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Heart Failure and Respiratory Hospitalizations Are Reduced in Patients With Heart Failure and Chronic Obstructive Pulmonary Disease With the Use of an Implantable Pulmonary Artery Pressure Monitoring Device

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Abstract

Background—Chronic obstructive pulmonary disease (COPD) is a frequent comorbidity in patients with heart failure (HF). Elevated pulmonary arterial (PA) pressure can be seen in both conditions and has been shown to predict morbidity and mortality.

Methods and Results—A total of 550 subjects with New York Heart Association functional class III HF were randomly assigned to the treatment (n = 270) and control (n = 280) groups in the CHAMPION Trial. Physicians had access to the PA pressure measurements in the treatment group only, in which HF therapy was used to lower the elevated pressures. HF and respiratory hospitalizations were compared in both groups. A total of 187 subjects met criteria for classification into the COPD subgroup. In the entire cohort, the treatment group had a 37% reduction in HF hospitalization rates ($P < .0001$) and a 49% reduction in respiratory hospitalization rates ($P = .0061$). In the COPD subgroup, the treatment group had a 41% reduction in HF hospitalization rates ($P = .0009$) and a 62% reduction in respiratory hospitalization rates (P

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= .0023). The rate of respiratory hospitalizations in subjects without COPD was not statistically different (P = .76).

Conclusions—HF management incorporating hemodynamic information from an implantable PA pressure monitor significantly reduces HF and respiratory hospitalizations in HF subjects with comorbid COPD compared with standard care.

Keywords

Heart failure; chronic obstructive pulmonary disease; implantable pulmonary artery pressure monitor; hospitalization

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are global epidemics and are leading causes of morbidity and mortality.[1–3] Both of these conditions are major public health problems and present a significant burden on the health care system.[4–10] COPD is a frequent comorbidity in patients with HF, but there are few reports that describe the clinical characteristics and outcomes in this population.[11–13] Elevated pulmonary arterial (PA) pressure can be seen in both conditions, particularly during exacerbation as the disease progresses, and has been shown to be a predictor of morbidity and mortality.[14–17] Despite current treatment regimens, hospital admission rates for both COPD and HF continue to increase. Improvements in outpatient management of patients with COPD and HF are needed to address the burden of increased exacerbations requiring hospitalizations. Earlier studies in subjects with HF have shown that increases in intracardiac and PA pressures occur before onset of clinical symptoms[18,19] and that early intervention in response to the elevated pressures decreases hospitalization rates.[20,21]

To our knowledge, no data exist that analyze the impact of an implantable hemodynamic monitoring device on COPD management and respiratory exacerbations requiring hospitalization. We studied a cohort of subjects enrolled in the Cardiomems Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Subjects (CHAMPION) trial who met criteria for classification into the COPD subgroup. The CHAMPION trial previously demonstrated that medical management incorporating hemodynamic information from an implantable PA pressure sensor was superior to standard care practices and significantly reduced HF hospitalization rates. In addition, this strategy led to significant decreases in PA pressures, fewer patients hospitalized for HF, more days alive outside of the hospital, improved quality of life, and a trend toward improved mortality in the treatment than in the control group.[22]

Studies have shown that pulmonary vascular disease is an important risk factor for respiratory exacerbations and mortality in patients with COPD.[23–25] In addition, studies have shown that elevated pulmonary hemodynamic variables are important predictors of hospitalization and mortality in HF patients with secondary pulmonary hypertension.[26–28] Although the benefit of PA pressure monitoring and its direct impact on the underlying pathophysiology and disease progression in acute decompensated HF requiring hospitalization is well understood, the potential role of PA pressure monitoring and its impact on the underlying pathophysiology and disease progression for respiratory exacerbations requiring hospitalization in patients with COPD has not been studied in detail

and is therefore less established. We acknowledge that the majority of acute exacerbations for COPD requiring hospitalization are directly caused by bacterial and viral infections as well as the other etiologies[29] and the ability for PA pressure monitoring and the optimization of outpatient HF medical management to alter these causes is less clear. We also acknowledge that titrations for diuretic therapy are not the mainstay for direct treatment of COPD exacerbations. However, we think that PA pressure monitoring in patients with HF may affect the precursor risk factors that may contribute to acute exacerbations of COPD requiring hospitalization and therefore PA pressure monitoring may be useful for indirect prevention of these events.

Specifically, studies have shown that increased PA pressures and pulmonary vascular stress contribute to worsening hypoxemia and increase the risk for further acute exacerbations of COPD requiring hospitalization.[23,24,30] In addition, it is well known that HF patients in general are at increased risk for pulmonary infections owing in part to the presence of excess volume and pulmonary congestion, which in turn may add hypoxia to the increased metabolic demands and is associated with worse outcomes.[2,31] Because outpatient HF medical management optimization through PA pressure monitoring is beneficial in preventing episodes of pulmonary congestion and excess volume, we think that this approach may indirectly reduce acute respiratory exacerbations requiring hospitalization as a result of lowering patient risk for pulmonary infections and/or worsening hypoxemia episodes that are directly affected by increased PA pressures, pulmonary vascular stress, and volume overload. Consequently, we hypothesized that a management strategy incorporating PA pressure monitoring may improve both clinical conditions, particularly in HF patients with comorbid COPD who are at increased risk for both HF and respiratory exacerbations.

To evaluate this concept, we compared HF and respiratory hospitalization rates in the entire CHAMPION cohort with the rates observed within the COPD and non-COPD subgroups. All patients in the CHAMPION trial were at high risk for HF hospitalizations, which was the primary focus of the trial. We hypothesized that a medical management strategy incorporating hemodynamic information from an implantable PA pressure sensor would likely result in a consistent treatment effect in reducing HF hospitalization rates in the COPD and non-COPD subgroups because both groups are at risk for HF. The COPD subgroup, however, was also at increased risk for respiratory exacerbations compared with the non-COPD subgroup. We therefore hypothesized that this strategy may also reduce the risk of respiratory exacerbations requiring hospitalization in COPD subjects in the treatment group. In contrast, this treatment effect would likely be diminished in non-COPD subjects because they are already at low risk for respiratory exacerbations.

Materials and Methods

Subjects

The trial enrolled subjects who were male or female ≥18 years of age, diagnosed with New York Heart Association (NYHA) functional class III heart failure for ≥3 months, regardless of left ventricular ejection fraction or cause, and had ≥1 heart failure hospitalization ≤12 months of the baseline visit. Subjects were excluded if they had an active infection, had a history of recurrent (> 1) pulmonary embolism or deep vein thrombosis, were unable to

tolerate right heart catheterization, experienced a major cardiovascular event (eg, myocardial infarction, stroke) ≤2 months of the baseline visit, had a cardiac resynchronization device (CRT) implanted ≤3 months before enrollment, or had stage IV or V chronic kidney disease (glomerular filtration rate [GFR] <25 mL min^{-1} 1.73 m^{-2}). The other inclusion and exclusion criteria have been described previously.[20] The Institutional Review Board of each participating center approved the study protocol, and every subject provided written informed consent.

COPD Classification Process

The criteria for COPD classification included a comprehensive review of each patient's clinical source documents and electronic case report forms collected during the CHAMPION trial. Patient medical histories, including whether or not a patient had a diagnosis of COPD, were determined by the patient's treating physician and recorded in the electronic case report form. A patient was included in the COPD cohort if the treating physician, who had full knowledge and access to his or her patient's medical information, made a determination that the patient had a history of COPD, including chronic productive cough, chronic wheezing, emphysema, or chronic bronchitis. These specific details for the medical history COPD criterion are the same used for COPD status in the OPTIMIZE-HF registry.[12]

In addition to the medical history criterion, detailed medication data was also collected in the electronic case report forms for all patients. We reviewed the medication data to identify patients receiving treatment with a β2-adrenergic agonist, corticosteroid, anticholinergic, leukotriene receptor antagonist, or a combination therapy at the time of patient enrollment. The documented indication for the medication as recorded by the treating physician had to specify COPD management for the medication criterion to be met. Patients meeting the COPD medical history criterion and/or the COPD medication criterion were included in the final COPD cohort.

Study Design

The CHAMPION trial was a prospective, multicenter (n = 64), randomized, single-blind clinical trial conducted in the USA designed to evaluate the safety and efficacy of the PA pressure monitoring system in subjects with HF. All subjects were on optimal HF drug and device therapies at the time of sensor implantation in accordance with American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) HF guidelines.[2] Eligible subjects underwent implantation of a PA pressure sensor, an integral part of the wireless implantable hemodynamic monitoring system (Cardiomems HF System; St Jude Medical, Atlanta, Georgia).

The PA pressure monitoring system has a passive wireless radiofrequency sensor without batteries or leads and has been described elsewhere.[20] Following the sensor implantation, subjects were hospitalized overnight for observation. Before hospital discharge, subjects were trained on how to operate the home electronic monitoring unit and instructed to take PA pressure measurements daily. Subjects were also randomized to either the treatment group, which allowed clinician access to the PA pressure readings that were obtained

through the PA pressure monitoring system, or the control group, from which access to PA pressure measurements was blocked. All subjects in the treatment and control groups recorded daily PA pressure readings. These measurements were transmitted through a modem or cellphone to a secure patient database. For subjects randomized to the treatment group, the goal was to lower PA pressures when elevated with the use of conventional HF treatment therapy, primarily diuretics and vasodilators. For subjects in the control group, physicians made changes to medical therapy in response to clinical signs and symptoms in accordance with their usual care practices.

Hospitalization Classification Process

All hospitalizations were reviewed and adjudicated by an independent blinded Clinical Events Committee (CEC). The CEC reviewed individual patient records, including admission and discharge summaries, progress notes, imaging results, and laboratory findings, including biomarkers when available. The CEC procedure for end point evaluation was consistent with the recommendations outlined by the Standardized Data Collection for Cardiovascular Trials Initiative Task Force.[32] HF hospitalizations were defined as an event that met all of the following criteria:

1. Admission to an inpatient unit or a visit to an emergency department that results in a ≥24-hour stay (or a date change if the time of admission/discharge is not available).
2. At least 1 new or worsening clinical symptom of HF.
3. At least 1 physical sign of HF.
4. Need for additional/increased HF therapy.
5. No other noncardiac or cardiac etiology identified for satisfying symptoms criterion 2 or signs criterion 3.

For hospitalizations not meeting the criteria above for HF in which respiratory-related etiology was suspected and patients presented with ≥1 signs or symptoms of respiratory distress, such as increased dyspnea, cough, sputum production, and/or infection, and underwent treatment targeted to alleviate these respiratory signs or symptoms, the CEC classified these events as respiratory hospitalizations. If a hospitalization satisfied both HF and respiratory hospitalization criteria, the CEC would defer classification to the disease that was the primary focus of the hospitalization according to the expert consensus of the committee as recommended by the Task Force.[32]

Statistical Analysis

The primary efficacy end point of this subgroup analysis was the rate of hospitalization related to HF and respiratory failure after insertion of the implant in the treatment group versus the control group. Comparison of demographic, laboratory, and hemodynamic analyses and comorbidities were performed with the use of an exact Wilcoxon rank sum test and a Fisher exact test. All values were expressed as mean ± SD. Subject hospitalization rates were analyzed with the use of the Andersen-Gill model, an extension of the Cox proportional hazards model for repeated event analyses.

Results

Hospitalizations

From September 2007 to October 2009, 550 subjects were randomly assigned to the treatment (n = 270) and control (n = 280) groups; 187 subjects met the COPD classification criteria for inclusion in the COPD subgroup. The mean follow-up time was 15 ± 7 months. The baseline characteristics of all subjects and subjects with COPD are presented in Tables 1 and 2 respectively. Patients with COPD had a higher prevalence of ischemic cardiomyopathy and other comorbidities compared with patients without COPD. Specifically, patients with COPD had a > 5% higher prevalence of coronary artery disease and history of myocardial infarction, diabetes, and atrial fibrillation compared with patients without COPD. These findings are consistent with data from other studies of HF and COPD.[12] Baseline hemodynamics for patients with and without COPD were elevated, with signs of moderate pulmonary hypertension in both groups. All patients were well treated according to ACCF/AHA HF guidelines[2] as required for inclusion in the study.

In the entire CHAMPION cohort, the treatment group had a 37% reduction in HF hospitalization rates (0.46 vs 0.73; hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.52–0.77; $P < .0001$) (Table 3). This treatment effect was consistent in patients with COPD and without COPD. In the subgroup of 187 subjects with comorbid COPD, the treatment group had a 41% reduction in HF hospitalization rates (0.55 vs 0.96; HR 0.59, 95% CI 0.44–0.81; $P = .0009$; Table 3; Fig. 1). In the subgroup of 363 subjects without COPD, the treatment group had a 34% reduction in HF hospitalization rates (0.41 vs 0.62; HR 0.66, 95% CI 0.51–0.85; $P = .0017$; Table 3; Fig. 2). In general, the COPD subgroup experienced higher HF hospitalization rates compared with the non-COPD subgroup.

In the entire CHAMPION cohort, the treatment group had a 49% reduction in respiratory hospitalization rates (0.07 vs 0.14; HR 0.51, 95% CI 0.32–0.83; $P = .0061$; Table 4). This treatment effect was substantially greater in subjects with COPD than without COPD. In the COPD cohort, the treatment group had a 62% reduction in respiratory hospitalization rates (0.12 vs 0.31; HR 0.38, 95% CI 0.21–0.71; $P = .0023$; Table 4; Fig. 3). In contrast, the treatment group in the non-COPD cohort experienced a nonsignificant reduction in respiratory hospitalization rates (0.05 vs 0.06; HR 0.88, 95% CI 0.40–1.98; $P = .7646$; Table 4; Fig. 4). However, the respiratory hospitalization rates for the entire COPD subgroup were significantly greater than the rates observed in the non-COPD subgroup.

HF Medication Changes

The average number of HF medication changes in the treatment group was compared with that of the control group after 6 months of follow-up. These data included up-titrations, down-titrations, starts of new medications, and stops of existing medications. In the COPD subgroup, treatment patients on average underwent 7.1 HF medication changes compared with only 3.7 HF medication changes in the control group over the 6 months of follow-up ($P < .0001$; Table 5). In the non-COPD subgroup, treatment patients on average underwent 7.9 HF medication changes compared with only 3.1 HF medication changes in the control group over the 6 months of follow-up ($P < .0001$; Table 5). This differential in favor of the

treatment group was predominantly driven by significantly more changes in diuretic therapies in response to elevated PA pressure data, which was available only in the treatment group.

Changes in PA Pressure

Using an area under the receiver operating characteristic curve (AUC) methodology to analyze changes in pulmonary artery pressure at 1 year of follow-up relative to baseline PA pressures obtained during the 1st week after randomization, the treatment group achieved significantly lower PA pressures than the control group for the entire cohort of subjects (−201.5 mm Hg–days in the treatment group vs 106.5 mm Hg–days in the control group; $P = .03$; Table 6). This differential of approximately −300 mm Hg–days in favor of the treatment group was consistently observed in patients with COPD and in patients without COPD. However, the AUC analysis in the COPD subgroup, which had a much smaller sample size than the non-COPD subgroup, was not statistically significant.

Discussion

Earlier studies have shown that the prevalence of COPD in HF subjects is high and ranges from 11% to 52% in North American patients and from 9% to 41% of European patients, with a higher prevalence in more recent studies.[33] Earlier randomized clinical trials in chronic HF have reported a lower prevalence of COPD of 10%–20%. The prevalence of COPD in the CHAMPION trial was high at 34% and is likely due in part to the higher risk study population enrolled in CHAMPION compared with other randomized clinical trials in HF that report COPD prevalence. Specifically, CHAMPION patients were all NYHA functional class III patients with ≥ 1 HF hospitalization in the previous year, whereas trials reporting a lower COPD prevalence typically enrolled ≥ 50% of patients who were NYHA functional class II without a previous HF hospitalization requirement. Registry data suggest that patients who are NYHA functional class III/IV have a significantly higher prevalence of COPD compared with patients who are NYHA functional class I/II.

The combination of these 2 diseases places a patient at increased risk for hospitalization and death.[11–13,35] Additionally, patients with HF and concomitant COPD present diagnostic challenges because both diseases have a progressive course with multiple exacerbations often requiring hospitalization. Clinically, physicians often have difficulty differentiating the etiology of symptoms in patients with COPD and HF because breathlessness and cough are commonly present in both diseases at the time of presentation. To our knowledge this is the 1st study analyzing the use of a continuous PA monitoring device to measure PA pressures in subjects with HF and comorbid COPD that evaluates the effect such a device has on hospitalization rates.

The Cardiomems HF System has previously been shown to be a novel therapeutic modality for the treatment of subjects with NYHA functional class III heart failure by reducing HF hospitalization rates, and it has been proven to be safe and well tolerated.[22] Earlier studies have shown that pulmonary vascular disease is an important risk factor for respiratory exacerbations and mortality in patients with COPD.[23–25] In addition, earlier studies have shown that elevated pulmonary hemodynamic variables are important predictors of

hospitalization and mortality in HF patients with secondary pulmonary hypertension.[26–28] The present subgroup analysis has shown for the 1st time that a management strategy incorporating hemodynamic information from an implantable PA pressure monitor significantly reduces the risk of both HF and respiratory hospitalizations, particularly in patients with comorbid COPD who are at increased risk for both HF and respiratory exacerbations.

Although the benefit of PA pressure monitoring and its direct impact on the underlying pathophysiology and disease progression in acute decompensated HF requiring hospitalization is well understood, this is the 1st analysis to evaluate the potential role of PA pressure monitoring and its impact on the underlying pathophysiology and disease progression for respiratory exacerbations requiring hospitalization. Our findings suggest that PA pressure monitoring in patients with HF and COPD affects the precursor risk factors that may contribute to acute respiratory exacerbations requiring hospitalization by lowering patient risk for pulmonary infections and/or worsening hypoxemia episodes that are directly affected by increased PA pressures, pulmonary vascular stress, and volume overload. By influencing these variables, PA pressure monitoring was beneficial in this study for preventing respiratory hospitalizations in HF patients with COPD.

It is important to emphasize that HF patients with comorbid COPD were at increased risk for HF and respiratory hospitalizations compared with patients without COPD. In particular, COPD subjects in the control group experienced the highest HF hospitalization rates (0.92) and respiratory hospitalization rates (0.31). These data suggest that increased filling pressures and congestion may have a cumulative detrimental effect in this high-risk population. It is not surprising that a management strategy incorporating hemodynamic information that effectively reduces filling pressures and pulmonary congestion would result in dual benefit for these high-risk patients with HF and COPD, resulting in a dramatic improvement for both HF and respiratory outcomes.

Study Limitations

Pulmonary function test data were not available in this study and were not part of the COPD classification criteria. Although our process was thorough and included a detailed evaluation of patient data including both medical histories and medication treatments consistent with other reported evaluations of patients with HF and COPD,[12] it is possible that some level of COPD misdiagnosis exists within these data. In addition, although the CEC adjudication process for hospitalizations was rigorous and followed recommended guidelines for HF trials, we acknowledge that distinguishing between HF and respiratory hospitalizations is difficult.

We think, however, that these concerns can be mitigated by (1) evaluating the statistical robustness of the reduction in respiratory hospitalizations observed in the COPD treatment group and (2) investigating whether variability of the treatment effect is observed when different COPD criteria are used to define the study population. A significant alteration of the distribution of respiratory hospitalizations would be required for the treatment effect to lose statistical significance. Under a tipping point analysis (Supplemental Table 1)

evaluating the potential impact of underreporting/misclassification of respiratory hospitalizations occurring in the treatment group only, 9 additional events would have to be added to the treatment group with no change in the control group for statistical significance to be lost. Under another tipping point analysis (Supplemental Table 2) evaluating the potential impact of overreporting/misclassification of respiratory hospitalizations in the control group only, 11 events would have to be removed from the control group with no change in the treatment group for statistical significance to be lost. To evaluate the validity of the COPD classification process and the subgroup analysis, we further evaluated respiratory hospitalization rates in patients that met each COPD criterion separately (medical history or current treatment with a COPD medication) to understand whether 1 COPD criterion was the primary driver for the event rate and/or the treatment effect relative to the other criterion (Supplemental Table 3). The results of this analysis showed that respiratory hospitalizations were consistent across each criterion and, importantly, that the treatment effect was consistently observed regardless of which COPD classification criteria were met. We think that these additional analyses help to confirm the robust statistical results of our findings and help to mitigate some of the inherent limitations of this study.

Conclusion

These data support the notion that physicians need to be more vigilant about optimizing HF treatment in this high-risk population and that targeting filling pressures is an effective strategy for improving clinical outcomes. Further investigation is required to examine the pathophysiologic relationships in greater detail among elevated filling pressures, HF, COPD, and respiratory exacerbations, and the implications in the development of new and effective treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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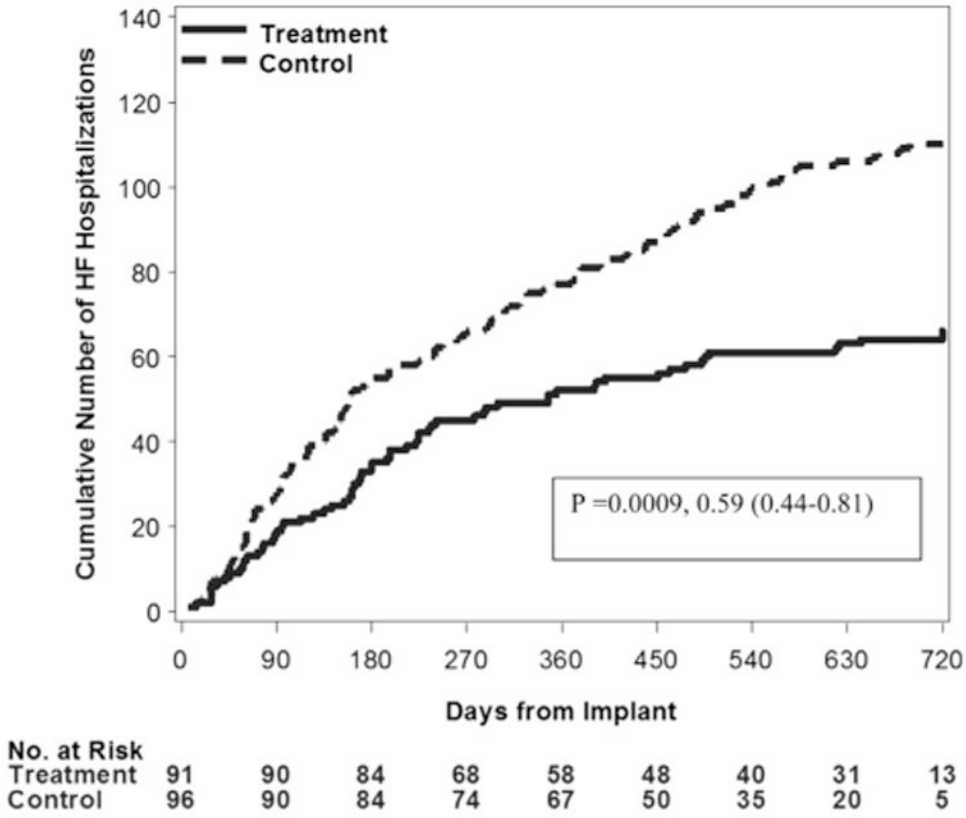

Fig. 1.

Cumulative heart failure (HF) hospitalizations after implantation in subjects with chronic obstructive pulmonary disease. *P* value, hazard ratio (treatment vs control), and 95% confidence interval were derived with the use of the Andersen-Gill model.

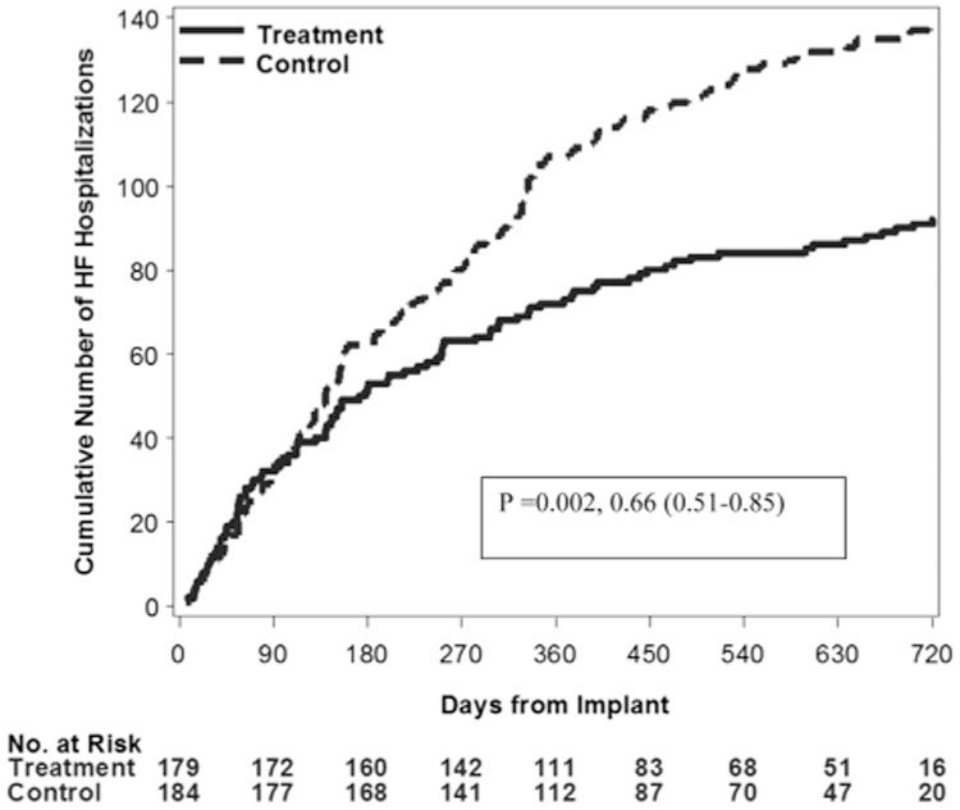

Fig. 2.

Cumulative heart failure (HF) hospitalizations after implantation in subjects without chronic obstructive pulmonary disease. *P* value, hazard ratio (treatment to control), and 95% confidence interval were derived with the use of the Andersen-Gill model.

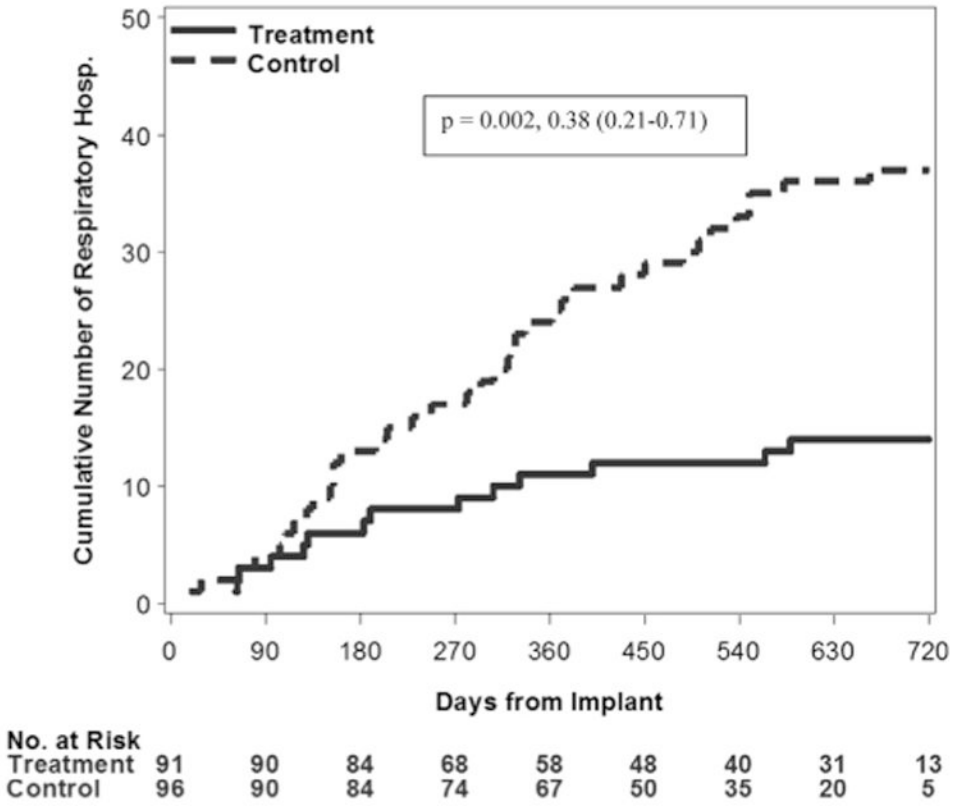

Fig. 3.

Cumulative respiratory hospitalizations after implantation in subjects with chronic obstructive pulmonary disease. P value, hazard ratio (treatment to control), and 95% confidence interval were derived with the use of the Andersen-Gill model.

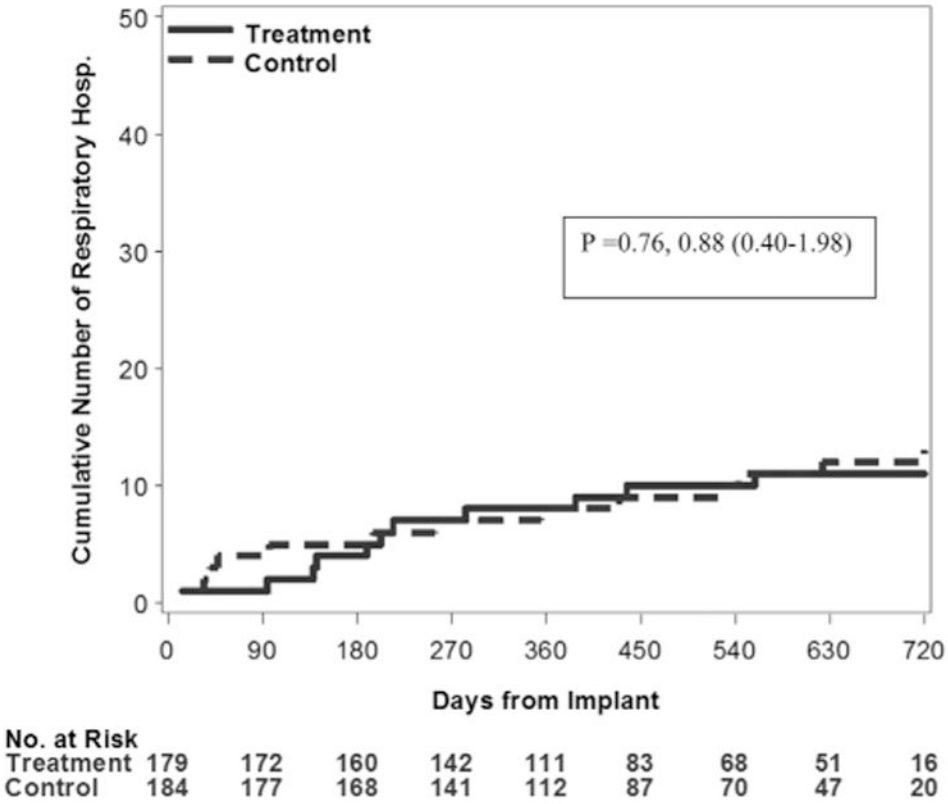

Fig. 4.

Cumulative respiratory hospitalizations after implantation in subjects without chronic obstructive pulmonary disease. *P* value, hazard ratio (treatment to control), and 95% confidence interval were derived with the use of the Andersen-Gill model.

Table 1
Baseline Characteristics of All Subjects (COPD vs No COPD)

	COPD (n = 187)	No COPD (n = 363)	*P* Value*
Demographics			
Age (y)	63 ± 11	61 ± 14	.16
Sex (% female)	30%	26%	.36
Race (% nonwhite)	20%	31%	<.01
BMI (kg/m^2)	32 ± 7.2	31 ± 7.2	.15
CRT/CRT-D implant	34%	35%	.78
ICD implant	41%	30%	.02
Ejection fraction (% ≥40%)	23%	21%	.59
Ischemic cardiomyopathy	67%	57%	.03
Laboratory and hemodynamic analysis			
Creatinine (mg/dL)	1.32 ± 0.42	1.40 ± 0.45	.03
GFR (mL^{-1} min 1.73 m^{-2})	62 ± 22	61 ± 23	.33
Systolic BP (mm Hg)	121 ± 21	123 ± 22	.71
Diastolic BP (mm Hg)	72 ± 13	72 ± 13	.77
Heart rate (beats/min)	74 ± 13	72 ± 12	.47
BUN (mg/dL)	28 ± 15	29 ± 18	.45
PA systolic pressure (mm Hg)	46 ± 15	44 ± 15	.40
PA diastolic pressure (mm Hg)	20 ± 8	19 ± 8	.18
PA mean pressure (mm Hg)	30 ± 10	29 ± 10	.30
PA wedge pressure (mm Hg)	19 ± 8	18 ± 8	.65
Cardiac output (L/min)	4.6 ± 1.4	4.5 ± 1.5	.22
Cardiac index (L min^{-1} m^{-2})	2.4 ± 0.7	2.3 ± 0.7	.18
PVR	2.8 ± 1.8	2.8 ± 2.0	.55
Comorbidities			
Hypertension	77%	78%	.83
Hyperlipidemia	80%	75%	.29
Coronary artery disease	78%	66%	<.01
History of myocardial infarction	55%	46%	.06
Diabetes mellitus	55%	46%	.06
Atrial tachycardia flutter/fibrillation	50%	44%	.21
Chronic kidney disease	21%	19%	.50
Pulmonary edema	18%	15%	.33
Cerebrovascular accident	12%	14%	.59
Hypotension	16%	11%	.11
Peripheral artery disease	15%	11%	.22
Cerebrovascular disease	11%	11%	1.00
HF medications			
ACEI/ARB	78%	78%	1.00
Beta-blocker	90%	91%	.64

	COPD (n = 187)	No COPD (n = 363)	*P* Value*
Aldosterone antagonist	43%	42%	.86
Nitrate	24%	21%	.51
Hydralazine	12%	13%	1.00
Diuretic: loop	93%	91%	.62
Diuretic: thiazide	11%	12%	.68
Diuretic: thiazide (PRN)	6%	7%	.86
COPD medications			
Any COPD medication	58%	–	–
β2-Adrenergic agonist	48%	–	–
Corticosteroid	33%	–	–
Anticholinergic	27%	–	–
Leukotriene receptor antagonist	6%	–	–

COPD, chronic obstructive pulmonary disease; BMI, body mass index; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator; GFR, glomerular filtration rate; BP, blood pressure; BUN, blood urea nitrogen; PA, pulmonary arterial; PVR, pulmonary vascular resistance; HF, heart failure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PRN, as needed.

Data are presented as n (%) or mean (SD).

* *P* value testing COPD subjects versus non-COPD subjects with the use of Exact Wilcoxon rank sum test for continuous measures and Fisher exact test for categoric measures.

Table 2
Baseline Characteristics of COPD Subjects

	Treatment (n = 91)	Control (n = 96)	All COPD Subjects (n = 187)	*P* Value*
Demographics				
Age (y)	63 ± 12	63 ± 11	63 ± 11	.70
Sex (% female)	33%	27%	30%	.43
Race (% nonwhite)	15%	24%	20%	.15
BMI (kg/m^2)	31 ± 7.8	32 ± 7.5	32 ± 7.2	.78
CRT/CRT-D implant	33%	34%	34%	.88
ICD implant	42%	39.6%	41%	.77
Ejection fraction (% ≥40%)	22%	24%	23%	.86
Ischemic cardiomyopathy	66%	68%	67%	.88
Laboratory and hemodynamic analysis				
Creatinine (mg/dL)	1.31 ± 0.43	1.33 ± 0.41	1.32 ± 0.42	.56
GFR ($mL\ min^{-1}\ 1.73\ m^{-2}$)	62 ± 21	62 ± 23	62 ± 22	.87
Systolic BP (mm Hg)	118 ± 21	124 ± 20	121 ± 21	.02
Diastolic BP (mm Hg)	70 ± 14	73 ± 12	72 ± 13	.11
Heart rate (beats/min)	75 ± 15	73 ± 11	74 ± 13	.67
BUN (mg/dL)	29 ± 17	28 ± 14	28 ± 15	.67
PA systolic pressure (mm Hg)	46 ± 15	45 ± 15	46 ± 15	.59
PA diastolic pressure (mm Hg)	19 ± 8	20 ± 9	20 ± 8	.93
PA mean pressure (mm Hg)	30 ± 10	30 ± 10	30 ± 10	.96
PA wedge pressure (mm Hg)	18 ± 7	19 ± 8	19 ± 8	.31
Cardiac output (L/min)	4.4 ± 1.3	4.9 ± 1.6	4.6 ± 1.4	.02
Cardiac index ($L\ min^{-1}\ m^{-2}$)	2.3 ± 0.6	2.5 ± 0.7	2.4 ± 0.7	.03
PVR	3.1 ± 2.2	2.5 ± 1.4	2.8 ± 1.8	.18
Comorbidities				
Hypertension	73%	81%	77%	.17
Hyperlipidemia	79%	80%	80%	.86
Coronary artery disease	78%	78%	78%	1.00
History of myocardial infarction	56%	54%	55%	.88
Diabetes mellitus	53%	56%	55%	.66
Atrial tachycardia flutter/fibrillation	53%	48%	50%	.56
Chronic kidney disease	23%	20%	21%	.60
Pulmonary edema	17%	20%	18%	.58
Cerebrovascular accident	8.8%	15%	12%	.26
Hypotension	18%	15%	16%	.69
Peripheral artery disease	15%	15%	15%	1.00
Cerebrovascular disease	7.7%	14%	11%	.24

Data are presented as n (%) or mean (SD). Abbreviations as in Table 1.

* *P* value testing COPD subjects versus non-COPD subjects with the use of Exact Wilcoxon rank sum test for continuous measures and Fisher exact test for categoric measures.

Table 3

Rate of Heart Failure Hospitalization (HF Hosp) Over Study Duration (Mean Follow-Up of 15 Months)

	Treatment			Control				
	n	HF Hosp	HF Hosp Rate (Annualized)	n	HF Hosp	HF Hosp Rate (Annualized)	RRR	*P* Value; HR (95% CI)*
Overall study	270	158	0.46	280	254	0.73	37%	<.0001; 0.63 (0.52–0.77)
Subjects with COPD	91	66	0.55	96	110	0.92	41%	.0009; 0.59 (0.44–0.81)
Subjects without COPD	179	92	0.41	184	144	0.62	34%	.0017; 0.66 (0.51–0.85)

RRR, relative risk reduction; COPD, chronic obstructive pulmonary disease.

**P* value, hazard ratio (HR; treatment to control), and 95% confidence interval (CI) derived with the use of the Andersen-Gill model.

Table 4

Rate of Respiratory Hospitalization (Resp Hosp) Over Study Duration (Mean Follow-Up of 15 Months)

	Treatment			Control				
	n	Resp Hosp	Resp Hosp Rate (Annualized)	n	Resp Hosp	Resp Hosp Rate (Annualized)	RRR	*P* Value; HR (95% CI)*
Overall study	270	25	0.07	280	50	0.14	49%	.0061; 0.51 (0.32–0.83)
Subjects with COPD	91	14	0.12	96	37	0.31	62%	.0023; 0.38 (0.21–0.71)
Subjects without COPD	179	11	0.05	184	13	0.06	13%	.7646; 0.88 (0.40–1.98)

Abbreviations as in Table 3.

**P* value, HR (treatment to control), and 95% CI derived with the use of the Andersen-Gill model.

Table 5

Average Number of Heart Failure Medication Changes After 6 Months of Follow-Up

	COPD Subgroup			Non-COPD Subgroup		
HF Medication	**Treatment**	**Control**	***P* Value**	**Treatment**	**Control**	***P* Value***
ACEI/ARB	0.78	0.36	.0028	0.84	0.48	.0011
Beta-blocker	0.6	0.48	.1966	0.72	0.54	.0276
Aldosterone antagonist	0.24	0.36	.6738	0.3	0.12	<.0001
Nitrate	0.42	0.18	.0005	0.54	0.18	<.0001
Hydralazine	0.24	0.12	.0814	0.36	0.18	<.0001
Diuretic: loop	3.78	1.86	<.0001	4.26	1.38	<.0001
Diuretic: thiazide	1.08	0.3	.0013	0.84	0.24	<.0001
Total	7.14	3.66	<.0001	7.92	3.06	<.0001

Abbreviations as in Table 1.

** P* value testing treatment vs control obtained by means of exact Wilcoxon rank sum test.

Table 6

One-Year Change from Baseline in Pulmonary Arterial Mean Pressures Average Area under the Receiver Operating Characteristic Curve (AUC) Analysis

	Treatment		Control		
	n	Mean mm Hg, Days ± SD	n	Mean mm Hg, Days ± SD	*P* Value*
Overall study	265	−201.5 ± 2,083	272	106.5 6 2,127	.03
Patients with COPD	89	−353.1 ± 2,302	93	−57.0 ± 1,862	.37
Patients without COPD	176	−124.8 ± 1,965	179	191.5 6 2,252	<.05

* *P* value according to analysis of covariance with the use of baseline pressure as the covariate.