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REVIEW

Safety and efficacy of baroreflex activation therapy for heart failure with reduced ejection fraction: a rapid systematic review

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Abstract

To retrieve and assess the available data in the literature about the safety and efficacy of baroreflex activation therapy (BAT) in heart failure with reduced ejection fraction (HFrEF) patients, through a rapid systematic review of clinical studies. Rapid systematic review of literature. Searched electronic databases included PubMed, EMBASE, CENTRAL, Scopus, and Web of Science using Mesh and free terms for heart failure and BAT. No language restriction was used for the searches. We included full peer reviewed publications of clinical studies (randomized or not), including patients with HFrEF undergoing BAT, with or without control group, assessing safety and efficacy outcomes. One reviewer conducted the analysis of the selected abstracts and the full-text articles, performed data extraction, and evaluated the methodological quality of the selected articles. The methodological quality was assessed according to the Cochrane Collaboration instruments. A descriptive summary of the results is provided. Of the 441 citations screened, 10 publications were included (three were only conference abstracts), reporting data from three studies. Only one study was a randomized clinical trial. Two studies reported a 6 month following, and the other study analysed outcomes up to 41 months. The procedure seems to be safe when performed by a well-trained multiprofessional team. An 86% rate of system and procedure-related complication-free was reported, with no cranial nerve injuries. Improvements in New York Heart Association class of heart failure, quality of life, 6 min walk test, and hospitalization rates, as well as in muscle sympathetic nerve activity. No meta-analysis was conducted because of the lack of homogeneity across studies; the results from each study are reported individually. BAT procedure seems to be safe if appropriate training is provided. Improvements in clinical outcomes were described in all included studies. However, several limitations do not allow us to make conclusive statements on the efficacy of BAT for HFrEF. New well-designed trials are still needed.

Keywords Baroreflex activation therapy; Heart failure; Rapid review

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Introduction

Mortality, morbidity, and healthcare costs related to heart failure with reduced ejection fraction (HFrEF) remain unacceptable high although the advances in the medical field.[1,2] The symptoms and the progression of the disease are promoted by sympathovagal imbalance, including an excessive activation of the sympathetic and inhibition of the parasympathetic nerves system.[3,4] In this context, baroreflex activation therapy (BAT), which is a treatment based on the stimulation of the baroreceptors located at the carotid sinus[5] and supposedly restores sympathovagal balance, has been reported in the literature.[6,7]

Large animal studies demonstrated a survival benefit when compared with untreated controls, as well as improvements in cardiac function, susceptibility to ventricular arrhythmias.[8–10] The first-in-human study,[6] which was a single-centre, open-label trial including 11 patients, was published in 2014. The study included patients with New York Heart Association (NYHA) Class III, ejection fraction lower than 40%,

optimized medical therapy, and ineligible for cardiac resynchronization. The results showed that BAT was safe and provided chronic improvements in muscle sympathetic nerve activity (MSNA), quality of life, and functional capacity.[6]

In 2015, the first randomized clinical trial (RCT) was published in the literature including 76 patients underwent to BAT and 70 controls. Similarly, the study showed that BAT is safe and improves functional capacity, quality of life, exercise capacity, N-terminal pro-brain natriuretic peptide, and possibly the burden of heart failure (HF) hospitalizations.[7]

Although the promising result, it is still unclear in the literature the effect of BAT in patients with HF. Thus, the aim of this study was to retrieve and assess the available data in the literature about the safety and efficacy of BAT in HFrEF patients, through a rapid systematic review of clinical studies.

Methods

Protocol and registration

This rapid review was designed using as guidance the Preferred Reporting Items for Systematic Reviews and Meta-analyses [11] and is registered in the PROSPERO (International Prospective Register of Systematic Reviews) database,[12] under the code [CRD42018114741].

Eligibility criteria

We included full peer reviewed publications of clinical studies (randomized or not), including patients with HFrEF undergoing BAT, with or without control group, assessing safety and efficacy outcomes. Abstracts from conferences were included if they provided enough information to judge eligibility and evaluate the outcomes. We excluded case reports and literature reviews.

Information sources and literature search

We searched the following electronic databases: PubMed, EMBASE, CENTRAL, Scopus, and Web of Science. In addition, we searched the references of the included articles manually, as well as performed a citation analysis of the included studies using Google Scholar. The initial search comprised the Mesh term 'Heart Failure' followed by its related entry terms and other free terms and free terms related to 'baroreflex activation therapy'. We did not use limits for language or date when conducting the searches.

Study selection

Titles and abstract of the retrieved articles were independently evaluated by one reviewer. Abstracts that do not provide enough information regarding the eligibility criteria will be kept for full-text evaluation. One reviewer evaluated full-text articles and determined study eligibility.

Data abstraction

One reviewer conducted data extraction and included study title, author, journal and year of publication, study design, population, inclusion and exclusion criteria, study arms and sample size, intervention description, outcomes definitions, measurement and results (as presented in the included studies), and follow-up period.

Risk of bias assessment

To assess the risk of bias of the RCT, we used the Cochrane Risk of Bias tool that considers bias related to selection, performance, detection, attrition, reporting, and other possible.[13] For the non-randomized studies, we used the ROBINS-I tool (Risk Of Bias In Non-randomized Studies—of Interventions), also from Cochrane Collaboration.[14] The following types of bias were considered: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measuring of outcomes, bias in selection of the reported result, and overall bias. The evaluation was conducted independently by one reviewer.

Synthesis

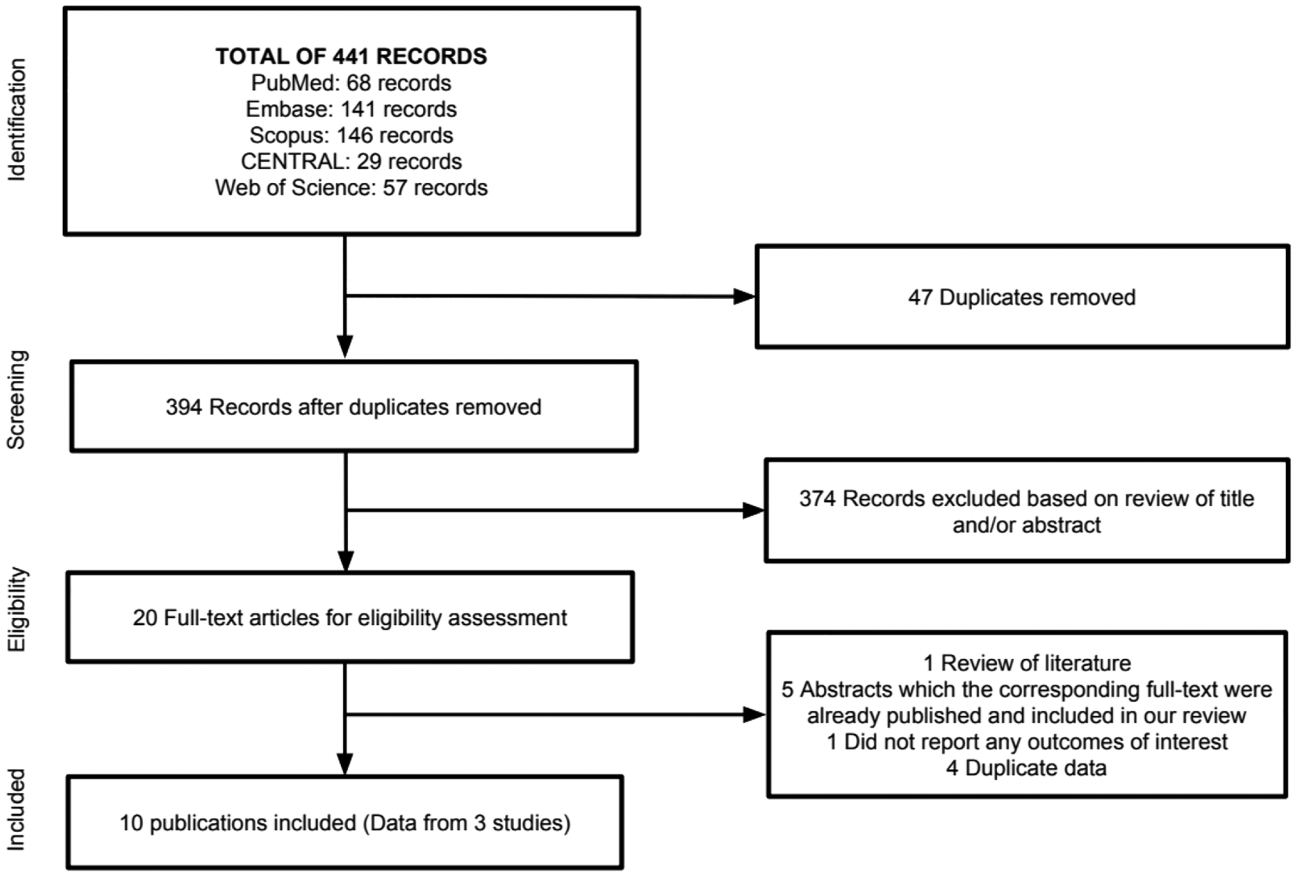
Descriptive analyses of studies will be performed including study characteristics and main results.

Results

Study selection

Our search strategies yielded 441 citations from the five electronic databases. After excluding duplicates and screening titles and abstracts for eligibility, 20 publications were kept for full-text evaluation. Finally, 10 publications were included in our rapid review, representing data from three studies. *Figure 1* demonstrates the study selection process.

Figure 1 Study selection process.



Study characteristics

First study (reported in three publications and one conference abstract)

Study from Gronda *et al.*[6] was the first-in-human study evaluating BAT for HFrEF published in the literature. The study included a series of 11 patients and reported a 6 month follow-up. A year later, another publication[15] reported the long-term follow-up of this study, including results at 12 and 21 ± 5 months after intervention. In 2016, another article[16] reporting data from the same study was published. However, this publication added data from nine controls, who were treated congestive HFrEF patients to assess the effects of chronic baroreceptor activation on arterial stiffness. In 2017, the authors published an abstract in a conference[17] reporting the 42 month follow-up of those 11 patients. The main characteristics of these publications are described in *Table 1*.

Second study (reported in four publications and one conference abstract)

Study from Abraham *et al.*[7], named HOPE4HF, was the first and only RCT found in the literature assessing BAT for HFrEF patients. The study included 140 patients, mostly men, with a mean ejection fraction of 24 ± 7%. Still in 2015, a sub-analysis of this RCT, study from Zile *et al.*[18] was published comparing patients with or without cardiac resynchronization therapy. In 2016, Weaver *et al.*[19] published the intraoperative experience and the 12 month safety and efficacy results of the HOPE4HF trial. A year after, Wachter *et al.*[20] presented an abstract in a conference reporting another sub-analysis of the HOPE4HF trial comparing patients with systolic blood pressure equal or lower to 16 mmHg with >16 mmHg. Last, Halbach *et al.*[21] published one more sub-analysis of the same trial in the literature, separating patients with or without coronary artery disease. The main characteristics of these publications are described in *Table 1*.

Third study (reported in one conference abstract)

Mueller-Ehmsen *et al.*[22] published an abstract in a conference reporting the European experience with BAT in HFrEF. The abstract included the results of 57 patients from centres in Germany, Italy, and France. We could not find a full text of this study; thus, we understand it was not published yet. The main characteristics of this study are described in *Table 1*.

Table 1 Studies characteristics

Study, Year	Study design	Population	Study arms, if applicable	Number of patients	Age (Mean ± SD)	Female *N* (%)	Hypertension *N* (%)	LVEF Mean ± SD (%)	Outcomes	Follow-up (months)
Gronda *et al.*,[6]	Single-centre, open-label study	HF patients NYHA Class III, EF < 40%, optimized medical therapy, and ineligible for CRT	Single arm	11	67 ± 9	3 (27.3)	NA	31 ± 7	MSNA, changes in NYHA functional class and quality-of-life score	1, 3, and 6
Gronda *et al.*,[15] —Long-term follow-up of Gronda *et al.*,[6]	Single-centre, open-label study	HF patients NYHA Class III, EF < 40%, optimized medical therapy, and ineligible for CRT	Single arm	11 (nine alive at the end of the follow-up)	67 ± 9	3 (27.3)	NA	31 ± 7	MSNA, baroreflex sensitivity data and hospitalization rate, changes in NYHA functional class and quality-of-life score	6 and 21.5 ± 4.2
Gronda *et al.*,[16] —Partially duplicated population with Gronda *et al.*,[6]	Single-centre, open-label study	NYHA Class III HFrEF patients	BAT	9	66 ± 8	1 (11.1)	NA	32.4 ± 8	Arterial stiffness—pulse wave velocity	3
			Control	9	68 ± 1	1 (11.1)		35.6 ± 6		
Gronda *et al.*,[17] —Long-term follow-up of Gronda *et al.*,[6] [Abstract]	Single-centre, open-label study	HF patients NYHA Class III, EF < 40%, optimized medical therapy, and ineligible for CRT	Single arm	11 (seven alive at the end of the follow-up)	NA	NA	NA	NA	MSNA, quality-of-life score, 6 min hall walk distance, LVEF, hospitalization	21.5 ± 4.7 and 41.5 ± 3.5
Abraham *et al.*,[7] HOPE4HF study	RCT	Chronic HF with LVEF of 35% or less	BAT—Barostim neo system	71	64 ± 7	9 (12.7)	19 (57.6)	24 ± 7	System-related and procedure-related major adverse neurological and cardiovascular events, changes in NYHA functional class, quality-of-life score, and 6 min hall walk distance	3 and 6
			Control—standard medical therapy	69	66 ± 1	11 (15.9)	21 (56.8)	25 ± 7		
Zile *et al.*,[18] —Sub-analyses of HOPE4HF study	RCT	Chronic HF with LVEF of 35% or less	CRT (divided in BAT and control)	45 (24 BAT and 21 control)	68 ± 9	9 (8.9)	8 (36.4)	24 ± 6	Changes in NYHA functional class, quality-of-life score, and 6 min hall walk distance	6
			No-CRT (divided in BAT and control)	95 (47 BAT and 48 control)	63 ± 1	16 (16.8)	32 (66.7)	25 ± 7		
Weaver *et al.*,[19] —Long-term	RCT	Chronic HF with LVEF of 35% or less	BAT—Barostim neo system	71	64 ± 7	9 (12.7)	19 (57.6)	24 ± 7	System-related and procedure-	12

(*Continues*)

Table 1 (continued)

Study, Year	Study design	Population	Study arms, if applicable	Number of patients	Age (Mean ± SD)	Female *N* (%)	Hypertension *N* (%)	LVEF Mean ± SD (%)	Outcomes	Follow-up (months)
follow-up of HOPE4HF study									related major adverse neurological and cardiovascular events, changes in NYHA functional class, quality-of-life score, and 6 min hall walk distance	
			Control—standard medical therapy	69	66 ± 1	11 (15.9)	21 (56.8)	25 ± 7		
Wachter *et al.*,[20] —Sub-analyses of HOPE4HF study [Abstract]	RCT	Chronic HF with LVEF of 35% or less	SBP ≤ 116 mmHg (divided in BAT and control)	71 (42 BAT and 29 control)	NA	NA	NA	NA	Changes in NYHA functional class, quality-of-life score, and 6 min hall walk distance	6
			SBP > 116 mmHg (divided in BAT and control)	69 (29 BAT and 40 control)	NA	NA	NA	NA		
Halbach *et al.*,[21] —Sub-analyses of HOPE4HF study	RCT	Chronic HF with LVEF of 35% or less	CAD (divided in BAT and control)	101 (52 BAT and 49 control)	NA	NA	NA	NA	Changes in NYHA functional class, quality-of-life score, and 6 min hall walk distance	6
			No-CAD (divided in BAT and control)	39 (19 BAT and 20 control)	NA	NA	NA	NA		
Mueller-Ehmsen *et al.*,[22] [Abstract]	Multicentre, open-label study	HF patients NYHA Class III, EF ≤ 40%	Single arm	57	NA	NA	NA	NA	Changes in NYHA functional class, quality-of-life score, HF medications and renal function	6

BAT, baroreflex activation therapy; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MSNA, muscle sympathetic nerve activity; NYHA, New York Heart Association; RCT, randomized controlled trial; SBP, systolic blood pressure.

Risk of bias

Risk of bias was assessed in Gronda *et al*.[6,15–17] and HOPE4HF[3,7,18–20] studies. We did not assessed risk of bias of the Mueller-Ehmsen *et al*.[22] because the abstract did not provide enough information to allow it. The study from Gronda *et al*. was considered of low risk of bias due to confounding, selection of participants, missing data, and selection of the reported result; and of moderate risk of bias due to classification of intervention, deviations from intended interventions, and measuring of outcomes. HOPE4HF trial was considered of low risk of bias related to selection, performance, detection, attrition, and reporting.

Synthesis of results

Safety

Both, study from Gronda and the HOPE4HF trial, used the same delivery system, the Barostim neo, CVRx, Inc, Minneapolis, MN, USA. The system consists of a pulse generator similar in size and shape to an implanted defibrillator coupled with a carotid sinus lead. The device is implanted subcutaneously in the right or left pectoral region with the lead tunnelled from a small (2.5–5 cm) cutaneous incision to affix over the ipsilateral carotid bifurcation. Safety related to this system has been previously reported[23] and comparable with a pacemaker. Study from Mueller-Ehmsen *et al*.[22] did not report details on the BAT system used; however, it mentions that the system safety profile is similar to a pacemaker. Thus, we believe they may have used the same system in their study. *Table 2* describes the system and procedure-related events reported in the included studies.

Efficacy

Changes in New York Heart Association class New York Heart Association HF class measurement was reported in all three studies and in nine of the 10 publications. Gronda *et al*.[6,15] reported improvements in NYHA class of HF at 3, 6, and 21.5 ± 4.2 month follow-ups. The report of the 4 year follow-up did not show data on this outcome. Improvements in class of HF were also demonstrated in the original publication[7] and all the sub-analyses[3,18–20] of the HOPE4HF study, in patients undergoing BAT at 6 months when compared with baseline. Similarly, the study from Mueller-Ehmsen *et al*.[22] also reported improvement of NYHA class of HF at 6 month follow-up. Detailed data on this outcome are shown on *Table 3*.

Quality of life Quality of life was measured in the three studies and reported in all publications. Improvements in this outcome were described in all comparison, except for patients making use of cardiac resynchronization therapy undergoing BAT, when compared with controls (patients making use of cardiac resynchronization therapy undergoing BAT) (P = 0.23). Details on quality of life measuring methods and results are described in *Table 3*.

Six minute walk test Six minute walk test was applied in all studies, and results were available in all publications. Most of the reported improvements in this outcomes, except for three patients group, are as follows: patients making use of cardiac resynchronization therapy undergoing BAT, when compared with controls (patients making use of cardiac resynchronization therapy not undergoing BAT) (P = 0.38); patients with systolic blood pressure $<$116 mmHg undergoing BAT, when compared with controls (patients with systolic blood pressure $<$116 mmHg not undergoing BAT) (P = 0.08); and patients without coronary artery disease undergoing BAT, when compared with patients without coronary artery disease not undergoing BAT (P = 0.84). These results are described in details in *Table 2*.

Hospitalization Hospitalization was described in two studies and seven publications. Most of the publications reported lower rates of hospitalization after BAT. There was no difference when compared patients making use of cardiac resynchronization therapy undergoing and not undergoing

Table 2 Summary of the reported system and procedure-related events reported in the included studies

Study, Year	Number of patients submitted to BAT	BAT system	System and procedure-related events
Gronda *et al*.,[6,15,16,23]	11	Barostim neo, CVRx, Inc, Minneapolis, MN, USA	One reported event. The patient experienced anaemia requiring a transfusion during the implant. The patient recovered with no residual effects.
HOPE4HF study,[3,7,18–20]	71	Barostim neo, CVRx, Inc, Minneapolis, MN, USA	The rate of freedom from system and procedure-related complications was 86% through 12 months. There were two MANCE events (hematomas) that occurred during the six first months after BAT. In addition, the study reported three more events: urinary tract infection secondary to urinary retention, hypotension, and transection of the transverse cervical skin nerve. The complications that did occur were generally mild and short-lived.
Mueller-Ehmsen *et al*.,[22]	57	Details are not reported in the abstract.	The abstract did not report any events neither data on safety. It is only mentioned that the system safety profile was similar to a pacemaker.

BAT, baroreflex activation therapy; MANCE, major adverse neurologic and cardiovascular events.

Table 3 Main efficacy summary results

Study, Year	Study arms, *N*	NYHA class	QoL	Six min hall walk distance (m)	Hospitalizations
Gronda *et al.*,[6]	BAT, 11	Baseline: 11 patients at Class III 3 month variation: six patients at Class II and five patients at Class I 6 month variation: one patient at Class III, two patients at Class II, and five patients at Class I $P < 0.001$ at both 3 and 6 month follow-up	Baseline: 33.4 ± 29.8 3 month variation: −1 1.7 ± 4.4 6 month variation: −10.6 ± 3.8 $P = 0.007$ Questionnaire: Minnesota Living with Heart Failure score	Baseline: 304.4 ± 49.6 3 month variation: +49.7 ± 15.7 6 month variation: +51.1 ± 25.6 $P = 0.05$	6 months before intervention: eight of the 11 patients were hospitalized (total of 125 days) 6 months after intervention: one of the 11 patients was hospitalized (total of 6 days)
Gronda *et al.*,[15] —Long-term follow-up of Gronda *et al.*,[6]	BAT, 9 (two of the 11 patients died)[a]	21.5 ± 4.2 month follow-up: all patients were at Class I	Baseline: 30.9 ± 27.8 6 month variation: −11.5 ± 4.6 21.5 ± 4.2 month variation: −13.2 ± 5.4 $P = 0.006$ Questionnaire: Minnesota Living with Heart Failure score	Baseline: 306.4 ± 52.4 6 month variation: +69.7 ± 24.4 21.5 ± 4.2 month variation: +58.4 ± 33.4 $P = 0.01$	12 months before intervention: 1.44 ± 1.3 days/month. Total of 155 days of hospitalization (all patients together) 6 months after intervention: 0.13 ± 0.33 days/month. Total of 7 days of hospitalization (all patients together) 21.5 ± 4.2 months after intervention: 0.27 ± 0.44 days/month. Total of 45 days of hospitalization (all patients together)
Gronda *et al.*,[17] —Long-term follow-up of Gronda *et al.*,[6] [Abstract]	BAT, 7 (four of the 11 patients died)[b]	Not reported	Baseline: 31.3 ± 26.0 21.5 ± 4.2 months: 1 7.7 ± 9.2 41.5 ± 3.5 months: 1 6.9 ± 7.7 $P < 0.05$ Questionnaire: Minnesota Living with Heart Failure score	Baseline: 306 ± 36.2 21.5 ± 4.2 months: 3 65 ± 36.2 41.5 ± 3.5 months: 425 ± 116 $P = 0.001$	Hospitalization rate (days/year/patient) Baseline: 17.18 21.5 ± 4.2 months: 0.93 41.5 ± 3.5 months: 0.87 $P < 0.001$
Abraham *et al.*,[7] HOPE4HF study	BAT, 71 Control, 69	6 months vs. baseline BAT ($n = 64$) Improved: 55% Same: 42% Worse: 3% Control ($n = 54$) Improved: 24% Same: 67% Worse: 9% $P = 0.002$	6 months vs. baseline BAT ($n = 64$): −17.4 ± 2.8 Control ($n = 54$): 2.1 ± 3.1 $P < 0.001$ Questionnaire: Minnesota Living with Heart Failure score	6 months vs. baseline BAT ($n = 56$): 59.6 ± 14.1 Control ($n = 43$): 1.5 ± 13.2 $P = 0.004$	6 months vs. baseline HF hospitalizations (n) BAT ($n = 57$): −0.49 ± 0.2 Control ($n = 50$): −0.05 ± 0.2 $P < 0.05$ HF hospitalizations (days) BAT ($n = 57$): −6.28 ± 2.7 Control ($n = 50$): 0.08 ± 1.7 $P < 0.05$
Zile *et al.*,[18]— Sub-analyses of HOPE4HF study	CRT BAT: 24 Control: 21	6 months vs. baseline CRT BAT: −0.7 ± 0.1	6 months vs. baseline CRT BAT: 9.3 ± 4.0	6 months vs. baseline CRT BAT: 16.4 ± 10.6	6 months vs. baseline HF hospitalizations (n) CRT

(*Continues*)

Table 3 (continued)

Study, Year	Study arms, *N*	NYHA class	QoL	Six min hall walk distance (m)	Hospitalizations
	No-CRT BAT: 47 Control:48	Control: −0.1 ± 0.2 $P < 0.001$ No-CRT BAT: −0.4 ± 0.1 Control: −0.2 ± 0.1 $P = 0.09$	Control: −0.9 ± 6.0 $P = 0.23$ No-CRT BAT: −21.6 ± 3.6 Control: 3.5 ± 3.7 $P < 0.001$ Questionnaire: Minnesota Living with Heart Failure score	Control: −3.5 ± 22.9 $P = 0.38$ No-CRT BAT: 85 ± 3.6 Control: 3.6 ± 16.3 $P = 0.003$	BAT: −0.42 ± 0.3 Control: −0.25 ± 0.3 $P = 0.78$ No-CRT BAT: −0.53 ± 0.2 Control: 0.05 ± 0.3 $P = 0.08$ HF hospitalizations (days) CRT BAT: −1.05 ± 1.2 Control: −0.13 ± 2.5 $P = 0.78$ No-CRT BAT: −8.89 ± 4.0 Control: 0.18 ± 2.2 $P = 0.09$
Weaver *et al.*,[19] —Long-term follow-up of HOPE4HF study	BAT, 71 Control, 69	12 months vs. baseline % improved BAT ($n = 56$): +45 Control ($n = 42$): +26 $P < 0.001$	12 months vs. baseline BAT ($n = 56$): −9.9 ± 2.9 Control ($n = 42$): 0.7 ± 2.9 $P = 0.003$	12 months vs. baseline BAT ($n = 50$): 5 8.5 ± 17.0 Control ($n = 39$): 13.4 ± 17.9 $P = 0.005$	Not reported
Wachter *et al.*,[20] —Sub-analyses of HOPE4HF study [Abstract]	SBP ≤ 116 mmHg BAT: 42 Control: 29 SBP > 116 mmHg BAT: 29 Control: 40	6 months vs. baseline SBP ≤ 116 mmHg BAT ($n = 37$): −0.5 ± 0.1 Control ($n = 22$): 0.0 ± 0.1 $P = 0.008$ SBP > 116 mmHg BAT ($n = 27$): −0.6 ± 0.1 Control ($n = 32$): −0.3 ± 0.1 $P = 0.03$	6 months vs. baseline SBP ≤ 116 mmHg BAT ($n = 37$): −18.7 ± 3.7 Control ($n = 22$): 4.6 ± 5.6 $P < 0.01$ SBP > 116 mmHg BAT ($n = 27$): −15.6 ± 4.5 Control ($n = 32$): 0.4 ± 3.6 $P = 0.007$ Questionnaire: Minnesota Living with Heart Failure score	6 months vs. baseline SBP ≤ 116 mmHg BAT ($n = 32$): 49.8 ± 14.9 Control ($n = 19$): − 20.8 ± 24.0 $P = 0.01$ SBP > 116 mmHg BAT ($n = 24$): 72.7 ± 26.4 Control ($n = 24$): 19.1 ± 13.5 $P = 0.08$	Not reported
Halbach *et al.*,[21] —Sub-analyses of HOPE4HF study	CAD BAT: 52 Control: 49 No-CAD BAT: 19 Control: 20	6 months vs. baseline CAD BAT ($n = 47$): −0.6 ± 0.1 Control ($n = 36$): −0.2 ± 0.1 $P = 0.003$ No-CAD BAT ($n = 17$): −0.4 ± 0.2 Control ($n = 18$): −0.1 ± 0.2	6 months vs. baseline CAD BAT ($n = 47$): −16.8 ± 3.4 Control ($n = 36$): 1.7 ± 4.1 $P < 0.001$ No-CAD BAT ($n = 17$): −18.9 ± 5.3 Control ($n = 18$): 2.9 ± 4.9 $P = 0.005$ Questionnaire: Minnesota Living with Heart Failure score	6 months vs. baseline CAD BAT ($n = 41$): 72.7 ± 17.2 Control ($n = 29$): − 6.6 ± 17.8 $P = 0.003$ No-CAD BAT ($n = 15$): 23.7 ± 21.9 Control ($n = 14$): 18.2 ± 16.6 $P = 0.84$	HF hospitalizations (n) CAD BAT ($n = 41$): −0.59 ± 0.26 Control ($n = 36$): 0.10 ± 0.28 $P = 0.058$ No-CAD BAT ($n = 16$): −0.25 ± 0.17 Control ($n = 14$): −0.43 ± 0.31 $P = 0.86$ HF hospitalizations (days) CAD BAT ($n = 41$): −7.32 ± 3.63

(*Continues*)

Table 3 (continued)

Study, Year	Study arms, *N*	NYHA class	QoL	Six min hall walk distance (m)	Hospitalizations
		$P = 0.21$			Control ($n = 36$): 0.95 ± 2.23 $P = 0.048$ No-CAD BAT ($n = 16$): −3.63 ± 2.80 Control ($n = 14$): −2.14 ± 1.73 $P = 0.677$
Mueller-Ehmsen *et al.*,[22] [Abstract]	BAT, 57	Baseline: 3.0 ± 0.0 6 month variation: −0.9 ± 0.1 $P < 0.001$ *N* available: 50	Baseline: 44.1 ± 22.1 6 month variation ($n = 49$): −14.4 ± 3.1 $P < 0.001$ Questionnaire: Minnesota Living with Heart Failure score	Baseline: 301.2 ± 81.2 6 month variation ($n = 43$): 85.2 ± 15.2 $P < 0.001$	Not reported

BAT, baroreflex activation therapy; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; NYHA, New York Heart Association; SBP, systolic blood pressure.
[a]Causes of death: one succumbed to septic shock that developed over pneumonia following a general decline in health 11.2 months post-activation. The second one, who was an insulin-dependent diabetic patient, died 16.2 months post-activation of electromechanical dissociation in the context of a new (first after BAT activation) episode of acute heart failure. Both patients suffered a post-ischaemic dilated cardiomyopathy.
[b]The abstract did not report the causes of death.

BAT, patients not making use of cardiac resynchronization therapy undergoing and not undergoing BAT, patients with coronary artery disease undergoing BAT or not, and patients without coronary artery disease undergoing BAT or not. Details on the hospitalization rates presented in each publication are described in *Table 2*.

Other reported outcomes

Besides the reported outcomes earlier, the publications from Gronda *et al.*[6,15–17] reported a serial measurement of MSNA. At a 6 month follow-up, the study demonstrated a reduction from 45.1 ± 7.7 to 31.3 ± 8.3 bursts/min and from 67.6 ± 12.7 to 45.1 ± 11.6 bursts/100 heartbeats, decreases of 31% and 33%, respectively ($P < 0.01$). The decrease was sustained through over the long-term follow-up (21.5 ± 4.2) with a difference of −15 ± 2.6 bursts/min ($P < 0.001$) and −24.7 ± 4.3 bursts/100 heartbeats ($P < 0.001$). At the 4 year follow-up, the study reported a measure of 26 ± 3, which was also significantly different from baseline ($P < 0.001$).

The study from Gronda *et al.*[16] also reported the effects of chronic carotid baroreceptor activation on arterial (aortic) stiffness in HFrEF. Aortic stiffness was evaluated by pulse wave velocity between the carotid and the femoral artery of the same side. The study reported non-significant change in pulse wave velocity at the third month evaluation after BAT. Similarly, no differences were reported in the control group.

The HOPE4HF[7] trial also reported the effects of BAT on systolic and diastolic blood pressure. It was observed an increase in systolic blood pressure, as well as pulse pressure in patients who underwent BAT, 6 months after intervention. In contrast, trends towards decreasing systolic blood pressure and pulse pressure were found in the control group. No effects on diastolic blood pressure were observed.

Discussion

This review summarized the available evidence on the use of BAT for patients with HFrEF. The results indicate that the therapy is safe and improves clinical outcomes such as NYHA class of HF, quality of life, 6 min walk test, and hospitalization rates, as well as in MSNA. The study evaluating arterial stiffness did not report any changes after therapy. The only RCT available reported an 86% rate of system and procedure-related complication-free, with no cranial nerve injuries.

The baroreceptors located at the carotid sinus have a well-known influence on the central autonomic nervous. Besides it, the sympathovagal imbalance plays in the progression of HF does. In this context, BAT consists in the stimulation of baroreceptors at the carotid sinus in order to decrease sympathetic and increase parasympathetic tone and, ultimately,

provide additional beneficial effects on patients with HFrEF.[3,24]

Up to now, most of the studies in human subjects evaluating BAT focused on patients with resistant hypertension. A recent meta-analysis[25] published in the literature assessing safety and efficacy of BAT in patients with resistant hypertension demonstrated that systolic and diastolic blood pressure decreased in patients who underwent BAT as early as 3 months and sustained up to 24 months after therapy.[25] The review included 12 studies in the qualitative analysis and five in the meta-analysis. In relation to the effects of BAT on blood pressure in patients with HFrEF, the HOPE4HF[7] trial has found that BAT significantly increased blood pressure, as well as pulse pressure. In the control group, the authors reported trends towards decreasing systolic blood pressure and pulse pressure. No effects on diastolic blood pressure were identified.

Previous data have shown that the MSNA is high in both HFrEF and severe hypertension ([26]), addressing similar autonomic imbalance in both conditions. In patients with advanced HFrEF, low systolic pressure is a marker of unfavourable outcomes. In relation to severe hypertensive patients, the persistency of high levels of blood pressure leads to unfavourable outcomes.

As said earlier, the systematic review evolving resistant hypertension patients[25] and the HOPE4HF trial[7] demonstrated opposite effects on blood pressure. BAT was demonstrated to rebalance the autonomic system restoring the appropriate physiological response. This result is unique in the device cardiovascular therapy setting.

In the HFrEF field, although the promising results, there is much yet to learn to achieve conclusive results about the use of BAT for HFrEF patients. Since the first-generation system, surgery duration, complexity, and the safety of BAT system have improved significantly. The available data indicate that, with proper training, the procedure is safe (19). In terms of efficacy, improvements in clinical outcomes have been reported in the included studies, as mentioned earlier. However, a pivotal trial is still need to make assertive conclusions.

This study has some limitations important to mention. Only three studies are available in the literature answering our review research question, and only one of them was designed as an RCT. In addition, three of the 10 included publications were only abstracts published in conferences and not peer review publications. The small sample size and the heterogeneity across the included studies lacked the power to make conclusive statements.

Importantly, we designed our study as a rapid systematic review. We did perform all the steps of a traditional systematic review; however, they were executed by only one reviewer. This approach has been previously described in the literature, and its value has been recognized by important organizations, such as the Cochrane Collaboration. A rapid review has a shorten time of execution, making it possible to obtain results timely and with reduced costs.

Despite those limitations, to our knowledge, this is the first review using a systematic methodology that aimed to retrieve and report the available data on the safety and efficacy of BAT for patients with HFrEF. We believe that our study can provide significant information to support future clinical trials and registries in this area.

In conclusion, the results of this review suggest that BAT is safe and improves clinical outcomes in HFrEF patients. Although the promising results, there is currently insufficient evidence on the safety and efficacy of BAT for patients with HFrEF to draw meaningful conclusions. Further high-quality RCTs with long-term follow-up are still needed in order to obtain conclusive results.

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire D, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation* 2014; **129**: e28–e292.
2. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CSP, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014; **63**: 1123–1133.
3. Halbach M, Fritz T, Madershahian N, Pfister R, Reuter H. Baroreflex activation therapy in heart failure with reduced ejection fraction: available data and future perspective. *Curr Heart Fail Rep* 2016; **13**: 71–76.
4. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *J Am Coll Cardiol* 2009; **54**: 375–385.
5. Ad N. Baroreflex activation therapy for patients with heart failure and low ejection fraction is safe and effective. *Semin Thorac Cardiovasc Surg* 2016; **28**: 329–330.
6. Gronda E, Seravalle G, Brambilla G, Costantino G, Casini A, Alsheraei A, Lovett EG, Mancia G, Grassi G. Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: a proof-of-concept study. *Eur J Heart Fail* 2014; **16**: 977–983.
7. Abraham WT, Zile MR, Weaver FA, Butter C, Ducharme A, Halbach M, Klug D, Lovett EG, Müller-Ehmsen J, Schafer JE, Senni M, Swarup V, Wachter R, Little WC. Baroreflex activation therapy for the treatment of heart failure with a

reduced ejection fraction. *JACC Heart Fail* 2015; **3**: 487–496.
8. Sabbah HN, Gupta RC, Imai M, Irwin ED, Rastogi S, Rossing MA, Kieval RS. Chronic electrical stimulation of the carotid sinus baroreflex improves left ventricular function and promotes reversal of ventricular remodeling in dogs with advanced heart failure. *Circ Heart Fail* 2011; **4**: 65–70.
9. Sabbah HN. Baroreflex activation for the treatment of heart failure. *Curr Cardiol Rep* 2012; **14**: 326–333.
10. Zucker IH, Hackley JF, Cornish KG, Hiser BA, Anderson NR, Kieval R, Irwin ED, Serdar DJ, Peuler JD, Rossing MA. Chronic baroreceptor activation enhances survival in dogs with pacing-induced heart failure. *Hypertension* 2007; **50**: 904–910.
11. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.
12. PROSPERO [Internet]. https://www.crd.york.ac.uk/prospero/ (19 June 2018).
13. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods Group, Cochrane. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **18**: d5928.
14. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016: i4919.
15. Gronda E, Seravalle G, Trevano FQ, Costantino G, Casini A, Alsheraei A, Lovett EG, Vanoli E, Mancia G, Grassi G. Long-term chronic baroreflex activation: persistent efficacy in patients with heart failure and reduced ejection fraction. *J Hypertens* 2015; **33**: 1704–1708.
16. Gronda E, Brambilla G, Seravalle G, Maloberti A, Cairo M, Costantino G, Lovett EG, Vanoli E, Mancia G, Grassi G. Effects of chronic carotid baroreceptor activation on arterial stiffness in severe heart failure. *Clin Res Cardiol* 2016; **105**: 838–846.
17. Gronda E, Costantino G, Alberti A, Baronio B, Staine T, Grassi G, Seravalle G, Vanoli E. Four years of baroreflex activation therapy in advanced heart failure: 3rd long-term follow-up report of a proof-of-concept study. https://esc365.escardio.org/Congress/Heart-Failure-2017-4th-World-Congress-on-Acute-Heart-Failure/Poster-Session-4-Devices-CRT-ICD-Surgery/153235-fouryears-of-baroreflex-activation-therapyin-advanced-heart-failure-3rd-longterm-follow-up-report-of-a-proof-of-concept-study (28 October 2018).
18. Zile MR, Abraham WT, Weaver FA, Butter C, Ducharme A, Halbach M, Klug D, Lovett EG, Müller-Ehmsen J, Schafer JE, Senni M, Swarup V, Wachter R, Little WC. 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**: 1066–1074.
19. Weaver FA, Abraham WT, Little WC, Butter C, Ducharme A, Halbach M, Klug D, Lovett EG, Madershahian N, Müller-Ehmsen J, Schafer JE, Senni M, Swarup V, Wachter R, Zile MR. Surgical experience and long-term results of baroreflex activation therapy for heart failure with reduced ejection fraction. *Semin Thorac Cardiovasc Surg* 2016; **28**: 320–328.
20. Wachter R, Abraham WT, Lindenfeld J, Weaver FA, Zannad F, Wilks S, Schafer JE, Zile MR. P1475Positive effects of baroreflex activation therapy in heart failure with reduced ejection fraction are independent of baseline blood pressure. *Eur Heart J* 2017; **38**: ehx502. P1475.
21. Halbach M, Abraham WT, Butter C, Ducharme A, Klug D, Little WC, Reuter H, Schafer JE, Senni M, Swarup V, Wachter R, Weaver FA, Wilks SJ, Zile MR, Müller-Ehmsen J. Baroreflex activation therapy for the treatment of heart failure with reduced ejection fraction in patients with and without coronary artery disease. *Int J Cardiol [Internet]* 2018; **266**: 187–192.
22. Mueller-Ehmsen J, Butter C, Halbach M, Klug D, Senni M, Lovett E, Gronda E. European experience with baroreflex activation therapy (BAT) in heart failure with reduced ejection fraction. https://esc365.escardio.org/Congress/Heart-Failure-2015/2nd-World-Congress-on-Acute-Heart-Failure-2015/Rapid-Fire-5-Chronic-heart-failure/115566-european-experience-with-baroreflex-activation-therapy-bat-in-heart-failure-with-reduced-ejection-fraction (27 October 2018).
23. Hoppe UC, Brandt M-C, Wachter R, Beige J, Rump LC, Kroon AA, Cates AW, Lovett EG, Haller H. 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**: 270–276.
24. Halbach M, Hickethier T, Madershahian N, Müller-Ehmsen J. Baroreflex activation therapy: a new treatment option for heart failure with reduced ejection fraction. *Expert Rev Cardiovasc Ther* 2014; **12**: 1465–1469.
25. Chunbin W, Fu S, Jing H. Efficacy and safety of baroreflex activation therapy for treatment of resistant hypertension: a systematic review and meta-analysis. *Clin Exp Hypertens* 2018; **40**: 501–508.
26. Grassi G. Assessment of sympathetic cardiovascular drive in human hypertension: achievements and perspectives. *Hypertension* 2009; **54**: 690–697.

Appendix

PubMed search—68 citations

Search	Query	Items found
#3	Search (#1 AND #2)	68
#2	Search "Heart Failure"[Mesh] OR "Cardiac Failure"[Title/Abstract] OR "Heart Decompensation"[Title/Abstract] OR "Decompensation, Heart"[Title/Abstract] OR "Heart Failure, Right-Sided"[Title/Abstract] OR "Heart Failure, Right Sided"[Title/Abstract] OR "Right-Sided Heart Failure"[Title/Abstract] OR "Right Sided Heart Failure"[Title/Abstract] OR "Myocardial Failure"[Title/Abstract] OR "Congestive Heart Failure"[Title/Abstract] OR "Heart Failure, Congestive"[Title/Abstract] OR "Heart Failure, Left-Sided"[Title/Abstract] OR "Heart Failure, Left Sided"[Title/Abstract] OR "Left-Sided Heart Failure"[Title/Abstract] OR "Left Sided Heart Failure"[Title/Abstract]	135 480
#1	Search "baroreflex activation"[Title/Abstract] OR barostim*[Title/Abstract] OR "baroreceptor stimulation"[Title/Abstract] OR "baroreceptor activation"[Title/Abstract] OR "carotid stimulation"[Title/Abstract] OR baroreceptor-activat*[Title/Abstract]	954

CENTRAL search—29 citations

‘"baroreflex activation" OR barostim* OR "baroreceptor stimulation" OR "baroreceptor activation" OR "carotid stimulation" OR baroreceptor-activat* in Title Abstract Keyword AND "Heart Failure" OR "Cardiac Failure" OR "Heart Decompensation" OR "Decompensation, Heart" OR "Myocardial Failure" OR "Congestive Heart Failure" in Title Abstract Keyword—(Word variations have been searched)’

Scopus search—146 citations

("baroreflex activation" OR barostim* OR "baroreceptor stimulation" OR "baroreceptor activation" OR "carotid stimulation" OR baroreceptor-activat*) AND ("Heart Failure" OR "Cardiac Failure" OR "Heart Decompensation" OR "Decompensation, Heart" OR "Myocardial Failure" OR "Congestive Heart Failure")

Web of Science search—57 citations

("baroreflex activation" OR barostim* OR "baroreceptor stimulation" OR "baroreceptor activation" OR "carotid stimulation" OR baroreceptor-activat*) AND ("Heart Failure" OR "Cardiac Failure" OR "Heart Decompensation" OR "Decompensation, Heart" OR "Myocardial Failure" OR "Congestive Heart Failure")

EMBASE search—141 citations

(’baroreflex activation’ OR barostim* OR ’baroreceptor stimulation’ OR ’baroreceptor activation’ OR ’carotid stimulation’ OR ’baroreceptor activat*’) AND (’heart failure’/de OR ’cardiac failure’/de OR ’heart decompensation’/de OR ’decompensation, heart’/de OR ’myocardial failure’/de OR ’congestive heart failure’/de)