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Pulmonary Artery Pressure-Guided Management of Patients With Heart Failure and Reduced Ejection Fraction

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ABSTRACT

BACKGROUND Despite increased use of guideline-directed medical therapy (GDMT), some patients with heart failure and reduced ejection fraction (HFrEF) remain at high risk for hospitalization and mortality. Remote monitoring of pulmonary artery (PA) pressures provides clinicians with actionable information to help further optimize medications and improve outcomes.

OBJECTIVES CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients trial) analyzed PA pressure-guided heart failure (HF) management in patients with HFrEF based on their ability to tolerate GDMT.

METHODS CHAMPION enrolled 550 patients with chronic HF regardless of left ventricular ejection fraction. A pre-specified sub-group analysis compared HF hospitalization and mortality rates between treatment and control groups in HFrEF patients (left ventricular ejection fraction ≤40%). Post hoc analyses in patients who tolerated GDMT were also performed. Hospitalizations and mortality were assessed using Andersen-Gill and Cox proportional hazards models.

RESULTS In 456 patients with HFrEF, HF hospitalization rates were 28% lower in the treatment group than in the control group (hazard ratio [HR]: 0.72; 95% confidence interval [CI]: 0.59 to 0.88; $p = 0.0013$), with a strong trend for 32% lower mortality (HR: 0.68; 95% CI: 0.45 to 1.02; $p = 0.06$). A 445-patient subset received at least 1 GDMT (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, or beta-blocker) at baseline; these patients had 33% lower HF hospitalization rates (HR: 0.67; 95% CI: 0.54 to 0.82; $p = 0.0002$) and 47% lower mortality (HR: 0.63; 95% CI: 0.41 to 0.96, $p = 0.0293$) than controls. Compared with controls, patients receiving both components of optimal GDMT ($n = 337$) had 43% lower HF hospitalizations (HR: 0.57; 95% CI: 0.45 to 0.74; $p < 0.0001$) and 57% lower mortality (HR: 0.43; 95% CI: 0.24 to 0.76; $p = 0.0026$).

CONCLUSIONS PA pressure-guided HF management reduces morbidity and mortality in patients with HFrEF on GDMT, underscoring the important synergy of addressing hemodynamic and neurohormonal targets of HF therapy. (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients [CHAMPION]; NCT00531661) (J Am Coll Cardiol 2017;70:1875-86) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin receptor blocker

CRT-D = cardiac resynchronization therapy with defibrillator

GDMT = guideline-directed medical therapy

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

PA = pulmonary artery

During the last 3 decades, significant progress has been made in the management of patients with heart failure (HF), focusing on pharmacological (1–8) and device-based therapies (9–12) to meet the challenges of this complex syndrome affecting an estimated 26 million people worldwide (13). In large randomized controlled trials (RCTs), these therapies have shown significant improvement in clinical outcomes, and have led to guideline-directed medical therapy (GDMT) recommendations. Conversely, patients unable to tolerate GDMT have a poor prognosis. The majority of RCTs in patients with HF have predominantly enrolled patients with reduced ejection fraction (HFrEF), and, to date, it is only in these patients that therapeutic drugs and devices have been proven effective. As a result of the large body of scientific evidence investigating the neurohormonal hypothesis of HF and the pathophysiological importance of excessive renin-angiotensin-aldosterone system and sympathetic nervous system activity (14–19), the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) (20) and European Society of Cardiology (ESC) (21) recommend broad use of GDMT for patients with HFrEF, as defined by left ventricular ejection fraction (LVEF) ≤40%.

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The strategy of achieving neurohormonal control of HF through the combination of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) with beta-blockers (BBs) represents a Class I recommendation by the ACCF/AHA/HFSA (20). Incremental to GDMT optimization, the addition of implantable cardioverter-defibrillators or cardiac resynchronization therapy with defibrillators is also a class I recommendation for select patients with HFrEF meeting specific cardiac rhythm requirements. Recently, a large RCT showed that replacement of ACEI/ARB with an angiotensin receptor-neprilysin inhibitor positively influenced outcomes and is the newest recommended approach for chronic HF management (22).

Despite these advances, morbidity and mortality in HF remain a major burden to patients, caregivers, and national health care systems (23,24). Acute decompensated HF results in more than 1 million hospital admissions per year in the United States (25,26), and this number has significantly increased over the past 20 years. In fact, mortality risk is directly associated with the number of decompensation episodes requiring intravenous rescue therapies, either in or out of the hospital (27). In this setting, a novel approach to HF management was recently proven effective, focusing on a strategy to further optimize the effectiveness of current, well-established therapies. Remote monitoring of intracardiac and pulmonary artery (PA) pressures using implantable devices can provide clinicians with access to actionable pathophysiological information, and help improve the serial decision-making process necessary to prevent HF hospitalizations and improve other clinical outcomes (28–31). Studies show that increases in cardiac filling pressures can often be detected several weeks before patients experience symptoms of worsening HF that require hospitalization, providing clinicians with a therapeutic time window necessary for effective intervention (32–35).

The CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA [New York Heart Association] functional Class III Heart Failure Patients) trial (NCT00531661) was a prospective, multicenter, randomized, single-blind clinical study in 550 patients that tested the impact of a PA pressure-guided HF management strategy using a wireless implantable hemodynamic monitoring system (CardioMEMS HF System, St. Jude Medical [now Abbott], Atlanta, Georgia) relative to HF management based on practice guidelines only (36). This pivotal trial met each of its primary and secondary endpoints (30,31), with consistent treatment effect sizes observed across several clinically relevant subgroups (37–41), leading to United States Food and Drug Administration approval of the CardioMEMS HF System in 2014 and guideline recommendation from the ESC (21). The CHAMPION trial enrolled a heterogeneous HF study group, regardless of LVEF or etiology, and was designed with a pre-planned analysis of outcomes based on baseline LVEF greater than, or less than or equal to 40%. Results from patients with HF with preserved ejection fraction (HFpEF) showed significant reductions in HF hospitalizations in the PA pressure-guided care group compared with traditional management strategies (37). No impact on mortality was shown in the small subgroup of patients with HFpEF.

Anecdotally, there is speculation that hemodynamic-guided care may be less useful in patients already benefitting from maximal GDMT. The CHAMPION trial required patients with HFrEF to already be treated with maximal dosing of appropriate neurohormonal antagonists, unless intolerance was documented. This design provides a unique opportunity to evaluate a potential differential impact of hemodynamic-guided HF management on

clinical outcomes based on variable use of GDMT in patients with HFrEF. Therefore, this report first details the pre-planned sub-group analysis examining the impact of the hemodynamic management strategy on HF hospitalization rates and survival in subjects with reduced ejection fraction (LVEF ≤40%). A post hoc analysis evaluating morbidity and mortality in subjects with HFrEF already benefitting from GDMT is then performed to explore the hypothesis that PA pressure-guided HF management is effective, even in patients with maximal neurohormonal antagonism.

METHODS

STUDY DESIGN. Between 2007 and 2009, the CHAMPION trial enrolled 550 patients with class III symptoms who had been hospitalized for HF in the prior year. Patients with any LVEF were included in the trial, but inclusion criteria for patients with HFrEF required established therapies with ACEI or ARB and BB at optimal or best-tolerated doses before randomization unless a contraindication or intolerance was documented. All patients underwent right heart catheterization evaluation with hemodynamic assessment and implantation of the PA pressure sensor before randomization to either the PA pressure-guided HF management strategy arm (treatment) or to the standard-of-care arm (control). Patients in both the treatment and control groups uploaded pressures daily, and were also treated according to clinical symptoms and signs of congestion and excess volume. Pressure information in the control group was not made available to investigators. All patients then remained in their randomized study groups until the last patient enrolled completed at least 6 months of study follow-up, resulting in approximately 797 patient-years (average of 18 months/patient) of follow-up. All hospitalizations and deaths were adjudicated by a clinical events committee blinded to randomized group assignment. The trial protocol was approved by local site institutional review boards, and each patient provided informed consent to volunteer for the study.

The central hypothesis of the CHAMPION trial and this HFrEF analysis was that medication adjustment guided by PA pressure would reduce the primary endpoint of HF hospitalizations compared to reliance solely on traditional management strategies, which could include daily weight measurements or monitoring of clinical symptoms and signs of congestion. The CHAMPION trial protocol gave investigators specific recommendations on how to use PA pressures to guide HF therapies for patients in the treatment arm (36,42), and detailed analyses of medication changes in the trial are published (42). Investigators were instructed to adjust medications, primarily using diuretic and vasodilator agents, to reduce PA pressures to recommended target ranges to reduce decompensation risk. When PA pressures were stable, investigators were encouraged to consider further optimization of GDMT in patients with HFrEF.

HF HOSPITALIZATION RATES AND SURVIVAL ANALYSES. The primary endpoint of HF hospitalization rates was compared in all patients with HFrEF (n = 456) over the complete randomized follow-up period, averaging 18 months. All-cause death was an observational endpoint in the trial, and was also evaluated over the same period. Given the significant reduction in HF hospitalizations and the strong trend for survival benefit, we also performed a retrospective exploratory analysis of mortality and morbidity in the subset of subjects with HFrEF who were on GDMT at enrollment. For this analysis, 2 overlapping subgroups of patients were identified to represent baseline GDMT usage: group 1, patients with HFrEF taking at least 1 ACEI/ARB or BB class ("at least 1 GDMT," n = 445); and group 2, patients with HFrEF taking both ACEI/ARB and BB ("optimal GDMT," n = 337). Eleven patients (2%) were excluded from this analysis due to complete intolerance of any GDMT at enrollment.

STATISTICAL ANALYSIS. Baseline characteristics, including patient demographics, medical histories, laboratory values, and hemodynamics, as well as background HF medical management are presented as counts and percentages for discrete variables and mean ± SD for continuous data. The Fisher exact test was used to compare proportions, and the Wilcoxon rank-sum test was used to compare continuous data. All changes made to HF medication during randomized follow-up, and the motivation for those changes, were documented by study investigators in an electronic database. Medication frequencies, the proportion of patients on HF therapies, and the total daily dose achieved after 6 months of follow-up were also analyzed and were previously reported in the HFrEF cohort (n = 456) (42).

Methods for analyzing hospitalization rates and mortality were pre-specified for the planned analysis in all patients with HFrEF. The Andersen-Gill extension of the Cox proportional hazards model (43,44), implemented to analyze recurrent events including hospitalization rates, the Cox proportional hazards model using the log-rank test, implemented to analyze time to death, and Kaplan-Meier methodology, used to plot survival estimates, were prospectively selected. Analyses compared HF hospitalization rates

TABLE 1 Demographic and Baseline Treatment Characteristics of All Patients Enrolled in the CHAMPION Trial With LVEF ≤40% (HFrEF)

	Treatment Group (n = 222)	Control Group (n =234)	p Value*
Demographics			
Age, yrs	60.0 ± 13.0	61.5 ± 12.7	0.1791
Male	166 (75)	179 (76)	0.7434
White	153 (69)	172 (74)	0.3013
Clinical findings			
BMI, kg/m^2	30.2 ± 6.2	30.0 ± 6.4	0.8612
Systolic BP, mm Hg	119.2 ± 21.9	121.9 ± 20.5	0.0818
Heart rate, beats/min	72.9 ± 12.8	73.9 ± 12.5	0.2412
Creatinine, mg/dl	1.41 ± 0.49	1.36 ± 0.42	0.5563
GFR, ml/min/1.73m^2	61.1 ± 22.8	62.3 ± 23.4	0.6973
BUN, mg/dl	29.8 ± 18.5	27.6 ± 16.1	0.4177
Ejection fraction, %	25.3 ± 8.1	23.2 ± 7.9	0.0025
Hemodynamics			
PA systolic pressure, mm Hg	44.8 ± 14.5	46.1 ± 15.3	0.4689
PA diastolic pressure, mm Hg	19.0 ± 8.7	19.8 ± 8.2	0.1752
PA mean pressure, mm Hg	29.3 ± 10.1	30.4 ± 10.2	0.2262
PA wedge pressure, mm Hg	17.9 ± 8.3	19.6 ± 8.3	0.0273
Cardiac output, l/min	4.42 ± 1.38	4.45 ± 1.49	0.8703
Cardiac index, l/min/m^2	2.10 ± 0.59	2.13 ± 0.63	0.5359
PVR, Wood units	2.92 ± 2.11	2.73 ± 1.84	0.6209
Medical history			
Ischemic cardiomyopathy	136 (61)	151 (65)	0.4978
COPD	64 (29)	69 (29)	0.9181
Coronary artery disease	146 (66)	177 (76)	0.0234
Diabetes mellitus	104 (47)	114 (49)	0.7083
History of MI	114 (51)	123 (53)	0.8513
Hyperlipidemia	168 (76)	184 (79)	0.5032
Hypertension	169 (76)	183 (78)	0.6554
History of atrial fibrillation	93 (42)	112 (48)	0.2211

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and survival between treatment and control groups in all patients with HFrEF.

To test the hypothesis that hemodynamic-guided care is effective in patients on GDMT, these outcomes were evaluated in GDMT groups 1 and 2. A step-down Bonferroni (Holm) procedure was used to account for multiplicity (45). Further multivariate analyses were performed to evaluate the potential impact of changes in neurohormonal antagonist or vasodilator agent dosing on survival benefit using a Cox proportional hazard model; these analyses were used both in the pre-planned sub-group analysis of all patients with HFrEF and for comparisons in groups 1 and 2 treatment and control subjects. Differences achieving $p < 0.05$ were considered statistically significant.

RESULTS

ANALYSIS OF ALL PATIENTS WITH HFrEF. Of the 550 patients enrolled in the CHAMPION trial, 456 (83%) had an LVEF ≤40% and represent the basic pre-specified analysis of hospitalization rates and survival for patients with HFrEF. Baseline clinical demographics and characteristics of the treatment and control groups are presented in Table 1. In general, patients had several pre-existing comorbid medical conditions and elevated PA pressures obtained during baseline assessment.

HF HOSPITALIZATION RATES AND SURVIVAL ANALYSES. After an average randomized follow-up of 18 months, HF hospitalization rates in the HFrEF population were 28% lower in the treatment group (162 hospitalizations, rate of 0.49 events/patient/year) compared with the control group (227 hospitalizations, rate of 0.69 events/patient/year; hazard ratio [HR]: 0.72; 95% confidence interval [CI]: 0.59 to 0.88; p = 0013) (Figure 1, Top). Survival analysis using Kaplan-Meier estimates (Figure 1, Bottom) showed 32% lower mortality in the treatment group (17.6%) compared with the control group (24.4%) after 18 months of randomized follow-up, which represented a strong trend favoring the treatment group (HR: 0.68; 95% CI: 0.45 to 1.02; p = 0.06).

Mortality in all patients with HFrEF was analyzed using a Cox proportional hazards model that included covariates for 6-month changes in daily dosages (mg) of ACEI/ARB and BB. Similar modelling was performed that included covariates for 6-month changes in daily dosages (mg) of nitrates and hydralazine. Adjusted for changes in neurohormonal antagonist doses in all patients with HFrEF, mortality comparing treatment versus control arms was 0.71 (95% CI: 0.47 to 1.07). The mortality HR, adjusted for changes in vasodilator agent doses for all HFrEF patients, was 0.70 (95% CI: 0.46 to 1.05).

ANALYSIS OF GDMT SUBGROUPS. Because a strong trend toward mortality benefit was observed in the complete cohort of patients with HFrEF, analysis in patients with HFrEF who were on GDMT was performed. Demographic characteristics of patients based on tolerance of GDMT were similar between treatment and control subjects for both groups 1 and 2 (Table 2). Average dosing of GDMT in patients who tolerated neurohormonal antagonists and used them at both baseline and at 6 months is shown in Table 3, with baseline total daily doses for ACEI/ARB averaging approximately 20 mg in enalapril equivalents, and for BB averaging approximately 30 mg in carvedilol equivalents. Significant diuretic agent dose increases (furosemide equivalents) were observed in both treatment and control subjects, resulting in similar total doses between groups at the end-randomized portion of the trial. Significant increases in vasodilator agent, ACEI/ARB, and BB doses were

observed only in the treatment group subjects. Hydralazine dose was not significantly changed in either treatment or control subjects in group 2 (Table 3).

HF hospitalization rates in group 1 (at least 1 ACEI/ARB or BB) were 33% lower in treatment compared with control patients (HR: 0.67; 95% CI: 0.54 to 0.82; p = 0.0002) (Central Illustration, A). Further improvements in hospitalization outcomes were observed in group 2 (both ACEI/ARB and BB) treatment patients compared with control (HR: 0.57; 95% CI: 0.45 to 0.73; p = 0.0002) (Central Illustration, A). Group 1 treatment patients had a 37% lower mortality rate compared with control subjects (HR: 0.63; 95% CI: 0.41 to 0.96; p = 0.0293), whereas group 2 treatment patients had a 57% lower mortality rate compared with control patients (HR: 0.43; 95% CI: 0.24 to 0.76; p = 0.0002) (Central Illustration, B).

IMPACT OF NEUROHORMONAL ANTAGONIST OR VASODILATOR AGENT DOSING. Mortality was analyzed using a Cox proportional hazards model that included covariates for 6-month changes in daily dosages (mg) of ACEI/ARB (enalapril equivalent) and BB (carvedilol equivalent). Additional modeling was performed, which included covariates for 6-month changes in daily dosages (mg) of nitrates and hydralazine. Similar to the entire HFrEF cohort, survival HRs for treatment versus control arms in group 1 and 2 subjects did not change appreciably after adjusting for either neurohormonal antagonist or vasodilator dosing changes (Table 4).

TABLE 1 Continued

	Treatment Group (n = 222)	Control Group (n =234)	p Value*
Treatment history			
ICD only	82 (37)	91 (39)	0.6998
CRT-D	85 (38)	93 (40)	0.7738
CRT-D or ICD	167 (75)	184 (79)	0.4363
Loop diuretic agent	206 (93)	215 (92)	0.7289
Loop diuretic agent dose, mg	97.8 ± 72.7	95.4 ± 73.3	0.6904
Thiazide diuretic agent	22 (10)	25 (11)	0.8778
Thiazide diuretic agent dose, mg	3.1 ± 2.5	3.4 ± 2.3	0.5643
Thiazide diuretic agent PRN	17 (8)	16 (7)	0.8569
Thiazide diuretic agent PRN dose, mg	3.0 ± 1.2	3.2 ± 1.6	0.9832
Nitrate	51 (23)	44 (19)	0.3000
Nitrate dose, mg	62.8 ± 31.1	50.3 ± 31.2	0.0271
Hydralazine	31 (14)	31 (13)	0.8915
Hydralazine dose, mg	123.0 ± 97.9	99.8 ± 62.5	0.6130
ACEI/ARB	173 (78)	183 (78)	1.0000
ACEI/ARB dose, mg	19.0 ± 17.4	20.1 ± 18.1	0.6580
BB	206 (93)	220 (94)	0.7063
BB dose, mg	28.6 ± 21.5	30.0 ± 23.0	0.7630
ACEI/ARB and BB-GDMT	163 (73)	174 (74)	0.8318
Aldosterone antagonist	105 (47)	101 (43)	0.3976
Aldosterone antagonist dose, mg	27.7 ± 13.0	31.0 ± 21.0	0.4002

Values are mean ± SD or n (%). *p value testing treatment vs. control from Wilcoxon rank-sum test or Fisher exact test.

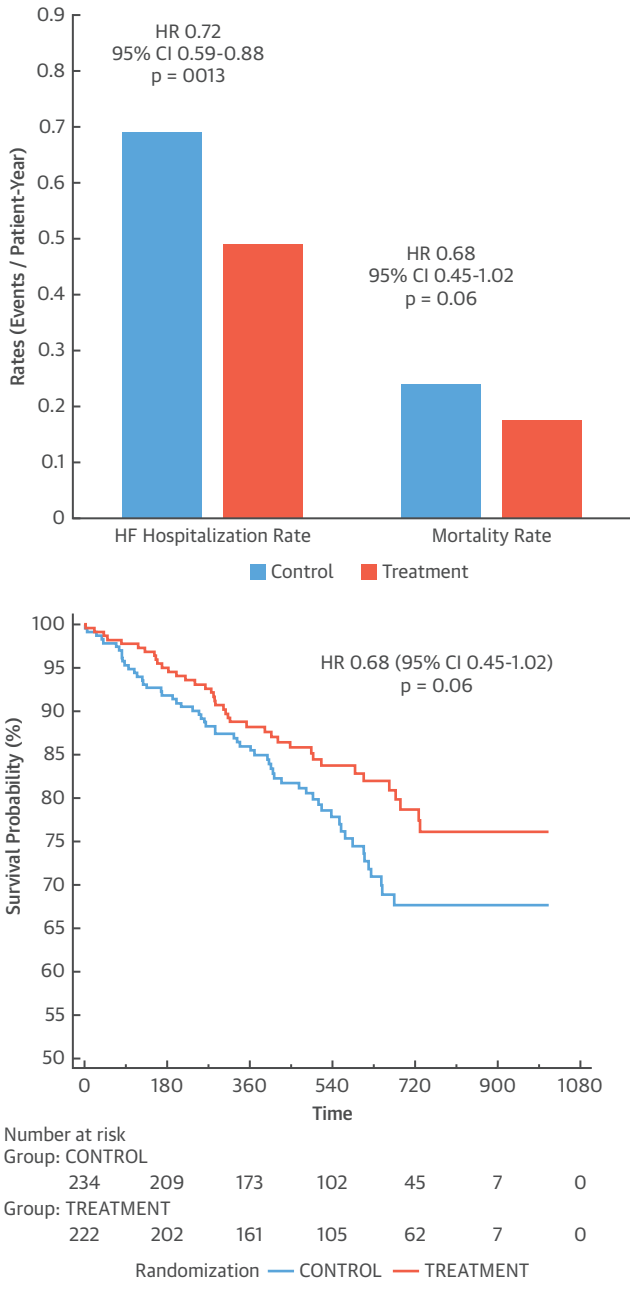
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; CHAMPION = CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients trial; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy with defibrillator; GDMT = guideline-directed medical therapy; GFR = glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PA = pulmonary artery; PRN = as needed; PVR = pulmonary vascular resistance.

DISCUSSION

Treatment group patients with HFrEF enrolled in the CHAMPION trial had significantly fewer HF decompensation events requiring a HF hospitalization, and had a strong trend toward reduced mortality compared with standard of care alone (control group). The hospitalization reduction and survival benefit seemed to be amplified by increasing application of GDMT. Additionally, as previously reported (42), investigators were able to further intensify neurohormonal antagonists, even in patients receiving maximally tolerated GDMT at baseline. However, the mortality benefit observed in patients receiving maximal GDMT at baseline was not entirely due to an ability to further optimize neurohormonal blockade.

The underlying pathophysiology of HF progression and acute decompensation is complex, involving numerous disease pathways, many of which are still not fully understood. It is clear that the process of HF decompensation requiring hospitalization has a negative impact on outcomes, with a majority of patients requiring further hospitalization in the next 6 to 12 months, as well as progression in the underlying disease process and higher mortality (27). It has long been hypothesized that prevention of acute decompensation would be a better management strategy for ambulatory patients with symptomatic HF, rather than reacting to a patient that is already decompensated (46). Many clinical trials focusing on intervention in patients with acute decompensated HF have failed to demonstrate a meaningful impact on outcomes (47). The current data further underscores the need for proactive prevention of decompensation and calls for an innovative look at management strategies. In general, RCTs have tested the safety and efficacy of a single drug or intervention. The novelty of the PA pressure-guided HF management strategy is that it may entail multiple simultaneous responses to PA pressure trends. Indeed, the same reduction in hospitalizations was observed in patients with HFpEF (37), in whom trials of a single intervention were all neutral or negative.

FIGURE 1 Clinical Outcomes of Pulmonary Artery Pressure-Guided Management in Patients With HFrEF



(Top) Heart failure (HF) hospitalization rates (events/patient-year) and mortality rate (deaths/patient-year) for all patients with heart failure with reduced ejection fraction (HFrEF) (n = 456) in the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial comparing treatment group patients **(orange bars)** with control group patients **(blue bars)**. Hazard ratios (HRs), 95% confidence intervals (CIs), and p value were obtained from the Andersen-Gill model for HF hospitalizations and from the Cox proportional hazards model for mortality. **(Bottom)** Kaplan-Meier survival plot for all patients with HFrEF (n = 456) in the CHAMPION trial comparing treatment group patients **(orange line)** with control group patients **(blue line)**. HR, 95% CI, and p value obtained from the Cox proportional hazards model.

In addition, management of chronic HF is often complicated by the presence of other comorbid conditions, each with their own set of complex clinical challenges. It is not surprising then that the successful management of patients with advanced chronic HF requires a comprehensive approach, involving use of multiple pharmacological and device therapies. However, determining more effective ways to reduce decompensation requiring hospitalization in the general HF population remains elusive (48-53). Innovative ideas that rely on new signals, such as changes in PA pressures using implantable hemodynamic monitoring, are now known to reduce HF hospitalization rates in both preserved and reduced ejection fraction. This is in contrast to the outcomes from multiple unsuccessful studies that attempted to reduce HF hospitalizations by basing clinical decision-making on less sensitive signals of worsening HF, such as daily weight measurements, frequent assessment of signs and symptoms of congestion, or nonhemodynamic device-based diagnostics (48-53).

Although there is little doubt regarding the safety, effectiveness, and overall benefit of neurohormonal antagonists at fixed doses to manage patients with HFrEF, there remains significant controversy regarding other HF drug classes, the magnitude of their benefit, which specific HF populations should be targeted, and exactly when and what dosages should be used. A fixed-dose approach to vasodilator therapy in a heterogeneous HFrEF study group resulted in only modest benefit (54,55). However, a more targeted approach of the fixed-dose vasodilator strategy in a less heterogeneous population of self-identified African Americans resulted in significant clinical benefit, including reduction in mortality (56). In the acute setting, higher fixed doses of loop diuretic agents failed to show significant benefit over lower fixed doses when evaluated in a prospective manner (57). This conflicting body of evidence shows the pragmatic complexity of using diuretic and vasodilator agents in the management of HF based only on early detection of patient symptoms or to alleviate acute hemodynamic abnormalities.

Although a fixed-dose approach to neurohormonal agents undoubtedly improves clinical outcomes, such an approach to diuretic and vasodilator agent management may not be optimal or even appropriate. It is possible that the primary culprit responsible for these mixed clinical trial results in heterogeneous study patients with HFrEF is due to the dosing strategy itself, and not the actual drug classes or their therapeutic mechanisms of action. Today, the availability of newer HF device

TABLE 2 Demographic and Baseline Treatment Characteristics for Patients With HFrEF on GDMT

	Group 1 (n = 445) At Least 1 ACEI/ARB or BB		Group 2 (n = 337) Both ACEI/ARB and BB	
	Treatment (n = 216)	Control (n = 229)	Treatment (n = 163)	Control (n = 174)
Demographics				
Age, yrs	59.7 ± 12.7	61.6 ± 12.7	58.6 ± 12.2	61.4 ± 12.9
Male	162 (75)	175 (76)	122 (75)	133 (76)
White	149 (69)	168 (73)	106 (65)	127 (73)
Clinical findings				
BMI, kg/m^2	30.3 ± 6.2	30.1 ± 6.4	30.6 ± 6.2	30.0 ± 6.6
Systolic BP, mm Hg	119.0 ± 21.3	122.2 ± 20.6	117.5 ± 20.4	122.6 ± 20.6
Heart rate, beats/min	72.9 ± 12.7	73.7 ± 12.5	72.1 ± 12.6	73.8 ± 12.5
Creatinine, mg/dl	1.41 ± 0.49	1.36 ± 0.42	1.36 ± 0.45	1.33 ± 0.39
GFR, ml/min/1.73m^2	61.2 ± 22.8	62.5 ± 23.5	64.4 ± 23.0	62.8 ± 21.6
BUN, mg/dl	29.9 ± 18.7	27.7 ± 16.3	27.6 ± 17.6	26.6 ± 15.8
Ejection fraction, %	25.3 ± 8.2	23.3 ± 7.9	24.9 ± 8.2	23.2 ± 7.8
Hemodynamics				
PA systolic, mm Hg	44.7 ± 14.5	45.9 ± 15.3	43.8 ± 14.6	44.8 ± 15.0
PA diastolic, mm Hg	18.9 ± 8.7	19.6 ± 8.0	18.5 ± 8.7	19.1 ± 7.7
PA mean, mm Hg	29.2 ± 10.2	30.2 ± 10.1	28.6 ± 10.3	29.5 ± 9.7
PA wedge, mm Hg	18.0 ± 8.4	19.5 ± 8.2	17.3 ± 8.1	19.1 ± 8.0
Cardiac output, l/min	4.43 ± 1.38	4.46 ± 1.49	4.59 ± 1.42	4.47 ± 1.54
Cardiac index, l/min/m^2	2.10 ± 0.59	2.14 ± 0.63	2.17 ± 0.61	2.13 ± 0.63
PVR, Wood units	2.86 ± 1.94	2.70 ± 1.78	2.78 ± 2.00	2.66 ± 1.86
Medical history				
Ischemic cardiomyopathy	133 (62)	148 (65)	96 (59)	113 (65)
COPD	60 (28)	69 (30)	43 (26)	49 (28)
Coronary artery disease	142 (66)	173 (76)	102 (63)	131 (75)
Diabetes mellitus	101 (47)	113 (49)	72 (44)	85 (49)
History of MI	112 (52)	121 (53)	80 (49)	89 (51)
Hyperlipidemia	163 (75)	180 (79)	116 (71)	139 (80)
Hypertension	165 (76)	180 (79)	124 (76)	138 (79)
Atrial fibrillation	88 (41)	108 (47)	61 (37)	84 (48)
Treatment history				
ICD only	79 (37)	90 (39)	61 (37)	64 (37)
CRT-D	83 (38)	89 (39)	59 (36)	73 (42)
CRT-D or ICD	162 (75)	179 (78)	120 (74)	137 (79)
Loop diuretic agent	201 (93)	210 (92)	155 (95)	164 (94)
Loop diuretic agent dose, mg	98.5 ± 73.3	95.1 ± 73.7	95.2 ± 77.4	88.3 ± 60.5
Thiazide diuretic agent	22 (10)	25 (11)	14 (9)	19 (11)
Thiazide diuretic agent dose, mg	3.1 ± 2.5	3.4 ± 2.3	3.6 ± 2.8	3.6 ± 2.6
Thiazide diuretic agent PRN	17 (8)	16 (7)	10 (6)	10 (6)
Thiazide PRN dose, mg	3.0 ± 1.2	3.2 ± 1.6	3.1 ± 1.4	3.2 ± 1.3
Nitrate	49 (23)	43 (19)	31 (19)	31 (18)
Nitrate dose, mg	62.9 ± 31.8	50.1 ± 31.5	61.6 ± 34.3	48.7 ± 33.4
Hydralazine	30 (14)	30 (13)	15 (9)	19 (11)
Hydralazine dose, mg	123.3 ± 99.6	102.1 ± 62.2	143.2 ± 120.3	80.9 ± 53.3
ACEI/ARB	173 (80)	183 (80)	163 (100)	174 (100)
ACEI/ARB dose, mg	19.0 ± 17.4	20.1 ± 18.1	19.0 ± 17.5	20.6 ± 18.3
BB	206 (95)	220 (96)	163 (100)	174 (100)
BB dose, mg	28.6 ± 21.5	30.0 ± 23.0	28.4 ± 21.9	31.0 ± 22.3
ACEI/ARB and BB	163 (75)	174 (76)	163 (100)	174 (100)
Aldosterone antagonist	104 (48)	100 (44)	85 (52)	75 (43)
Aldosterone antagonist dose, mg	27.8 ± 13.0	30.8 ± 21.0	27.7 ± 13.2	30.8 ± 20.5

Values are mean ± SD or n (%).

Abbreviations as in Table 1.

TABLE 3 Changes in HF Drug Therapy

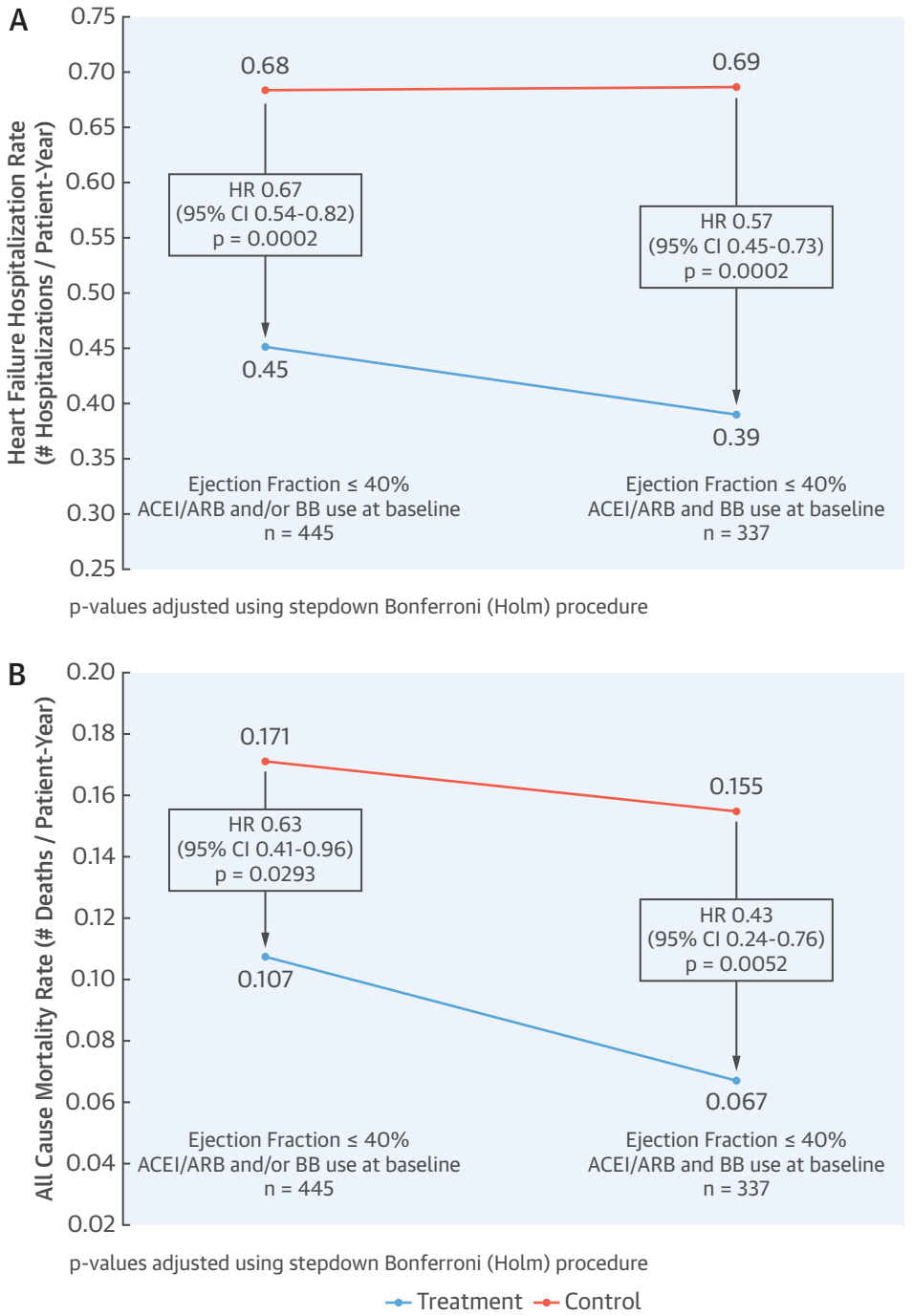
Patients on at Least 1 ACEI/ARB or BB at Baseline (Group 1) After 6 Months of Hemodynamic-Guided HF Management							
		Treatment Group (n = 216)			Control Group (n = 229)		
	Drug	Baseline	6 Months	p Value*	Baseline	6 Months	p Value*
Diuretic agents	Loop diuretic agent (furosemide equivalent)	96.2 ± 70.1	118.1 ± 94.0	0.0005	91.7 ± 63.6	109.8 ± 89.7	0.0002
	Thiazide diuretic agent (stand) (metolazone equivalent)	2.92 ± 1.98	3.92 ± 4.04	0.5234	3.47 ± 2.38	3.49 ± 3.06	1.0000
	Thiazide diuretic agent (PRN)	3.05 ± 1.20	3.20 ± 1.29	1.0000	3.18 ± 1.61	3.26 ± 1.24	0.8750
Vasodilator agents	Nitrate	64.3 ± 33.4	86.5 ± 58.3	0.0004	48.0 ± 30.4	50.7 ± 32.1	0.3750
	Hydralazine	125.0 ± 100.9	157.6 ± 99.4	0.0009	104.9 ± 60.9	129.4 ± 93.2	0.0850
Neurohormonal antagonists	ACEI or ARB (enalapril equivalent)	19.4 ± 17.9	22.7 ± 22.2	0.0051	20.1 ± 18.3	20.4 ± 19.5	0.6121
	BB (carvedilol equivalent)	29.1 ± 21.7	32.9 ± 23.7	0.0011	29.6 ± 22.8	30.8 ± 23.2	0.3091
	Aldosterone antagonist (spironolactone equivalent)	27.8 ± 13.0	27.0 ± 22.0	0.5514	30.8 ± 21.0	30.9 ± 30.2	0.3703
Patients on Both ACEI/ARB and BB Therapy at Baseline (Group 2) After 6 Months of Hemodynamic-Guided HF Management							
		Treatment Group (n = 163)			Control Group (n = 174)		
	Drug	Baseline	6 Months	p Value*	Baseline	6 Months	p Value*
Diuretic agents	Loop diuretic agent (furosemide equivalent)	93.4 ± 73.2	107.7 ± 79.6	0.0082	88.3 ± 60.5	108.6 ± 85.8	<0.0001
	Thiazide diuretic agent (stand) (metolazone equivalent)	3.27 ± 1.99	4.41 ± 4.16	0.6250	3.62 ± 2.63	3.64 ± 3.50	1.0000
	Thiazide diuretic agent (PRN)	3.19 ± 1.41	2.92 ± 1.25	1.0000	3.21 ± 1.27	3.71 ± 1.40	0.5000
Vasodilators	Nitrate	63.5 ± 36.1	84.4 ± 60.1	0.0078	45.4 ± 31.1	48.9 ± 33.6	0.3125
	Hydralazine	148.0 ± 123.3	166.6 ± 124.2	0.1875	88.4 ± 51.3	104.6 ± 74.3	0.2500
Neurohormonal antagonists	ACEI or ARB (enalapril equivalent)	19.3 ± 18.0	22.0 ± 21.5	0.0312	20.6 ± 18.6	20.5 ± 19.2	0.7909
	BB (carvedilol equivalent)	28.7 ± 22.0	33.6 ± 24.7	0.0004	30.8 ± 22.5	31.0 ± 22.2	0.9537
	Aldosterone antagonist (spironolactone equivalent)	26.9 ± 10.7	26.3 ± 18.9	0.5459	30.8 ± 20.5	30.4 ± 29.7	0.1708

Values are mean ± SD. *p value testing baseline dose to 6-month dose using paired Wilcoxon tests within groups for patients on drug at baseline and 6-month visit.
HF = heart failure; other abbreviations as in Table 1.

technologies, such as implantable hemodynamic management systems, has shifted our therapeutic target from treatment of acute hemodynamic abnormalities to ongoing management of cardiac filling pressures in the ambulatory setting. This updated ambulatory hemodynamic hypothesis can uniquely explain certain aspects of disease progression in HF that were previously unknown or unobtainable. For example, baseline PA diastolic pressure predicted HF events in both the treatment and control groups, and directional changes in PA pressure can be used to predict both HF hospitalization risks (58) and mortality (59). These new insights help provide a window into the time-dependent progression of HF, from a period of stability to that of acute decompensation that cannot be adequately addressed through fixed-dose neurohormonal control alone or the use of diuretic and vasodilator therapy in response to signs and symptoms of congestion.

In the CHAMPION trial, 445 patients with HFrEF entered the study already well-treated, with a background of maximally tolerated doses of GDMT, including at least 1 ACEI/ARB or BB, and 337 of these patients were using both ACEI/ARB and BB therapies. For these patients, continuation of neurohormonal antagonists alone was not sufficient to prevent progression of their HF syndrome. Integration of fixed-dose neurohormonal control coupled with dynamic modulation of ambulatory PA pressures, primarily with diuretic and vasodilator agents, resulted in a synergistic therapeutic strategy that addressed HF disease progression more broadly than the neurohormonal or prior acute hemodynamic hypotheses alone. When evaluated in a randomized setting in a large cohort of patients, this strategy of PA pressure-guided HF management resulted in large, clinically and statistically significant treatment effects that reduced HF hospitalizations and mortality by 33% and 43%, respectively, in patients taking at least 1 ACEI/ARB or BB at baseline and by 43% and 57%, respectively, in patients taking both ACEI/ARB and BB at baseline compared with continued neurohormonal management alone. Notably, this strategy of PA pressure-guided HF management has recently been shown to lower PA pressures (60) and reduce HF hospitalization rates and comprehensive HF costs (61) in real-world populations of patients with chronic HF.

CENTRAL ILLUSTRATION **Pulmonary Artery Pressure-Guided Heart Failure Management**



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(A) Heart failure hospitalization rates compared between subjects randomized to the treatment group **(blue line)** versus the control group **(orange line)** in patients with heart failure with reduced ejection fraction (HFrEF) treated with at least 1 of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) or beta-blocker (BB) (group 1, n = 445) and patients receiving both ACEI/ARB and beta-blocker therapy (group 2, n = 337). **(B)** All-cause mortality rates compared between subjects randomized to the treatment group **(blue line)** versus the control group **(orange line)** in group 1 patients (n = 445) and group 2 patients (n = 337). Hazard ratio (HR), 95% confidence interval (CI), and p value obtained from the Cox proportional hazards model using the stepdown Bonferroni (Holm) procedure to account for multiplicity.

TABLE 4 Unadjusted Mortality and Mortality Adjusted for Absolute Changes in HF Medication Dose Over 6 Months

	Group 1 EF ≤40% and at Least 1 ACEI/ARB or BB (n = 445)	Group 2 EF ≤40% and Both ACEI/ARB and BB (n = 337)
Unadjusted mortality	0.63 (0.41–0.96)	0.43 (0.24–0.76)
Mortality adjusted for changes in neurohormonal antagonist doses*	0.65 (0.43–0.99)	0.45 (0.25–0.80)
Mortality adjusted for changes in vasodilator agent doses†	0.64 (0.42–0.98)	0.44 (0.25–0.78)

Values are hazard ratio (95% confidence interval) from Cox proportional hazards model for mortality. *Model includes covariates for 6-month changes in daily dosages (mg) of ACEI/ARB and beta-blockers. †Model includes covariates for 6-month changes in daily dosages (mg) of nitrates and hydralazine.

EF = ejection fraction; other abbreviations as in Tables 1 and 3.

STUDY LIMITATIONS. Although the CHAMPION trial prospectively planned to evaluate clinical outcomes by baseline ejection fraction, the current analysis of the ability of patients with HFrEF to tolerate neurohormonal antagonist therapies was not explicitly prospectively planned. Thus, these findings should be viewed as hypothesis-generating and supportive of the concept, outlined by Zile et al. (59), concerning the impact of adequate PA pressure treatment on mortality rates. Despite this limitation, the magnitude of the treatment effect was significant and consistently observed, even in patients who were maximally treated with all available neurohormonal antagonists, including mineralocorticoid receptor antagonists, as a requirement for inclusion in the trial. In addition, the combination of angiotensin-neprilysin inhibition was not available at the time of the CHAMPION Trial.

CONCLUSIONS

Initiation of a PA pressure-guided HF management strategy, even in patients already receiving maximally tolerated background medical and device therapies, was able to achieve large, consistent treatment benefits in HF hospitalizations and mortality. Additional post-market investigations are underway to definitively validate this new synergistic therapeutic strategy, which integrates target-dose neurohormonal control coupled with dynamic modulation of ambulatory PA pressures.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with HFrEF, guiding medication and device-based therapy by measurement of PA pressure reduces hospitalizations and mortality.

TRANSLATIONAL OUTLOOK: Additional investigations are needed to validate the impact on morbidity and mortality of a clinical management strategy for patients with HFrEF that integrates neurohormonal inhibition with PA pressure measurements in routine clinical practice.

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