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Autonomic regulation device therapy in heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Heart failure with reduced ejection fraction (HFrEF) represents a significant public health burden associated with incremental health care costs. Given the limitations associated with pharmacological autonomic regulation therapy (ART), device-based autonomic neuromodulation is on the horizon now for ART in those patients. This systematic review aimed primarily to determine the effect of ART by devices on functional status and quality of life (QOL) in patients with HFrEF. We performed a meta-analysis of five randomized controlled trials (1074 patients) comparing ART by devices versus optimal medical therapy (OMT) in HFrEF. We assessed pooled estimates of odds ratio (OR) for improvement in New York Heart Association (NYHA) class and mean differences (MD) in 6-minute hall walk distance (6-MHWD), Minnesota Living with Heart Failure Questionnaire (MLHFQ) score, N-terminal pro b-type natriuretic peptide (NT-proBNP) levels, and left ventricular end-systolic volume index (LVESVi) with their 95% confidence intervals (CIs) at 6-month follow-up. Compared to OMT alone, ART by devices in HFrEF significantly improves NYHA class (OR 2.26, 95% CI 1.33 to 3.83, $P = 0.003$), increases 6-MHWD (MD 45.53 m, 95% CI 30.61 to 60.45, $P < 0.00001$), improves MLHFQ score (MD − 10.59, 95% CI − 20.62 to − 0.57, $P = 0.04$) with neutral effect on NT-proBNP levels (MD − 236.5 pg/ml, 95% CI − 523.86 to 50.87, $P = 0.11$) and LVESVi (MD − 1.01 ml/m^2, 95% CI − 4.49 to 2.47, $P = 0.57$). We concluded that device-based neuromodulation therapy significantly improves functional status and quality of life in patients with HFrEF.

Keywords Autonomic regulation · Devices · Heart failure

Abbreviations

6-MHWD	6-minute hall walk distance
ART	Autonomic regulation therapy
CI	Confidence interval
HFrEF	Heart failure with reduced ejection fraction
LVESVi	Left ventricular end-systolic volume index
MD	Mean difference
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
QOL	Quality of life

Introduction

Affecting approximately 25 million patients worldwide, heart failure (HF) remains a major global health problem [1]. Despite advanced strategies which have improved prognosis of such patients, overall mortality rates remain high at figures approaching 50% death rate at 5 years [2]. The autonomic nervous system (ANS) plays a central role in maintaining hemodynamics in patients with HF. Reduced cardiac output leads to activation of many cardiovascular reflexes and neurohormonal axis including the renin-angiotensin-aldosterone (RAAS) system ending up with stimulation of the sympathetic nervous system (SNS) [3]. Enhanced SNS activation is well-known denominator in patients with heart failure with reduced ejection fraction (HFrEF) with

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some recent research work implicating it as a potential pathophysiologic mechanism in patients with heart failure and preserved ejection fraction (HFpEF) as well [4]. Initially, increased SNS activity leads to improvement in cardiac output through a positive chronotropic and inotropic effects, however, by time, this chronic stimulation of SNS leads to a state of progressive myocardial fibrosis, autonomous neurohormonal activation and heightened liability for arrhythmias [5]. In addition to this dysregulation in SNS, withdrawal of parasympathetic nervous system (PNS) signals has also been reported in patients with HF [6], including but not limited to reduced ganglionic vagal activity and receptor density [7]. All these factors lead to a state of "sympathovagal imbalance" which is thought to be the underlying culprit for a worse long-term outcome in those patients. Considering the significant role of ANS in HF pathogenesis, there has been an enormous interest in ANS modulation as part of HF therapy armamentarium. The beneficial effects of guideline-directed medical therapies in HF as ß-blockers and RAAS inhibitors are thought to be related, at least in part, to ANS modulation with a resultant reduction in arrhythmogenesis and reverse left ventricular remodeling [8]. However, there are many drawbacks in the pharmacological modulation of the ANS such as the nonspecific sympatholysis induced by drugs, the lack to selectively modulate each limb of the ANS, and known side effects of medications [9]. These limitations have fueled the development of novel percutaneous device therapies that could reverse the above-mentioned "sympathovagal imbalance" by either enhancing the PNS signals or inhibiting the SNS overactivation. They include vagal nerve stimulation (VNS), spinal cord stimulation (SCS), baroreceptor activation therapy (BAT), and renal denervation (RDN) [10]. Few randomized controlled trials (RCTs) examined the role of such devices in patients with HFrEF, and these trials were not powered to detect differences between groups concerning hard endpoints such as mortality. Instead, they used many patient-centered outcomes that are of particular relevance to patients with HF such as New York Heart Association (NYHA) class change, quality of life (QOL) score metrics, and 6-minute hall walk distance (6-MHWD), in addition to some surrogate endpoints such as cardiac biomarkers and LV remodeling. Interestingly, these trials have yielded inconsistent results, calling the whole idea of ANS modulation by percutaneous devices in patients with HFrEF into question. Based on these facts and taking into consideration that patient-centered outcomes are gaining great acceptance now among clinical trialists [11], we conducted this systematic review and meta-analysis to provide such information.

Methods

This meta-analysis was conducted according to available statements for design, analysis, and reporting of meta-analyses of randomized studies [12]. The protocol was registered in PROSPERO with ID (CRD42018085931) [13].

Search strategy and selection criteria

We searched PubMed, The Cochrane Library, and Scopus (anytime up to February 2018) for randomized controlled trials evaluating autonomic regulation device therapy in HFrEF. We used search terms that provide the highest attainable sensitivity in detecting trials exploring such issue. We used terms "Vagal nerve stimulation" AND "Heart failure," "Renal denervation" AND "Heart failure," " Spinal cord stimulation" AND "Heart failure," "Baroreflex activation" AND "Heart failure," "Autonomic regulation therapy" AND "Heart failure." MeSH terms were used whenever possible.

Eligibility criteria (PICOS) and exclusions

Population Patients with HFrEF, with ejection fraction (EF) ≤ 40% and New York Heart Association (NYHA) class III despite optimal medical therapy

Intervention Any autonomic regulation device therapy

Control Optimal medical therapy without intervention

Primary outcome Improvement of New York Heart Association (NYHA) functional class by at least one point and change in 6-minute hall walk distance (6-MHWD) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) at 6-month follow-up

Secondary outcome Change in levels of NT-proBNP levels and left ventricular end-systolic volume index (LVESVi) at 6-month follow-up

Study design Randomized controlled trials

We excluded non-English studies and conference papers.

Screening and data extraction

EndNote was used for removal of duplications; after that, two independent reviewers performed screening to include records that meet inclusion criteria (excluding irrelevant records by titles and abstracts). A full-text screening was done after that to include only relevant records that meet inclusion criteria. Divergences were resolved by consensus. Search results are summarized using a PRISMA flow chart. Data extraction was done by two independent reviewers according to a predefined form list; then, a third reviewer was included to resolve any discrepancy if a consensus cannot be reached.

Risk of bias assessment

The risk of bias of the selected studies was evaluated independently by two reviewers using the Cochrane's Risk of Bias Assessment Tool which assesses sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. The reviewers assigned a low, high, or unclear risk of bias for each category.

Statistical analysis

Statistical analysis and graphs were performed using Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. For changes in MLHFQ QOL score, 6-MHWD, NT-proBNP levels, and LVESVi, the analysis was done using inverse variance method based on a random-effect model to calculate mean differences with their 95% confidence intervals. For NYHA class improvement outcome, the Mantel-Haenszel method was used based on a random-effect model to determine odds ratio with its 95% confidence interval. The odds ratio for improvement in NYHA class outcome was chosen because it is associated with less heterogeneity in meta-analyses than risk differences or relative risks [14]. To enhance the robustness of our results, we used a random-effect model since it is more conservative than a fixed-effect model, as it considers the variability between studies [15]. Plot digitizer software (version 2.6.8) was used to extract necessary data whenever they were only available through figures. Standard deviations (SD) of the differences in MLHFQ QOL score and 6-MHWD outcomes in the DEFEAT-HF study [16] were borrowed from Abraham et al.'s study [17, 18] (up to the registered due date for completion of this meta-analysis [13], we did not receive a conclusive response from the DEFEAT-HF authors after we contacted them to obtain these missing data). Data for NT-proBNP [reported in various studies using median(s) and range(s)] have been transformed to mean(s) and standard deviation(s) in order to facilitate data pooling in a consistent format [19, 20]. Assessment of heterogeneity was done first by rough visual inspection of forest plots; evidence of heterogeneity was considered to exist if chi-square P value was < 0.1. Heterogeneity across trials was assessed using the I^2 measure, with values interpreted as follows: 0% means no observed heterogeneity; 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively [21]. In case of considerable heterogeneity, we performed a sensitivity analysis by excluding study/studies thought to be the cause of such heterogeneity.

Results

Search results

Our search retrieved 276 unique articles. Following the abstract screening, only 52 titles were eligible for full-text screening. Finally, five RCTs [16, 17, 22–24] with a total of 1074 patient were found to be eligible for the final analysis (Fig. 1). The summary of the included studies and their main results are shown in Table 1, and the baseline characteristics of their populations are shown in Table 2.

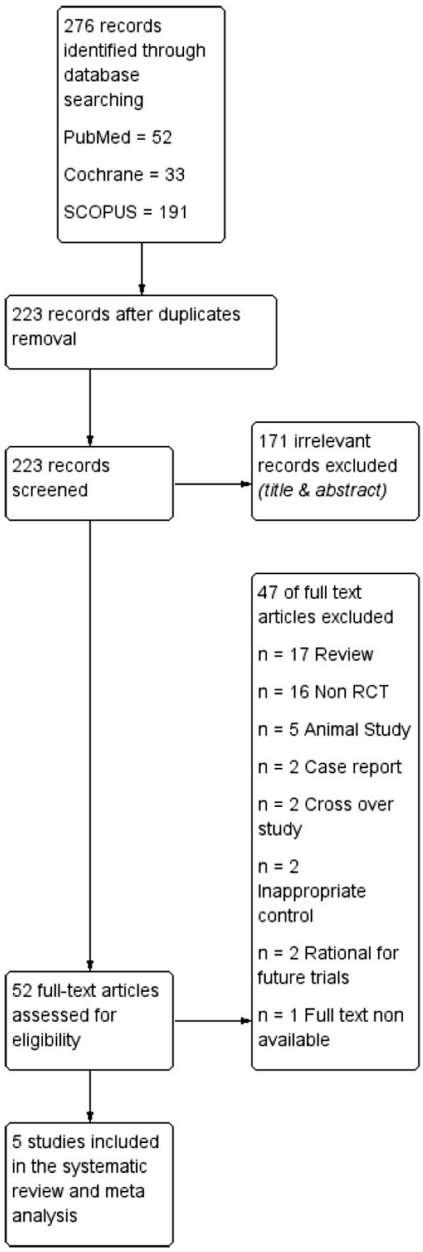

Fig. 1 A PRISMA flow chart of study selection

Table 1 Summary of the included studies

Study ID	Design	Population	Patients randomized	Crossover or parallel	Main findings
DEFEAT-HF trial [16]	Single-blind RCT	EF ≤ 35%, NYHA class III despite medical therapy	66	Parallel	No significant change in the LVESVi in patients receiving SCS ($P = 0.30$). Changes in NYHA, MLHFQ, and 6-MHWD were non-significant as well.
Abraham et al [17]	Non-blinded RCT	EF ≤ 35%, NYHA class III despite medical therapy	146	Parallel	Significant improvements in 6-MHWD ($P = 0.004$), MLHFQ ($P < 0.001$), and NYHA class ranking ($P = 0.002$ for change in distribution). Also, NT-proBNP levels were significantly reduced ($P = 0.02$).
NECTAR-HF trial [22]	Double-blind RCT	EF ≤ 35%, NYHA class II or III despite medical therapy	95	Parallel	No significant change in the LVESVi in patients receiving VNS ($P = 0.36$). However, there were significant improvements in MLHFQ ($P = 0.04$) and NYHA class ($P = 0.03$).
INOVATE-HF trial [23]	Non-blinded RCT	EF ≤ 40%, NYHA class III despite medical therapy	707	Parallel	At 6-month follow-up, there were significant improvements in NYHA class ($P < 0.01$) and 6-MHWD ($P < 0.01$) but LVESVi did not significantly change ($P = 0.38$).
Chen et al [24]	Non-blinded RCT	EF ≤ 40%, NYHA class II to IV despite medical therapy	60	Parallel	There were significant improvements in 6-MHWD ($P = 0.04$) and NYHA class ($P < 0.001$). Also, NT-proBNP levels were significantly reduced ($P < 0.001$).

6-MHWD 6-minute hall walk distance, *EF* ejection fraction, *LVESVi* left ventricular end-systolic volume index, *MLHFQ* Minnesota Living with Heart Failure Questionnaire, *NT-proBNP* N-terminal pro b-type natriuretic peptide, *NYHA* New York heart association, *RCT* randomized controlled trial, *SCS* spinal cord stimulation, *VNS* vagal nerve stimulation

Quality of included studies

The included studies were qualitatively at low risk of bias according to the Cochrane risk of bias assessment tool. The summary of quality assessment domains of included studies is shown in (Fig. 2).

Primary outcomes

Improvement in NYHA class

This outcome was reported in all the five finally included studies. However, four studies reported this outcome in a categorical manner (improved/non-improved). Only Chen et al.'s study [24] reported this outcome as a continuous variable. Up to the registered due date for completion of this meta-analysis [13], we did not receive any response from authors after we contacted them to obtain the categorical expression of these data. Therefore, we excluded Chen et al.'s study from the final meta-analysis of this outcome.

More patients in the device arm significantly improved their NYHA class by at least one point compared to the control arm [252 patients versus 98 patients in the device and control arm respectively, odds ratio 2.26, 95% CI 1.33 to 3.83, $P = 0.003$; Fig. 3a], with moderate heterogeneity between studies ($P = 0.1$; $I^2 = 51\%$). Subsequent sensitivity analysis after exclusion of the DEFEAT-HF study [16] resolved heterogeneity ($P = 0.4$; $I^2 = 0\%$) maintaining the favorable effect of autonomic regulation device therapy for improvement of NYHA class compared to the control group [odds ratio 2.51, 95% CI (1.82 to 3.46), $P < 0.00001$; Fig. 3d] (see "Discussion" for further details).

Change in 6-MHWD

This outcome was reported in four out of the five finally included studies. There was a significant increase in 6-MHWD in the device arm compared to the control arm [MD 45.53 m, 95% CI (30.61 to 60.45), $P < 0.00001$; Fig. 3b]; the pooled studies were homogeneous ($P = 0.58$; $I^2 = 0\%$).

Change in MLHFQ QOL score

This outcome was reported in three out of the five finally included studies. There was a trend towards significantly improved MLHFQ score in the device arm compared to the

Table 2 Baseline characteristics of included studies' population

Study ID		DEFEAT-HF trial [16]	Abraham et al. [17]	NECTAR-HF trial [22]	INOVATE-HF trial [23]	Chen et al. [24]
Age (years), mean (SD)	Device	58 ± 11*	64 ± 11	59.8 ± 12.2	61.7 ± 10.5	48.5 ± 8.4
	Control	66 ± 11	66 ± 12	59.3 ± 10.1	60.9 ± 11.2	50.5 ± 7.7
Gender, male (%)	Device	32 (76.2)	62 (87)	56 (89)	339 (77.8)	22 (73.3)
	Control	20 (83.3)	58 (84)	26 (81)	219 (80.8)	24 (80)
BMI (kg/m^2), mean (SD)	Device	31 ± 6	29 ± 5	28.6 ± 5.9*	30.4 ± 6.1	24.2 ± 2.8
	Control	29 ± 6	29 ± 5	31.2 ± 5.1	30.6 ± 6.4	23.6 ± 2.4
Resting HR (bpm), mean (SD)	Device	No statistically significant difference between groups †	73 ± 11	68.2 ± 13.2	72.5 ± 12.2	78.6 ± 10.6
	Control		75 ± 12	71.3 ± 12.9	71.4 ± 11.5	79.7 ± 12.6
SBP (mmHg), mean (SD)	Device	114 ± 19	115 ± 18	118 ± 17	117.7 ± 17.4	110.6 ± 16.5
	Control	119 ± 16	119 ± 17	115 ± 16	118.6 ± 18.5	108.6 ± 12.8
DBP (mmHg), mean (SD)	Device	70 ± 10	72 ± 11	73 ± 10	71.7 ± 10.9	70.5 ± 11.1
	Control	70 ± 11	73 ± 11	73 ± 13	72.5 ± 10.3	68.9 ± 9.1
Heart failure etiology, (ischemic) *N* (%)	Device	25 (59.5)	47 (66.2)	44 (70)	255 (58.5)	6 (20)
	Control	12 (50)	47 (68.1)	20 (63)	173 (63.8)	5 (16.7)
NYHA-III, *N* (%)	Device	42 (100)	70(98.6)	51 (80.9)	436 (100)	Reported as means (SD) ‡
	Control	24 (100)	69 (100)	22 (68.8)	271 (100)	
LVEF (%), mean (SD)	Device	29 ± 5	24 ± 7	30.5 ± 6.0	23.9 ± 6.7	31.1 ± 5.7
	Control	29 ± 5	25 ± 7	30.8 ± 4.2	25.2 ± 7.3	31.9 ± 6.0
LVESVi (ml/m^2), mean (SD)	Device	52.5 ± 23	NR	89.4 ± 33.8	106.0 ± 41.8	NR
	Control	62.7 ± 16.2		94.8 ± 22.6	100.6 ± 40.5	
6-MHWD (meters), mean (SD)	Device	309 ± 118	297 ± 79	NR	304.1 ± 111.5	285.5 ± 84.3
	Control	352 ± 118	308 ± 85		317.0 ± 178.4	274 ± 43.2
MLHFQ, mean (SD)	Device	51 ± 20	51 ± 21*	44.4 ± 22.2	NR	NR
	Control	45 ± 18	43 ± 22	42.8 ± 25.1		
NT-proBNP (pg/ml), mean (SD)	Device	1281 ± 2215	1422 ± 1026	879 ± 245	NR	1519 ± 599.3
	Control	2137 ± 1706.1	1172 ± 502	882 ± 239		1595 ± 707
RAAS blocker use, *N* (%)	Device	38 (90.5)	56 (79)	51 (81)	383 (87.8)	30 (100)
	Control	22 (91.7)	54 (79)	24 (75)	246 (90.8)	30 (100)
Beta-blockers use, *N* (%)	Device	40 (95.2)	62 (87)	59 (94)	409 (93.8)	28 (93.3)
	Control	23 (95.8)	58 (85)	30 (94)	251 (92.6)	29 (96.7)
Diuretics use, *N* (%)	Device	40 (95.2)	66 (93)	54 (86)	336 (77.1)	21 (70)
	Control	22 (91.7)	53 (78)	32 (100)	205 (75.6)	24 (80)
CRT, *N* (%)	Device	NR	24 (33.8)	5 (7.9)	145 (33.3)	NR
	Control		21 (30.4)	4 (12.5)	95 (35)	
ICD, *N* (%)	Device	32 (67.2)	63 (88.7)	51 (80.9)	215 (49.3)	NR
	Control	17 (70.8)	59 (85.5)	22 (68.7)	127 (46.9)	

* $p < 0.05$ vs. other groups, † not reported numerically in the DEFEAT-HF trial, ‡ device arm 3.2 ± 0.5 and control arm 3.1 ± 0.4; *6-MHWD* 6-minute hall walk distance, *BMI* body mass index, *bpm* beats per minute, *CRT* cardiac resynchronization therapy, *DBP* diastolic blood pressure, *HR* heart rate, *ICD* implantable cardiac defibrillator, *LVEF* left ventricular ejection fraction, *MLHFQ* Minnesota Living with Heart Failure Questionnaire, *NYHA* New York Heart Association, *NR* not reported, *RAAS* renin-angiotensin-aldosterone system, *SD* standard deviation, *SBP* systolic blood pressure

control arm [MD − 10.59, 95% CI (− 20.62 to − 0.57), $P = 0.04$; Fig. 3c]; however, the pooled studies were heterogeneous ($P = 0.04$; $I^2 = 69\%$). Subsequent sensitivity analysis after exclusion of Abraham et al.'s study [17] resolved heterogeneity ($P = 0.55$; $I^2 = 0\%$) and resulted in neutral overall effect over this outcome [MD − 5.65, 95% CI (− 13.04 to 1.73), $P = 0.13$; Fig. 3e].

Secondary outcomes

Change in NT-proBNP levels

This outcome was reported in four out of the five finally included studies. There was no significant difference between the device and the control arms regarding the change in NT-

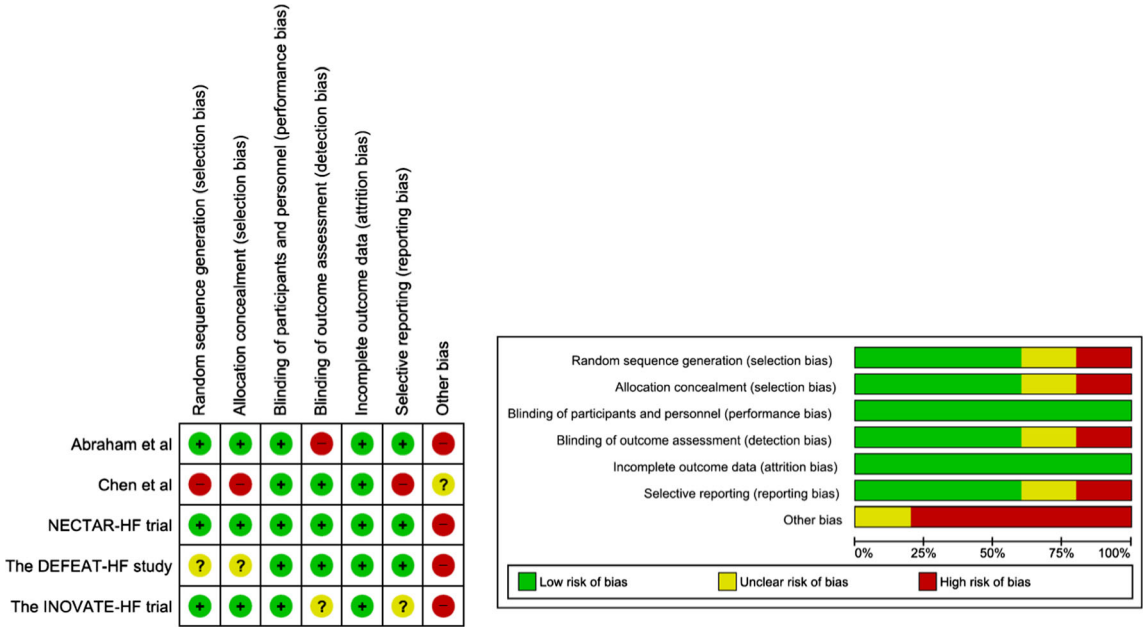

Fig. 2 Quality assessment of included studies and risk of bias

proBNP levels from baseline to 6 months follow-up [MD − 236.5 pg/ml, 95% CI (− 523.86 to 50.87), $P = 0.11$; Fig. 4a]; and the pooled studies were heterogeneous ($P < 0.00001$; $I^2 = 91\%$). Multiple sensitivity analyses did not resolve heterogeneity for this outcome (see "Discussion" for further details).

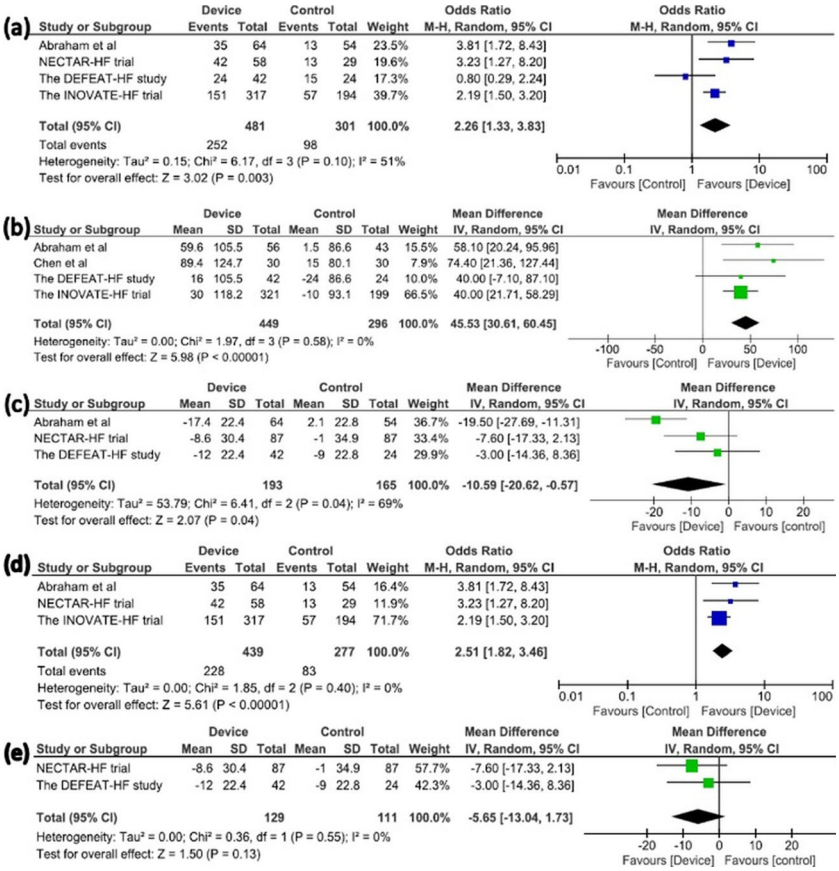

Fig. 3 Primary outcomes and sensitivity analyses. Forest plots with individual and summary estimates of the OR with 95% CI of improvement in NYHA class (a), MD with 95% CI of 6-MHWD (b), MLHFQ (c), OR with 95% CI of improvement in NYHA class *after exclusion* of DEFEAT-HF study (d) and MD with 95% CI of MLHFQ *after exclusion* of Abraham et al. study (e). A random-effect model was applied to estimate OR and MD with their 95% CIs. Squares and diamond sizes are proportional to study weight. Inter-study heterogeneity, separately reported for each outcome, was tested using Cochran's χ^2 test and the I^2 test (see text for details). CI confidence interval, MD mean difference, 6-MHWD 6-minute hall walk distance, MLHFQ Minnesota Living with Heart Failure Questionnaire, NYHA New York Heart Association, OR Odds ratio

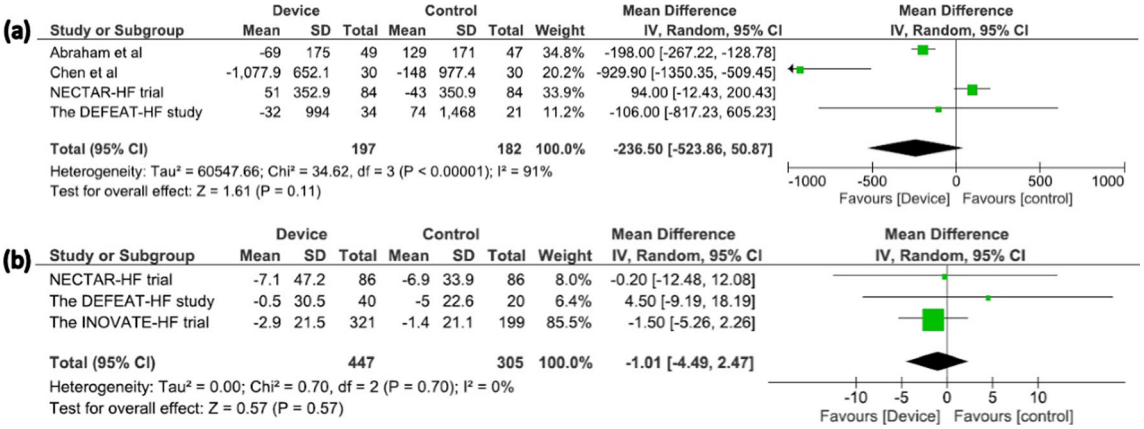

Fig. 4 Secondary outcomes. Forest plots with individual and summary estimates of the MD with 95% CI of changes in NT-proBNP levels (a) and changes in LVESVi (b). A random-effect model was applied to estimate MD with its 95% CI. Squares and diamond sizes are proportional to study weight. Inter-study heterogeneity, separately reported for each outcome, was tested using Cochran's χ^2 test and the I^2 test (see text for details). CI confidence interval, LVESVi left ventricular end-systolic volume index, MD mean differences, NT-proBNP N-terminal pro b-type natriuretic peptide

Change in LVESVi

This outcome was reported in three out of the five finally included studies. There was no significant difference between the device and the control arms regarding the change in LVESVi from baseline to 6 months follow-up [MD − 1.01 ml/m^2, 95% CI (− 4.49 to 2.47), $P = 0.57$; Fig. 4b]; and the pooled studies were homogeneous ($P = 0.7$; $I^2 = 0\%$).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis addressing the idea of ANS modulation by percutaneous devices in patients with advanced HFrEF. The present meta-analysis suggests that autonomic regulation device therapy significantly improves functional status, 6-MHWD and, potentially, QOL metrics in those patients, but does not have a significant impact on NT-proBNP levels or LVESVi (as a surrogate marker for LV remodeling) at 6-month follow-up.

Various societies' guidelines for managing HFrEF still do not endorse any of the included devices for ANS modulation due to lack of robust safety and efficacy data. However, our findings are reassuring and pave the way for future pivotal RCTs with larger sample sizes and more extended follow-up periods that provide power to detect differences in hard clinical endpoints.

We opted for the selection of three patient-centered outcomes as the 1^{ry} endpoint of this meta-analysis because of two main reasons. First, we strongly believe that improving patients' symptoms and QOL should be among the primary objectives of any innovative therapy for HF. Second, most studies exploring these devices had small calculated sample sizes that did not allow for adequate power to detect differences in hard outcomes such as mortality. Our pooled results were consistent with the main findings from the included studies, and the overall message of this meta-analysis is that "from the patient's perspective, this idea works well".

It is first useful and noteworthy to reflect on our findings in the context of the baseline characteristics of included studies' population; they were homogenous patients with advanced HFrEF who were still symptomatic despite background optimal and contemporary HF therapies including cardiac resynchronization therapy (CRT) in some (Table 2). The fact that these devices, albeit acting on different points within the ANS, caused a significant additional improvement in functional status and QOL among such optimally managed patients makes sense and implies (with a reasonable degree of evidence and statistical power) that the overall concept is still alive and valid for further clinical research after refinement of stimulation parameters.

Importantly, two out of the three outcome components of the 1^{ry} endpoint showed moderate to high levels of heterogeneity. The moderate between-trials heterogeneity regarding the improvement of NYHA class outcome could be explained if we take into account that the DEFEAT-HF study [16] had the smallest sample size among all included studies. Moreover, it did not set functional status change as a primary endpoint, leading to a non-significant effect of the device therapy over NYHA class change among its participants, and even when included in the pooled estimate, it did not affect the overall statistical significance of this outcome. Not surprisingly, sensitivity analysis (after exclusion of DEFEAT-HF study) resolved heterogeneity entirely and resulted in a higher level of significantly improved NYHA class in the pooled estimate (Fig. 3d). Regarding MLHFQ QOL score outcome, the high and significant heterogeneity among studies is most probably due to the fact that Abraham et al.'s study [17] was adequately powered to set QOL metrics as a 1^{ry} endpoint. This contrasted

with the DEFEAT-HF study [16] and the NECTAR-HF trial [22], both of which included QOL metrics as a 2^{ry} endpoint. Subsequent sensitivity analysis of this outcome (after exclusion of Abraham et al.'s study) not only resolved heterogeneity but also made this outcome to fall somewhat short of statistical significance (Fig. 3e).

The finding that autonomic regulation device therapy did not significantly affect levels of NT-proBNP was not expected, given the significant improvement in functional status experienced by those patients, and the reason for this remains elusive. One explanation might lie in some non-reported baseline population characteristics that affected NT-proBNP levels, which may have resulted in unmeasured confounders leading finally to heterogeneous treatment effects. Interestingly, the results of previous studies examining BNP measurement as a surrogate for functional status and drug efficacy in patients with HFrEF are conflicting [25]. More recent data concluded that the value of NT-proBNP in predicting potential treatment responses remains unclear [26], making some commentators to strongly question its role as an endpoint in HF trials [27]. Our findings clearly add to the accumulating body of evidence supporting skepticism about using NT-proBNP levels as a surrogate endpoint in future HF trials (with the caveat that this debate is much more complex than it seems).

This meta-analysis showed that autonomic regulation device therapy did not significantly decrease LVESVi at 6-month follow-up, and this merits discussion. Going back to, and based on, the pivotal trials of cardiac resynchronization therapy (CRT) which showed an early and robust beneficial cardiac remodeling effect in the first 6 months and beyond [28], some of the included studies used change in LVESVi at 6 months as their 1^{ry} endpoint such as the DEFEAT-HF study [16] and the NECTAR-HF trial [22]. They hypothesized that, like CRT, 6 months might be sufficient to show an effect on LV remodeling, but they failed to prove their hypothesis. Taking into consideration that CRT and autonomic regulation device therapies are mechanistically different, one should realize that it may not be appropriate to compare both, and thus, the 6-month randomized period of these trials may have been too short to detect changes in cardiac remodeling. Therefore, our meta-analysis suggests that a longer follow-up period (12 to 18 months) should be planned for any effect on LV remodeling to be seen using autonomic regulation device therapies.

From the safety standpoint, the finally included five studies in this meta-analysis reported safety outcome in a non-uniform manner that did not allow for data extraction. For instance, both Chen et al.'s study [24] and the DEFEAT-HF study [16] just reported (in their text) that safety monitoring committees did not find any serious adverse events related to the procedure or the system. The other three studies [17, 22, 23] used "rate of freedom from procedure- or system-related complications" as the primary safety objective (and these data were, understandably, reported only in one arm of each study, i.e., the device arm; therefore, no comparator arm has been made available). The adverse event-free rates at 6 months were 90.6%, 85.9%, and 85% for the INOVATE-HF trial [23], Abraham et al. [17], and the NECTAR-HF trial [22] respectively (meeting predefined criteria of statistical significance for all).

Few limitations to this study deserve mention and some discussion. First, our analysis was based on aggregate data extracted from original publications, but not on patient-level data. This prevented us from conducting in-depth subgroup analyses. Second, included RCTs were different in designs; one of them (NECTAR-HF trial) was double-blinded, another one (DEFEAT-HF study) was single-blinded, while the others were non-blinded. Third, although we understand that including studies of devices with different physiologic effects may be suggested as a limitation, Ioannidis et al. [29] stated that merging different interventions into the same class is an acceptable methodological solution in such a situation. We do feel that any specific differences between the included devices do not contradict with the facts that they have a main common mechanism of action (*that is to restore the sympathovagal balance in those patients percutaneously*) and that they are used in a very homogeneous patient population; thus, it makes sense to merge them into one class. Moreover, we aimed primarily to evaluate the merits of the overall idea like what has been done in meta-analyses on the new oral anticoagulants (NOACs) [30, 31] that merged them into one class even though they are chemically different drugs with one of them (dabigatran) having a different mechanism of action from the others. Fourth, all included studies in the current meta-analysis were carried out before the era of angiotensin-receptor-neprilysin inhibitor (ARNI) [32] widespread use in HFrEF. It may be interesting to see if the beneficial effect of such devices will hold against a background HF therapy that includes ARNI, a promising next-step area for clinical investigation.

Conclusion

In patients with HFrEF, modulation of ANS using percutaneous devices significantly improves functional status and, potentially, quality of life but has a neutral effect over NT-proBNP and LVESVi. Our findings may ease the use of such devices on a compassionate case-by-case basis until adequately powered pivotal RCTs explore the impact of these devices on hard clinical outcomes. This may provide solutions for this subset of patients who have limited options.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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