outcome measure					
10. Were relevant outcome measures established a priori?	Yes	No	Yes	Yes	No
11. Were outcome assessors blinded to the intervention that patients received?.	No	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Partial	Partial	Partial	No
13. Were the relevant outcomes measured before and after intervention?	Yes	Yes	Yes	Yes	Yes
Statistical Analysis					
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Unclear
Results and Conclusions					
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	No	No	No
16. Was the loss to follow-up reported?	Yes	Unclear	Yes	Yes	Unclear
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Partial	Yes	Yes	Yes
18. Were adverse events reported?	Partial	Partial	Yes	Yes	No
19. Were the conclusions of the study supported by results?	No	No	Yes	No	No
Competing interest and source of support					
20. Were both competing interest and source of support for the study reported?	Yes	Yes	Yes	Yes	Yes
Overall Risk of bias	**Low**	**High**	**Low**	**Low**	**High**

Table A-5: Evidence profile: efficacy and safety Baroreceptor Activation Therapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Barostim Activation Therapy	standard therapy (or BAT-off)	Relative (95% CI)	Absolute (95% CI)		
Reduction of systolic 24-hour AMBP												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	44	0	-	mean 8 mmHg lower (2 lower to 14 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction of office SBP												
2	observational studies	serious [a]	not serious	not serious	serious [b]	none	74	0	-	mean 23 mmHg lower (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT
Reduction in the number of CV events – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Procedure-related serious adverse events												
2	observational studies	serious [a]	not serious	not serious	serious [b]	none	24 events in 74 patients				⨁◯◯◯ VERY LOW	CRITICAL
Device-related serious adverse events												
2	observational studies	serious [a]	not serious	not serious	serious [b]	none	4 events in 74 patients				⨁◯◯◯ VERY LOW	CRITICAL

[a] *not blinded, no adjusted for confounding*

[b] *small sample size, wide confidence intervals*

[c] *First generation device, different operating mechanism and safety profile; not in clinical use anymore*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

Abbreviations: *AMBP = Ambulatory blood pressure, CI = confidence interval, SBP = systolic blood pressure*

Applicability table

Table A-6: Summary table characterising the applicability of BAT studies

Domain	Description of applicability of evidence
Population	The main body of evidence assessed patients with resistant hypertension. TRH is difficult to diagnose due to the possibility of secondary reasons for hypertension, or apparent resistant hypertension, due to lacking compliance or therapy adherence. While most studies states to have diagnosed TRH by use of AMBP and office BP to rule out white coat hypertension, therapy adherence was not assessed by most studies. It is, therefore, possible that the study population is overestimating TRH prevalence. The trials excluded several comorbidities, which are more common in patients with TRH patients. It is unclear whether BAT is safe to use in patients with these comorbidities.
Intervention	The studies described BAT as add-on therapy for the treatment of TRH. While the implantation of the stimulation device was explained in almost all studies, changes in additional therapeutic regimens were not explicitly mentioned by the studies. Physicians were free to change the anti-hypertensive dosages and medication, which was not adjusted for potential confounding.
Comparators	The included studies described BAT compared to a sham procedure for the first generation device. No comparative evidence was available for the second generation device, despite European market-authorization since 2011. For neither of the devices, studies compared BAT in relation to standard therapeutic management, thus benefits in comparison to standard therapy in terms of reduction of CV events could not be evaluated.
Outcomes	The most critical outcome for the assessment of a potential benefit of the BAT is a reduction in the number of CV events, as compared to standard therapy. This outcome was not evaluated by any of the studies. Furthermore, it is recommended to assess a reduction in BP by use of AMBP measurements rather than office BP measurements, to allow evaluating day-night differences, and overall BP reduction of a day, rather than a single measurement once a day. Only one study on the second generation device including 44 patients assessed AMBP.
Setting	While the studies on the first generation device reflected geographical diversity, the studies on the second generation device were all based in Europe, two of them in Germany and one in Austria. The geographical focus of the published literature is in Germany and the Netherlands. However, ongoing trials from Nordic countries and France indicate European diversity of study settings. Data from the US context is only available from the first generation device. Evidence from other high-income countries is lacking. The procedures took place in hospital operating rooms, which reflects the clinical setting where the technology is deployed.

List of ongoing randomised controlled trials

Table A-7: List of ongoing controlled trials of baroreceptor activation therapy for resistant hypertension

Identifier/ Trial name	Study design	Enrollment	Status	Primary completion date	Conditions	Intervention/ Comparison	Primary Outcome	Sponsor
NCT02572024/ The Nordic BAT Study	Allocation: Randomize, Intervention Model: Parallel Assignment, Masking: Double (Investigator, Outcomes Assessor), Primary Purpose: Treatment	100	Recruiting	11/2020	Resistant Hypertension	Device: BAT|Other: Placebo	✿ Change in systolic ambulatory BP in response to BAT therapy ✿ Change in home BP in response to BAT therapy ✿ Change in office blood pressure in response to BAT therapy ✿ Change in autonomic function in response to BAT therapy	Helsinki University Central Hospital, Skane University Hospital|Sahlgrenska University Hospital, Sweden|Karolinska Institutet|Odense University Hospital| University of Oslo| Helsinki University
NCT01679132 BAROSTIM NEO HTN Pivotal Trial	Allocation: RandomizedIntervention Model: Parallel Assignment; Masking: None (Open-Label); Primary Purpose: Treatment	310	Active, not recruiting	09/2017	Uncontrolled Hypertension	Device: Neo Baroreflex Activation Therapy System|Other: Standard of care medical management only	✿ Primary Safety Objective ✿ Primary Efficacy	Industry CVRx, Inc.
NCT02364310, ESTIM-rHTN	Economic Evaluation; Allocation: Randomized; Intervention Model: Parallel AssignmentMasking: None (Open Label), Primary Purpose: Treatment	128	Recruiting	11/2018	Hypertension	Device: BAT with Barostim neo™	12th month SBP (mmHg) measured on ABPM, adjusted on baseline SBP, to compute the incremental cost-effective ratio	Central Hospital, Nancy, France
NCT03179800 CALM- 2	Allocation: Randomized; Intervention Model: Crossover Assignment; Masking: Triple (Participant, Care Provider, Outcomes Assessor); Primary Purpose: Treatment	300	Recruiting	05/2020	Resistant Hypertension	Device: MobiusHD|Other: Sham Implantation	Primary Effectiveness Endpoint – Change in mean 24-hr sABP from baseline to 180-day	Industry Vascular Dynamics, Inc.

Literature search strategies

Search strategy for Cochrane

Search Name: Baroreflex activation for treatment-resistant hypertension	
Search Date: 06/12/2017 18:31:18.492	
ID	Search
#1	MeSH descriptor: [Hypertension] explode all trees
#2	hypertens* (Word variations have been searched)
#3	(high* or heighten* or rais* or elevat* or increas*) near blood pressure* (Word variations have been searched)
#4	#1 or #2 or #3
#5	resistant or resistent (Word variations have been searched)
#6	#4 and #5
#7	(resistant or resistent) near (hypertens* or ((high* or heighten* or rais* or elevat* or increas*) near blood pressure*)) (Word variations have been searched)
#8	#6 or #7
#9	MeSH descriptor: [Baroreflex] explode all trees
#10	baro*reflex (Word variations have been searched)
#11	MeSH descriptor: [Pressoreceptors] explode all trees
#12	presso*receptor* (Word variations have been searched)
#13	Baro*receptor* (Word variations have been searched)
#14	#9 or #10 or #11 or #12 or #13
#15	stimul* or activat* (Word variations have been searched)
#16	MeSH descriptor: [Electric Stimulation Therapy] explode all trees
#17	#15 or #16
#18	#14 and #17
#19	BAT:ti,ab,kw
#20	BaroStim (Word variations have been searched)
#21	Rheos (Word variations have been searched)
#22	CVRx (Word variations have been searched)
#23	(baro*receptor* or presso*receptor* or baro*reflex* or caroti*) near (stimul* or activat*) (Word variations have been searched)
#24	#18 or #19 or #20 or #21 or #22 or #23
#25	#8 and #24
Total: 39 Hits	

Search strategy for CRD

Search Name: Baroreflex activation for treatment-resistant hypertension	
Search Date: 06/12/2017	
ID	Search
1	MeSH DESCRIPTOR Hypertension EXPLODE ALL TREES
2	(hypertens*)
3	((high* OR heighten* OR rais* OR elevat* OR increas*) NEAR blood pressure*)
4	#1 OR #2 OR #3
5	MeSH DESCRIPTOR Baroreflex EXPLODE ALL TREES

6	(baro*reflex*)
7	MeSH DESCRIPTOR Pressoreceptors EXPLODE ALL TREES
8	(presso*receptor*)
9	(Baro*receptor*)
10	MeSH DESCRIPTOR Electric Stimulation Therapy EXPLODE ALL TREES
11	(BAT)
12	(BaroStim)
13	(Rheos)
14	(CVRx)
15	((baro*receptor* OR presso*receptor* OR baro*reflex* OR caroti*) NEAR (stimul* OR activat*))
16	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	#4 AND #16
Total: 12 Hits	

Search strategy for Embase

Search Name: Baroreflex activation for treatment-resistant hypertension	
Search Date: 06/12/2017	
No.	Query Results
#31	#12 AND #30
#30	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
#29	((baro*receptor* OR presso*receptor* OR baro*reflex* OR caroti*) NEAR/2 (stimul* OR activat*)):ti,ab
#28	cvrx:df
#27	rheos:dn,df
#26	barostim:dn
#25	bat:ti,ab
#24	'baroreflex activation therapy'/exp
#23	#19 AND #22
#22	#20 OR #21
#21	'electrotherapy'/exp
#20	stimul* OR activat*
#19	#13 OR #14 OR #15 OR #16 OR #17 OR #18
#18	baro*receptor*:ti,ab
#17	presso*receptor*:ti,ab
#16	'pressoreceptor'/exp
#15	baro*reflex:ti,ab
#14	'carotid sinus pressoreceptor reflex'/exp
#13	'pressoreceptor reflex'/exp
#12	#10 OR #11
#11	'treatment resistant hypertension'/exp
#10	#8 OR #9
#9	((resistant OR resistent) NEAR/1 (hypertens* OR 'high* blood pressure*' OR 'heighten* blood pressure*' OR 'rais* blood pressure*' OR 'elevat* blood pressure*' OR 'increas* blood pressure*')):ti,ab
#8	#4 AND #7
#7	#5 OR #6
#6	resistent
#5	resistant

#4	#1 OR #2 OR #3
#3	((high* OR heighten* OR rais* OR elevat* OR increas*) NEAR/2 'blood pressure*'):ti,ab
#2	hypertens*:ti,ab
#1	'hypertension'/exp
Total: 390 Hits	

Search strategy for Medline

Search Name: Baroreflex activation for treatment-resistant hypertension		
Search Date: 06/12/2017		
No.	Query Results	Results
1	exp Hypertension/	254,475
2	hypertens*.mp.	492,259
3	((high* or heighten$3 or rais$3 or elevat$3 or increas$3) adj3 blood pressure*).mp.	61,786
4	1 or 2 or 3	518,692
5	resist#nt.mp.	414,308
6	4 and 5	8,194
7	(resist#nt adj (hypertens* or ((high* or heighten$3 or rais$3 or elevat$3 or increas$3) adj3 blood pressure*))).mp.	3,175
8	6 or 7	8,194
9	exp Baroreflex/	5,931
10	baro?reflex.ti,ab.	8,188
11	exp Pressoreceptors/	8,220
12	presso?receptor*.ti,ab.	112
13	Baro?receptor*.mp.	7,798
14	9 or 10 or 11 or 12 or 13	18,240
15	(stimul* or activat*).mp.	2,869,881
16	exp Electric Stimulation Therapy/	76,618
17	15 or 16	2,903,276
18	14 and 17	6,985
19	BAT.ti,ab.	1,2451
20	BaroStim.ti,ab.	16
21	Rheos.ti,ab.	34
22	CVRx.ti,ab.	11
23	((baro?receptor* or presso?receptor* or baro?reflex* or caroti*) adj2 (stimul* or activat*)).mp.	2,276
24	18 or 19 or 20 or 21 or 22 or 23	19,933
25	8 and 24	264
26	remove duplicates from 25	239
Total: 239 Hits		

Ludwig Boltzmann Institut
Health Technology Assessment