Baroreflex Stimulation Devices

Medical Policy #: 02.02.19
Original Effective Date: January 2016
Reviewed: January 2022
Revised: January 2022

DESCRIPTION

Baroreceptors are pressure sensors contained within the walls of the carotid arteries. They are part of the autonomic nervous system that regulates basic physiologic functions such as heart rate and blood pressure. When these receptors are stretched, which occurs with increases in blood pressure, the baroreflex is activated. Activation of the baroreflex signals the brain, which responds by inhibiting sympathetic nervous system output and increasing parasympathetic nervous system output. The effect of this activation is to reduce heart rate and blood pressure, thereby helping to maintain homeostasis of the circulatory system.

The use of baroreflex stimulation devices (also known as baroreflex activation therapy) is a potential alternative treatment for resistant hypertension and heart failure. Both hypertension and heart failure are relatively common conditions and are initially treated with medications and lifestyle changes. A substantial portion of patients are unresponsive to conventional therapy and treating these patients is often challenging, expensive, and

can lead to adverse events. As a result, there is a large unmet need for additional treatments.

Treatment Resistant Hypertension

Clinical Context and Therapy Purpose
The purpose of baroreflex stimulation devices is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medical therapy or other anti-hypertensive treatments (i.e., radiofrequency ablation of renal sympathetic nerves), in patients with treatment-resistant hypertension.

Populations
The relevant population of interest is individuals with treatment-resistant hypertension.

Interventions
The therapy being considered is baroreflex stimulation (also known as baroreflex activation therapy). Implanted devices provide electrical stimulation of the baroreceptors in the carotid arteries. Activating the baroreflex inhibits the sympathetic nervous system, causing various physiologic changes, including lowering blood pressure (BP).

Patients with treatment-resistant hypertension are actively managed by cardiologists in an outpatient clinical setting; baroreflex stimulation devices would be implanted in an inpatient hospital setting.

Comparators
Comparators of interest include optimal medical therapy and other hypertension treatments (i.e., radiofrequency ablation of renal sympathetic nerves).

Patients with treatment-resistant hypertension are actively managed by cardiologists in an outpatient clinical setting.

Outcomes
The general outcomes of interest are overall survival (OS), functional outcomes, quality of life, hospitalizations, medication use, and treatment-related morbidity.

Available literature has followed patients for up to 28 months, but in practice, patients with treatment-resistant hypertension would require long-term follow-up by cardiologists.

Randomized Controlled Trials
The Rheos® pivotal RCT evaluated the efficacy of baroreflex stimulation for lowering BP. Bisognano et. al. (2011) reported on this double-blind trial, which included patients with treatment-resistant hypertension defined as at least 1 systolic BP (SBP) measurement of 160 mm Hg or more with diastolic BP (DBP) measurement of 80 mm Hg or more after at least 1 month of maximally tolerated medical therapy. A total of 322 patients had the Rheos system implanted, and 265 patients underwent randomization. Participants were randomized in a 2:1 fashion to the device turned on or off for a 6-month

period. After 6 months, all patients had the device turned on. The primary efficacy endpoints were the percentage of patients achieving at least a 10 mm Hg decrease in SBP at 6 months (acute efficacy) and the percentage of patients who maintained their BP response over the 6- to 12-month study period (sustained efficacy). Primary safety outcomes were defined thresholds for procedural safety (at least 82% of patients free from procedural adverse events at 30 days), therapy safety (not more than 15% excess treatment-related adverse events in the experimental group), and device safety (at least 72% of patients free from procedural or therapy-related adverse events at 12 months).At 6 months, 54% of patients in the stimulation group had an SBP decrease of 10 mm Hg or more compared with 46% of patients in the control group (p=.97), indicating that the primary acute efficacy outcome was not met. The primary sustained efficacy outcome was met, with 88% of patients who responded at 6 months maintaining a response at 12 months. A secondary efficacy outcome (the percentage of patients reaching target SBP) showed a significant between-group difference. A total of 42% of the patients in the active treatment group reached a target SBP of 140 mm Hg compared with 24% in the control group (p=.005). For the primary procedural safety endpoint, the predefined threshold of 82% was not met. At 30 days, the percentage of patients free of procedural adverse events was 74.8%. The primary safety endpoint for therapy safety was met, with a similar percentage of patients free of treatment-related adverse events at 6 months (91.7% vs. 89.3%; p<.001 for noninferiority). The primary safety endpoint for device safety was also met, with 87.2% of patients free of device-related adverse events at 12 months, exceeding the predefined threshold of 72%.

Bakris et. al. (2012) reported on additional data in an extension of the Rheos trial.[5,] A total of 276 (86%) of the 322 implanted patients consented to long-term open-label follow-up. After a mean follow-up of 28 months, 244 (88%) of 276 were clinically significant responders. Response was defined as sustained achievement of the target SBP (≤ 140 mm Hg, or ≤ 130 mm Hg for patients with diabetes or renal disease), or a reduction in SBP of 20 mm Hg or more from device activation. Alternatively, patients could qualify as responders if their implanted device was deactivated and if they had an increase in SBP of at least 20 mm Hg in the 30 days after device deactivation. The extension study lacked a comparison group.

Observational Studies

Several uncontrolled observational studies have also been published. Scheffers et. al. (2010) reported on the largest of these, the Device Based Therapy in Hypertension Extension Trial (DEBuT-HT), which was a multicenter, single-arm feasibility study of the Rheos baroreflex activation therapy system. This trial enrolled 45 patients with treatment-resistant hypertension defined as a BP greater than 160/90 mm Hg despite treatment with at least 3 antihypertensive drugs, including a diuretic. The planned follow-up was 3 months, with a smaller number of patients followed up to 2 years. In 37 patients completing the 3-month protocol, office SBP was reduced by 21 mm Hg (p<.001) and DBP was reduced by 12 mm Hg (p<.001). There was a smaller reduction in 24-hour ambulatory BP (n = 26), with a decrease of 6 mm Hg in SBP (p=.10) and a decrease of 4 mm Hg in DBP (p=.04). In 26 patients followed for 1 year, the declines in office BP were

30 mm Hg for systolic (p<.001) and 20 mm Hg for diastolic (p<.001). For ambulatory BP (n = 15), the 1-year declines were 13 mm Hg for systolic (p<.001) and 8 mm Hg for diastolic (p=.001). A total of 7 (16.7%) of 42 patients experienced adverse events. Three patients required device removal due to infection, 1 experienced perioperative stroke, 1 experienced tongue paresis due to hypoglossal nerve injury, 1 had postoperative pulmonary edema, and 1 required reintervention for device explantation.

Wallbach et. al. (2016) published a single-arm study using the second-generation Neo device to treat uncontrolled hypertension. The study reported on 44 patients with resistant hypertension, defined as an office BP ≥ 140 mm Hg or ≥ 130 mm Hg for patients with chronic kidney disease and proteinuria, despite treatment with at least 3 antihypertensive medications including a diuretic. Mean baseline office BP was 171/91 mm Hg. After 6 months of baroreflex activation therapy, mean office BP decreased to 151 mm Hg over 82 mm Hg (pre to post, p<.001). At 6 months, the mean number of BP medications used per patient decreased from 6.5 at baseline to 6.0 (p<.03). One procedure-related major adverse event occurred, a contralateral stroke. Ten (23%) of the 44 patients experienced a minor procedure-related complication. The most common minor adverse events were disturbance of wound healing (n = 5 [11%]) and postoperative hematoma (n = 4 [9%]). One patient had revision surgery but explantation was not needed.

Section Summary
A Randomized control trial (RCT) has evaluated baroreflex stimulation devices. This trial, which compared the first-generation Rheos device plus medical management with medical management alone, met some but not all of its efficacy endpoints. Baroreflex stimulation-treated patients were no more likely to achieve at least a 10 mm Hg decrease in SBP at 6 months, but were more likely to reach the target SBP of 140 mm Hg or less at 6 months. The trial met 2 of its 3 predefined safety endpoints (therapy safety and device safety but not procedural safety). In addition, several uncontrolled studies have reported short-term reductions in BP, together with adverse events such as infection, hypoglossal nerve injury, and wound complications. Additional RCTs, particularly those using the second-generation device, are needed to draw conclusions about safety and efficacy.

Treatment Resistant Heart Failure

Clinical Context and Therapy Purpose
The purpose of baroreflex stimulation devices is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medical therapy in patients with treatment-resistant heart failure.

Populations
The relevant population of interest is individuals with treatment-resistant heart failure.

Interventions
The therapy being considered is baroreflex stimulation (also known as baroreflex activation therapy). Implanted devices provide electrical stimulation of the baroreceptors

in the carotid arteries. Activating the baroreflex inhibits the sympathetic nervous system, causing various physiologic changes, including lowering BP.

Patients with treatment-resistant heart failure are actively managed by cardiologists in an outpatient clinical setting; baroreflex stimulation devices would be implanted in an inpatient hospital setting.

Comparators
Comparators of interest include optimal medical therapy, implantable devices, and transplantation.

Patients with treatment-resistant heart failure are actively managed by cardiologists in an outpatient clinical setting.

Outcomes
The general outcomes of interest are OS, functional outcomes, quality of life, hospitalizations, medication use, and treatment-related morbidity.

Available literature has followed patients for up to 12 months, but in practice, patients with treatment-resistant heart failure would be followed by cardiologists for the rest of their lives.

Systematic Reviews
In 2020, Cai et. al. published a meta-analysis evaluating the efficacy of baroreflex activation therapy for heart failure. The meta-analysis included 4 RCTs and concluded that baroreflex activation therapy significantly improves quality of life score, 6-minute hall walk distance, New York Heart Association (NYHA) class, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and duration of hospitalization compared to control. However, the 4 RCTs included in the analysis all represented the same patient population from the Hope for Heart Failure (HOPE4HF) study (NCT01471860 and NCT01720160), and did not account for the overlapping population between studies. Therefore, this meta-analysis likely overestimated the true effect of baroreflex activation therapy. The HOPE4HF RCT and post hoc/subgroup analyses are summarized below.

Randomized Controlled Trials
In 2019, the Barostim Neo System was the first device to receive premarket approval through the U.S. Food and Drug Administration's (FDA's) Expedited Access Pathway (see Regulatory section). The safety and effectiveness data reviewed by the FDA was reported in the Barostim Neo-Baroreflex Activation Therapy for Heart Failure (BeAT-HF) trial. The BeAT-HF examined the safety and effectiveness of baroreflex activation therapy in heart failure patients with reduced ejection fraction using an Expedited and Extended Phase design. In the Expedited Phase, baroreflex activation therapy plus guideline-directed medical therapy was compared at 6â¯months post-implant to guideline-directed medical therapy alone using 3 intermediate end points: 6-minute hall walk distance, Minnesota Living with Heart Failure Questionnaire, and NT-proBNP. The

rate of heart failure morbidity and cardiovascular mortality was compared between the arms to evaluate early trending using predictive probability modeling. In the Expedited Phase, investigators randomized 264 intended use patients. The primary safety endpoint was major adverse neurological and cardiovascular event free rate, which was only measured in the baroreflex group; the lower bound of the one-sided 95% CI of the event-free rate had to be > 85%. Results analysts were blinded to arm assignment. At 6 months, the major adverse neurological and cardiovascular event -free rate was 96.8% (121 of 125 patients), and the one-sided 95% lower bound was 92.8% (p<.001). Effectiveness endpoint results are summarized in the table below. The FDA concluded from these results that the system was safe for the intended use population, and all effectiveness endpoints showed a statistically significant benefit for baroreflex activation therapy plus guideline-directed medical therapy compared to guideline-directed medical therapy alone.

6-Month Change from Baseline for Effectiveness Endpoints in the BeAT-HF Expedited Phase Trial

	6MHWD		QOL[a]		NT-proBNP	
	BAT + GDMT	GDMT	BAT + GDMT	GDMT	BAT + GDMT	GDMT
n	118	120	120	125	120	123
Mean (SD)	48.6 (66.3)	-7.9 (88.4)	-20.7 (25.4)	-6.2 (20.1)	-21.1% (0.4)	3.3% (0.3)
95% CI	36.5 to 60.7	-23.9 to 8.1	-25.3 to -16.1	-9.8 to -2.7	-32.3% to -8.2%	-8.9% to 17.2%
Difference	60.1		-14.1		-24.6%	
95% CI	40.3 to 79.9		-19.2 to -8.9		-37.6% to -8.7%	
p-value	<.001		<.001		.004	

6MHWD: 6-minute hall walk distance; BAT: Barostim therapy; BeAT-HF: Barostim Neo-Baroreflex Activation Therapy for Heart Failure; CI: confidence interval; GDMT: guideline based medical treatment; NA: not applicable; NT-proBNP: N-terminal pro-B-type natriuretic peptide; QOL: quality of life; SD: standard deviation.
[a] Measured by the Minnesota Living With Heart Failure Quality of Life questionnaire.

BeAT-HF includes an extended phase in which the heart failure morbidity and cardiovascular mortality end point is based on an expected event rate of 0.4 events/patient/year in the guideline-directed medical therapy arm. This trial is ongoing.

Halbach et. al. (2018) published a post hoc subgroup analysis from HOPE4HF evaluating baroreflex activation treatment for heart failure in patients with and without coronary artery disease (CAD). Patients (N = 146) from 45 centers with left ventricular ejection fraction < 35% and NYHA Class III were randomized to the baroreflex activation treatment group (n = 76) or control group (n = 70). The rate of system- or procedure-related major adverse neurological or cardiovascular events was 3.8% for the CAD group and 0% for no-CAD group (p>.99), while the system- or procedure-related complication rate was 11.5% for patients with CAD and 21.1% for those without CAD (p=.44). In the baroreflex activation group, from baseline to 6 months, quality of life scores decreased by 16.8 ± 3.4 points for CAD patients and by 18.9 ± 5.3 for no-CAD patients; NYHA Class decreased by 0.6 ± 0.1 for CAD patients and by 0.4 ± 0.2 for no-CAD patients. Left ventricular ejection fraction increased by 1.2 ± 1.4 for the CAD group and 5.2 ± 1.9 for

the no-CAD group. No interaction was found between the presence of CAD and effect of baroreflex activation therapy (p>.05). The study was limited by its small sample size and by the subgroup analysis not being prespecified. Overall, the limitations of this RCT included a relatively small sample size for a common condition, relatively short intervention period, and lack of blinding; some of the positive findings on the subjective patient-reported outcomes might have been due at least in part to a placebo effect. Additional RCTs with larger sample sizes and longer follow-up are needed to confirm these positive findings.

Weaver et. al. (2016) reported 12-month results for 101 (69%) of 146 patients from this RCT. No additional system- or procedure-related major adverse neurologic and cardiovascular events occurred between 6 and 12 months. Moreover, outcomes for NYHA functional class improvement, quality of life score, and 6-minute walk distance were all significantly better in the treatment group than in the control group at 12 months. This analysis had a substantial amount of missing data.

Abraham et. al. (2015) reported on 1 RCT, the HOPE4HF study, that evaluated baroreflex stimulation for the treatment of heart failure. This trial was nonblinded and included 146 patients with NYHA class III heart failure and an ejection fraction of ≤ 35% despite guideline-directed medical therapy. Patients were randomized to baroreflex stimulation (Barostim Neo System) plus medical therapy (n = 76) or to continued medical therapy alone (n = 70) for 6 months. The primary safety outcome was the proportion of patients free from major adverse neurologic and cardiovascular events. The trialists specified 3 primary efficacy endpoints: changes in NYHA functional class, quality of life-score, and 6-minute walk distance. The overall major adverse neurologic and cardiovascular events-free rate was 97.2%; rates were not reported separately for the baroreflex stimulation and control groups. In terms of the efficacy outcomes, there was significant improvement in the baroreflex stimulation group versus the control group on each of the 3 outcomes. Significantly more patients in the treatment group (55%) improved by at least 1 level in NYHA functional class than in the control group (24%; p<.002). Mean quality of life scores, as assessed by the Minnesota Living with Heart Failure Questionnaire, improved significantly more in the treatment group (–17.4 points) than in the control group (2.1 points; p<.001). Similarly, mean 6-minute walk distance improved significantly more in the treatment group (59.6 meters) than in the control group (1.5 meters; p=.004.).

Section Summary

The available evidence for baroreflex activation therapy for heart failure includes 2 RCTs and a post hoc subgroup analysis of a RCT. All trials compared baroreflex stimulation plus medical therapy with medical therapy alone in patients with heart failure. The 2019 RCT, the expedited trial that was used by the FDA to approve the Barostim Neo System, demonstrated that the system is safe and effective for its intended use population; however, the extended trial is still underway, and longer-term outcomes have not yet been determined. A 2018 RCT found a low rate of major adverse events and met all 3 efficacy endpoints (improvements in NYHA functional class, quality of life, and 6-minute walk distance). However, the study had methodologic limitations, including lack

of blinding, a relatively small sample size for a common condition, and relatively short intervention period.

Summary of Evidence
For individuals who have treatment-resistant hypertension who receive baroreflex stimulation therapy, the evidence includes a RCT and several small uncontrolled studies. Relevant outcomes are overall survival (OS), functional outcomes, quality of life, hospitalizations, medication use, and treatment-resistant morbidity. The uncontrolled studies have reported short-term reductions in BP in patients treated with baroreflex stimulation devices, as well as adverse events such as infection, hypoglossal nerve injury, and wound complications. The RCT comparing baroreflex stimulation with continued medical management met some efficacy endpoints but not others, as well as 2 of its 3 predefined safety endpoints. Additional RCTs are needed to permit conclusions on efficacy and safety. Baroreflex stimulation for treatment-resistant hypertension is accessible only through a Humanitarian Device Exemption for patients who previously participated in a pivotal trial. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have treatment-resistant heart failure who receive baroreflex stimulation therapy, the evidence includes 2 RCTs and a post hoc subgroup analysis of a RCT. Relevant outcomes are overall survival (OS), functional outcomes, quality of life, hospitalizations, medication use, and treatment-resistant morbidity. The expedited phase of the 2019 RCT was used by the U.S. FDA to approve the Barostim Neo System. The trial demonstrated that the system is safe and effective for its intended use population in the short term; however, the extended trial is still underway, and longer-term outcomes have not been determined. A 2018 RCT met all 3 efficacy endpoints but had methodologic limitations, incomplete blinding, a relatively small sample size for a common condition, and a short intervention period. A second, larger, RCT designed to assess the effects of the intervention on mortality, safety, function, and quality of life outcomes is underway. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Heart Association
In 2017, the American Heart Association (AHA) issued a joint guideline for the management of high blood pressure in adults with the American College of Cardiology and multiple other organizations. This guideline notes that studies have not provided sufficient evidence to support the use of baroreceptor pacing for managing resistant hypertension.

National Institute for Health and Excellence (NICE)
In 2015, the National Institute for Health and Excellence (NICE) issued a interventional procedures guidance that included the following recommendations:

- Current evidence on the safety and efficacy of implanting a baroreceptor stimulation device for resistant hypertension is inadequate. Therefore, this procedure should only be used in the context of research.
- Further research on implanting a baroreceptor stimulation device for resistant hypertension should document patient selection in detail and should specify the devices and techniques used, and any adjunctive therapies. It should describe the changes in blood pressure that are considered to result from baroreceptor stimulation, and those that might be caused by other factors. Outcomes should include the duration of effect of baroreceptor stimulation; device durability; and the complications of hypertension, such as myocardial infarction and stroke.

Regulatory Status
In 2014, the Barostim Neo™ Legacy System received a humanitarian device exemption from the U.S. Food and Drug Administration for use in patients with treatment-resistant hypertension who received Rheos® Carotid Sinus leads as part of the Rheos® pivotal trial and were considered responders in that trial.

In 2019, Barostim Neo™ was granted premarket approval (PMA P180050) and is indicated for the improvement of symptoms of heart failure (i.e., quality of life, six-minute hall walk, and functional status) for patients who remain symptomatic despite treatment with guideline-directed medical therapy, are New York Heart Association (NYHA) Class III or Class II (with a recent history of Class III), and have a left ventricular ejection fraction ≤35% and a N-terminal pro-B-type natriuretic peptide (NT-proBNP) <1600 pg/ml, excluding patients indicated for Cardiac Resynchronization Therapy according to the American Heart Association/American College of Cardiology/European Society of Cardiology guidelines.

PRIOR APPROVAL

Not Required.

POLICY

See Related Medical Policies
- 02.02.17 Cardiac Contractility Modular Therapy
- 02.02.21 Cardiac Hemodynamic Monitoring for the Management of Heart Failure in the Outpatient Setting
- Noninvasive Heart Failure and Arrhythmia Management and Monitoring System

The use of baroreflex implanted stimulation devices (Barostim Neo™ Legacy System or Barostim Neo™) is considered **investigational** for all indications, including but not limited to the treatment of hypertension and heart failure, because the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0266T Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)
- 0267T Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)
- 0268T Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)
- 0269T Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)
- 0270T Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)
- 0271T Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)
- 0272T Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day)
- 0273T Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming

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POLICY HISTORY		
Date	**Reason**	**Action**
January 2022	Annual Review	Policy Revision, New Policy Created

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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