



## Increased frequency of occurrence of bendopnea is associated with poor outcomes in heart failure outpatients

Hakkı Kaya , Anıl Şahin , Hakan Güneş , Lütfü Bekar , Ahmet Çelik , Yüksel Çavuşoğlu , Vedat Çaldır , Hasan Güngör & Mehmet Birhan Yılmaz on behalf of TREAT-HF Investigators

To cite this article: Hakkı Kaya , Anıl Şahin , Hakan Güneş , Lütfü Bekar , Ahmet Çelik , Yüksel Çavuşoğlu , Vedat Çaldır , Hasan Güngör & Mehmet Birhan Yılmaz on behalf of TREAT-HF Investigators (2020): Increased frequency of occurrence of bendopnea is associated with poor outcomes in heart failure outpatients, Acta Cardiologica, DOI: [10.1080/00015385.2020.1797303](https://doi.org/10.1080/00015385.2020.1797303)

To link to this article: <https://doi.org/10.1080/00015385.2020.1797303>



Published online: 19 Aug 2020.



Submit your article to this journal [↗](#)



Article views: 1



View related articles [↗](#)



View Crossmark data [↗](#)

## Increased frequency of occurrence of bendopnea is associated with poor outcomes in heart failure outpatients

Hakkı Kaya<sup>a</sup>, Anıl Şahin<sup>b</sup>, Hakan Güneş<sup>c</sup>, Lütfü Bekar<sup>d</sup>, Ahmet Çelik<sup>e</sup>, Yüksel Çavuşoğlu<sup>f</sup>, Vedat Çaldır<sup>g</sup>, Hasan Güngör<sup>h</sup> and Mehmet Birhan Yılmaz<sup>i</sup>; on behalf of TREAT-HF Investigators

<sup>a</sup>Department of Cardiology, Faculty of Medicine, Canakkale Onsekiz Mart University, Canakkale, Turkey; <sup>b</sup>Antalya Training and Research Hospital, Cardiology Clinics, Antalya, Turkey; <sup>c</sup>Department of Cardiology, Faculty of Medicine, Sıtcu Imam University, Kahramanmaraş, Turkey; <sup>d</sup>Department of Cardiology, Faculty of Medicine, Hitit University, Çorum, Turkey; <sup>e</sup>Department of Cardiology, Faculty of Medicine, Mersin University, Mersin, Turkey; <sup>f</sup>Department of Cardiology, Faculty of Medicine, Osmangazi University, Eskişehir, Turkey; <sup>g</sup>Cardiology Clinic, Baskent University Konya Hospital, Konya, Turkey; <sup>h</sup>Department of Cardiology, Faculty of Medicine, Adnan Menderes University, Aydın, Turkey; <sup>i</sup>Department of Cardiology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

### ABSTRACT

**Background:** Relationship between the frequency of occurrence of bendopnea during the daily life of heart failure (HF) outpatients and clinical outcomes has never been evaluated before.

**Methods:** Turkish Research Team-Heart Failure (TREAT-HF) is a network between HF centres, which undertakes multicentric observational studies in HF. Herein, the data including stable 573 HF patients with reduced ejection fraction out of seven HF centres were presented. A questionnaire was filled by the patients, with the question 'Do you experience shortness of breath while tying your shoelace?', assessing the presence and frequency of bendopnea.

**Results:** To the question related to bendopnea, 48% of the patients answered 'yes, every time', 31% answered 'yes, sometimes', and 21% answered 'No'. Patients were followed for an average of  $24 \pm 14$  months, and the patients who answered 'yes, every time' and 'yes, sometimes' to the bendopnea question were found having increased risk for both HF-related hospitalisations (HR:3.2,  $p < .001$ - HR:2.8,  $p = .005$ ) and composite outcome consisting of 'HF-related hospitalisations and all-cause death in the multi-variate analysis (HR:3.1,  $p < .001$ - HR:3.0,  $p < .001$ ). Kaplan Meier analysis for HF-related hospitalisation, all-cause death, and the composite of these were provided for these three groups, yielding significant and graded divergence curves with the best prognosis in 'no' group, with the moderate prognosis in 'sometimes' group, and with the worst prognosis in the 'every time' group.

**Conclusion:** For the first time in the literature, our study shows that the increased frequency of bendopnea occurrence in daily life is associated with poor outcomes in HF outpatients.

### ARTICLE HISTORY

Received 16 June 2020; Accepted 12 July 2020

### KEYWORDS

Bendopnea; coronary artery disease; heart failure; hospitalisation; mortality; education level

## Introduction

Heart failure (HF) is a complex clinical syndrome, which can develop as a common result of many heart diseases affecting approximately 26 million people worldwide [1]. This syndrome, which is quite complicated both in diagnoses and treatment, can manifest itself with recurrent hospitalisations and high mortality rates [2]. Despite technological advances in diagnostic tests, clinical evaluation is the cornerstone of clinical evaluation in the management of HF patients.

Shortness of breath is the most basic symptom in HF patients, and subtypes such as exercise dyspnoea, orthopnea, paroxysmal nocturnal dyspnoea have long been considered as HF symptoms [3]. A new

symptom, called bendopnea, was introduced by Thibodeau et al., which was described as shortness of breath within the first 30 sec. after leaning forward [4]. Thibodeau et al. also associated bendopnea with increased filling pressures, and then their subsequent research associated bendopnea with poor outcomes in HF outpatients [5]. HF course is a dynamic process for pathophysiological reasons. Symptoms such as orthopnea, paroxysmal nocturnal dyspnoea, and bendopnea, which are particularly related to increased filling pressures, may appear and disappear from time to time in HF patients due to the variable course of filling pressures [6–8]. In this study, we aimed to evaluate the relationship between the frequency of occurrence of

bendopnea and long-term prognosis in HF outpatients, for the first time in the literature.

## Materials and methods

Turkish Research Team-Heart Failure (TREAT-HF) is a network that has been undertaking multicentric, observational cohort studies in HFrEF (Heart failure with reduced ejection fraction) outpatients, established with the collaboration of seven qualified HF centres in Turkey. TREAT-HF cohorts II-III-IV enrolled consecutive stable HFrEF outpatients in preset days (preset day of a week) per-protocol (predefined by the primary investigator) of Decembers of years 2015-2016-2017 respectively along with a questionnaire which evaluates several data including the presence of bendopnea. For the question 'do you experience shortness of breath while tying your shoelace?' in the questionnaire asked to evaluate bendopnea, three answers were available to patients. These are 1- 'Yes, every time', 2- 'Yes, sometimes', 3- 'No'. Thanks to this question, patients were able to do the self-assessment of bendopnea.

In the cohorts, exclusion criteria were determined such as patients who did not answer the question associated with bendopnea; pregnant women; patients with acute myocardial ischaemia within the last 30 days or acute myocarditis; patients with less than one month history of acute heart failure requiring hospitalisation; patients who were on uptitration phase of life-saving medications; patients with cancer and/or life expectancy <1 year, severe aortic, mitral, pulmonary valve disease; and patients who were unable or unwilling to lean forward to assess for bendopnea.

Patient's data including age, gender, level of education, comorbidities such as diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), NYHA class, laboratory data, 12-lead resting electrocardiogram, echocardiographic data, and presence of bendopnea were recorded on the case report forms.

Out of 761 consecutive HF outpatients who answered the questionnaire, 684 patients accepted to respond to the bendopnea question (see flow chart – Figure 1). Outcomes concerning all-cause death and HF-related hospitalisation during a mean follow up of  $24 \pm 14$  months after the index visit were assessed by an independent study coordinator who gathered and reviewed hospital's medical records and made necessary phone calls for outcome data. Defined events were made anonymous with the deletion of any identifying criteria for the patient and sent to the main

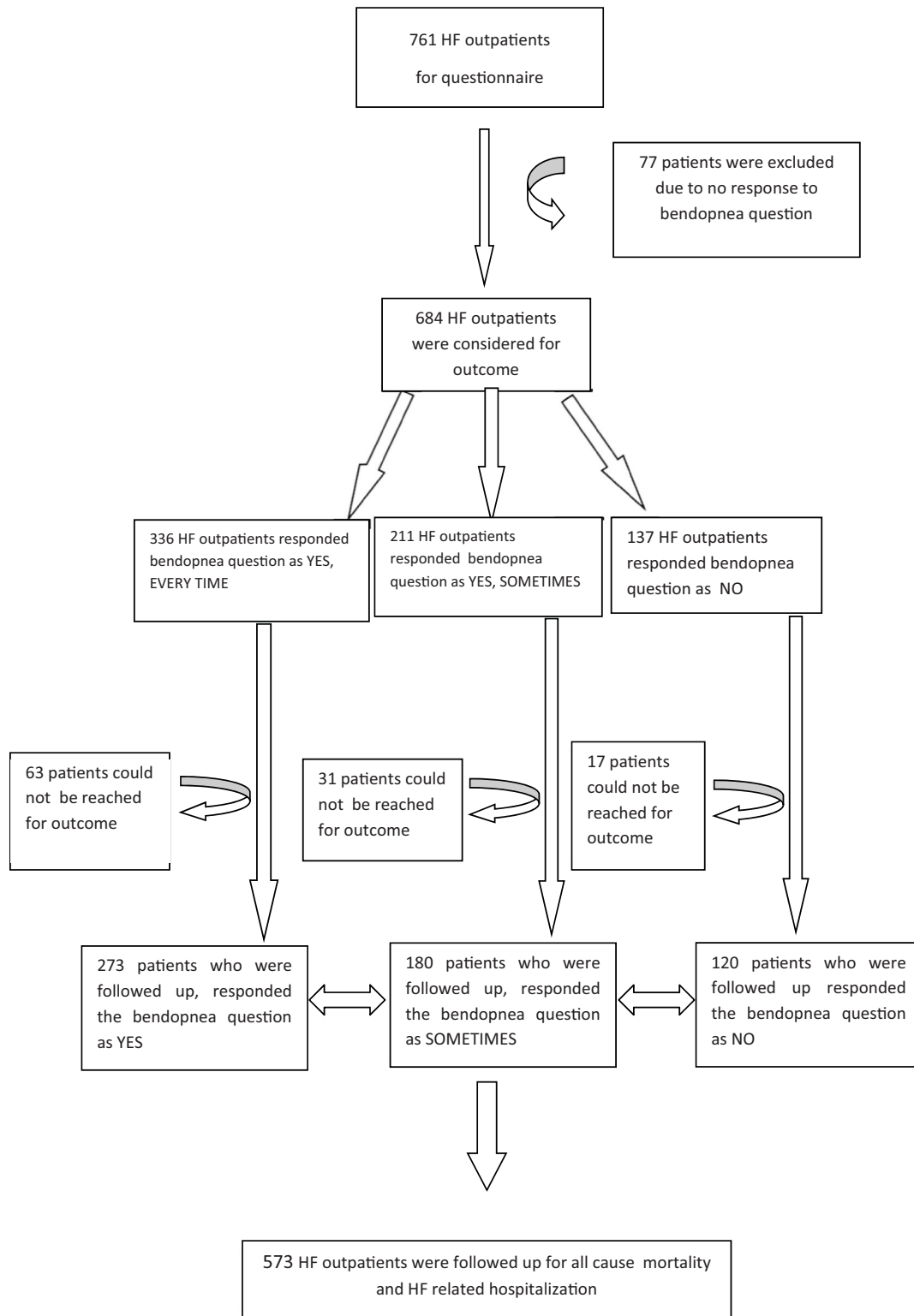
centre. All the events were adjudicated by an experienced author who was blinded to patients, centres and the current analysis.

Outcomes were defined as all-cause death, HF-related hospitalisation and the composite outcome of all-cause death or HF-related hospitalisation. HF-related hospitalisation was defined as the presence of clinical signs or symptoms of HF that are severe enough to require the use of intravenous furosemide of at least 40 mg within 2 h of admission along with hospitalisation in either a ward or CCU/ICU lasting more than three days. HT was defined as blood pressure  $>140/90$  mm Hg on more than two occasions during office measurements or being on antihypertensive treatment. DM was defined as fasting blood sugar  $\geq 126$  mg/dl or being on antidiabetic treatment. All venous blood samples were obtained upon patients' presentations before the questionnaire.

Echocardiographic examinations were performed by experienced echocardiographers as a part of routine clinical practice. Left ventricle ejection fraction (LVEF) was calculated using the modified Simpson method. Chamber sizes were defined according to the appropriate guidelines [9]. Right ventricular (RV) dimensions were evaluated according to the actual guidelines [9], and hence, midcavity and/or basal RV diameter above and below the reference range in the apical four-chamber view at end-diastole were taken into account. The left atrium (LA) size was measured at the end ventricular systole by M-mode linear dimension, obtained from the parasternal long-axis view. Systolic pulmonary artery pressure (sPAP) was calculated as shown previously [10]. Written informed consent was obtained from all patients, and the study was approved by the local ethics committee.

## Statistical analysis

The Kolmogorov–Smirnov test was used to verify the normality of the distribution of continuous variables which were expressed as mean  $\pm$  SD or median (min-max) in the presence of abnormal distribution, and categorical variables expressed as percentages. Comparisons between groups of patients were made by use of chi-square or Fisher's exact test for categorical variables, one-way ANOVA was used for normally distributed continuous variables. Levene's test was used to assess the homogeneity of the variances. Also,  $p < .05$  was considered statistically significant. When an overall significance was observed, pairwise posthoc tests were performed using Tukey's test if the variances were homogeneous or Tamhane T2 test was



**Figure 1.** Patient flow chart.

performed if they were not homogeneous. Kruskal-Wallis test was used when the distribution was skewed. We used univariate analyzes to quantify the association of variables with HF-related hospitalisation, all-cause death, and composite outcome, separately.

Variables found to be statistically significant in the univariate analyzes and other potential confounders were used in a multivariate cox proportional-hazards model with the forward stepwise method to determine the independent prognostic factors for HF-related

hospitalisation, all-cause death and the composite outcome of these. Kaplan-Meier curves were used to display death, HF-related hospitalisation and composite outcome in three patient groups that are defined as 'yes-every time', 'yes-sometimes', and 'no' groups, according to the patients' responses to the question associated with bendopnea. All statistical procedures were performed using SPSS software version 14.0 (SPSS Inc., Chicago, IL).

## Results

Patients were classified into three groups according to their responses for the bendopnea question; 273

(48%) patients' responses were 'yes, every time' (Group I), 180 (31%) patients' responses were 'yes, sometimes' (Group II), and 120 (21%) patients' responses were 'No' (Group III). Baseline characteristics, which included the demographic and clinic data of patients were presented in Table 1. The mean age was  $66 \pm 12$ . The average age of patients in Group I is higher than those in Group II, and those in Group II have a higher average age than those in Group III. The rates of the female patient, diabetes patient, as well as, patients whose functional capacity is NYHA class III or ambulatory IV, are higher in group I than group II and higher in group II than group III. CAD rates similar within Group I and Group II are

**Table 1.** Baseline characteristics, laboratory and echocardiographic parameters, medications and outcomes.

Characteristics	Patients' responses to the question associated with bendopnea				p
	All patients n = 573	Yes, every time (Group I) (n = 273)	Yes, sometimes (Group II) (n = 180)	No (Group III) (n = 120)	
Age (years)	66 ± 12	68 ± 11 <sup>*‡</sup>	64 ± 12 <sup>&amp;</sup>	60 ± 14	<.001
Height (cm)	167 ± 8	166 ± 7	167 ± 11	168 ± 7	.252
Weight (kg)	76 ± 14	77 ± 15	76 ± 14	75 ± 14	.666
Female (%)	180 (31%)	105 (39%)	48 (27%)	27 (23%)	.002
Graduation from university (%)	47 (8%)	19 (7%)	19 (10%)	9 (7%)	.381
Hypertension (%) (n = 564)	208 (37%)	110 (41%)	63 (36%)	35 (29%)	.077
DM (%) (n = 564)	161 (29%)	98 (36%)	41 (23%)	22 (18%)	<.001
CAD (%) (n = 564)	281 (50%)	141 (52%)	94 (54%)	46 (38 %)	.017
AF (%) (n = 559)	132 (24%)	75 (28%)	32 (19%)	25 (21%)	.064
COPD (%) (n = 564)	135 (24%)	68 (25%)	43 (25%)	24 (20%)	.515
NYHA III-ambulatory IV (%) (n = 522)	219 (42%)	147 (56%)	49 (33%)	23 (21%)	<.001
QRS duration (ms) (n = 559)	119 ± 31	119 ± 30	120 ± 31	114 ± 31	.247
Heart rate (min) (n = 559)	81 ± 18	82 ± 18	79 ± 18	82 ± 18	.312
<b>Laboratory parameters</b>					
Glucose (mg/dl)	111 (60-598)	112 (61-598)	111 (60-538)	109 (65-406)	.184
Urea (mg/dl)	36 (8-272)	39 (10-272)	31 (8-200)	33 (10-229)	.125
Creatinine (mg/dl)	1.1 (0.4-6.6)	1.2 (0.5-4.9)	1.1 (0.4-6.6)	1.1 (0.6-4.8)	.726
Sodium (mmol/L)	137 ± 10	137 ± 9	137 ± 14	138 ± 4	.765
NT pro BNP (pg/mL)	1080 (0-3500)	1481 (40-3395)	699 (0-3500)	1034 (90-3500)	.053
Potassium (mmol/L)	4.6 ± 0.6	4.6 ± 0.6	4.6 ± 0.6	4.6 ± 0.6	.426
Haemoglobin(g/dl)	13 ± 2	13 ± 2	13 ± 2	13 ± 2	.221
<b>Echocardiographic parameters</b>		(n = 557)			
LA diameter (mm)	45 ± 6	45 ± 6	44 ± 6	44 ± 6	.126
LV diastolic diameter (mm)	58 ± 8	58 ± 8	57 ± 8	58 ± 9	.878
LV systolic diameter (mm)	46 ± 10	46 ± 10	46 ± 10	47 ± 11	.895
EF (%)	32 ± 8	31 ± 8 <sup>*</sup>	33 ± 8	32 ± 8	.006
RV dilatation (%)	191 (34%)	86 (33%)	60 (34%)	45 (39%)	.486
sPAP (mmHg)	43 ± 14	45 ± 14 <sup>‡</sup>	40 ± 14	40 ± 13	.002
<b>Medications</b>	(n = 547)				
Beta blocker(%)	454 (83%)	211 (82%)	144 (84%)	99 (83%)	.848
ACEI/ARB	376 (69%)	174 (68%)	118 (69%)	84 (71%)	.851
MRA (%)	258 (47%)	126 (49%)	77 (45%)	55 (46%)	.675
Ivabradine (%)	79 (15%)	33 (14%)	21 (13%)	25 (21%)	.136
Diuretics (%)	384 (70%)	203 (79%)	104 (61%)	77 (65%)	<.001
Digoxine (%)	132 (24%)	67 (26%)	37 (22%)	28 (24%)	.568
Statin (%)	216 (40%)	95 (37%)	70 (41%)	51 (43%)	.484
<b>Outcomes</b>					
Death (%)	222 (39%)	146 (53%)	53 (29%)	23 (19%)	<.001
HF related hospitalisations (%)	385 (67%)	232 (85%)	121 (67%)	32 (27%)	<.001
<b>Composite Outcome</b>					
Death or HF related hospitalisations (%)	448 (78%)	260 (95%)	145 (81%)	48 (36%)	<.001

The bold values represents as Statistically significant  $p < .05$  values.

DM: Diabetes mellitus; CAD: Coronary artery disease; AF: Atrial fibrillation; COPD: Chronic obstructive pulmonary disease NYHA: New york heart association; BNP: Brain natriuretic peptid; LA: Left atrium; LV: Left ventricle; EF: Ejection fraction; RV: Right ventricle; SPAP: Systolic pulmonary artery pressure; ACEI: Angiotensinogen converting enzyme inhibitor; ARB: Angiotensin receptor blocker; MRA: Mineralocorticoid receptor antagonist; HF: Heart failure.

\* $p < .05$  for post-hoc analysis between group I and group II.

‡ $p < .05$  for post-hoc analysis between group I and group III.

& $p < .05$  for post-hoc analysis between group II and group III.

**Table 2.** Univariate and multivariate cox regression analyses for predicting HF-related hospitalisations.

Variables	Univariate			Multivariate		
	p	HR	(95% CI)	p	HR	(95% CI)
Bendopnea (every time)	<.001	3.881	2.679–5.622	<.001	3.199	1.678–6.100
Bendopnea (sometimes)	<.001	2.828	1.913–4.181	.005	2.762	1.357–5.623
Coronary Artery Disease	<.001	1.566	1.277–1.920	.018	1.573	1.080–2.289
NT Pro-BNP levels	<.001	1.002	1.001–1.003	.002	1.003	1.001–1.006
Graduation from University	.040	0.687	0.481–0.982	<.001	0.302	0.159–0.575
NYHA class III- ambulatory IV	.001	1.445	1.171–1.783			
Age	.028	1.009	1.001–1.018			
Hypertension	.027	1.270	1.028–1.568			
Diabetes Mellitus	.002	1.412	1.133–1.761			
Atrial Fibrillation	.090	1.226	0.969–1.550			
QRS Duration	<.001	1.006	1.003–1.009			
Ejection Fraction	.025	0.987	0.975–0.998			
RV Dilatation	<.001	1.458	1.176–1.808			
Haemoglobin levels	.040	0.950	0.904–0.998			
Usage of MRA	.187	0.870	0.707–1.070			

All the variables from Table 1 were examined and only those significant at  $p < .250$  level are shown in univariate analysis. Multivariate Cox proportional-hazards model including all the variables in univariate analysis and also variables found to be significantly different between groups I,II and III with forward stepwise method. CI: Confidence interval; HR: Hazard ratio, Abbreviations in Table 1.

significantly higher than group III. The sPAP average is similar in group II and III, while is higher in group I. There is no difference between all three groups in terms of the use of drugs other than diuretics, while the rate of diuretic use is higher in patients in group I than patients in group II and group III.

During follow-up of  $24 \pm 14$  months (up to 48 months), 222 (39%) patients died, 385 (67%) patients experienced at least one HF-related hospitalisation, and 448 (78%) patients died or experienced HF-related hospitalisation. The rates of death, HF-related hospitalisation and composite outcome of death or HF-related hospitalisation were found to be higher in group I than group II, while higher in group II than group III (Table 1).

A univariate analysis comparing those with and without HF-related hospitalisations during follow up was displayed in Table 2. Older age, presence of HT, DM, CAD, poor NYHA III- ambulatory IV functional class, AF, RV dilatation, higher NT pro-BNP levels, higher QRS duration, lower haemoglobin levels, and lower EF in patients with HF-related hospitalisation were noted. Patients, who graduated from university and those who used mineralocorticoid receptor antagonists (MRA) were less likely to have HF-related hospitalisations, while the patients who responded to the question of bendopnea as 'yes, every time' and 'yes, sometimes' showed more tendency, in the univariate analysis. However, in the multivariate Cox proportional-hazards model with a forward stepwise method, for the variables found to be statistically significant in the univariate analysis and variables found to be significantly different between the group I, II and III (Table 2), the occurrence of bendopnea every time and sometimes, also, being a university graduate, CAD, NT

pro BNP level remained independently associated with the risk of HF-related hospitalisation following adjustment. The univariate and multivariate cox regression analyses for HF-related hospitalisation in Table 2 were applied separately and in the same way for all-cause death and composite outcome consisting of all-cause death and HF-related hospitalisation, and the results were presented in Table 3 and Table 4, respectively.

Kaplan Meier analyzes were done for HF-related hospitalisation, all-cause death, and the composite of these, and all of the three Kaplan Meier analyzes yielded significant results and graded divergence curves with the best prognosis in 'no' group, the moderate in 'sometimes' group, and the worst in the 'every time' group (Figure 2(A–C),  $p < .001$ ).

## Discussion

Our study, for the first time in the literature, showed that bendopnea, which recently entered literature, had a higher risk of HF-related hospitalisations and all-cause deaths in the groups answering 'yes, every time' than in the groups answering 'yes, sometimes' and 'no', while there was the higher risk in the group answering 'yes, sometimes' than the group answering 'no'.

After Thibodeau et al. introduced bendopnea into HF literature and showed the relationship of bendopnea with left ventricular filling pressures, they showed that bendopnea was independently associated with HF-related hospitalisation and death in the 3rd month through a study of 179 heart failure outpatients [4,5]. Unlike these studies, the presence of bendopnea was not observed by the physician in our study, instead of that, the patients were asked a question of tying

**Table 3.** Univariate and multivariate cox regression analyses for predicting all cause death.

Variables	Univariate			Multivariate		
	p	HR	(95% CI)	p	HR	(95% CI)
<b>Coronary Artery Disease</b>	.001	1.578	1.206–2.063	.021	1.637	1.076–2.489
<b>NYHA class III-ambulatory IV</b>	<.001	1.914	1.434–2.553	.015	1.676	1.106–2.541
Bendopne (every time)	<.001	3.881	2.679–5.622			
Bendopne (sometimes)	.024	1.756	1.076–2.866			
Age	<.001	1.025	1.013–1.037			
Hypertension	<.001	1.825	1.395–2.386			
Diabetes Mellitus	<.001	1.730	1.312–2.282			
Atrial Fibrillation	.036	1.377	1.020–1.857			
QRS Duration	.142	1.003	0.999–1.008			
Heart Rate	.123	1.006	0.999–1.013			
COPD	.171	1.260	0.905–1.755			
Ejection Fraction	.213	0.990	0.975–1.006			
RV Dilatation	.001	1.639	1.229–2.186			
sPAP	.196	1.007	0.997–1.017			
NT Pro-BNP levels	.186	1.002	1.001–1.003			
Haemoglobin levels	.149	0.954	0.895–1.017			
Usage of MRA	.153	1.224	0.927–1.617			

All the variables from Table 1 were examined and only those significant at  $p < 0.250$  level are shown in univariate analysis. Multivariate Cox proportional-hazards model including all the variables in univariate analysis and also variables found to be significantly different between groups I, II and III with forward stepwise method. CI: Confidence interval; HR: Hazard ratio, Abbreviations in Table 1.

**Table 4.** Univariate and multivariate cox regression analyses for predicting composite outcome.

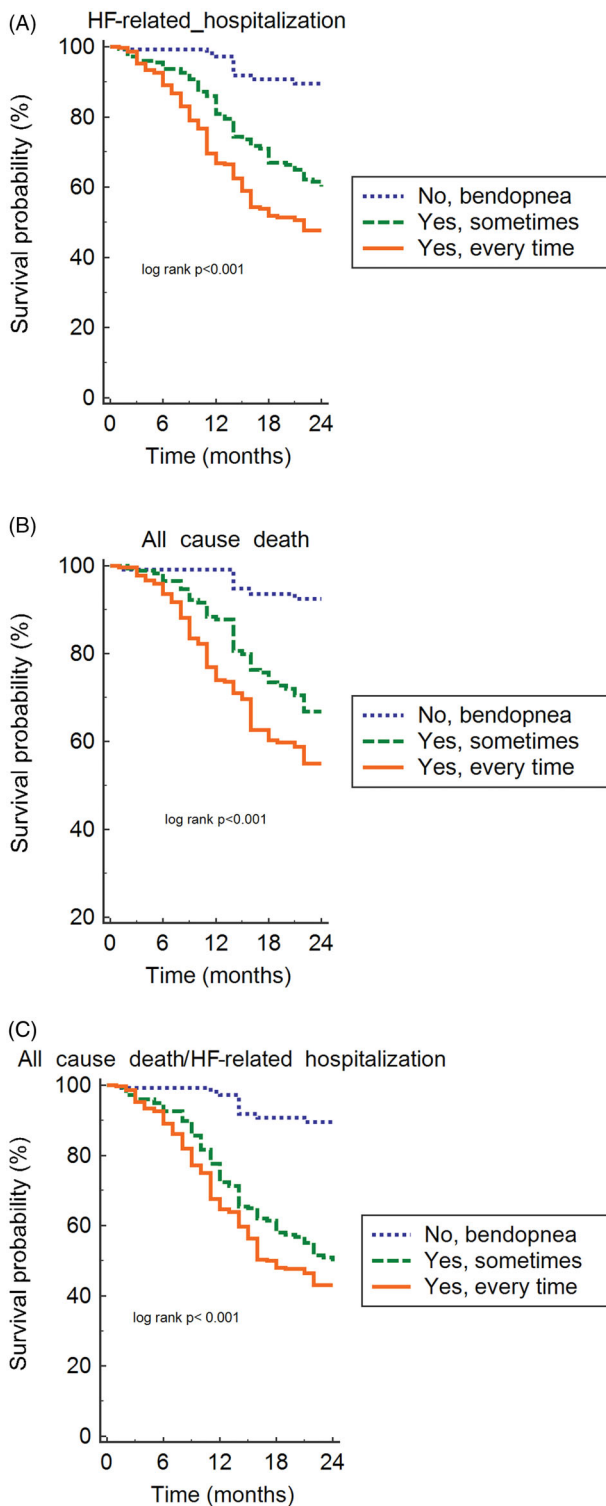
Variables	Univariate			Multivariate		
	p	HR	(95% CI)	p	HR	(95% CI)
<b>Bendopnea (every time)</b>	<.001	3.256	2.356–4.500	<.001	3.095	1.768–5.774
<b>Bendopnea (sometimes)</b>	<.001	2.537	1.803–3.569	<.001	3.024	1.588–5.760
<b>Coronary Artery Disease</b>	<.001	1.653	1.368–1.997	<.001	1.912	1.364–2.680
<b>NT Pro-BNP levels</b>	.001	1.002	1.001–1.003	.024	1.002	1.001–1.003
<b>Graduation from University</b>	.116	0.758	0.537–1.071	<.001	0.317	0.168–0.598
NYHA class III- ambulatory IV	<.001	1.403	1.152–1.710			
Age	.010	1.010	1.002–1.018			
Hypertension	<.001	1.382	1.139–1.676			
Diabetes Mellitus	<.001	1.445	1.180–1.771			
Atrial Fibrillation	.064	1.227	0.988–1.525			
QRS Duration	.001	1.005	1.002–1.008			
Ejection Fraction	.070	0.990	0.979–1.001			
RV Dilatation	<.001	1.521	1.237–1.845			
Haemoglobin levels	.039	0.952	0.909–0.996			

All the variables from Table 1 were examined and only those significant at  $p < .250$  level are shown in univariate analysis. Multivariate Cox proportional-hazards model including all the variables in univariate analysis and also variables found to be significantly different between groups I,II and III with forward stepwise method. CI: Confidence interval; HR: Hazard ratio, Abbreviations in Table 1.

shoes to evaluate bendopnea. The fact that bendopnea is dependent only on patient evaluation without physician control is one of the limitations of our study, yet it enabled us to make a separation between the groups of patients with bendopnea being seen more frequently and more rarely. According to Thibodau et al, bendopnea is associated with pulmonary capillary wedge pressure (PCWP) and right atrium pressure (RAP), and as we know, cardiac filling pressures such as PCWP and RAP are non-stable, dynamic pressures [4,6–8,11]. Furthermore, there have been studies in the literature which evaluate the treatment regulation of HF outpatients based on the PCWP follow-up [12,13]. We hypothesise that patients whose ventricular filling pressures are constantly high or at borderline feel short of breath every time they lean forward, while

the patients whose ventricular filling pressures are normal and rising from time to time feel sometimes short of breath when they lean forward during the periods of high pressure. Furthermore, in the study of Thibadeu et al. 28% of the 102 patients who were initially referred for cardiac catheterisation were diagnosed with bendopnea, while 35% of the 46 patients who were evaluated and decided to undergo catheterisation were diagnosed with bendopnea [4]. This is an indication that bendopnea is lost and appeared in the same patient from period to period. Therefore, it is important to evaluate the frequency of emergence of bendopnea in the same patient.

In all three Kaplan Meier statistical analyzes for HF-related hospitalisations, all-cause deaths, and their composite outcome, according to patients' self-



**Figure 2.** (A) Kaplan Meier Curve for heart failure-related hospitalisation. (B) Kaplan Meier Curve for all-cause death. (C) Kaplan Meier Curve for all-cause death and heart failure-related hospitalisation (composite outcome).

evaluation of bendopnea, the increased frequency of bendopnea occurrence was shown to be associated with poor prognosis for all three outcomes (Figure 2(A–C)). According to the Cox Regression analysis

conducted in our study, the appearance of shortness of breath while leaning forward in the groups of ‘every time’ and ‘sometimes’ was found to be significant in both univariate and multivariate analysis for HF-related hospitalisations, also they were found significant in univariate analysis for all-cause deaths but lost their significance in multivariate analysis. However, for the composite outcome of all-cause deaths and HF related hospitalisation, the occurrence of bendopnea every time and sometimes was shown to increase the risk through both univariate analysis and multivariate analysis, and this risk was shown to be higher in patients who responded the bendopnea question as ‘Yes, every time’ than those who responded as ‘Yes, sometimes’.

The results of our study were similar to that of Thibodeu et al. which was the only study with HF outpatients, but the differences from this study were that our study involved approximately 3 times the number of patients, it was multicentered study, the duration of follow-up was longer, and most importantly, the relationship of bendopnea with outcomes was evaluated according to the frequency of occurrence in the patients [5].

It is possible that higher mean age, CAD and DM rates in the group of patients who felt bendopnea more often may be associated with poor diastolic function and higher filling pressures in older HF patients with more comorbidities [14–16]. In line with the study of Thibodeu et al. the proportion of women in the bendopnea patient group was found to be higher in our study and this may be speculated that women may be more likely to have lower symptom thresholds. In our study without invasive measurements, the higher rate of patients with RV dilatation and the sPAP average in the patients with bendopnea may be echocardiographic indicators of increased RA pressure, and this can be explanatory for higher diuretic usage rates in the bendopnea group.

An interesting result of our study, which may be the topic of new research, is that higher education levels reduce the risk of HF-related hospitalisation, which is shown in a multi-variate analysis. This result may be due to the higher level of education leading to higher disease awareness and correspondingly higher medical and non-medical treatment compliance. In this study, CAD and Nt probnp levels were found to be independent predictors for HF-related hospitalisation and composite outcome, while CAD and NYHA class were found to be independent predictors for all-cause deaths. The relationship between



these parameters and HF prognosis has been known for a long time and the results of our study are consistent with the literature [17–22].

Our study has some limitations. First of all, the bendopnea assessment in our study is less specific than that of Thibadeu et al. because the bendopnea assessment in our study was not performed by a physician, the bendopnea question in the questionnaire was answered by the patients, and the patients' self-assessment for bendopnea was realised. However, the reliability of this method was not tested. Although the patients who were unable to lean forward due to myoskeletal system problems were excluded from the study, the patients who were experiencing shortness of breath by leaning forward due to noncardiac reasons may have mistakenly evaluated as bendopnea. Also, unfortunately, waist and hip circumference measurements, which may affect the occurrence of bendopnea in the patients, were not included in the study, but the height and weight of the patients were presented in the study, and no difference was found between the groups. Also, in this self-assessment we applied in our study, the duration of the emergence of bendopnea was unfortunately not determined. However, in other bendopnea studies, the average duration of bendopnea to occur is 10 sec [23], and in the classical definition of bendopnea, the duration of shortness of breath is stated as 30 sec [4]. The question for the time required for the person to tie his shoelace, which we used to evaluate bendopnea in our study, is around average 20–30 sec, and this method seems acceptable given the average bendopnea emergence times in other studies. Another limitation of our study is related to echocardiographic parameters. Although the relationship of bendopnea with LV filling pressures is known, the measurements of inferior vena cava, which is an echocardiographic indicator of RA pressure, and the parameters of LV diastolic function evaluation, which is an echocardiographic indicator of PCWP, were unfortunately not included in our study.

In conclusion, bendopnea was associated with increased HF-related hospitalisations and high mortality rates in HF outpatients. Also, our study that has the highest number of patients and the longest follow-up period on this issue in the literature showed for the first time that the increased frequency of occurrence of bendopnea in daily life was also associated with poor outcomes in HF outpatients. If our study is supported by new studies, it will also contribute to the development of a fairly simple but

valuable method of evaluating the prognosis of HF patients.

### Disclosure statement

No potential conflict of interest was reported by the author(s).

### References

- [1] Ponikowski P, Anker SD, AlHabib KF, et al. Heart failure: preventing disease and death worldwide. *ESC Heart Fail.* 2014;1(1):4–25.
- [2] Jessup M, Brozena S. Heart failure. *N Engl J Med.* 2003;348(20):2007–2018.
- [3] McKee PA, Castelli WP, McNamara PM, et al. The natural history of congestive heart failure: the Framingham study. *N Engl J Med.* 1971;285(26):1441–1446.
- [4] Thibodeau JT, Turer AT, Gualano SK, et al. Characterization of a novel symptom of advanced heart failure: bendopnea. *JACC Heart Fail.* 2014;2(1):24–31.
- [5] Thibodeau JT, Jenny BE, Maduka JO, et al. Bendopnea and risk of adverse clinical outcomes in ambulatory patients with systolic heart failure. *Am Heart J.* 2017;183:102–107.
- [6] Rome MP, Majetich N, Binkley PF, et al. Left ventricular performance during the course of a day and meals in dilated cardiomyopathy and heart failure. *Am J Med Sci.* 1989;298(5):289–294.
- [7] Agostoni P, Guazzi M, Doria E, et al. Pulmonary hemodynamic and tidal volume changes during exercise in heart failure. *Ital Heart J.* 2002;3(2):104–108.
- [8] Desai AS, Bhimaraj A, Bharmi R, et al. Ambulatory hemodynamic monitoring reduces heart failure hospitalizations in "real-world" clinical practice. *J Am Coll Cardiol.* 2017;69(19):2357–2365.
- [9] Lang RM, Bierig M, Devereux RB, Chamber Quantification Writing Group; American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology, et al. Recommendations for chamber quantification. *Eur J Echocardiogr.* 2006;7(2):79–108.
- [10] Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation.* 1984;70(4):657–662.
- [11] Drazner MH, Velez-Martinez M, Ayers CR, et al. Relationship of right- to left-sided ventricular filling pressures in advanced heart failure: insights from the ESCAPE trial. *Circ Heart Fail.* 2013;6(2):264–270.
- [12] Kochav SM, Flores RJ, Truby LK, et al. Prognostic Impact of Pulmonary Artery Pulsatility Index (PAPI) in patients with advanced heart failure: insights from the ESCAPE trial. *J Card Fail.* 2018;24(7):453–459.

- [13] Adamson PB, Abraham WT, Bourge RC, et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Heart Fail.* 2014; 7(6):935–944.
- [14] Lehrke M, Marx N. Diabetes mellitus and heart failure. *Am J Cardiol.* 2017;120(15):37–47.
- [15] Slivnick J, Lampert BC. Hypertension and heart failure. *Heart Fail Clin.* 2019;15(4):531–541.
- [16] Baeza-Trinidad R, Isaula-Jimenez O, Peinado-Adiego C, et al. Prevalence of Bendopnea in general population without heart failure. *Eur J Intern Med.* 2018;50: e21–e22.
- [17] Schou M, Gustafsson F, Kistorp CN, et al. Prognostic usefulness of anemia and N-terminal pro-brain natriuretic peptide in outpatients with systolic heart failure. *Am J Cardiol.* 2007;100(10):1571–1576.
- [18] Windram JD, Loh PH, Rigby AS, et al. Relationship of high-sensitivity C-reactive protein to prognosis and other prognostic markers in outpatients with heart failure. *Am Heart J.* 2007;153(6):1048–1055.
- [19] Davarzani N, Sanders-van Wijk S, Karel J, et al. N-terminal Pro-B-type natriuretic peptide-guided therapy in chronic heart failure reduces repeated hospitalizations-results from TIME-CHF. *J Card Fail.* 2017; 23(5):382–389.
- [20] Lala A, Desai AS. The role of coronary artery disease in heart failure. *Heart Fail Clin.* 2014;10(2):353–365.
- [21] Di Tanna GL, Wirtz H, Burrows KL, et al. Evaluating risk prediction models for adults with heart failure: a systematic literature review. *PLoS One.* 2020;15(1): e0224135.
- [22] Chioncel O, Lainscak M, Seferovic PM, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2017;19(12):1574–1585.
- [23] Pranata R, Yonas E, Chintya V, et al. Clinical significance of bendopnea in heart failure-Systematic review and meta-analysis. *Indian Heart J.* 2019;71(3): 277–283.