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Interventions Linked to Decreased Heart Failure Hospitalizations During Ambulatory Pulmonary Artery Pressure Monitoring

Maria R. Costanzo, MD,[a] Lynne W. Stevenson, MD,[b] Philip B. Adamson, MD,[c] Akshay S. Desai, MD,[b] J. Thomas Heywood, MD,[d] Robert C. Bourge, MD,[e] Jordan Bauman, MS,[c] William T. Abraham, MD[f]

ABSTRACT

OBJECTIVES This study sought to analyze medical therapy data from the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III Heart Failure) trial to determine which interventions were linked to decreases in heart failure (HF) hospitalizations during ambulatory pulmonary artery (PA) pressure-guided management.

BACKGROUND Elevated cardiac filling pressures, which increase the risk of hospitalizations and mortality, can be detected using an ambulatory PA pressure monitoring system before onset of symptomatic congestion allowing earlier intervention to prevent HF hospitalizations.

METHODS The CHAMPION trial was a randomized, controlled, single-blind study of 550 patients with New York Heart Association functional class III HF with a HF hospitalization in the prior year. All patients undergoing implantation of the ambulatory PA pressure monitoring system were randomized to the active monitoring group (PA pressure-guided HF management plus standard of care) or to the blind therapy group (HF management by standard clinical assessment), and followed for a minimum of 6 months. Medical therapy data were compared between groups to understand what interventions produced the significant reduction in HF hospitalizations in the active monitoring group.

RESULTS Both groups had similar baseline medical therapy. After 6 months, the active monitoring group experienced a higher frequency of medications adjustments; significant increases in the doses of diuretics, vasodilators, and neurohormonal antagonists; targeted intensification of diuretics and vasodilators in patients with higher PA pressures; and preservation of renal function despite diuretic intensification.

CONCLUSIONS Incorporation of a PA pressure-guided treatment algorithm to decrease filling pressures led to targeted changes, particularly in diuretics and vasodilators, and was more effective in reducing HF hospitalizations than management of patient clinical signs or symptoms alone. (J Am Coll Cardiol HF 2016;4:333–44)

From the [a]Advocate Heart Institute, Naperville, Illinois; [b]Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts; [c]Global Research and Development, St. Jude Medical, Austin, Texas; [d]Scripps Clinic, La Jolla, California; [e]University of Alabama at Birmingham, Birmingham, Alabama; and the [f]Division of Cardiology, The Ohio State University, Columbus, Ohio. Dr. Costanzo has received travel expenses from St. Jude Medical and consulting fees for membership in the Steering Committee of the LAPTOP-HF trial, which is sponsored by St. Jude Medical and the Advocate Heart Institute; and received research support from St. Jude Medical. Dr. Stevenson received travel expenses from St. Jude Medical and Brigham and Women's Hospital; and received research support from St. Jude Medical. Dr. Adamson was the Co-Principal Investigator of the CHAMPION trial; and is currently Medical Director and Vice President for Medical Affairs, Global Research and Development for St. Jude Medical. Dr. Desai has received consulting honoraria from St. Jude Medical; is a consultant for Merck, Relypsa, and Novartis; and received research grants from Novartis. Dr. Heywood has received research support from Medtronic and St. Jude Medical; fellowship support from St. Jude Medical; speaking honoraria from Medtronic, St. Jude Medical, and Biotronik; and has

ABBREVIATIONS AND ACRONYMS

AA = aldosterone antagonist

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin receptor blocker

BB = beta blocker

GDMT = guideline-directed medical therapy

HF = heart failure

LVEF = left ventricular ejection fraction

PA = pulmonary artery

Higher cardiac filling pressures in patients with heart failure (HF) are associated with higher risk for hospitalizations and mortality (1,2). Regardless of left ventricular ejection fraction (LVEF), filling pressures rise more than 2 weeks before rehospitalization (3). In the COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) study, active adjustment in medications in response to elevated filling pressures transmitted by an implanted device decreased hospitalizations more effectively than therapy guided only by clinical signs and symptoms of congestion (4). In patients with an estimated baseline pulmonary artery (PA) diastolic pressure higher than 25 mm Hg the risk of HF events decreased by 50% if the pressure was subsequently lowered below 25 mm Hg (5). However, COMPASS-HF (6) lacked definitions for target "optivolemia" filling pressures and therapy algorithms. As a result, high filling pressures at baseline generally remained high throughout the study, during which the average estimated PA diastolic pressure was 28 ± 7 mm Hg (5). Ambulatory monitoring of intracardiac pressures is only useful if it can be translated into effective interventions.

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HF management guided by monitoring of PA pressure was refined in the CHAMPION trial (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III Heart Failure) to include guidelines on how to treat elevated PA pressures to achieve protocol-defined target filling pressure ranges with titration of diuretics and vasodilators (7). This study compared HF hospitalization rates in patients whose therapy was guided by PA pressures (active monitoring group) with patients whose uploaded PA pressures were not available to the clinicians. In this "blind therapy group," investigators adjusted therapy according to usual clinical information. In CHAMPION, PA pressure-guided HF management was associated with a 28% reduction in HF hospitalization rates after 6 months and 37% after an average follow-up of 15 months relative to management guided by clinical assessment alone (8).

We analyzed the frequency and rationale for medication changes in relationship to PA pressure data obtained during the CHAMPION trial to determine what interventions were linked to decreased hospitalizations during ambulatory PA pressure-guided management, and what baseline PA pressure and therapies delivered were associated with benefit.

METHODS

STUDY DESIGN. The study design and main results of the CHAMPION trial have been previously published in detail (7,8). Briefly, from 64 U.S. study sites the trial enrolled 550 New York Heart Association functional class III patients who had been hospitalized for HF in the previous year. Patients were enrolled regardless of LVEF or HF etiology and were required to already be taking all appropriate guideline-directed medical and device therapies (GDMT) (9). The CHAMPION trial was a randomized, controlled, single-blind study with all patients undergoing right heart catheterization and implantation of the wireless hemodynamic monitoring system (CardioMEMS HF System, St. Jude Medical, Inc., Atlanta, Georgia) (10–12). For all patients, physicians had access to baseline hemodynamic information from the right heart catheterization. After device implantation, patients were randomized 1:1 to the active monitoring group or to the blind therapy group. All patients in both groups were instructed to transmit daily PA pressure readings from home. Real-time PA pressure information from home monitoring was available to physicians only for patients randomized to the active monitoring group. The primary endpoint for the CHAMPION trial was HF hospitalization rates, which were evaluated at 6 months of follow-up. All hospitalizations and deaths were adjudicated by a clinical events committee blinded to study group assignment.

Protocol recommendations for PA pressure-guided HF management. Patients in both arms were treated according to clinical symptoms and signs of excessive volume, including daily weight measurements. The central hypothesis was that medication adjustment guided by PA pressure would reduce HF hospitalizations compared with reliance solely on clinical symptoms and signs. CHAMPION trial investigators were given specific recommendations on

consulted for St. Jude Medical, Medtronic, and Biotronik. Dr. Bourge has received grant support and consulting honoraria from CarioMEMS and St. Jude Medical. Mr. Bauman is employed by St. Jude Medical in Global Research and Development. Dr. Abraham has received consulting fees from CardioMEMS/St. Jude Medical for roles as Co-Principal Investigator for the CHAMPION trial and Principal Investigator for the LAPTOP-HF trial; and has received speaker honoraria and travel fees from St. Jude Medical.

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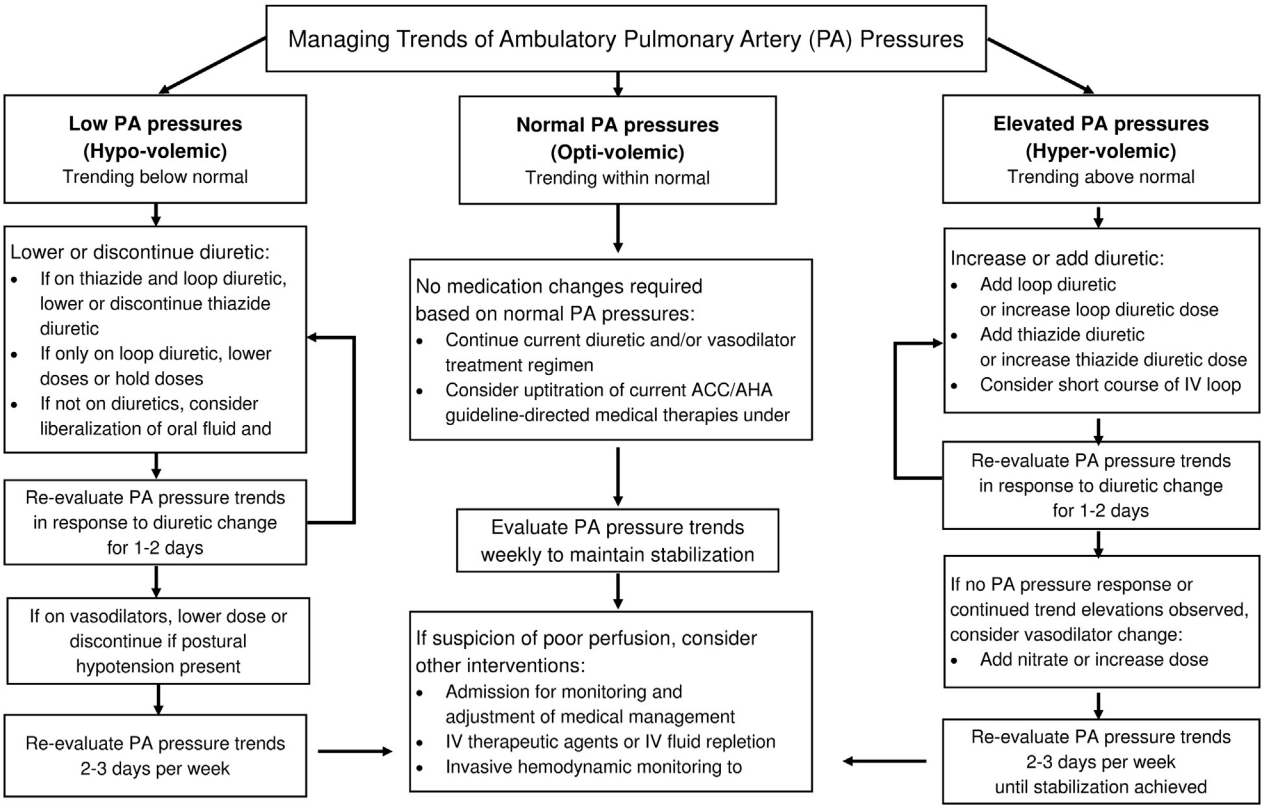
FIGURE 1 Pulmonary Artery Pressure Treatment Guidelines



The PA pressure treatment guidelines for the CHAMPION trial used a treatment algorithm in response to patient hemodynamic trend data. The low PA pressure and elevated PA pressure algorithms implemented change protocols for diuretic and/or vasodilator therapies to achieve hemodynamic stabilization. In the presence of normal PA pressures, continuation of existing patient treatment regimens with consideration for further uptitration of guideline-directed medical therapy was recommended. ACC = American College of Cardiology; AHA = American Heart Association; CHAMPION = CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III Heart Failure; IV = intravenous; PA = pulmonary artery.

how to use PA pressures to guide HF therapies (Figure 1). The study protocol instructed investigators to reduce PA pressures to a target range by adjusting diuretics or vasodilators. The target for PA diastolic pressure of 8 mm Hg to 20 mm Hg and/or PA mean pressure 10 mm Hg to 25 mm Hg were used. It was anticipated that knowledge of PA pressure might facilitate further optimization of GDMT in patients with HF and reduced EF, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), aldosterone antagonists (AAs), all of which can also contribute to lower PA pressures, and beta blockers (BBs), titration of which may be facilitated by knowledge that PA pressures are stable.

ANALYSES AND STATISTICAL METHODS. Results for this analysis are provided for the entire study population regardless of LVEF and presented for patients with reduced LVEF only when appropriate. The percentage of patients in the active monitoring and blind therapy groups receiving ACEI/ARB, BB, AA, nitrates, hydralazine, loop diuretics, and daily and as-needed thiazide diuretics at baseline and at 6 months were evaluated (13). Differences between groups were analyzed using the Fisher exact test.

Outpatient medication changes were tracked during the 6 months of follow-up, including whether the dose was increased or decreased, and were compared between groups using the Wilcoxon rank sum test.

The total daily doses for each HF drug therapy class were also calculated at baseline and after 6 months, converting to equivalents for enalapril, carvedilol, AA spironolactone, furosemide, and metolazone. Conversion details are provided in Online Tables 1 and 2.

Estimates for the frequency of medication changes, including dose increases or decreases, occurring during the 6 month follow-up period, were also

related to baseline PA diastolic pressure for the randomized groups using the Poisson regression methodology (14). The regression estimates for medication changes were then plotted across the range of baseline PA diastolic pressure for each group.

Data are summarized as frequencies and percentages for categorical variables. Continuous variables are presented as mean ± standard deviation. For all statistical analysis, significance levels were 2-sided with a p value <0.05. All statistical analyses were performed using SAS version 9.2 or higher (Cary, North Carolina).

TABLE 1 Baseline Patient Profile

	Treatment Group (n = 270)	Control Group (n = 280)	p Value*
Demographics			
Age, yrs	61.3 ± 13	61.8 ± 12.7	0.5924
Male	194 (72)	205 (73)	0.7745
White	196 (73)	205 (73)	0.9236
Laboratory findings			
BMI, kg/m^2	30.5 ± 6.5	30.9 ± 7.3	0.6235
Systolic BP, mm Hg	121.2 ± 22.5	123.2 ± 21	0.1280
Heart rate, beats/min	72.4 ± 12.9	73 ± 12.1	0.4870
Creatinine, mg/dl	1.4 ± 0.47	1.35 ± 0.42	0.5558
GFR, ml/min/1.73 m^2	60.4 ± 22.5	61.8 ± 23.2	0.5635
BUN, mg/dl	29.6 ± 18	28.1 ± 16.2	0.6323
Ejection fraction >40%	48 (18)	45 (16)	0.6496
Hemodynamics			
PA systolic pressure, mm Hg	44.3 ± 14.2	45.4 ± 15.2	0.5276
PA diastolic pressure, mm Hg	18.6 ± 8.5	19.3 ± 8.1	0.2676
PA mean pressure, mm Hg	28.9 ± 9.9	29.9 ± 10	0.3016
Cardiac output, l/min	4.48 ± 1.41	4.56 ± 1.54	0.5420
Cardiac index, l/min/m^2	2.13 ± 0.6	2.17 ± 0.64	0.4553
PVR, Wood Units	2.88 ± 2.02	2.7 ± 1.82	0.4744
Medical history			
Ischemic cardiomyopathy	158 (59)	174 (62)	0.4327
Chronic obstructive pulmonary disease	76 (28)	83 (30)	0.7078
Coronary artery disease	182 (67)	202 (72)	0.2290
Diabetes mellitus	130 (48)	139 (50)	0.7337
History of MI	134 (50)	137 (49)	0.9320
Hyperlipidemia	204 (76)	218 (78)	0.5458
Hypertension	207 (77)	220 (79)	0.6100
History of atrial fibrillation	120 (44)	135 (48)	0.3932
Treatment history			
ICD only	88 (33)	98 (35)	0.5889
CRT-D	91 (34)	99 (35)	0.7201
CRT-D or ICD	179 (66)	197 (70)	0.3145
ACE/ARB	205 (76)	222 (79)	0.3584
Beta blocker	243 (90)	256 (91)	0.6595
ACE/ARB and beta blocker, GDMT	188 (70)	205 (73)	0.3955

Values are mean ± SD or n (%). *p value testing treatment versus control obtained from exact Wilcoxon rank sum test (continuous variables) and Fisher exact test (categorical values).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; BMI = body mass index; BUN = blood urea nitrogen; CRT-D = cardiac resynchronization therapy; GDMT = guideline-directed medical therapy; GFR = glomerular filtration rate; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; PA = pulmonary artery; PVR = pulmonary vascular resistance.

RESULTS

Patients enrolled in the CHAMPION trial had a mean age of 62 ± 13 years (Table 1). Per the 2013 American College of Cardiology Foundation/American Heart Association HF guideline definitions, HF was associated with reduced LVEF (≤40%) in 83% of patients (mean LVEF, 24.3 ± 8.0%) and preserved LVEF (>40%) in 17% of patients (mean LVEF, 53.6 ± 8.1%). At baseline there were no differences between active monitoring and blind therapy groups in the percentage of patients receiving each drug class or their total daily dose equivalents for the entire study population or the reduced LVEF subgroup (Table 2).

INTERVENTIONS DURING ACTIVE HEMODYNAMIC MONITORING. Frequency of HF drug therapy changes. More than twice as many medication changes occurred in the active monitoring group compared with the blind therapy group during the 6-month primary study follow-up period (2,468 vs. 1,061; p < 0.0001), as shown in Figure 2. Diuretics were the most frequently adjusted medications in both groups, although the number of dose changes were significantly higher in the active monitoring than in the blind therapy group (1,547 vs. 585; p < 0.0001). Fewer adjustments of other medication types were observed, but more frequent changes were made in the active monitoring than in the blind therapy group for direct vasodilators and for the GDMT neurohormonal antagonists (p < 0.05 for each drug class).

The frequency of decreases in medication doses from baseline to 6 month was significantly greater (p < 0.05) in the active monitoring group than in the blind therapy group. The higher frequency in medication decreases is accounted for by a greater number of diuretic dose reductions in the active monitoring than in the blind therapy group (Figure 3).

Changes in diuretic dosing and renal function. Diuretic doses were changed approximately 3 times as often in the active monitoring group. After 6 months, there were significant increases in the total daily loop diuretic dose compared with baseline for both treatment groups. For patients on therapy at baseline and at 6 months of follow-up, the increases in furosemide-equivalent dose in the active monitoring group was 25.9 mg (+27% change from baseline; p < 0.01) versus the 14.3 mg in the blind therapy group (+15% change of baseline; p < 0.01) (Table 3). As recommended in the study protocol, more diuretic changes occurred in patients with higher baseline PA diastolic pressure (Figure 4). The relationship between higher PA diastolic pressures and the number of diuretic changes was more apparent in the

TABLE 2 Heart Failure Drug Therapy at Baseline: Prevalence and Total Daily Dose

HF Drug Class	Drug	Active Monitoring Group (n = 270) n (%)	Active Monitoring Group (n = 270) Total Daily Dose (mg)	Blind Therapy Group (n = 280) n (%)	Blind Therapy Group (n = 280) Total Daily Dose (mg)	Analysis p Value*	Analysis p Value†
Diuretics	Loop diuretic	248 (92)	98.4	258 (92)	101.6	0.99	0.66
	Thiazide diuretic (ongoing)	30 (11)	3.27	35 (12)	3.70	0.69	0.50
	Thiazide diuretic (as needed)	20 (7)	3.19	18 (6)	3.35	0.74	0.75
Vasodilators	Nitrate	64 (24)	64.2	56 (20)	53.0	0.30	0.08
	Hydralazine	36 (13)	136.5	33 (12)	105.1	0.61	0.16
	ACE inhibitor or ARB	205 (76)	20.2	222 (79)	21.4	0.36	0.55
Neurohormonal antagonists	Beta blocker	243 (90)	28.7	256 (91)	31.5	0.66	0.22
	Aldosterone antagonist	117 (43)	29.2	114 (41)	32.0	0.55	0.32

HF Drug Class	Drug	Active Monitoring Group LVEF ≤40% Subgroup (n = 222) n (%)	Active Monitoring Group LVEF ≤40% Subgroup (n = 222) Total Daily Dose (mg)	Blind Therapy Group LVEF ≤40% Subgroup (n = 234) n (%)	Blind Therapy Group LVEF ≤40% Subgroup (n = 234) Total Daily Dose (mg)	Analysis p Value*	Analysis p Value†
Diuretics	Loop diuretic	206 (93)	97.7	215 (92)	95.3	0.7289	0.7363
	Thiazide diuretic (ongoing)	22 (10)	3.14	25 (11)	3.41	0.8778	0.7042
	Thiazide diuretic (as needed)	17 (8)	3.01	16 (7)	3.18	0.8569	0.7417
Vasodilators	Nitrate	51 (23)	62.7	44 (19)	50.3	0.3000	0.0559
	Hydralazine	31 (14)	123.0	31 (13)	99.8	0.8915	0.2701
	ACE inhibitor or ARB	173 (78)	19.0	183 (78)	20.1	1.0000	0.5749
Neurohormonal antagonists	Beta blocker	206 (93)	28.6	220 (94)	30.0	0.7063	0.5100
	Aldosterone antagonist	105 (47)	27.7	101 (43)	31.0	0.3976	0.1785

*p value testing treatment versus control prevalence obtained from Fisher exact test. †p value testing treatment versus control total daily dose obtained from exact Wilcoxon rank sum test.

HF = heart failure; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

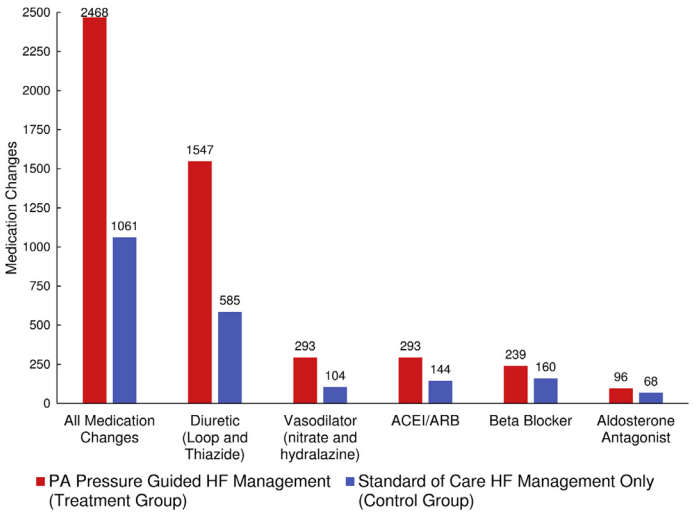
active monitoring than in the blind therapy group. Across the range of baseline PA diastolic pressures, the estimated frequency of diuretic changes made by investigators in the active monitoring group was 2.8 times greater than in the blind therapy group (incidence rate ratio [IRR]: 2.78; 95% confidence interval: 2.53 to 3.06; $p < 0.0001$).

Baseline estimated glomerular filtration rate was similar in the 2 groups (Table 1). After 6 months of follow-up, there were no significant changes in serum creatinine or estimated glomerular filtration rate between the active monitoring and blind therapy groups (Table 4). Separate analysis of the 297 patients (54%) with chronic kidney disease at baseline (estimated glomerular filtration rate <60 ml/min/1.73 m^2) also found no change in renal function compared between groups.

Use of direct vasodilators. During 6 months of follow-up, vasodilator therapies were adjusted in 116 patients (43%) in the active monitoring group and 47 patients (17%) in the blind therapy group. Only 5% of the patients with vasodilator change did not have a diuretic change. The active monitoring group had an increase in nitrate dose from baseline (17.5 mg [+27% change from baseline]; $p < 0.01$) and hydralazine dose from baseline (33.3 mg [+24% change from baseline]; $p < 0.01$). No changes from baseline were observed in the blind therapy group for these therapies (Table 3). More vasodilator changes occurred in active monitoring patients who had higher baseline PA diastolic pressure (Figure 5). Across the range of baseline PA diastolic pressures, the frequency of vasodilator changes in the active monitoring group was 3.0 times greater than in the blind therapy group (IRR: 2.97; 95% confidence interval: 2.39 to 3.73; $p < 0.0001$).

The percentage of blind therapy patients given nitrates increased from 19% to 22% after 6 months, whereas nitrate therapy nearly doubled in the active monitoring group (24% to 42%; $p < 0.01$) (Table 5). Therefore, the total daily dose of nitrate therapy was higher in the active monitoring group compared with the blind therapy patients at the end of 6 months (70.5 vs. 53.7 mg; $p = 0.02$). Hydralazine therapy also almost doubled in the active monitoring group (13% to 23%; $p < 0.01$), whereas the blind therapy group had no significant change in use of this drug. Despite higher use in the active treatment group, the average

FIGURE 2 Frequency of Medication Changes by Drug Class



Total HF medication changes occurring during the 6-month follow-up period were compared between the active monitoring group (PA pressure-guided HF management added to standard of care management of patient clinical signs and symptoms) **(red bars)** and the blind therapy group (HF management including only standard assessment of weights and patient-reported symptoms) **(blue bars)**. In addition, medication changes by HF drug class were compared between groups. ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; HF = heart failure; PA = pulmonary artery.

daily dose of hydralazine was not different between treatment groups. Similar findings were observed in the subgroup of patients with reduced LVEF (Table 5).

Increased dosing of neurohormonal antagonists. The active monitoring group experienced significant increases from baseline in doses of ACEI/ARB (+4.23 mg; $p < 0.01$), BB (+3.40 mg; $p < 0.01$), and AA (+3.71 mg; $p = 0.03$). No significant changes were observed in the blind therapy group for these therapies (Table 3).

There were 456 patients with a LVEF ≤40% at the time of enrollment. Baseline use of GDMT was excellent as shown in Table 2. For patients on therapy at baseline and at 6 months of follow-up (paired test), the active monitoring group patients with reduced LVEF had increases in ACEI/ARB (+3.32 mg; $p < 0.01$), BB (+3.79 mg; $p < 0.01$), and AA (+4.26 mg; $p = 0.02$). Again, no changes in GDMT from baseline were observed in the blind therapy group (Table 3).

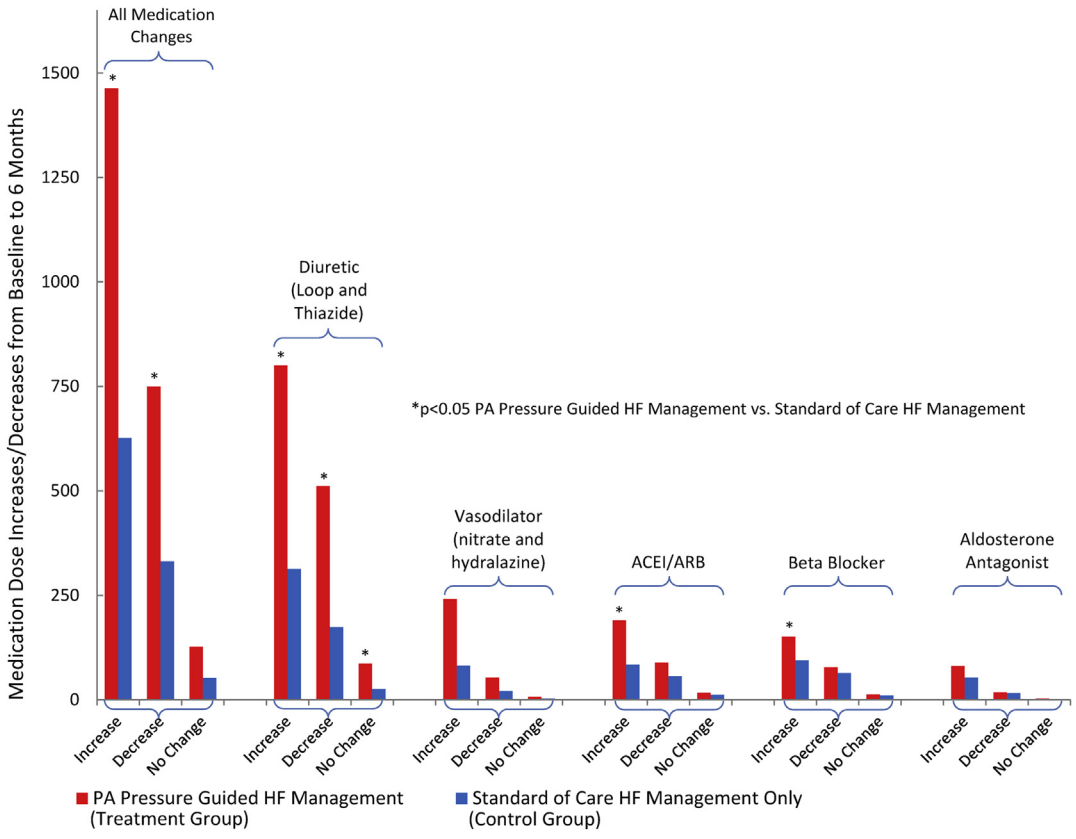
Identification of patients at higher risk needing diuretic changes. Patients who were considered to require diuretic dose adjustment during the 6 months follow-up were at higher risk of events, whether PA pressures were known or not. HF hospitalization rates in patients with diuretic changes were 38% lower in the active monitoring group than in the blind therapy group (IRR: 0.62; 95% confidence interval: 0.46 to 0.83; $p = 0.0014$). Only 49 patients (18%) in the active monitoring group had no diuretic changes and these were patients with lower initial PA diastolic pressures (median, 13 mm Hg; interquartile range, 9.0 to 17.3 mm Hg). This group had the lowest HF hospitalization rate at 0.21 events per year. The blind therapy group had more patients (n = 107, 38%) deemed not to need diuretic changes based on signs and symptoms alone. Interestingly, patients without diuretic change in the blind therapy group had significantly higher PA diastolic pressure (median, 17 mm Hg; interquartile range, 12.3 to 23.0 mm Hg) and a higher HF hospitalization rate of 0.39 events per year, compared with the 0.21 events per year among patients without diuretic change in the active monitoring group. Although the difference in hospitalization rates in this limited subset was not statistically significant, the 45% lower HF hospitalization rate during active monitoring in the "low diuretic intervention group" suggests that risk-stratification into a "low diuretic intervention group" was less accurate on the basis of clinical information alone.

DISCUSSION

This analysis of pharmacologic interventions and ambulatory PA pressures completes the circle, linking reduction of elevated PA pressures to reduced hospitalization rates through a more frequent adjustment of diuretic and vasodilator medications compared with changes triggered by clinical signs and symptoms alone. In patients with HF with reduced EF, PA pressure-guided medication management occurred on the background of GDMT and actually allowed higher dosing of neurohormonal antagonists. Patients with higher baseline PA pressures in the active treatment group had both a greater frequency of therapeutic interventions and greater reduction in HF events throughout the duration of the CHAMPION trial. This analysis underscores the vital importance of specifying both the targets of therapeutic interventions and the algorithm guiding such interventions to validate a new management strategy. This specific information is essential to effectively translate the strategy used in the CHAMPION trial into clinical practice.

AMBULATORY CARDIAC PRESSURES AS TARGET FOR THERAPY. The association of high filling pressures with poor outcomes has long been recognized in chronic HF (15). However, altering prognostic markers does not necessarily improve prognosis (16). For some of these variables, more severe derangement may

FIGURE 3 Frequency of Medication Increases and Decreases by Drug Class



Increases and decreases in all classes of HF medications during the 6-month follow-up period were compared between the active monitoring group **(red bars)** and the blind therapy group **(blue bars)**. The greater number of medication decreases in the active monitoring group is entirely caused by a greater number of reductions in diuretic doses. **No Change** represents instances where a medication was changed (e.g., dose frequency, route, etc.) that resulted in no net daily dose equivalent change. Abbreviations as in Figures 1 and 2.

indicate more advanced disease unresponsive to further intervention (6). Previous disenchantment with treatment of hemodynamics arose when the target for treatment focused on low cardiac output by using inotropic therapies, which consistently worsened outcomes (17). In contrast, a large and consistent database now available from trials of ambulatory hemodynamic monitoring indicates that elevated filling pressures not only track advancing disease but provide targets for intervention that can often avert hospitalization (18,19). Reductions in filling pressures directly translate to reduced hospitalization risk, which predicts a favorable impact on HF disease progression. In the primary CHAMPION trial manuscript, the reduction in PA pressures from baseline to 6 months (secondary endpoint in the trial) was greater in the active monitoring than in the blind therapy group (8). The current analysis of medication use in the CHAMPION trial connects higher PA pressures to higher event rates and demonstrates that purposeful lowering of those pressures with proactive treatment reduces HF event rates.

TITRATION OF THERAPY. Adjustment of diuretics. Diuretics were most frequently adjusted in response to ambulatory monitoring of PA pressures, and the number of changes in the doses of these medications was closely related to PA pressure levels at baseline. This is congruent with the fact that when patients are allowed to decompensate and are hospitalized they have evidence of congestion requiring administration of intravenous diuretics to alleviate fluid overload regardless of LVEF (20–22).

This concept also applies to the 90 days following hospital discharge in which diuretics accounted for more than 60% of all medication changes, typically in response to weight changes (23). Although

TABLE 3 Changes in Heart Failure Drug Therapy Total Daily Dose

		Active Monitoring Group (n = 270)			Blind Therapy Group (n = 280)		
HF Drug Class	**Drug**	**Baseline**	**6 Months**	**p Value***	**Baseline**	**6 Months**	**p Value***
Diuretics	Loop diuretic	96.8 ± 73.9 (223)	122.7 ± 101.5 (223)	<0.01	98.0 ± 74.6 (241)	112.4 ± 90.3 (241)	<0.01
	Thiazide diuretic (standing)	3.18 ± 1.90 (18)	4.29 ± 3.53 (n = 18)	0.17	3.54 ± 2.56 (22)	3.42 ± 3.01 (22)	0.71
	Thiazide diuretic (as needed)	3.22 ± 1.27 (19)	3.36 ± 1.32 (19)	0.58	3.35 ± 1.77 (18)	3.42 ± 1.47 (18)	0.85
Vasodilators	Nitrate	65.4 ± 36.9 (58)	82.9 ± 58.1 (58)	<0.01	51.7 ± 34.2 (51)	55.4 ± 36.7 (51)	0.14
	Hydralazine	140.1 ± 113.1 (34)	173.4 ± 110.5 (34)	<0.01	108.0 ± 64.0 (29)	130.0 ± 91.9 (29)	0.16
Neurohormonal antagonists	ACE inhibitor or ARB	20.7 ± 19.6 (189)	24.9 ± 24.5 (189)	<0.01	21.6 ± 20.5 (203)	21.6 ± 21.0 (203)	0.94
	Beta blocker	29.3 ± 22.0 (228)	32.7 ± 24.7 (228)	<0.01	31.4 ± 28.6 (240)	32.0 ± 28.3 (240)	0.54
	Aldosterone antagonist	27.0 ± 11.0 (101)	30.8 ± 20.0 (101)	0.03	32.8 ± 22.3 (99)	35.5 ± 29.3 (99)	0.14
		Active Monitoring Group LVEF ≤40% Subgroup (n = 222)			**Blind Therapy Group LVEF ≤40% Subgroup (n = 234)**		
HF Drug Class	**Drug**	**Baseline**	**6 Months**	**p Value***	**Baseline**	**6 Months**	**p Value***
Diuretics	Loop diuretic	95.5 ± 69.4 (185)	118.3 ± 92.9 (185)	0.0004	92.0 ± 63.3 (201)	109.6 ± 88.9 (201)	**0.0007**
	Thiazide diuretic (standing)	2.92 ± 1.98 (13)	3.92 ± 4.04 (13)	0.3512	3.47 ± 2.38 (14)	3.49 ± 3.06 (14)	0.9796
	Thiazide diuretic (as needed)	3.05 ± 1.20 (16)	3.20 ± 1.29 (16)	0.5805	3.18 ± 1.61 (16)	3.26 ± 1.24 (16)	0.8489
Vasodilators	Nitrate	64.1 ± 32.7 (45)	85.3 ± 57.2 (45)	0.0028	48.3 ± 30.0 (39)	50.9 ± 31.7 (39)	0.2750
	Hydralazine	124.6 ± 99.2 (30)	162.3 ± 101.1 (30)	0.0011	102.1 ± 61.5 (27)	125.7 ± 93.4 (27)	0.1579
	ACE inhibitor or ARB	19.4 ± 17.9 (158)	22.7 ± 22.2 (158)	0.0053	20.1 ± 18.3 (168)	20.4 ± 19.5 (168)	0.7544
Neurohormonal antagonists	Beta blocker	29.1 ± 21.7 (193)	32.9 ± 23.7 (193)	0.0017	29.6 ± 22.8 (206)	30.8 ± 23.2 (206)	0.2503
	Aldosterone antagonist	26.9 ± 10.9 (91)	31.2 ± 20.5 (91)	0.0241	31.9 ± 22.0 (90)	34.9 ± 29.8 (90)	0.1407

Values are mean ± SD (n). *p value testing baseline dose to 6-month dose using paired Student *t* test within groups.
Abbreviations as in Tables 1 and 2.

weight-based monitoring at home will remain a component of HF management, intensified surveillance of weight changes at home has not consistently improved outcomes when tested in prospective clinical trials (24). Weight changes track reliably with fluid status during short time periods, such as hospitalization and the first week after discharge, but the "target" weight or "dry" weight diverges increasingly over time. This target can change for reasons other than volume, such as an increase with higher caloric intake or a decrease with cardiac cachexia. With this in mind aggregate analyses show weight gain is insensitive and the magnitude of change in most decompensating patients is <2 pounds. This change is within the range of normal variability for many patients and is not routinely actionable (25). Conversely, remotely obtained PA pressures consistently provide a valid signal for early warning of impending decompensation in the outpatient setting allowing intervention to prevent hospitalizations (26). The time course of the rise in cardiac filling pressures, generally detectable about 2 to 4 weeks before a hospitalization, is consistent across experiences with 2 different devices, in 2 different trials conducted over 2 different time periods (5). Furthermore, the ability to track pressures daily from home provides a "complete" disease management system allowing rapid response in medication change that can be continued until the pressures are lowered to the range of hemodynamic stability. This knowledge led to more increases and decreases in medication dosing in the active monitoring group of the

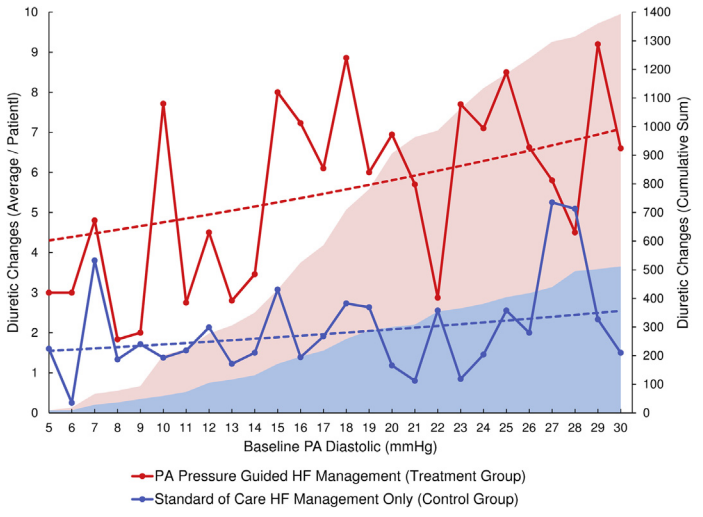
CHAMPION trial. Notably, not only the frequency of medications increases, but also that of decreases was significantly higher in the active monitoring than in the blind therapy group. The fact that the higher frequency of decreases in the active monitoring group was exclusively caused by a greater number of reductions in diuretic doses may explain why the greater number of medication changes in the active monitoring group was not associated with a greater worsening of renal function at 6 months compared with the blind therapy group.

Adjustment of direct vasodilators. The protocol specified use of vasodilators to reduce PA pressures when elevations persisted despite intensification of diuretic therapy or when circulating volume was not clearly elevated. Vasodilator adjustments were made more often in the active monitoring group mostly in those with the highest baseline PA pressures. Nitrates and hydralazine decrease systemic vascular resistance and intracardiac filling pressures and are considered useful for therapy of symptomatic HF with reduced LVEF (27,28). In CHAMPION, however, these medications were adjusted in a similar manner for both patients with HF with reduced EF (mean of 1.1 change per patient) and patients with HF with preserved EF (mean of 1.0 change per patient). The optimal use of direct vasodilators to supplement or replace increases in diuretic doses has not been established.

Adjustment of neurohormonal antagonists in HF with reduced ejection fraction. The high prevalence of baseline GDMT in the CHAMPION study was consistent with other contemporary trials and the benefit of ambulatory PA pressures to guide therapy occurred in addition to the benefits of excellent GDMT (6,8). The small but significant increase in ACEI and BB dosing may have contributed to improved outcomes observed in the active monitoring arm. Interestingly, improvement in outcomes in trials of B-type natriuretic peptide-guided therapy has also been ascribed to increases in neurohormonal antagonists' dosing (29). Ambulatory hemodynamic monitoring provides more specific guidance compared with biomarkers, because ACEI and ARB may lower filling pressures through further vasodilation, and knowledge of PA pressures may help to safely uptitrate BB agents. In the future, knowledge of PA pressures may be particularly helpful to personalize titration of neurohormonal antagonists in patients with a recent history of hemodynamic instability.

STRATEGY OF HF MANAGEMENT USING AMBULATORY PA PRESSURE MONITORING. Trials testing management strategies rather than single interventions are complicated by the need for protocols to clearly identify appropriate therapeutic targets. This is important because a disease management strategy includes the identification of the signal, implementation of an intervention, and ability to reassess the impact of the intervention. This requires rapid

FIGURE 4 Impact of Baseline PA Diastolic Pressure on Diuretic Changes



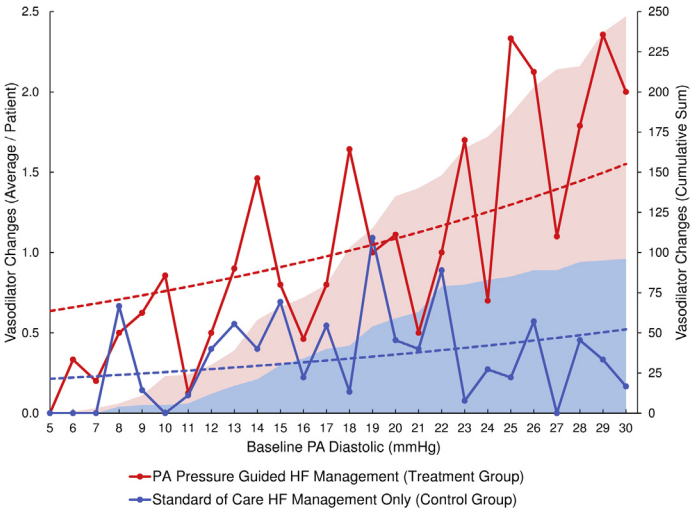
Shown on the primary y-axis to the left are the average number of diuretic changes per patient at each baseline PA diastolic pressure (x-axis) between the PA pressure-guided HF management **(solid red line)** and standard of care HF management **(solid blue line)** groups. Poisson regression estimates of the number of diuretic changes per patient are depicted with **dotted lines** for each group. The cumulative sum of the total number of diuretic changes with increasing PA diastolic pressure are displayed on the secondary y-axis to the right using **shaded areas**. Abbreviations as in Figures 1 and 2.

TABLE 4 Renal Function

All Patients	Active Monitoring Group (N = 270)	Blind Therapy Group (N = 280)	p Value*
Baseline creatinine	1.40 ± 0.47 (270)	1.35 ± 0.42 (280)	0.56
Creatinine change from baseline to 6 months	0.10 ± 0.45 (230)	0.07 ± 0.38 (235)	0.28
Baseline GFR	60.4 ± 22.5 (270)	61.8 ± 23.2 (280)	0.56
GFR change from baseline to 6 months	-3.1 ± 17.0 (230)	-1.0 ± 16.4 (235)	0.20
Patients With Chronic Kidney Disease at Baseline (eGFR <60)			
	Active Monitoring Group (N = 150)	**Blind Therapy Group (N = 147)**	**p Value***
Baseline creatinine	1.7 ± 0.41 (150)	1.6 ± 0.34 (147)	0.40
Creatinine change from baseline to 6 months	0.1 ± 0.54 (128)	0.1 ± 0.44 (123)	0.99
Baseline GFR	43.5 ± 9.09 (150)	44.4 ± 9.12 (147)	0.46
GFR change from baseline to 6 months	1.0 ± 14.48 (128)	0.6 ± 12.60 (123)	1.00

Values are mean ± SD (n). *p value testing treatment versus control obtained from exact Wilcoxon rank sum test. Abbreviation as in Table 1.

FIGURE 5 Impact of Baseline PA Diastolic Pressure on Vasodilator Changes



Shown on the primary y-axis to the left are the average number of vasodilator changes per patient at each baseline PA diastolic pressure (x-axis) between the PA pressure-guided HF management **(solid red line)** and standard of care HF management **(solid blue line)** groups. Poisson regression estimates of the number of vasodilator changes per patient are depicted with **dotted lines** for each group. The cumulative sum of the total number of vasodilator changes with increasing PA diastolic pressure are displayed on the secondary y-axis to the right using **shaded areas**. Abbreviations as in Figures 1, and 2.

kinetics of the marker used for assessment, which has complicated trials using biomarkers that do not respond immediately to therapy intensification. The ESCAPE trial had a specific target pulmonary capillary wedge pressure of 16 mm Hg in hospitalized patients, but interventions often included intravenous inotropic therapy rather than vasodilators, and there was no outpatient surveillance of PA pressures after discharge (30). The CHAMPION trial, in which PA pressures were consistently monitored over time, included a protocol specifying both the desired PA pressure ranges and the sequence of interventions with diuretics and vasodilators to achieve and maintain the target PA pressures in ambulatory patients.

STUDY LIMITATIONS. Although there was systematic prospective collection of interventions made in responses to PA pressures in the active monitoring group, there are gaps in the information related to such actions. The initial interventions triggered by the right heart catheterization information in both groups before randomization and the interventions made during hospitalization after randomization were not captured. This may have altered the magnitude of the difference in outcomes observed between the active monitoring and the blind therapy group. Medication

TABLE 5 Heart Failure Drug Therapy at 6 Months: Prevalence and Total Daily Dose

		Active Monitoring Group (n = 270)		Blind Therapy Group (n = 280)		Analysis	
HF Drug Class	Drug	n (%)	Total Daily Dose (mg)	n (%)	Total Daily Dose (mg)	p Value*	p Value†
Diuretics	Loop diuretic	239 (89)	123.8	251 (90)	110.6	0.68	0.13
	Thiazide diuretic (standing)	53 (20)	3.68	41 (15)	3.65	0.14	0.96
	Thiazide diuretic (as needed)	33 (12)	3.50	30 (11)	3.59	0.59	0.84
Vasodilators	Nitrate	113 (42)	70.5	65 (23)	53.7	<0.01	0.02
	Hydralazine	61 (23)	145.6	42 (15)	128.7	0.03	0.40
Neurohormonal antagonists	ACE inhibitor or ARB	203 (75)	24.3	212 (76)	21.5	0.92	0.19
	Beta blocker	236 (87)	32.7	246 (88)	32.2	0.90	0.82
	Aldosterone antagonist	130 (48)	30.2	124 (44)	34.1	0.39	0.18
		Active Monitoring Group LVEF ≤40% Subgroup (n = 222)		**Blind Therapy Group LVEF ≤40% Subgroup (n = 234)**		**Analysis**	
HF Drug Class	**Drug**	**n (%)**	**Total Daily Dose (mg)**	**n (%)**	**Total Daily Dose (mg)**	**p Value***	**p Value†**
Diuretics	Loop diuretic	199 (90)	120.0	209 (89)	107.8	1.0000	0.1794
	Thiazide diuretic (standing)	41 (18)	3.79	32 (14)	3.67	0.2012	0.8833
	Thiazide diuretic (as needed)	28 (13)	3.32	25 (11)	3.18	0.5605	0.6974
Vasodilators	Nitrate	92 (41)	69.6	51 (22)	49.4	<0.0001	0.0121
	Hydralazine	52 (23)	145.0	38 (16)	122.5	0.0600	0.2847
Neurohormonal antagonists	ACE inhibitor or ARB	167 (75)	22.4	178 (76)	20.3	0.9131	0.3406
	Beta blocker	199 (90)	32.9	211 (90)	30.8	0.8774	0.3655
	Aldosterone antagonist	117 (53)	30.6	111 (47)	32.9	0.3027	0.4441

*p value testing treatment versus control prevalence obtained from Fisher exact test. †p value testing treatment versus control total daily dose obtained from exact Wilcoxon rank sum test.
Abbreviations as in Tables 1 and 2.

changes during HF hospitalizations were not recorded as part of the available medication dataset. Because there were more HF hospitalizations in the blind therapy group, some interventions triggered by clinical signs and symptoms may not be accounted for in this group. However, the greater number of ambulatory medication interventions in the active monitoring group resulted in a greater net change in overall medication doses between discharge and 6 months. Despite these factors, ambulatory monitoring of PA pressures still resulted in significant reduction in HF hospitalization rates after 6 months of follow-up (8).

CONCLUSIONS

The CHAMPION trial with the specified protocol has validated the concept that knowledge of ambulatory PA pressures leads to more interventions that reduce HF events compared with standard clinical assessment. Decreases in PA pressures are clearly associated with decreased HF hospitalizations. The current study is focused on the degree and nature of the interventions made.

It is not known, however, how much the target filling pressures should vary for individual patients, such as those with a chronic mismatch between right- and left-sided filling pressure elevation (31). The current relationship between PA pressures and HF hospitalizations suggests that lower filling pressures are better throughout the range represented in the CHAMPION trial. Most medication interventions in CHAMPION were adjustments in diuretics, but 43% of patients in the active monitoring group did also have significant changes in direct vasodilator doses. It is not known when vasodilators would be more effective than diuretics to maintain lower filling pressures. Neither is it known how titration of ACEIs/ARBs and BBs should be modulated by knowledge of ambulatory filling pressures that are too high or too low.

Ambulatory hemodynamic monitoring is now available for incorporation into routine HF management to guide interventions to decrease filling pressures, improve quality of life, and decrease hospitalizations not only for HF, but for associated diagnoses, such as pulmonary disease, which can be exacerbated by congestion (32). Expanding clinical experience and data for analysis will provide new insight into how best to achieve these goals. The current analysis validates the target pressure ranges and the algorithm for intervention that can be used as a starting point to reduce HF hospitalizations and improve patient outcomes in previously hospitalized New York Heart Association functional Class III patients.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Maria Rosa Costanzo, Advocate Heart Institute, Edward Heart Hospital, 801 South Washington Street, Naperville, Illinois 60566. E-mail: Mariarosa.costanzo@advocatehealth.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Use of implantable hemodynamic monitoring devices in ambulatory patients has revealed that cardiac filling pressures rise weeks before the onset of signs and symptoms of heart failure decompensation. The absolute rate of heart failure hospitalizations is highest with high baseline pulmonary artery pressures but the relative reduction of events with pressure-guided therapy is similar regardless of baseline pressures. The CHAMPION trial has demonstrated how diuretics and vasodilators were adjusted according to pulmonary artery pressure levels to reduce heart failure-related hospitalizations compared with management based only on usual clinical assessment.

TRANSLATIONAL OUTLOOK: The analysis presented here is essential to understand what interventions were triggered by pulmonary artery pressure measurements to reduce pulmonary artery pressures and hospitalizations. This analysis underscores the vital importance of specific algorithms and target pressure ranges for pulmonary artery pressure-guided management to effectively translate the strategy used in the CHAMPION trial into clinical heart failure management.

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KEY WORDS heart failure, hemodynamic monitoring, hospitalization, pulmonary artery pressure

APPENDIX For supplemental tables, please see the online version of this article.