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# Current and future use of neuromodulation in heart failure

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Autonomic imbalance is a common finding in heart failure (HF) with reduced ejection fraction (HFrEF). Addressing different targets within the autonomic nervous systems has been evaluated in patients with HF, including renal sympathetic denervation, vagal nerve stimulation, and baroreceptor activation therapy (BAT). Although all are pathophysiologically plausible and promising, only BAT shows sufficient evidence for implementation into clinical practice in randomized controlled trials. Baroreceptor activation therapy can be used in patients with symptomatic HFrEF despite optimal guideline-directed medication and device therapy. This article reviews the current and future use of neuromodulation in HF and provides an overview on current guideline recommendations and clinical practice.

## Neuromodulation in heart failure

Autonomic imbalance is a common finding in heart failure (HF) with reduced ejection fraction (HFrEF).[1] Chronic activation of the sympathetic autonomic nervous system, as well as vagal withdrawal, is a key maladaptive mechanism in HF development.[2] Modulating the autonomic imbalance, therefore, has gained importance in recent years.[3,4] Addressing different targets within the autonomic nervous systems has been evaluated in patients with HF, including renal sympathetic denervation (RDN), vagal nerve stimulation (VNS), and baroreceptor activation therapy (BAT).[5] Also, medical treatment with digitalis glycosides at lower dosages with lower target levels than traditionally used in HFrEF is considered to increase the sensitivity of carotid sinus baroreceptors and activate central vagal nuclei, resulting in an increase of parasympathetic tone. This is currently being investigated in the DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure (DIGIT-HF) trial[6] and the Digoxin Evaluation in Chronic heart failure: Investigational Study In Outpatients in the Netherlands (DECISION) trial (clinicaltrials.gov NCT03783429).

## Renal sympathetic denervation

Renal sympathetic denervation was initially performed to treat refractory arterial hypertension, but presented conflicting results in larger trials.[7] The REACH-Pilot study represented a proof-of-concept study on seven patients with a mean left ventricular (LV) ejection fraction (LVEF) of 43%,[8] followed by the RDT-PEF study in 25 patients with HF with preserved ejection fraction (HFpEF) patients.[9] Interestingly, this method addresses HFrEF and HFpEF patients from the beginning. In the randomized IMPROVE-HF-I study, RDN was safe in HFrEF patients, but did not result in significant changes in cardiac sympathetic nerve activity as measured using iodine-123 meta-iodobenzylguanidine at 6 months.[10] Renal sympathetic denervation might have an impact on LV function and functional capacities in patients with HFrEF, but larger studies would be required to prove a robust effect on endpoints.[11]

## Vagal nerve stimulation

Vagal nerve stimulation was first evaluated for safety and feasibility in 32 patients with HFrEF in the CardioFit

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study.[12] However, the NECTAR-HF study, a randomized, blinded, sham-controlled trial failed to improve the primary endpoint of change in LV end-systolic diameter and other secondary parameters like LV end-systolic volume, LVEF, peak $VO_2$, and N-terminal pro-brain natriuretic peptide (NT-proBNP). Only quality of life (QoL) (measured by the Minnesota living with HF questionnaire and the SF-36) and New York Heart Association (NYHA) functional class showed significant improvement.[13] In addition, the long-term follow-up of the NECTAR-HF study did not show a long-standing efficacy of VNS.[14] The ANTHEM-HF trial randomized patients with HFrEF to the right or left vagus with the primary endpoint of change in LVEF or LV end-systolic volume.[15] A long-term follow-up of patients enrolled in the ANTHEM-HF trial was recently published and showed beneficial effects on LVEF and 6 min walking distance throughout a follow-up period of at least 42 months.[16]

The largest randomized trial on VNS in HF was the INOVATE-HF trial enrolling 707 patients with a 3:2 randomization to VNS vs. control. The primary endpoint of mortality or HF hospitalization was not significantly different among both groups.[17]

To date, despite promising preclinical results, VNS did not show significant benefit in HF patients and has not been implemented into clinical routine.[18] The multicentre, open-label, randomized clinical ANTHEM-HFrEF trial (clinicaltrials.gov: NCT03425422) is currently enrolling up to 800 participants and evaluating the primary endpoint of safety and cardiovascular mortality and HF hospitalization.

## Baroreflex activation therapy

As for RDN, BAT (*Figure 1*) was originally used for refractory arterial hypertension.[19] Applying BAT to HF patients, the proof-of-concept study initially included 11 patients with HFrEF and NYHA functional Class III showing improvement in HF symptoms, 6 min walk distance, and LVEF after 3 and 6 months,[20] and later confirmed in a long-term follow-up of 2 years.[21] HOPE4HF, a randomized trial in 146 patients with HFrEF, demonstrated significant improvement in NYHA functional class, HF questionnaire score, and 6 min walking distance, as well as in NT-proBNP levels.[22] Enrolling 408 patients with HFrEF and NYHA functional Class III or II (having recently been III), the randomized BeAT-HF trial showed that BAT was safe and significantly improved QoL, functional capacity, and reduced NT-proBNP.[23] A recent meta-analysis confirmed consistent results and clinically meaningful improvement throughout the trials using BAT in patients with HFrEF.[24]

The benefit of BAT is, therefore, well founded in patients with HFrEF. Nevertheless, due to the strong pathophysiological association of arterial hypertension and HFpEF, BAT especially represents a promising therapy option in patients with HFpEF, too. The use of BAT in HFpEF should, therefore, be further investigated.

## Heart failure guidelines, current indications, and use of baroreceptor activation therapy

Based on the results of the BeAT-HF study demonstrating safety and significantly improved QoL, exercise capacity, and NT-proBNP levels in HFrEF patients,[23] in August 2019, the FDA approved BAT with the Barostim Neo System as indicated for patients with advanced HF who are not suited for treatment with other HF devices such as cardiac resynchronization therapy (CRT). The FDA granted the Barostim Neo System a breakthrough device designation to expedite evidence generation and the agency's review of the device. As part of the approval, the FDA required the manufacturer to continue the randomized BeAT-HF study to investigate the potential of the therapy to reduce mortality and HF hospitalizations. These pivotal results from the ongoing post-approval phase of the BeAT-HF study regarding endpoints for morbidity and mortality will be completed in 2022, unblinding and publication are expected in 2023.

Currently, despite the observed improvements of QoL and exercise capacity, BAT is not mentioned in the 2013 ACC/AHA Guidelines for the management of HF or the 2017 and 2021 update thereof.[25,26] Also the 2017 and 2021 Canadian Guidelines for the management of HF[27,28] do not mention specific devices for chronic HF other than CRT and implantable cardioverter defibrillator.

The 2021 ESC guidelines for the diagnosis and treatment of HF state that BAT has been 'shown to offer a modest improvement in effort capacity and QoL. However, currently, the evidence is considered insufficient to support specific guideline recommendations for a reduction in mortality or hospitalization for these and a variety of other implantable electrical therapeutic technologies'.[29]

This statement in the 2021 ESC guidelines (and also the neglect of BAT in other guidelines) has to be viewed in the context that in general, current HFrEF guidelines are focused on treatments that improve morbidity and mortality. Therefore, some treatments that are safe, improve patients' QoL, but have not (yet) proven an effect on morbidity and mortality, are not or only marginally mentioned in HFrEF guidelines. However, improving QoL is highly relevant to patients with HFrEF, and some even favour QoL over longevity.[30] Thus, in patients with advanced HFrEF without indication for CRT and not indicated yet, or not suited for heart transplantation or ventricular assist device (VAD) implantation, BAT provides a safe and effective approach for improving symptoms and QoL. The reduction of circulating levels of the prognostic marker NT-proBNP also points to the potential of also improving prognosis. However, the results of the post-approval phase of the BeAT-HF study have to be awaited.

Implantation rates of the Barostim Neo System were growing worldwide in 2021 despite negative COVID-related impact globally. Reimbursement in Germany is mostly on case-by-case basis determined by

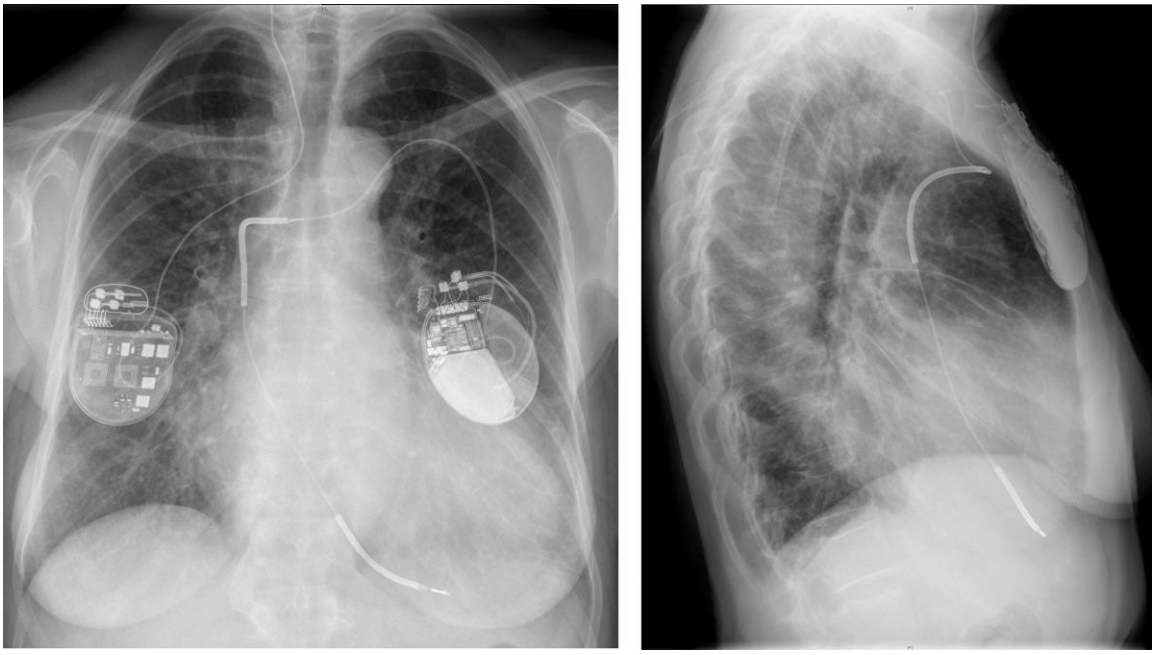

**Figure 1** Chest X-ray showing a patient with a baroreflex activation therapy device (right pectoral device).

medical necessity. In the USA, the Barostim Neo System is indicated for the improvement of HF symptoms, QoL, 6 min hall walk, and functional status, for patients who remain symptomatic despite treatment with guideline-directed medical therapy, are NYHA Class III or Class II (who had a recent history of Class III), have an LVEF ≤35%, an NT-proBNP <1600 pg/mL, and excluding patients indicated for CRT according to AHA/ACC/ESC guidelines.

## Perspective and future use of baroreceptor activation therapy

If the ongoing pivotal BeAT-HF study described in more detail above will show significant reduction of mortality and/or HF hospitalization endpoints in early 2023, broader application of BAT during the upcoming years is expected in patients with HFrEF and persisting EF <35% despite guideline-directed therapies.

Besides the BeAT-HF outcome trial, also additional data on LV remodelling during BAT are expected from the BiRD-HF registry currently ongoing in Germany (DRKS-ID: DRKS00013297). This study includes HFrEF patients implanted *de novo* with a Barostim Neo System within 30 days before consent that is not yet activated; and implant has to meet the CE-Mark approved indications and contraindications for Barostim Neo System in the treatment of HF, i.e. NYHA Class III and LVEF ≤35% despite being treated with the appropriate HF guideline-directed therapy. Patients who received a CRT within 6 months of activation, or are scheduled or have a Class I indication for CRT, are not eligible for BiRD-HF. The primary endpoint is the change in LV end-systolic volume index (LVESVi) from baseline through 6 months of follow-up measured by 3D echocardiography (as assessed by a core lab). The key secondary endpoint is the change in LVEF from baseline to 6 months; additional endpoints include NYHA class, QoL, biomarkers, 6 min hall walk, and healthcare utilization. BiRD-HF aims to include 102 patients to get 83 patients with complete baseline and 6-month LVESVi assessment. Thus, BiRD-HF is supplementary to BeAT-HF and will provide valuable additional data on reverse remodelling by BAT in patients with HFrEF.

In parallel to the conduct of the BeAT-HF and BiRD-HF studies, BAT is further developed to accomplish a less invasive, novel interventional implantation technique avoiding the surgical approach to the carotid sinus (*Figure 2*). This minimally invasive technique using ultrasound imaging to guide placement of the stimulation lead near the targeted carotid baroreceptors was first applied in humans in June 2021. The ongoing BATwire Implant Kit study (clinicaltrials.gov NCT04600791) prospectively investigates the new implantation technique in patients with HFrEF fulfilling the BAT indication enrolled at up to 25 US sites. The study will evaluate the implant experience, safety, and effectiveness of the BATwire kit. All subjects will be implanted, and the device will be activated before being discharged. Follow-up visits will occur at up to 12 months post-implant. The primary outcome is freedom from serious adverse events related to the implantation of the lead using the BATwire Implant Kit through 30 days post-implant or attempted implant as well as the improvement in 6 min hall walk at 6 months. If successfully completed, this study will pave the way for even broader application of BAT in the future.

Telemedicine and remote monitoring are of increasing importance in the management of patients with HF.[31]

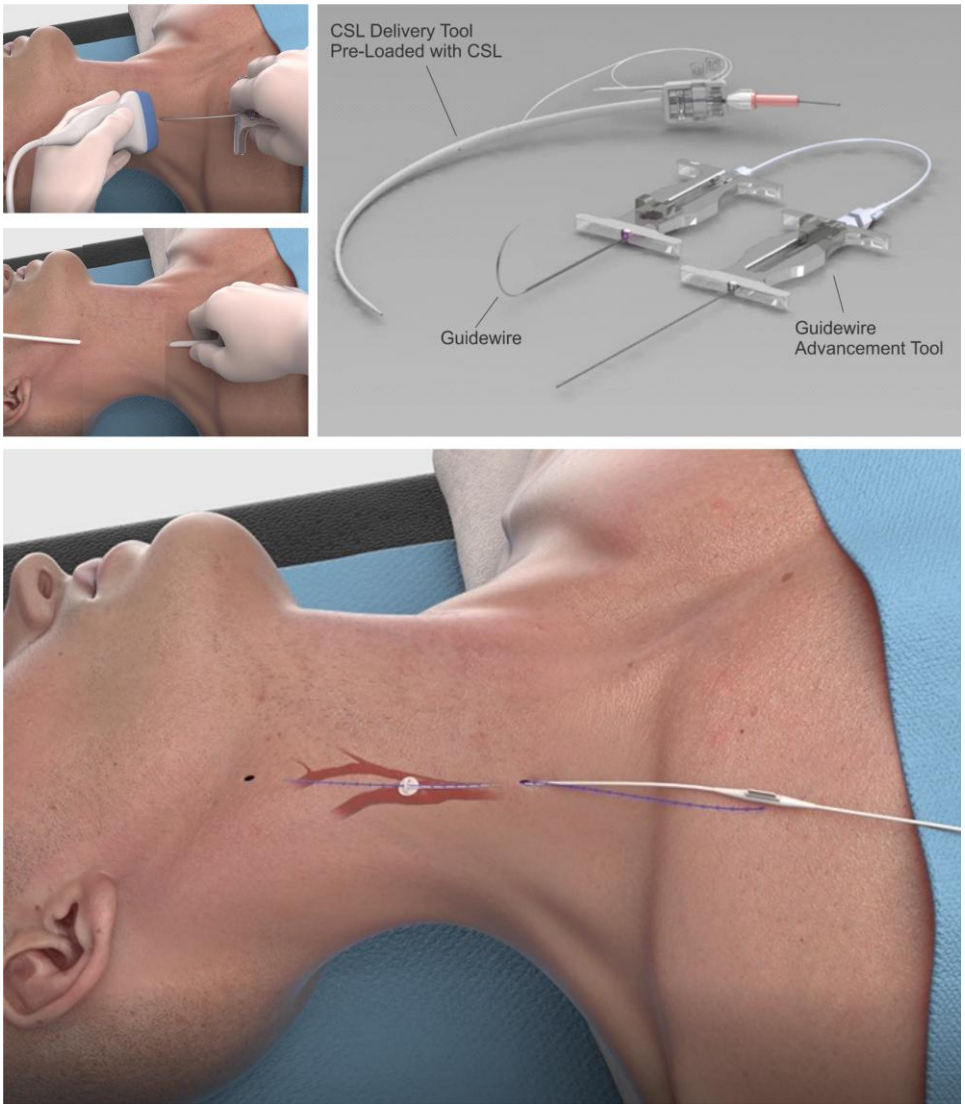


**Figure 2** Minimally invasive technique using ultrasound imaging to guide placement of the stimulation lead near the targeted carotid baroreceptors (Courtesy L. Gaelle, CVRx).

The implementation of telemedical care should therefore also be expedited in patients with neuromodulation in HFrEF.

## Clinical practice

Careful patient characterization is crucial for patient selection. *Figure 3* presents an exemplary workflow for the identification of patients eligible for BAT. Importantly, patients should first receive guideline-recommended and established therapies for HFrEF.[29] This includes but is not exclusively limited to optimal HF medication,[32] contemporary valvular heart disease management, defibrillator therapy, CRT,[33] or VAD. Baroreceptor activation therapy may be considered especially in patients with narrow QRS (<130 ms) or broader QRS (≥130 ms) of non-left bundle branch block morphology. Even though CRT is a powerful therapy in patients with HFrEF and left bundle branch block, the majority of patients with HFrEF are not candidates for CRT. Only ~20% of patients with HFrEF have a QRS of ≥120 ms.[34] Baroreceptor activation therapy, therefore, represents an additional option beyond CRT.

Contraindications for BAT should be ruled out during diagnostic work-up. Contraindications for implantation of a Barostim Neo device include: (i) bilateral carotid bifurcations located above the level of the mandible, (ii) baroreflex failure or autonomic neuropathy, (iii) uncontrolled, symptomatic cardiac bradyarrhythmias, (iv) carotid atherosclerosis with stenosis >50% (determined by ultrasound or angiography), and (v) ulcerative plaques in the carotid artery (determined by ultrasound or angiography).

Patients implanted with BAT should receive close clinical follow-up. In order to expand the existing evidence, enrolment of patients with BAT in clinical registries is strongly recommended.

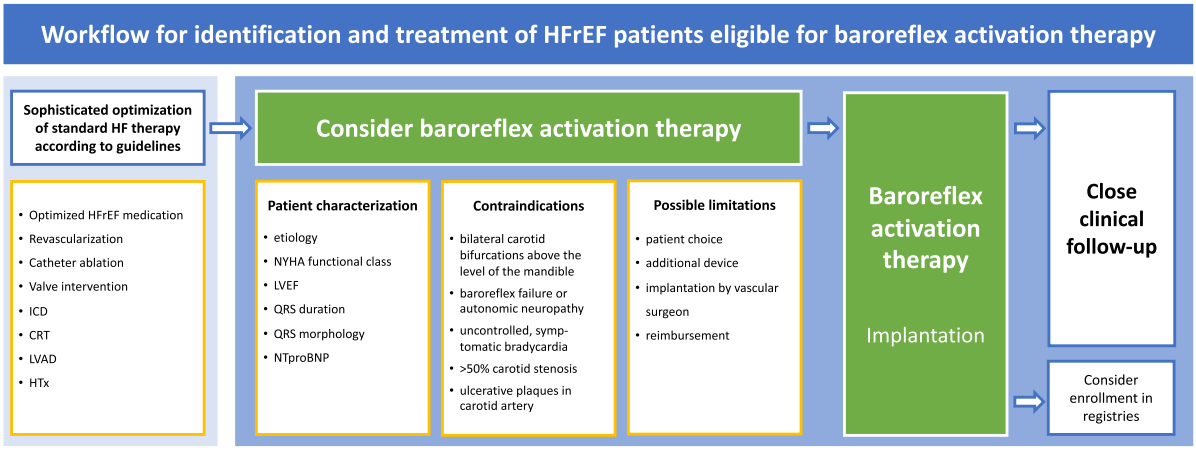


**Figure 3** Exemplary workflow for identification of patients with heart failure with reduced ejection fraction eligible for baroreflex activation therapy. HFrEF, heart failure with reduced ejection fraction; HF, heart failure; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device; HTx, heart transplantation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

## Conclusions

Neuromodulation in HF was addressed using RND, VNS, and BAT. Although all of these were pathophysiologically plausible and promising, only BAT showed sufficient evidence for implementation into clinical practice in randomized controlled trials. Baroreceptor activation therapy can be used in patients with symptomatic HFrEF despite optimal guideline-directed medication and device therapy. The benefit of BAT in patients with HFpEF remains to be proven in upcoming trials.

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## Data availability

No new data were generated or analysed in support of this research.

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