ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 284–294
Published online 8 October 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14190

ORIGINAL ARTICLE

Baroreflex activation therapy in advanced heart failure therapy: insights from a real-world scenario

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Abstract

Aims Baroreflex activation therapy (BAT) is an innovative treatment option for advanced heart failure (HFrEF). We analysed patients' BAT acceptance and the outcome of BAT patients compared with HFrEF patients solely treated with a guideline-directed medical therapy (GDMT) and studied effects of sacubitril/valsartan (ARNI).

Methods In this prospective study, 40 HFrEF patients (71 ± 3 years, 20% female) answered a questionnaire on the acceptance of BAT. Follow-up visits were performed after 3, 6, and 12 months. Primary efficacy endpoints included an improvement in QoL, NYHA class, LVEF, HF hospitalization, NT-proBNP levels, and 6MHWD.

Results Twenty-nine patients (73%) showed interest in BAT. Ten patients (25%) opted for implantation. BAT and BAT + ARNI patients developed an increase in LVEF (BAT +10%, *P*-value (*P*) = 0.005*; BAT + ARNI +9%, *P* = 0.049*), an improved NYHA class (BAT −88%, *P* = 0.014*, BAT + ARNI −90%, *P* = 0.037*), QoL (BAT +21%, *P* = 0.020*, BAT + ARNI +22%, *P* = 0.012*), and reduced NT-proBNP levels (BAT −24%, *P* = 0.297, BAT + ARNI −37%, *P* = 0.297). BAT HF hospitalization rates were lower (50%) compared with control group patients (83%) (*P* = 0.020*).

Conclusions Although BAT has generated considerable interest, acceptance appears to be ambivalent. BAT improves outcome with regard to LVEF, NYHA class, QoL, NT-proBNP levels, and HF hospitalization rates. BAT + ARNI resulted in more pronounced effects than ARNI alone.

Keywords Heart failure; Autonomic nervous system; Baroreceptor; Baroreflex activation therapy

Received: 27 May 2022; Revised: 1 September 2022; Accepted: 21 September 2022
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Introduction

The prognosis of patients suffering from advanced heart failure (HF) with a reduced ejection fraction (HFrEF) is still poor.[1] Chronic HF results in a sustained activation of the sympathetic autonomic nervous system (ANS),[2,3] which is associated with an apoptosis of cardiomyocytes, myocardial fibrosis, further limitations of systolic pump function,[4,5] increased coronary venous epinephrine levels, and an increased mortality.[6]

Because patients' adherence to HF drug therapy seems to require an improvement,[7] HF device therapy might be a promising addition. Within the last years, different approaches of neuromodulation have been studied [spinal cord stimulation,[8] direct vagal stimulation,[9,10] baroreflex activation therapy (BAT),[11–13] cardiac contractility modulation (CCM)[14–16]]. Only BAT and CCM have emerged as suitable therapeutic options.[11–16]

BAT is delivered by a pacemaker-like device (Barostim neo system, CVRx, Inc., Minneapolis, MN, USA). By stimulating the carotid bifurcation BAT therapy intends to restore the neurohormonal balance in HFrEF patients.[17,18] In a proof-of-concept study, a reduction of muscular sympathetic nerve activity (MSNA) by BAT has been demonstrated.[11] Further studies have shown significant improvements in quality of life (QoL), New York Heart Association functional class (NYHA class), 6-min hall walk distance (6MHWD), and NT-proBNP levels in BAT patients.[11–13] Thus, BAT represents a promising

new device to improve HFrEF patients' outcome and healthcare costs. However, due to a lack of evidence, BAT and CCM are still perceived as 'devices under evaluation'.[19] In addition, there have been major guideline-relevant advances in HF drug therapy recently, affecting the ANS and cardiac reverse remodelling,[19] that have not yet been considered in the aforementioned studies.[11–13] The aim of this prospective study was to gain further knowledge about BAT from a real-world setting, not only in terms of effectiveness in conjunction with novel HF medications [angiotensin-receptor neprilysin inhibitor (ARNI) sacubitril/valsartan] but also with regard to the acceptance of an additional device therapy for HF.

Methods

In this single-centre prospective study, 40 consecutive HFrEF patients from our outpatient HF department eligible for BAT according to the inclusion criteria of the study by *Abraham et al*.[5] and willing to take part were included. A self-designed standardized questionnaire was used to evaluate patients' acceptance of an additional device implantation. Follow-up (FU) visits were performed after 3, 6, and 12 months. Primary efficacy endpoints included an improvement in QoL (EQ-5D-5L), NYHA class, LVEF, HFrEF hospitalization rate, NT-proBNP levels, and 6MHWD. The study was performed in compliance with the principles outlined in the Declaration of Helsinki and approved by the Institutional Ethics Committee (Reg. No. 2017-215). The study was registered at clinicaltrials.gov (NCT03230643).

Patient management

During routine clinical appointments at our centre, HFrEF patients were informed about BAT. At baseline, a patient history was obtained. To verify their clinical indication for BAT supply all patients underwent physical examinations, transthoracic echocardiography (TTE), duplex ultrasonography of the carotids, blood collections, a 6MHWD test, and blood pressure measurements. In addition, HF medications were evaluated for completeness. BAT eligibility was defined by HFrEF with an impaired ejection fraction $\leq$35% and dyspnoea (NYHA class III) despite an optimized medical HF therapy for more than 3 months. ARNIs had to be titrated up to the maximum tolerated dose 3 months prior to inclusion. Patients were divided into two groups. Patients who decided for a BAT device implantation were admitted as inpatients (BAT group). Patients who decided against a BAT device implantation served as control group. BAT device implantations were performed as part of clinical routine. The implantation procedure followed a protocol that has been described in detail in a prior study.[20] One month after implantation, the device was activated.

Follow-up

After discharge (control group) and BAT activation (BAT group) FU visits were scheduled at 3, 6, and 12 months including interviews, physical examinations, a standardized questionnaire (EQ-5D-5L), blood sample collections, a TTE, a 6MHWD test, and blood pressure measurements. In BAT patients, an additional device interrogation was performed. Unscheduled visits were conducted, if required.

Endpoint

We aimed to analyse patients' acceptance of BAT and outcome in comparison with HFrEF patients solely treated with a GDMT. Effects of ARNIs and cardiac resynchronization therapy (CRT) on BAT response were evaluated.

Data collection

Data on patient characteristics, medication, symptoms, and complications were compiled from patient records and discharge letters. Procedural parameters and clinical aspects concerning the implantation of the BAT device were taken from surgery reports and procedure-related documents.

Statistical analysis

All statistical analyses were performed with SPSS, version 27 (SPSS, Inc., Chicago, IL, USA). Continuous variables between the groups (BAT and control) were compared by employing an unpaired two-sided Student's *t*-test. Differences in continuous parameters between baseline and FU were analysed by paired Student's *t*-test. Categorical data were examined by Fisher's exact test. Data are presented as mean ± SD or percentage value unless stated otherwise. A P-value < 0.05 was considered statistically significant.

Results

Patient characteristics

The study population consisted of 40 consecutive HFrEF patients (71 ± 3 years old, 20% female) with an indication for BAT. At baseline, a mean LVEF of 27 ± 1% was measured. All patients suffered from dyspnoea (NYHA class III). The NT-proBNP value averaged 2302 ± 460 pg/mL. 6-MHWD

amounted to 281 ± 23 m. All patients received GDMT according to HF guidelines[1] at the maximum tolerated dose for more than 3 months prior to inclusion. Fifteen patients (38%) were treated with ARNIs. Thirty-four patients were CRT non-responders (85%). Baseline characteristics of all patients and group differences (Control vs. BAT) are summarized in *Table 1*.

Baseline characteristics (ARNI vs. BAT)

Characteristics are shown in *Table 2*.

Patients' awareness of and interest in BAT

As evaluated by the self-designed standardized questionnaire, the majority of patients (95%, 38 patients) had not been informed about BAT before. Only 5% (two patients) had heard or read about BAT in advance. After detailed information and explanations, 29 patients (73%) spontaneously declared great interest, nine patients (23%) requested time to think about it, and only one patient (3%) rejected BAT from the outset. A subgroup analysis of those interested in BAT (29 patients, 73%) showed that only 12 patients (42%) specifically desired an implantation. Despite detailed medical information and examinations, the majority of patients still requested

Table 1 Baseline characteristics

Characteristics	All patients (n = 40)	Control (n = 30)	BAT (n = 10)	P-value
Age (years)	71 ± 3	71 ± 2	71 ± 4	0.960
Gender, female	6 (20%)	4 (13%)	2 (20%)	0.244
BMI (kg/m^2)	27 ± 2	27 ± 5	31 ± 4	0.885
LVEF (%)	27 ± 1	29 ± 1	23 ± 2	**0.004***
NT-proBNP (pg/mL)	2302 ± 460	2044 ± 359	2532 ± 1167	0.683
6MHWD (m)	281 ± 23	297 ± 24	234 ± 44	0.210
ICM	30 (75%)	22 (73%)	8 (80%)	0.258
DCM	10 (25%)	8 (27%)	2 (20%)	0.258
ARNIs	15 (38%)	9 (30%)	6 (60%)	0.096
Hypertension	38 (95%)	29 (97%)	9 (90%)	0.268
Diabetes mellitus	13 (33%)	8 (27%)	5 (50%)	0.128
AT/AF	20 (50%)	15 (50%)	5 (50%)	0.220
VAs	10 (25%)	6 (20%)	4 (40%)	0.141
ICD	5 (13%)	4 (13%)	1 (10%)	0.343
CRT-D	34 (85%)	25 (83%)	9 (90%)	0.326
GFR ≥ 30 mL/min/1.73 m^2	40 (100%)	30 (100%)	10 (100%)	1.000

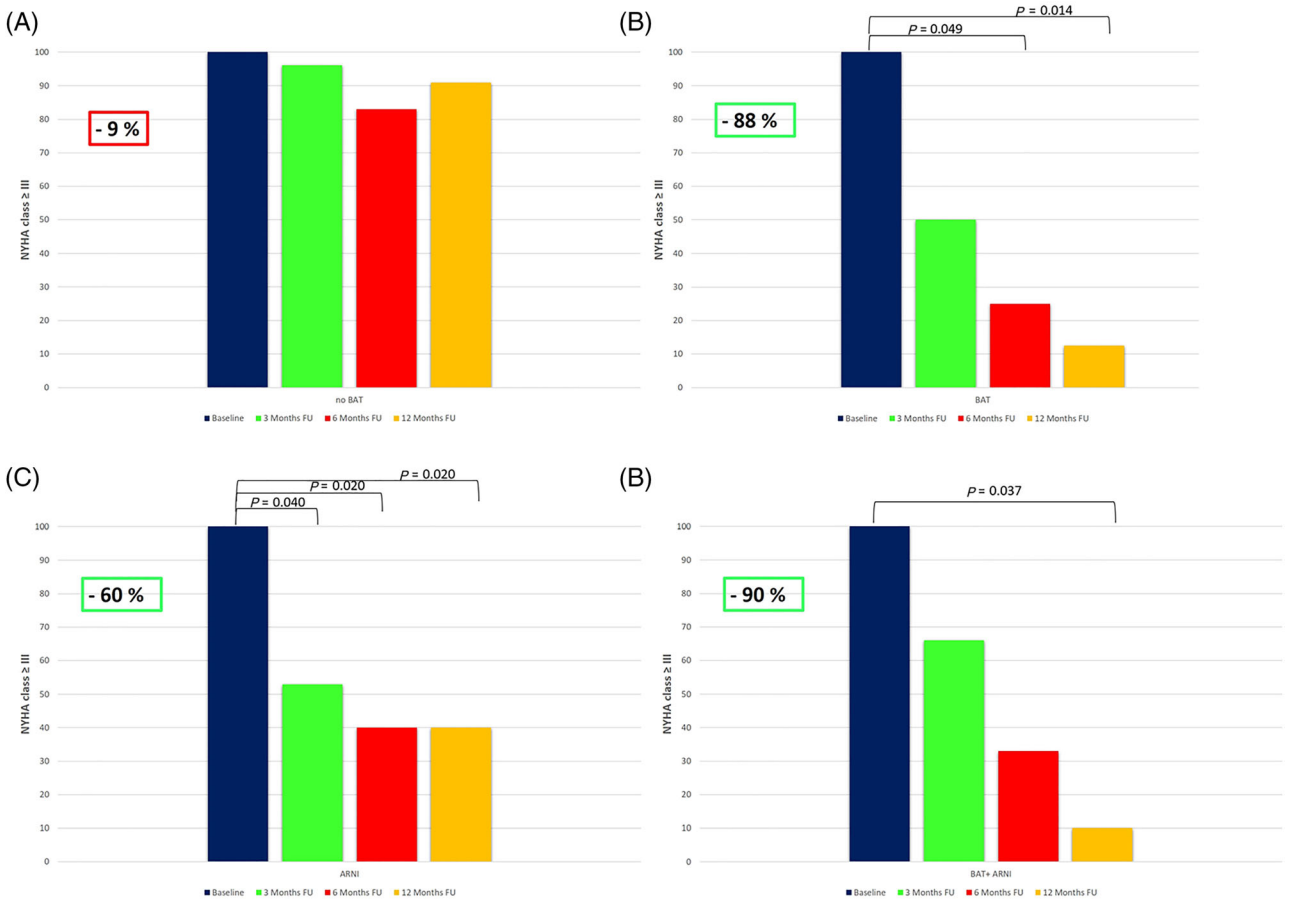
6MHWD, 6-min hall walk distance; ARNIs, sacubitril/valsartan; AT/AF, atrial fibrillation; BMI, body mass index; CRT-D; cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator; ICM, ischaemic cardiomyopathy; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; VAs, ventricular arrhythmias.
Continuous variables are shown as the mean ± SD and categorical variables as the number (%).
*Statistical significance.

Table 2 Baseline characteristics (ARNI group vs. BAT group)

Characteristics	ARNI (n = 15)	BAT (n = 10)	P-value
Age (years)	66 ± 8	71 ± 4	0.370
Gender, female	3 (20%)	2 (20%)	0.254
BMI (kg/m^2)	27 ± 2	31 ± 4	0.872
LVEF (%)	26 ± 5	23 ± 2	0.225
NT-proBNP (pg/mL)	2256 ± 32	2532 ± 1167	0.843
6MHWD (m)	291 ± 32	234 ± 44	0.292
ICM	9 (60%)	8 (80%)	0.202
DCM	6 (40%)	2 (20%)	0.201
Hypertension	15 (100%)	9 (90%)	0.214
Diabetes mellitus	7 (47%)	5 (50%)	0.160
AT/AF	5 (33%)	5 (50%)	0.178
VAs	2 (13%)	4 (40%)	0.129
ICD	2 (13%)	1 (10%)	0.327
CRT-D	12 (80%)	9 (90%)	0.306
GFR ≥ 30 mL/min/1.73 m^2	15 (100%)	10 (100%)	1.000

6MHWD, 6-min hall walk distance; ARNIs, sacubitril/valsartan; BMI, body mass index; CRT-D; cardiac resynchronization therapy defibrillator; DCM, dilated cardiomyopathy; AT/AF, atrial fibrillation; ICD, implantable cardioverter defibrillator; ICM, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; VAs, ventricular arrhythmias.
Continuous variables are shown as the mean ± SD and categorical variables as the number (%).

Figure 1 Effects of BAT on NYHA class.



further information and were interested in alternative therapeutic options. Patients who were initially undecided (nine patients, 23%) considered BAT as a possible future treatment option and wanted further information and time for consideration. Detailed information is visualized in *Figure S1*.

Procedural data and complications

All patients who opted for a BAT device (10 patients, 25%) were successfully implanted as part of routine clinical practice. No severe adverse events occurred. One month after implantation, the device was activated with a gradual up-titration of the stimulation energy during the course of 3–6 months.

Follow-up data

Effects of BAT on NYHA class

At baseline, all patients suffered from dyspnoea (NYHA class III). In contrast to the control group, BAT patients developed a significant improvement in NYHA class over time. At the 3-month FU, significantly more control group patients complained about dyspnoea, NYHA III, in contrast to BAT patients. Similar group differences were observed at the 6-month and 12-month FU. Details are presented in *Figure 1*.

Effects of BAT on QoL

In contrast to the control group, BAT patients developed a significant increase in QoL (*Figure 2*).

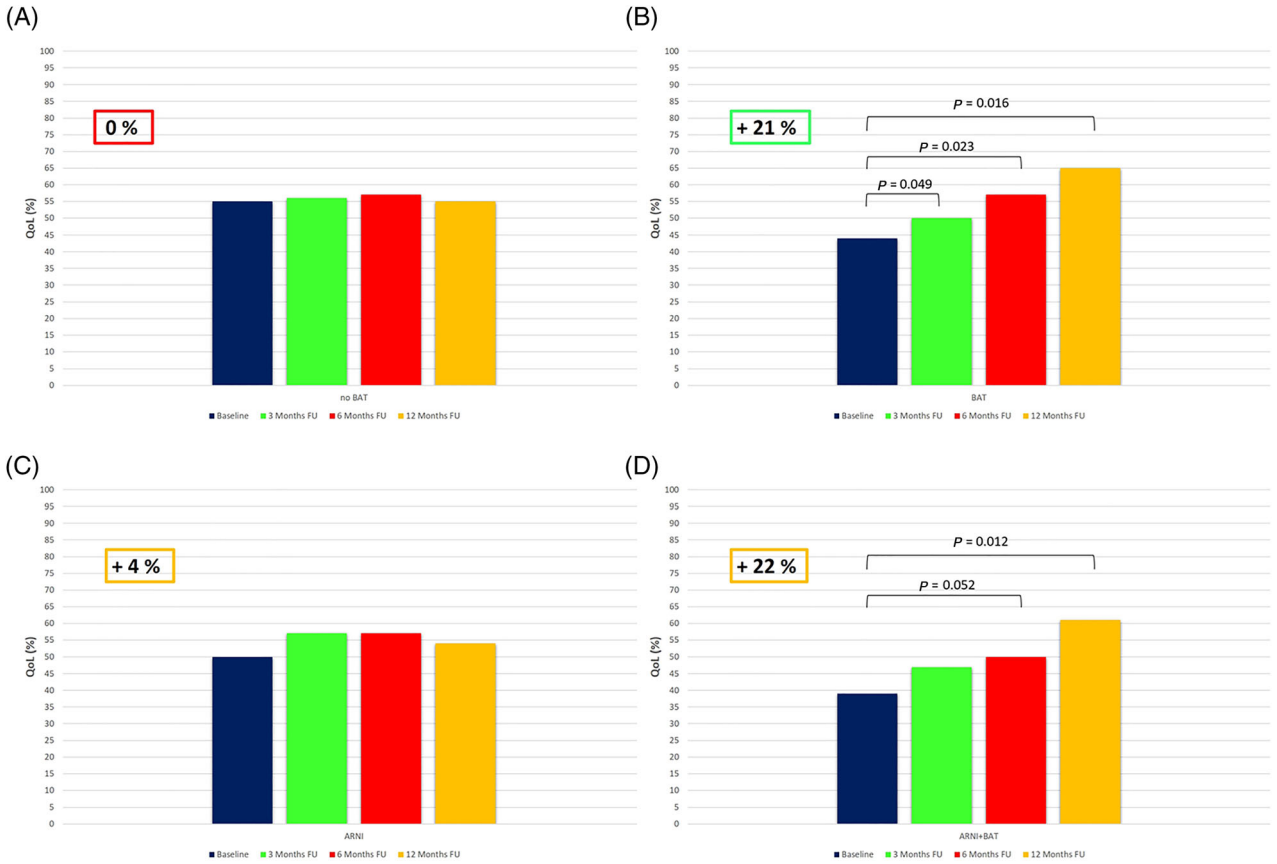
Effects of BAT on NT-proBNP levels

Control group patients presented with a significant increase in NT-proBNP levels. In BAT patients, an NT-proBNP level reduction was observed (*Figure 3*).

Effects of BAT on LVEF

In contrast to control group patients, BAT patients showed a significant increase in LVEF at the 3-month FU already. A further improvement was observed at the 6-month and at the 12-month FU. Control group patients did not develop changes in LVEF, even after 12 months (*Figure 4*).

Figure 2 Effects of BAT on QoL.



Effects of BAT on 6MHWD

The 6MHWD in control group patients ($control_{6MHWD\ BL}$ 297 ± 24 m $_{to\ 12mFU}$ 329 ± 50 m, +11%, $P = 0.159$) was comparable with BAT patients ($control_{6MHWD\ BL}$ 234 ± 44 m $_{to\ 12mFU}$ 271 ± 43 m, +16%, $P = 0.140$) ($P = 0.368$).

Effects of BAT on hospitalization rate

HF hospitalization rates of BAT patients (50%) were significantly lower compared with control group patients (83%) ($P = 0.020$*). During the observation period of 12 months, control group patients were hospitalized an average of three times for worsening HF, BAT patients an average of only one time.

Impact of ARNIs on patient outcome

Effects of ARNIs/BAT + ARNIs on NYHA class

ARNI-treated patients presented with a significant reduction in NYHA class at the 3-month, 6-month, and 12-month FU. Over time, effects were more pronounced in the BAT group compared with the ARNI cohort of patients. BAT + ARNI patients developed the strongest NYHA class reduction (*Figure 1*).

Effects of ARNIs/BAT + ARNIs on QoL

In ARNI patients, no relevant changes in QoL were reported. Thus, QoL differed between the BAT group and the ARNI cohort of patients in favour of the BAT group. BAT + ARNI-treated patients showed a significant increase in QoL at the 6-month and 12-month FU (*Figure 2*).

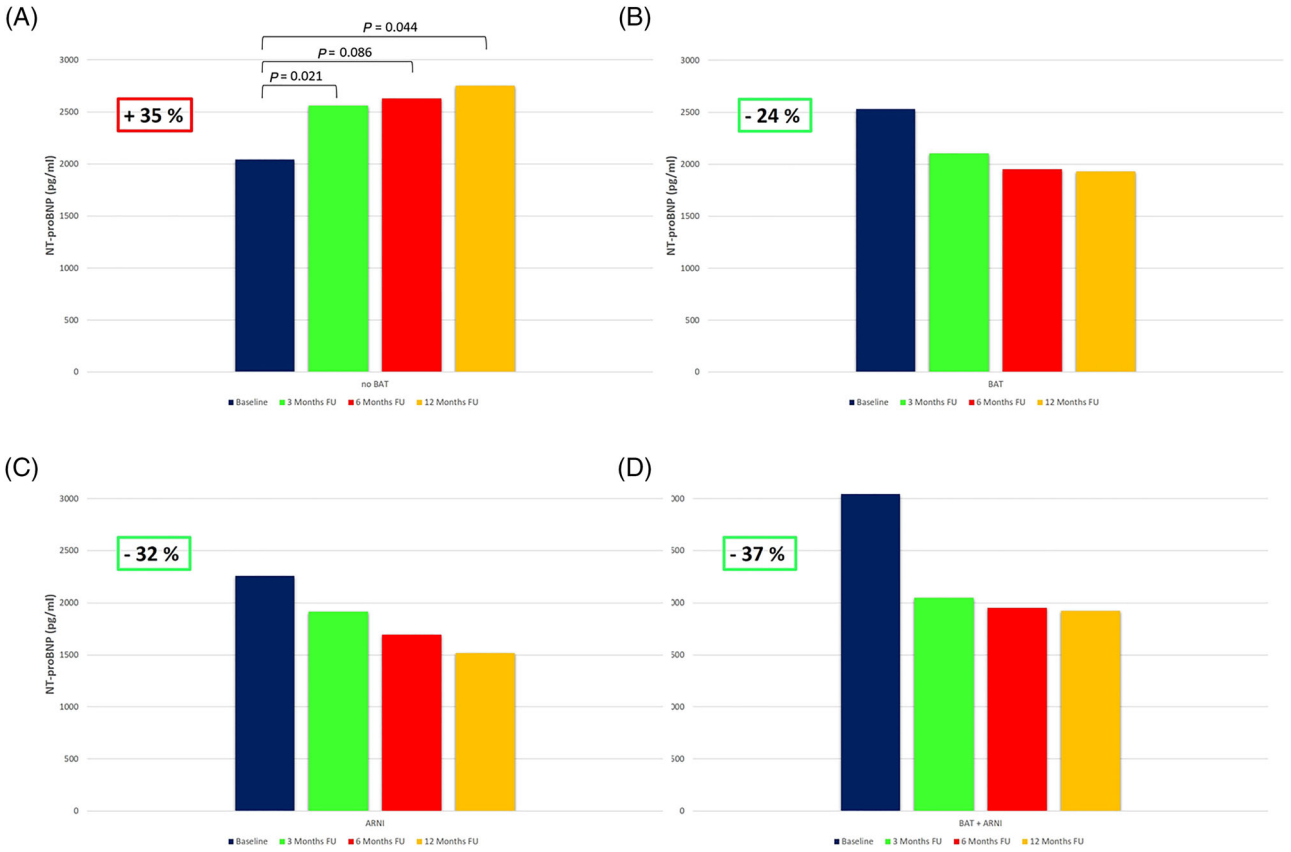
Effects of ARNIs/BAT + ARNIs on NT-proBNP levels

ARNI patients developed a 32% reduction in NT-proBNP levels. Thus, NT-proBNP levels were improved in both groups but differed between BAT and ARNI group patients in favour of the latter. BAT + ARNI patients presented with the highest reduction in NT-proBNP levels (*Figure 3*).

Effects of ARNIs/BAT + ARNIs on LVEF

ARNI-treated patients presented with a significantly improved LVEF at the 6-month and 12-month FU. Compared with the ARNI group, BAT patients developed a higher increase in LVEF at the 12-month FU. Patients who received BAT in addition to ARNIs showed a significant increase in

Figure 3 Effects of BAT on NT-proBNP levels.



LVEF, similar to that observed in the BAT cohort of patients (*Figure 4*).

Effects of ARNIs/BAT + ARNIs on 6MHWD

ARNI group patients as well as patients with BAT + ARNIs showed no significant increase in 6MHWD (BAT + ARNI $_{6MHWD\ BL}$ 318 ± 38 m $_{to\ 12mFU}$ 312 ± 48 m, −2%, *P*-value = 0.859) during the follow-up period. The 6MHWD did not differ significantly between BAT (+16%) and ARNI-treated patients (+1%) (BAT vs. ARNI, 12-month FU, *P* = 0.674).

First, BAT seems to be a rather unknown therapeutic tool in HFrEF patients, but arouses great interest among them. However, agreement to implantation is moderate.

Second, BAT is associated with a significant improvement in NYHA class, QoL, NT-proBNP levels, LVEF, and hospitalization rates.

Third, effects of BAT and ARNIs seem to be comparable.

Fourth, the combination of BAT and ARNIs leads to more pronounced effects than ARNIs alone.

Fifth, even under CRT therapy, HFrEF patients seem to benefit from BAT.

Discussion

Main findings

To the best of our knowledge, this is the first study not only evaluating BAT in a real-world scenario in HFrEF patients in terms of outcome, proving the longest FU in a study of this extent so far, but also analysing BAT acceptance and effects of ARNIs on the BAT response.

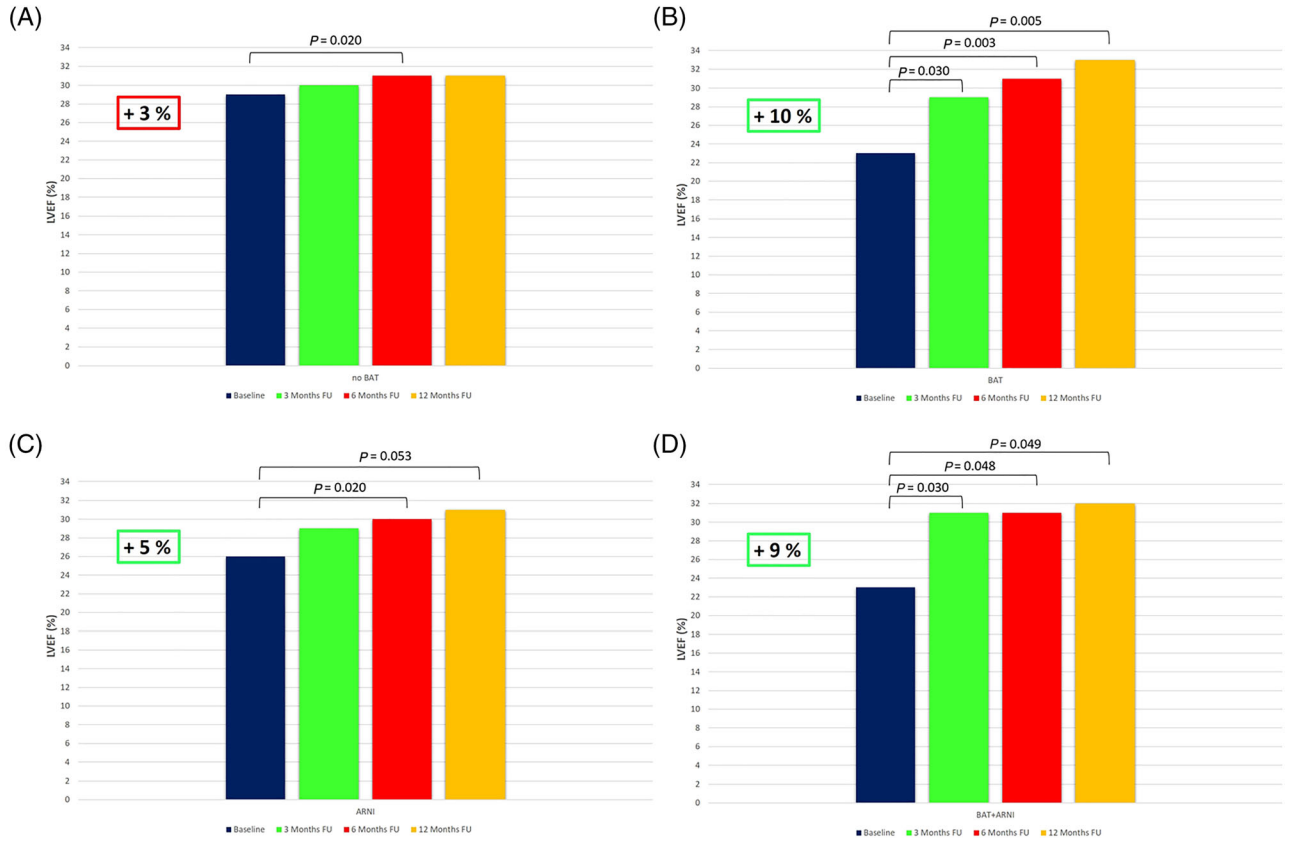
This study has five major findings:

Impact of BAT on patients' outcome

Because the inclusion criteria of our study are predominantly the same as those of the *HOPE4HF* study,[12] the results can be compared directly. Important to note, the FU duration was only 6 months in the *HOPE4HF* study[12] in contrast to our study with FU appointments at 3, 6, and 12 months. Long-term results of the *BeAT-HF* study are pending.[13]

DOI: 10.1002/ehf2.14190

Figure 4 Effects of BAT on LVEF.



Clinical effects

In contrast to NYHA class improvements in the *HOPE4HF* study with 55% of patients reporting on significant changes at the 6-month FU,[12] we documented similar but earlier effects at the 3-month FU already (50% change in distribution) and even more extensive effects at the 12-month FU with 80% of patients experiencing significant improvements (*Figure 1*). As the *BeAT-HF* study reports on a 34% improvement in NYHA class, these finding is in line with our results.[13] Most likely due to our small cohort as well as more advanced HF in our patients compared with the *BeAT-HF* study population, no significant changes in 6MHWD were achieved. However, a significant increase in QoL was documented (*Figure 2*). In the *HOPE4HF* study, the between-group difference in QoL score was −20 points and −14 points in the BeAT-HF study, favouring BAT each.[12,13] Thus, these results are also in accordance with our data. In line with our results (−33%), the *HOPE4HF* study documented a significantly reduced hospitalization rate in BAT patients (−78%). The slightly lower reduction in HF hospitalization rates in our BAT patients might be explained by more advanced stages of HF in our study population. Study results of the *BeAT-HF* study regarding hospitalization rates are pending.[13]

Effects on biomarkers

In contrast to an increase in NT-proBNP levels in the control group, BAT therapy reduced NT-proBNP levels by about 24% (*Figure 3*). These findings are in line with the *HOPE4HF*[12] and the *BeAT-HF* study (−25%).[13] Thus, in our study, even the critically ill patients with much higher NT-proBNP levels of 2302 ± 460 pg/mL compared with patients in the *BeAT-HF* study benefitted from BAT. This should be noted in particular against the background that, after an interim analysis of the first study results of the *BeAT-HF* study, only patients with NT-proBNP levels below 1.600 pg/mL were considered, as they seemingly benefit more from BAT.[13] Nevertheless, our cohort of patients is far too small to draw valid conclusions in this regard.

Effects on echocardiographic parameters

Regarding the LVEF, our study demonstrates a significantly improved LVEF under BAT therapy (+10%) (*Figure 4*). In the *HOPE4HF* study, echocardiographic analyses indicated a non-significant trend towards an improved LVEF in the BAT

group.[12] The *BeAT-HF* trial did not assess left ventricular structure or function.[13]

Comparison to alternative neuromodulatory approaches

CCM therapy represents another neuromodulatory therapy option for HF patients with NYHA class III–IV exertional dyspnoea despite GDMT, an LVEF between 25 and 45%, and a narrow QRS complex <130 ms.[14–16] In contrast to the BAT device leading to an activation of the ANS via a carotid sinus stimulation lead, CCM therapy consists of non-excitatory electrical signals delivered to the heart by two to three leads during the absolute refractory period.[14] CCM improves exercise tolerance ($V0_2max$) and QoL.[14] The composite of cardiovascular death and HF hospitalization rates is reduced.[14] In patients with an LVEF below 35%, CCM can be integrated into a device with an ICD (Integra CCM-D).[14,15] Clinical effectiveness was greater in CCM patients with an LVEF between 35 and 45%.[14] These results match those obtained in the BeAT-HF study.[13] Both the highly impaired LVEF and elevated NT-proBNP levels can be considered to reflect advanced HF. The reason for the poorer outcome of this specific cohort of patients with BAT and CCM may be due to advanced remodelling processes with marked, irreversible fibrosis. For this reason, all available therapeutic options should be explored early in HF patients to avoid missing the optimal time for an additional HF device implantation to improve patients' outcome. Nonetheless, we observed beneficial effects of BAT in patients with advanced HF, too.

Additional impact of ARNIs on patients' outcome

Recommendations regarding the establishment of HF therapy have changed. Current HF guidelines[19] recommend an extended basic drug therapy consisting of a beta-blocker (BB),[21] a sodium-glucose co-transporter 2 inhibitor (SGLT2-I),[22] a mineralocorticoid receptor antagonist (MRA),[23] and an angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin receptor-neprilysin inhibitor (ARNI).[24] In addition, new drugs such as the soluble guanylate cyclase (sGC) stimulator vericiguat have been added.[19] In contrast to earlier BAT studies,[11–13] we are the first explicitly analysing the impact of ARNIs on patients' outcome. In our study, at baseline, 38% of patients were on therapy with ARNIs dosed out to maximum tolerability. In the *BeAT-HF* trial, ARNIs were titrated up during the study so that only after 6 months, 38% of patients had ARNIs.[13] SGLT-I and vericiguat had not yet been approved for HF treatment.

In our study, ARNIs led to similar effects as BAT therapy, although these appear to be more pronounced under BAT therapy, particularly with regard to improvements in LVEF, NYHA class, and QoL (*Figures 1*, *2, and 4*). The extent of ARNI-induced NYHA class and LVEF improvement in our study is comparable with that observed in previous ARNI studies.[24] In our study, ARNIs seem to have a greater impact on NT-proBNP levels than BAT (*Figure 3*). The amount of NT-proBNP reduction is in line with a previous study analysing the effects of ARNIs in HFrEF patients.[25] The combination of BAT and ARNIs leads to more pronounced therapeutic effects than a therapy with ARNIs alone indicating an additive effect of BAT and ARNIs (*Figures 1–4*).

Concerning aspects of cardiac remodelling time in ARNI patients, a meta-analysis by Wang *et al*. reports on significant cardiac reverse remodelling processes at 3 months already with even more pronounced effects over time.[26] These observations are in line with the PROVE-HF study by Januzzi *et al*., as they revealed a correlation between reduced NT-proBNP levels and an improved LVEF at the 6-month follow up with even more pronounced effects at the 12-month follow-up.[25]

This may be one reason why we see a significant improvement in NYHA class and LVEF as well as a further reduction in NT-proBNP levels in the ARNI cohort of patients during the 12-month observation period despite a completed up-dosing of ARNIs 3 months prior to inclusion (*Figures 1*, *3, and 4*).

No significant changes were observed in the ARNI group with regard to QoL (*Figure 2*). Lewis *et al*. analysed health-related QoL outcomes in PARADIGM-HF and demonstrated that ARNIs are associated with an improved QoL by 4 months after randomization, which persisted throughout 36 months.[27] These results match our findings as well as in our study ARNIs were already up-titrated more than 3 months prior to inclusion.

BAT may be primarily considered in an early stage of HF, when cardiac remodelling processes are still expected. There are similar considerations for ARNI therapy. Wang *et al*. stated that ARNIs should be prescribed as early as possible.[26]

As our cohort of patients is small, further studies are needed to investigate the effect of BAT under extended HF medication in detail.

Impact of CRT on patients' outcome

BAT and CRT are two different approaches to improve HF and to reduce cardiac remodelling processes. Zile *et al*. demonstrated that BAT effects were most pronounced in patients not treated with CRT, although changes in efficacy endpoints in the CRT group favoured BAT as well.[28] In this subgroup analysis of the HOPE4HF study, the trend seems to be in favour of a more pronounced benefit with respect to QoL, NYHA class, and LVEF in non-CRT subjects at the 6-month FU.[28] Concerning parameters such as NYHA class, NT-proBNP levels, and the number of HF hospitalizations no differences were observed.[28] Based on the results of this

subgroup analysis, patients with a class I indication for CRT were excluded for BAT treatment in the *BeAT-HF* trial.[13] The rationale is that CRT per se may influence sympathovagal balance to the heart and vessels and thus affects the potential benefit of BAT.[28–33]

DeMazumder *et al*.[33] and Gademan *et al*.[31] have demonstrated that CRT has salutary effects on both the sympathetic and parasympathetic nervous systems, which act to restore the sympathovagal balance in patients with HFrEF.

It has been demonstrated that CRT acutely reduces MSNA in clinical responders.[31] Other studies stated that CRT acutely increased baroreflex sensitivity and heart rate variability.[33]

In addition, a recent study examined the effect of CRT on cholinergic signalling in patients with HFrEF and animal models of HFrEF suggesting that remodelling of cholinergic signalling is an important mechanism underlying HFrEF and that CRT enhances sympathovagal balance in these patients.[33]

Thus, patients treated with CRT may have less sympathetic/parasympathetic imbalance even when they have NYHA class III symptoms of HF. This may explain the observed differences in the response to BAT in patients with a CRT compared with those without.

Nevertheless, the authors of a current meta-analysis including the *HOPE4HF* as well as the *BeAT-HF* cohort of patients report on clinical meaningful improvements consequent across the range of patients studied including CRT patients.[32] These results are in line with our results. In our study, most patients were CRT non-responders (*Table 1*). The majority of CRT patients benefitted significantly from BAT therapy, also regarding QoL, NYHA class, and LVEF (*Figures 1–4*). Further studies are needed to analyse the interaction of both forms of therapy in more detail. In particular, the therapeutic gap between GDMT and ventricular assist devices (VAD) or heart transplantations (HTX) in CRT non-responders remains an interesting potential area of BAT application.

Impact of coronary artery disease on patients' outcome

In our study, there was no evidence of differences in response to BAT depending on the presence of ICM or DCM. These findings act in concert with a prior study.[32,34] However, our BAT group is certainly too small to reveal minor statistical differences.

Patients' acceptance of BAT

Although BAT therapy shows promising results in HF treatment and patients initially communicated a strong interest in BAT, only 10 patients (25%) opted for device implantation (*Figure S1*). As the majority of patients had an implanted ICD or CRT device before, the option to integrate BAT into these devices might be beneficial for patients' acceptance. A more detailed analysis is needed in this regard. Unfortunately, screening data from the *HOPE4HF* or *BeAT-HF* study are not available for comparison in this context.[12,13]

Future perspective and clinical outlook

BAT is newly mentioned in the current HF guidelines.[19] However, evidence for a reduction in mortality and hospitalization based on randomized controlled trials is still pending. In order to improve the selection of patients who will benefit most from BAT, many questions have yet to be answered. Differences in treatment response depending on whether DCM or ICM is present have not yet been satisfactorily worked out. The role of BAT in CRT non-responders as an additional therapeutic option (bridge to VAD or HTX) remains ambivalent. It is unclear whether HF patients with a preserved ejection fraction (HFpEF) might also benefit from BAT. New HF drugs, for example, SGLT2-I, have become standard of care in HF treatment. Their impact on the ANS and thus the therapeutic outcome of BAT in this context have not been studied so far. Precise effects of BAT on cardiac remodelling and fibrosis and thus potential therapeutic influences of BAT on cardiac arrhythmias remain unclear.

Beyond that, further device innovations (smaller device, easier implantation, combination with an ICD or CRT in one device, telemonitoring option, etc.) are also to be welcomed.

Conclusions

Although interest in BAT among symptomatic patients suffering from otherwise untreatable advanced HF seems to be present, the acceptance of an additional device implantation is low. However, in this real-world scenario, patients opting for BAT were rewarded with a superior outcome, even when innovative drugs were already applied.

Particularly because of the small number of patients in our study, future prospective, randomized studies are required specifying BAT indications in subgroups to direct guideline recommendations.

Limitations

Because of the small patient population in our study, we report on initial observations. Future prospective, randomized studies are required specifying BAT indications in subgroups to direct guideline recommendations. Soft clinical endpoints as, for example, NYHA class and QoL may be subject to

patients' certainly subjective perception. Although ARNIs had to be titrated up to the maximum tolerated dose 3 months prior to inclusion, further ARNI induced cardiac remodelling processes during the observation period of our study cannot be excluded. This may influence the study result of the BAT + ARNI group to some extent.

Acknowledgements

We acknowledge support by the DFG Open Access Publication Funds of the Ruhr-Universität Bochum.

Open Access funding enabled and organized by Projekt DEAL.

Conflict of interest

None declared.

Funding

The study was supported by the Faculty of Medicine at Ruhr-Universität Bochum, Germany (FoRUM programme F914-2017).

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1: Patients' Awareness of and Interest in BAT.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members; Document Reviewers. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF: The task force for the diagnosis and treatment of acute and chronic HF of the European Society of Cardiology (ESC). Developed with the special contribution of the HF Association (HFA) of the ESC. *Eur J Heart Fail*. 2016; **18**: 891–975.
2. Ferguson DW, Abboud FM, Mark AL. Selective impairment of baroreflex-mediated vasoconstrictor responses in patients with ventricular dysfunction. *Circulation*. 1984; **69**: 451–460.
3. Florea VG, Cohn JN. The autonomic nervous system and HF. *Circ Res*. 2014; **114**: 1815–1826.
4. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in HF physiology, pathophysiology, and clinical implications. *J Am Coll Cardiol*. 2009; **54**: 1747–1762.
5. van Bilsen M, Patel HC, Bauersachs J, Böhm M, Borggrefe M, Brutsaert D, Coats AJS, de Boer RA, de Keulenaer GW, Filippatos GS, Floras J, Grassi G, Jankowska EA, Kornet L, Lunde IG, Maack C, Mahfoud F, Pollesello P, Ponikowski P, Ruschitzka F, Sabbah HN, Schultz HD, Seferovic P, Slart RHJA, Taggart P, Tocchetti CG, Van Laake LW, Zannad F, Heymans S, Lyon AR. The autonomic nervous system as a therapeutic target in HF: A scientific position statement from the Translational Research Committee of the HF Association of the European Society of Cardiology. *Eur J Heart Fail*. 2017; **19**: 1361–1378.
6. Brunner-La Rocca HP, Esler MD, Jennings GL, Kaye DM. Effect of cardiac sympathetic nervous activity on mode of death in congestive HF. *Eur Heart J*. 2001; **22**: 1136–1143.
7. Setoguchi S, Choudhry NK, Levin R, Shrank WH, Winkelmayer WC. Temporal trends in adherence to cardiovascular medications in elderly patients after hospitalization for HF. *Clin Pharmacol Ther*. 2010; **88**: 548–554.
8. Zipes DP, Neuzil P, Theres H, Caraway D, Mann DL, Mannheimer C, Van Buren P, Linde C, Linderoth B, Kueffer F, Sarazin SA, DeJongste MJL, DEFEAT-HF Trial Investigators. Determining the feasibility of spinal cord neuromodulation for the treatment of chronic systolic HF: The DEFEAT-HF study. *JACC Heart Fail*. 2016; **4**: 129–136.
9. Zannad F, De Ferrari GM, Tuinenburg AE, Wright D, Brugada J, Butter C, Klein H, Stolen C, Meyer S, Stein KM, Ramuzat A, Schubert B, Daum D, Neuzil P, Botman C, Castel MA, D'Onofrio A, Solomon SD, Wold N, Ruble SB. Chronic vagal stimulation for the treatment of low ejection fraction HF: Results of the NEural Cardiac TherApy foR HF (NECTAR-HF) randomized controlled trial. *Eur Heart J*. 2015; **36**: 425–433.
10. Gold MR, Van Veldhuisen DJ, Hauptman PJ, Borggrefe M, Kubo SH, Lieberman RA, Milasinovic G, Berman BJ, Djordjevic S, Neelagaru S, Schwartz PJ, Starling RC, Mann DL. Vagus nerve stimulation for the treatment of HF: The INOVATE-HF trial. *J Am Coll Cardiol*. 2016; **68**: 149–158.
11. 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 HF: A proof-of-concept study. *Eur J Heart Fail*. 2014; **16**: 977–983.
12. Abraham WT, Zile MR, Weaver FA, Butter C, Ducharme A, Halbach M, Klug D, Lovett EG. Baroreflex activation therapy for the treatment of HF with a reduced ejection fraction. *JACC Heart Fail*. 2015; **3**: 487–496.
13. Zile MR, Lindenfeld J, Weaver FA, Zannad F, Galle E, Rogers T, Abraham WT. Baroreflex activation therapy in patients with HF with reduced ejection fraction. *J Am Coll Cardiol*. 2020; **76**: 1–13.
14. Abraham WT, Kuck KH, Goldsmith RL, Lindenfeld J, Reddy VY, Carson PE, Mann DL, Saville B, Parise H, Chan R, Wiegn P, Hastings JL, Kaplan AJ, Edelmann F, Luthje L, Kahwash R, Tomassoni GF, Gutterman DD, Stagg A, Burkhoff D, Hasenfuß G. A randomized controlled trial to evaluate the safety

and efficacy of cardiac contractility modulation. *JACC Heart Fail*. 2018; **6**: 874–883.
15. Wiegn P, Chan R, Jost C, Saville BR, Parise H, Prutchi D, Carson PE, Stagg A, Goldsmith RL, Burkhoff D. Safety, performance, and efficacy of cardiac contractility modulation delivered by the 2-lead optimizer smart system: The FIX-HF-5C2 study. *Circ Heart Fail*. 2020; **13**: e006512.
16. Anker SD, Borggrefe M, Neuser H, Ohlow MA, Röger S, Goette A, Remppis BA, Kuck KH, Najarian KB, Gutterman DD, Rousso B, Burkhoff D, Hasenfuss G. Cardiac contractility modulation improves long-term survival and hospitalizations in HF with reduced ejection fraction. *Eur J Heart Fail*. 2019; **21**: 1103–1113.
17. Floras JS. Sympathetic nervous system activation in human HF: Clinical implications of an updated model. *J Am Coll Cardiol*. 2009; **54**: 375–385.
18. Mann JA, Abraham WT. Cardiac contractility modulation and baroreflex activation therapy in HF patients. *Curr Heart Fail Rep*. 2019; **16**: 38–46.
19. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021; **42**: 3599–3726 Erratum in: Eur Heart J. 2021 Oct 14; PMID: 34447992. McDonagh TA, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF. Eur Heart J. 2021. PMID: 34447992.
20. 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 HF with reduced ejection fraction. *Semin Thorac Cardiovasc Surg*. 2016; **28**: 320–328.
21. CIBIS-II Investigators and Committees. The cardiac insufficiency bisoprolol study II (CIBIS-II): A randomised trial. *Lancet*. 1999; **353**: 9–13.
22. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Belohavek J, Böhm M, Chiang C-E, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Duat A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM, DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019; **381**: 1995–2008.
23. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. *N Engl J Med*. 1999; **341**: 709–717.
24. Docherty KF, Vaduganathan M, Solomon SD, McMurray JJV. Sacubitril/valsartan: Neprilysin inhibition 5 years after PARADIGM-HF. *JACC Heart Fail*. 2020; **8**: 800–810.
25. Januzzi JL Jr, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, Camacho A, Piña IL, Rocha RA, Shah AM, Williamson KM, Solomon SD, PROVE-HF Investigators. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA*. 2019; **322**: 1085–1095.
26. Wang Y, Zhou R, Lu C, Chen Q, Xu T, Li D. Effects of the angiotensin-receptor neprilysin inhibitor on cardiac reverse remodeling: Meta-analysis. *J Am Heart Assoc*. 2019; **8**: e012272.
27. Lewis EF, Claggett BL, McMurray JJV, Packer M, Lefkowitz MP, Rouleau JL, Liu J, Shi VC, Zile MR, Desai AS, Solomon SD, Swedberg K. Health-related quality of life outcomes in PARADIGM-HF. *Circ Heart Fail*. 2017; **10**: e003430.
28. 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 HF with a reduced ejection fraction: Safety and efficacy in patients with and without cardiac resynchronization therapy. *Eur J Heart Fail*. 2015; **17**: 1066–1074.
29. Mortara A, Vanoli E. Baroreceptor activation therapy: The importance of targeting the right patient: Who needs to be treated? *Eur J Heart Fail*. 2015; **17**: 1000–1002.
30. Fantoni C, Raffa S, Regoli F, Giraldi F, La Rovere MT, Prentice J, Pastori F, Fratini S, Salerno-Uriarte JA, Klein HU, Auricchio A. Cardiac resynchronization therapy improves heart rate profile and heart rate variability of patients with moderate to severe HF. *J Am Coll Cardiol*. 2005; **46**: 1875–1882.
31. Gademan MG, van Bommel RJ, Ypenburg C, Haest JC, Schalij MJ, van der Wall EE, Bax JJ, Swenne CA. Biventricular pacing in chronic HF acutely facilitates the arterial baroreflex. *Am J Physiol Heart Circ Physiol*. 2008; **295**: H755–H760.
32. Coats AJS, Abraham WT, Zile MR, Lindenfeld JA, Weaver FA, Fudim M, Bauersachs J, Duval S, Galle E, Zannad F. Baroreflex activation therapy with the Barostim™ device in patients with heart failure with reduced ejection fraction: A patient level meta-analysis of randomized controlled trials. *Eur J Heart Fail*. 2022. https://doi.org/10.1002/ejhf.2573
33. DeMazumder D, Kass DA, O'Rourke B, Tomaselli GF. Cardiac resynchronization therapy restores sympathovagal balance in the failing heart by differential remodeling of cholinergic signaling. *Circ Res*. 2015; **116**: 1691–1699.
34. 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 HF with reduced ejection fraction in patients with and without coronary artery disease. *Int J Cardiol*. 2018; **266**: 187–192.