ORIGINAL RESEARCH

Echocardiographic Assessment of Pulmonary Artery Systolic Pressure and Outcomes in Ambulatory Heart Failure Patients

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***Background*—**Pulmonary hypertension (PH) in patients with heart failure (HF) is associated with worse outcomes and is rapidly being recognized as a therapeutic target. To facilitate pragmatic research efforts, data regarding the prognostic importance of noninvasively assessed pulmonary artery systolic pressure (PASP) in stable ambulatory patients with HF are needed.

***Methods and Results*—**We examined the association between echocardiographic PASP and outcomes in 417 outpatients with HF (age, 54±13 years; 60.7% men; 50.4% whites; 24.9% with preserved ejection fraction). Median PASP was 36 mm Hg (interquartile range [IQR]: 29, 46). After a median follow-up of 2.6 years (IQR: 1.7, 3.9) there were 72 major events (57 deaths; 9 urgent heart transplants; and 6 ventricular assist device implantations) and 431 hospitalizations for HF. In models adjusting for clinical risk factors and therapy, a 10-mm Hg higher PASP was associated with 37% higher risk (95% CI: 18, 59; $P<0.001$) for major events, and 11% higher risk (95% CI: 1, 23; $P=0.039$) for major events or HF hospitalization. The threshold that maximized the likelihood ratio for both endpoints was 48 mm Hg; those with PASP ≥48 mm Hg (N=84; 20.1%) had an adjusted hazard ratio of 3.33 (95% CI: 1.96, 5.65; $P<0.001$) for major events and 1.47 (95% CI: 1.02, 2.11; $P=0.037$) for major events or HF hospitalization. Reduced right ventricular systolic function had independent prognostic utility over PASP for adverse outcomes. Right atrial pressure and transtricuspid gradient both contributed to risk.

***Conclusions*—**Elevated PASP, determined by echocardiography, identifies ambulatory patients with HF at increased risk for adverse events. **(*J Am Heart Assoc*. 2014;3:e000363 doi: 10.1161/JAHA.113.000363)**

Key Words: echocardiography • heart failure • mortality • outcomes • pulmonary hypertension

Pulmonary hypertension (PH) is common among patients with heart failure (HF) and predicts worse clinical outcomes,[1–12] The gold standard for diagnosis of PH is a mean pulmonary artery pressure ≥25 mm Hg on right heart catheterization (RHC).[13] However, RHC is an invasive procedure with associated risks,[14] significantly limiting its utility for routine detection and monitoring of PH in HF. Therefore, RHC is primarily used to evaluate end-stage (Stage D) HF patients for advanced therapies.[15,16] However, considering the prevalence of PH in HF patients who are stable on medical therapy (Stage C HF),[13] its impact on outcomes,[17] and the need to develop targeted therapies for PH in HF,[17] alternative methods for routine PH detection and serial monitoring are needed for the large population of Stage C HF patients.

Doppler echocardiography is a noninvasive, widely available imaging modality that can be used to estimate the pulmonary artery systolic pressure (PASP), most commonly by calculating the transtricuspid gradient from the regurgitant jet velocity.[18] Studies comparing RHC with echocardiographic estimates of PASP in HF patients have demonstrated a summary sensitivity and specificity of ≈90% and 70%, respectively, for diagnosis of PH,[19] suggesting that echocardiographic assessment could be an acceptable alternative. However, studies reporting outcomes in HF patients with echocardiographically determined PASP are limited to either advanced HF patients,[1] hospitalized patients,[20] referrals for suspected HF,[8] analyses of data available in an electronic data warehouse,[11] or mixed in- and outpatient populations,[6,12] using varied definitions for PH.[1,6,8,11,12,20] Data for the most prevalent group of HF patients, ie, those with Stage C HF treated on an outpatient basis, are particularly lacking,

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Accompanying Table S1, Figures S1 and S2 are available at http://jaha.ahajournals.org/content/3/1/e000363/suppl/DC1

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thus significantly limiting our ability to estimate potential treatment effects and plan research efforts in this population. In this study, we sought to assess the association between echocardiographic PASP and outcomes in ambulatory patients with HF.

Methods

Study Population

We collected data on patients older than 18 years who were treated at a tertiary care specialty outpatient HF clinic and were on stable therapy for >1 month. Patients with complex congenital heart disease, previous heart or other solid organ transplantation, previous or scheduled ventricular assist device implantation, known cardiac infiltrative disease, stage D HF requiring continuous inotropic support on an outpatient basis, pulmonary hypertension from causes other than left-sided heart disease (non-Group-2 pulmonary hypertension), or other comorbidities that significantly reduce life expectancy were excluded. The diagnosis of HF with preserved left ventricular ejection fraction (LVEF) required a clinical diagnosis of HF, a B-type natriuretic peptide level >200 pg/mL, and echocardiographic evidence of diastolic dysfunction. Baseline echocardiographic data were available in 469 patients; of these, 417 (88.9%) had a tricuspid regurgitation signal of adequate quality to calculate PASP and were included in the present analysis. Chronic pulmonary disease was defined as physician diagnosis of chronic obstructive lung disease, interstitial lung disease, or sarcoidosis. Sleep apnea was defined as physician diagnosis of sleep apnea with or without use of continuous positive airway pressure therapy. The study has been approved by the Institutional Review Board.

Echocardiography

Transthoracic echocardiograms performed as part of outpatient care were assessed; studies performed during hospitalizations or for acute indications were not considered. For the purposes of this study, all echocardiograms were reanalyzed independently of clinical reports by an experienced echocardiographer blinded to clinical data. Measurements were performed according to the American Society of Echocardiography (ASE) standards. All patients had dedicated 2-dimensional and color Doppler imaging to exclude right ventricular outflow tract obstruction or pulmonary stenosis. PASP was estimated from the tricuspid regurgitant jet velocity using the modified Bernoulli equation and adding the estimated right atrial pressure (RAP) on the basis of inferior vena cava (IVC) diameter and collapsibility. We assigned RAP using a classification scheme that has been validated in an advanced HF cohort[21]: IVC ≤2 cm and >50% collapsibility, 5 mm Hg; IVC >2 cm and ≥50% collapsibility, 10 mm Hg; IVC >2 cm and <50% collapsibility, 15 mm Hg; and IVC >2 cm and no collapsibility, 20 mm Hg. We assumed RAP 10 mm Hg for cases with IVC ≤2 cm and ≤50% collapsibility. Chamber quantification and right ventricular systolic function measurements, including right ventricular fractional area change (RVFAC) and tricuspid annular plane systolic excursion (TAPSE), were performed as recommended by ASE.[22,23] Mitral and tricuspid regurgitation were graded semiquantitatively into none/trace, mild, mild-to-moderate, moderate-to-severe, and severe.[24]

Study Outcomes

We collected data on: (1) major clinical events (death, heart transplantations, and ventricular assist device implantations); (2) hospitalizations for HF; and (3) all-cause hospitalizations. The primary endpoint was defined as the time to first major event, defined as death, urgent (UNOS status 1A) transplantation, or ventricular assist device implantation. The secondary endpoint was defined as the time to first major event or HF hospitalization, whichever occurred first. Patients who received heart transplants as UNOS status 1B (N=2) were censored as alive at the time of transplant for analysis purposes. Additional outcomes analyzed were the rates of HF and all-cause hospitalizations. Data were collected through medical record review including inpatient records and all outpatient notes from any specialty including data on hospitalizations in other hospitals, information obtained from family members, direct patient inquiry during follow-up, and Social Security Death Index. To ensure complete capture of hospitalizations, we (1) reviewed all medical records carefully, including outpatient visits to any provider, to assess for any notation of interim hospitalizations at an outside institution, and (2) directly asked patients about interim admissions every 6 months as part of the surveillance process. All hospital records were individually reviewed and the reason for admission was manually adjudicated on an individual encounter basis, regardless of ICD codes.

Statistical Analysis

The correlation of baseline characteristics with PASP was assessed with Spearman's rank correlation. Event-free survival was estimated by the Kaplan-Meier method. The association of PASP with the primary and secondary endpoints was examined with unadjusted and adjusted Cox proportional hazards models. According to the framework of Hsieh and Lavori,[25] our cohort had 84% power to detect an increase in risk for major events by ≥30% for every 10-mm Hg higher PASP at the 2-sided α=0.05 based on a data-driven R^2≤0.1 of PASP with clinical covariates. We evaluated PASP

both as a continuous variable and as a categorical variable after identifying a cut-off point. Form of association (linear versus nonlinear) in continuous analysis was examined with fractional polynomials and restricted cubic splines.[26] The proportionality of hazards was examined using the Schoenfeld residuals. To identify a cut-off point of PASP that optimized model fit (based on the likelihood ratio) for major events, we used a spline model with "step" function as described by Sauerbrei et al[27] We also evaluated predefined, clinically relevant cut-off points. The association of PASP with hospitalization rates was examined with negative binomial regression models to account for overdispersion. Based on previous literature,[28–30] we considered characteristics known to be associated with HF outcomes, including age, gender, race, etiology, systolic blood pressure, LVEF, serum sodium, blood urea nitrogen, hemoglobin, and treatment (angiotensin-modulating agents, β-blockers, aldosterone antagonists, implantable defibrillator and/or biventricular pacemaker), in all adjusted models. To evaluate for collinearity between covariates we examined the correlation matrix of coefficients after each regression and the variance inflation factors against an external dependent variable. Missing covariate values (overall, 1.7% of values) were imputed using multiple imputations by chained equations and estimates from 20 imputed datasets were combined.[31] Because of the large number of covariates relative to the number of events, which might be a source of model instability and bias, we have repeated the main regression analyses using bootstrap replications (N=1000) to examine the stability of our estimation results in a sensitivity analysis.[32] To evaluate for the impact of RAP on outcomes, we additionally performed a regression analysis with RAP and transtricuspid gradient as separate components.

In secondary analyses, we examined the association of PASP with outcomes in race and sex subgroups and in patients with reduced (<45%) versus preserved (≥45%) LVEF based on the index echocardiogram. We additionally examined for incremental impact of right ventricular systolic dysfunction as expressed by reduced RVFAC or reduced TAPSE in subsets with available data. For the latter analysis, we defined reduced RVFAC (<35%) and reduced TAPSE (<1.6 cm) using the ASE-proposed cut-offs.[23] Since clinical trials in HF are often designed with short- to intermediate-term outcomes, to facilitate future research efforts we also estimated the proportion of eligible patients, event rates, and numbers of patients required to screen and enroll to detect a prespecified relative risk reduction (RRR) of 25% at 1 year for the primary and secondary endpoint using various PH eligibility definitions. Finally, we have evaluated a random 10% sample of echocardiograms (N=42) for agreement of PASP estimates between clinical echocardiogram reports and independent readings for research purposes. For this analysis, we entered the mean PASP value when a range of PASP was reported in clinical reports. We used (1) Bland-Altman analysis to assess bias and limits of agreement and (2) Lin's concordance coefficient to assess correlation. All analyses were performed using STATA version 12.1 (StataCorp LP).

Results

Patient Characteristics and Outcomes

The baseline clinical and echocardiographic characteristics of patients are summarized in Table 1. The mean age was 54±13 years; 60.7% were men, 50.4% were white, and 47.2% were black. Mean LVEF was 35±15%, with one-quarter of patients having preserved (≥45%) LVEF. Most patients were receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (83.3%) and beta-blockers (92.5%), whereas 42.9% were on aldosterone antagonists and two-thirds had an implantable defibrillator. Median PASP was 36 (interquartile range 29, 46) mm Hg. The proportion of patients with PASP ≥35, ≥40, ≥45, and ≥50 mm Hg was 54.2%, 37.2%, 26.4%, and 17.3%, respectively. Right atrial pressure was estimated at 5, 10, 15, and 20 mm Hg in 13.2%, 60.2%, 21.1%, and 5.5% of patients, respectively.

Black race, lower LVEF, and worse renal function were associated with higher PASP (Table 2). Among echocardiographic characteristics, larger left ventricular volumes, more severe mitral regurgitation, and larger left atrium were associated with higher PASP. BNP levels positively correlated with PASP. Clinical covariates and LVEF explained only 9.4% of the variation in PASP (R^2=0.094).

Median follow-up was 2.6 (interquartile range 1.7, 3.9) years, for a total of 1107 patient-years. During follow-up, there were 72 major clinical events (17.3%) including 57 deaths, 9 urgent heart transplantations, and 6 ventricular assist device implantations (4 as bridge-to-transplant and 2 as destination therapy). Six of 57 death (10.5%) events were derived from Social Security Death Index. The annualized event rate for the primary endpoint was 6.5%. Event-free survival at 1, 2, and 3 years was 92.9%, 88.2%, and 83.7%, respectively. An additional 94 patients were admitted with decompensated HF, for a total of 166 secondary endpoint events (39.8%). Survival free from major events and HF hospitalization was 74.6%, 66.7%, and 61.0% at 1, 2, and 3 years, respectively. A total of 431 admissions for HF occurred in 151 unique patients during follow up (39 per 100 patient-years) among 990 all-cause admissions (89 per 100 patient-years) in the entire cohort. Patients not included in the analysis because of inadequate tricuspid regurgitation signal (N=52) had similar outcomes (annualized primary endpoint rate 5.8%; P=0.66) compared to those included.

Table 1. Clinical and Echocardiographic Characteristics at Baseline (n=417)

Characteristic	Value
Clinical characteristics	
Age, y	54±13
Men, n (%)	253 (60.7)
Race	
White, n (%)	210 (50.4)
Black, n (%)	197 (47.2)
Other, n (%)	10 (2.4)
Body mass index, kg/m^2	30.4±7.2
Ischemic heart disease, n (%)	154 (36.9)
Diabetes mellitus, n (%)	125 (30.0)
Chronic pulmonary disease, n (%) *	60 (14.4)
Sleep apnea, n (%)	64 (15.4)
Left ventricular ejection fraction, %	35±15
Left ventricular ejection fraction ≥45%, n (%)	104 (24.9)
Systolic blood pressure, mm Hg	113±19
Blood urea nitrogen, mg/dL	18 (13, 26)
Creatinine, mg/dL	1.2 (1.0, 1.5)
Sodium, mEq/L	138±3
Hemoglobin, g/dL	13.1±1.8
Brain natriuretic peptide, pg/mL†	247 (79, 750)
Treatment, n (%)	
β-blockers	383 (92.5)
ACE inhibitors or ARB	345 (83.3)
Aldosterone antagonists	179 (42.9)
Defibrillator/CRT	277 (67.2)
Echocardiographic characteristics	
Pulmonary artery systolic pressure, mm Hg	38 (29, 46)
Left ventricular volume at diastole (indexed), mL/m^2	90 (66, 123)
Left ventricular volume at systole (indexed), mL/m^2	57 (39, 89)
Mitral regurgitation (moderate-to-severe or higher), n (%)	101 (24.2)
Tricuspid regurgitation (moderate-to-severe or higher), n (%)	89 (21.3)
Left atrial volume (indexed), mL/m^2	30 (22, 41)
Tricuspid annular plane excursion, cm‡	1.6 (1.0, 1.9)
Right ventricular are at diastole, cm^2§	20 (17, 26)
Right ventricular are at systole, cm^2§	12 (10, 17)
Right ventricular fractional area change, %§	38±12

Data are expressed as mean±SD, number (percentage), or median (interquartile range). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CRT, cardiac resynchronization therapy.
*Chronic obstructive lung disease, interstitial lung disease, or sarcoidosis.
†Available in 259 of 417 (62.1%) participants.
‡Available in 362 of 417 (86.8%) participants.
§Available in 376 of 417 (90.2%) participants.

Table 2. Correlation of Patient Characteristics With PASP (n=417)

Characteristic	Spearman's Rho	*P* Value
Age	0.08	0.12
Male gender	0.00	0.96
Black race	0.16	0.001
Body mass index	0.01	0.90
Ischemic heart disease	−0.01	0.78
Diabetes mellitus	0.08	0.081
Chronic pulmonary disease	−0.02	0.74
Sleep apnea	0.02	0.71
Left ventricular ejection fraction	−0.21	<0.001
Systolic blood pressure	−0.03	0.52
Blood urea nitrogen	0.19	<0.001
Creatinine	0.16	0.001
Sodium	−0.06	0.21
Hemoglobin	−0.08	0.10
Brain natriuretic peptide*	0.35	<0.001
β-blocker use	−0.03	0.59
ACE inhibitor or ARB use	−0.03	0.50
Aldosterone antagonist use	0.05	0.34
Defibrillator/CRT	0.07	0.15
Left ventricular volume at diastole (indexed)	0.12	0.019
Left ventricular volume at systole (indexed)	0.16	0.002
Mitral regurgitation (0 to 4)	0.41	<0.001
Tricuspid regurgitation (0 to 4)	0.45	<0.001
Left atrial volume (indexed)	0.31	<0.001
Tricuspid annular plane excursion, cm†	0.00	0.99
Right ventricular are at diastole, cm^2‡	0.20	<0.001
Right ventricular are at systole, cm^2‡	0.19	<0.001
Right ventricular fractional area change‡	−0.10	0.054

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CRT, cardiac resynchronization therapy; PASP, pulmonary artery systolic pressure.
*Available in 259 of 417 (62.1%) participants.
†Available in 362 of 417 (86.8%) participants.
‡Available in 376 of 417 (90.2%) participants.

Association of Pulmonary Artery Systolic Pressure With Outcomes

The association between PASP and risk for primary or secondary endpoints was approximately linear, with risk increasing by 43% (95% CI: 27, 62) for the primary endpoint and 24% (95% CI: 14, 36) for the secondary endpoint for every 10-mm Hg increase in PASP in univariable models (Table 3). In models adjusting for clinical risk factors and therapy, a 10-

Table 3. Association of Pulmonary Artery Systolic Pressure at Baseline With Outcomes

Outcome	Univariable HR or RR (95% CI)	*P* Value	Multivariable* HR or RR (95% CI)	*P* Value
Continuous analysis: relative risk expressed per 10 mm Hg of PASP				
Primary endpoint (major clinical event)†	1.43 (1.27 to 1.62)	<0.001	1.37 (1.18 to 1.59)	<0.001
Secondary endpoint (major clinical event or HF hospitalization)	1.24 (1.14 to 1.36)	<0.001	1.11 (1.01 to 1.23)	0.039
Rate of HF hospitalizations	1.36 (1.15 to 1.61)	<0.001	1.21 (1.05 to 1.41)	0.010
Rate of all-cause hospitalizations	1.18 (1.07 to 1.30)	0.001	1.09 (1.00 to 1.20)	0.049
Categorical analysis: relative risk comparing PASP ≥48 mm Hg vs <48 mm Hg				
Primary endpoint (major clinical event)	4.17 (2.62 to 6.63)	<0.001	3.33 (1.96 to 5.65)	<0.001
Secondary endpoint (major clinical event or HF hospitalization)	2.24 (1.61 to 3.10)	<0.001	1.47 (1.02 to 2.11)	0.037
Rate of HF hospitalizations	3.05 (1.77 to 5.27)	<0.001	2.31 (1.39 to 3.84)	0.001
Rate of all-cause hospitalizations	1.98 (1.44 to 2.73)	<0.001	1.65 (1.20 to 2.26)	0.002

ACE indicates angiotensin-converting enzyme; CI, confidence interval; HF, heart failure; HR, hazard ratio; PASP, pulmonary artery systolic pressure; RR, relative risk.
*Adjusted for clinical characteristics: age, gender, race, ischemic etiology, systolic blood pressure, sodium, blood urea nitrogen, left ventricular ejection fraction, hemoglobin, medications (β-blocker, ACE inhibitor or angiotensin receptor blocker, aldosterone antagonist), cardioverter defibrillator, and cardiac resynchronization therapy.
†Death, left ventricular assist device implantation, or urgent (UNOS IA) heart transplantation.

mm Hg higher PASP was associated with 37% higher risk (95% CI: 18, 59; *P*<0.001) for the primary endpoint and 11% higher risk (95% CI: 1, 23; *P*=0.039) for the secondary endpoint (Table 3). Higher PASP at baseline was strongly associated with higher rates of HF and all-cause hospitalizations (Table 3).

PASP ≥48 mm Hg was the optimal cut-off for prediction of major clinical events. Event-free survival at 3 years was 59.6% for patients with PASP ≥48 mm Hg (N=84, 20.1%) versus 90.3% for patients with PASP <48 mm Hg (N=333, 79.9%), Figure 1. The corresponding HF hospitalization-free survival was 39.8% and 66.5%, respectively. Patients with PASP ≥48 mm Hg had higher rates of HF-related (75 versus 31 per 100 patient-years; *P*<0.001) and all-cause (138 versus 79 per 100 patient-years; *P*<0.001) hospitalizations during follow-up. The increased risk for adverse events associated with PASP

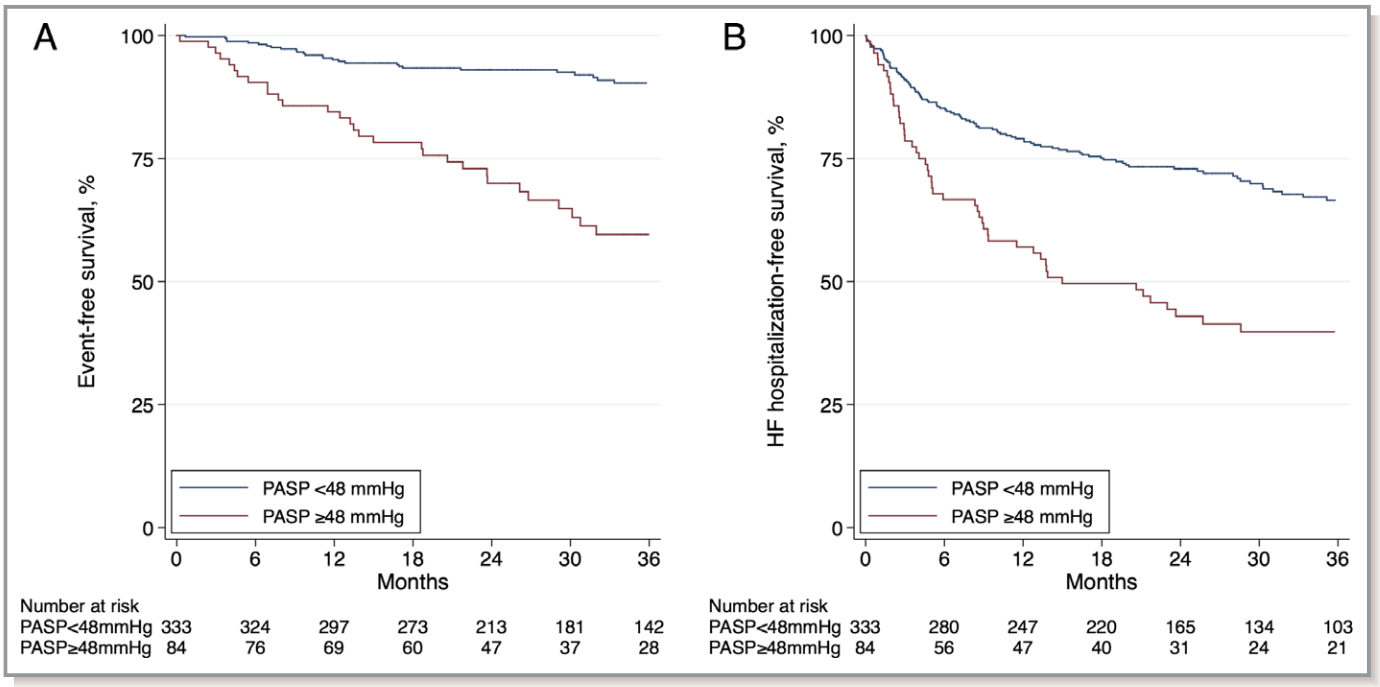

Figure 1. Association between pulmonary hypertension and outcomes. survival free from (A) major clinical events (death, left ventricular assist device implantation or urgent heart transplantation) and (B) major clinical events or hospitalization for heart failure (HF) according to echocardiography-derived pulmonary artery systolic pressure (PASP) at baseline.

≥48 mm Hg persisted in models adjusting for clinical characteristics (Table 3).

In sensitivity analyses using bootstrap estimation, the 95% confidence intervals for the association of PASP with outcomes widened only minimally over standard estimation and the level of significance did not change for most associations (Table S1). However, the multivariable associations for the secondary endpoint and all-cause hospitalizations crossed the nominal significance threshold and retained only borderline significance. The results were similar with percentile-based CIs. No significant bias in the point estimates was detected.

Subgroup Analyses

The risk associated with higher PASP was not different across sex and race for the primary (P=0.96 and P=0.38 for interaction, respectively) and secondary endpoints (P=0.32 and P=0.94 for the interaction terms, respectively), Figure 2. Similarly, there was no sex- or race-based differential association of PASP with HF or all-cause hospitalizations (data not shown). In patients with HF with LVEF (≥45%), the risk associated with PASP was more pronounced compared to reduced LVEF (<45%) for the primary (P=0.033 for the interaction term) and secondary (P=0.049 for the interaction term) outcome, Figure 2. However, the number of events in the preserved LVEF subgroup was small, precluding confirmation of this trend in multivariable analyses (non-estimable parameters).

Impact of Right Ventricular Systolic Function

Among 376 patients with available data on RVFAC (90.2% of cohort), 152 (40.4%) had reduced RVFAC (<35%). Reduced RVFAC was associated with higher risk for major events independent of elevated PASP (HR 2.40; 95% CI: 1.46, 3.94; P=0.001), Figure 3. However, this association was attenuated in models adjusting for clinical risk factors (HR 1.43; 95% CI: 0.88, 2.32; P=0.15). Reduced RVFAC was also associated with higher risk for major event or HF hospitalization (HR 2.08; 95% CI: 1.50, 2.88; P<0.001); this association retained significance in models adjusting for clinical risk factors (HR 1.47; 95% CI: 1.00, 2.15; P=0.049).

Among 362 patients with available data on TAPSE (86.8% of cohort), 177 (48.9%) had reduced TAPSE (<1.6 cm). Reduced TAPSE was not associated with higher risk for major events after adjusting for PASP (HR 1.13; 95% CI: 0.69, 1.87; P=0.62), Figure S1. Reduced TAPSE was associated with higher risk for major event or HF hospitalization in models including PASP (HR 1.61; 95% CI: 1.15, 2.26; P=0.005), but this association was attenuated in models additionally adjusting for clinical risk factors (HR 1.42; 95% CI: 0.97, 2.06; P=0.71).

Estimated Right Atrial Pressure Versus Transtricuspid Gradient and Outcomes

In regression analyses with RAP and transtricuspid gradient entered as separate components, both RAP and transtricuspid

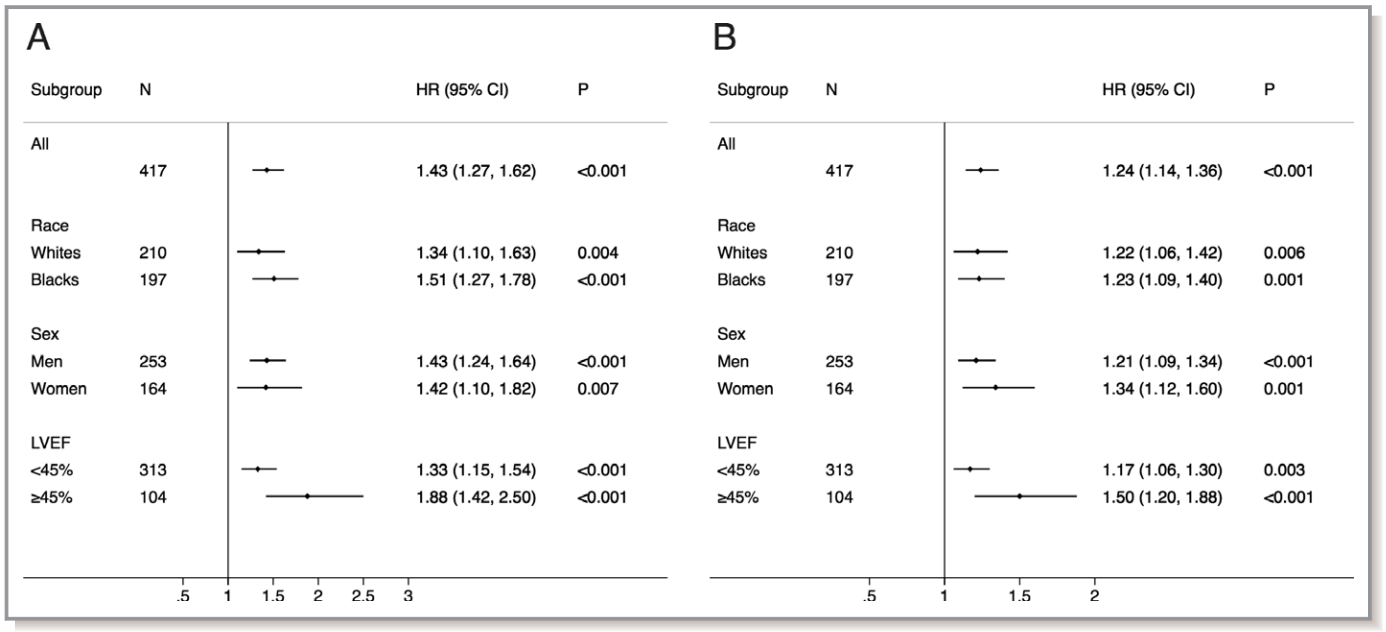

Figure 2. Impact of pulmonary hypertension in major subgroups. Relative risk for (A) major clinical events (death, left ventricular assist device implantation or urgent heart transplantation) and (B) major clinical events or hospitalization for heart failure per 10 mm Hg of pulmonary artery systolic pressure (PASP) at baseline in gender, race, and ejection fraction based subgroups. CI indicates confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.

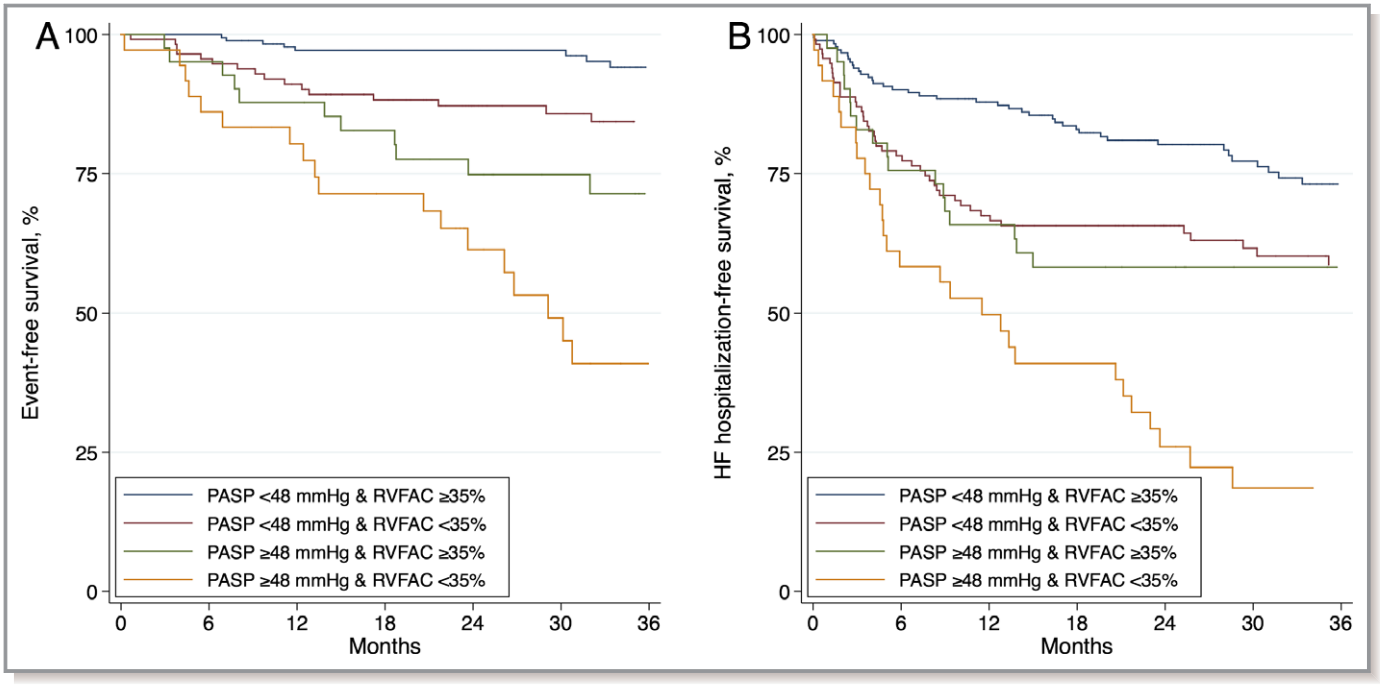

Figure 3. Incremental prognostic value of right ventricular systolic function assessed by right ventricular fractional area change. Survival free from (A) major clinical events (death, left ventricular assist device implantation or urgent heart transplantation) and (B) major clinical events or hospitalization for heart failure (HF) according to echocardiography-derived pulmonary artery systolic pressure (PASP) and right ventricular fractional area change (RVFAC) at baseline. Right ventricular systolic function had independent and incremental prognostic value.

gradient independently predicted major clinical events and this association persisted in multivariable models (Table 4). The association between RAP and outcomes was linear. The association of both RAP and transtricuspid gradient with outcomes was attenuated when the endpoint of interest was set to major event or HF hospitalization, but the highest RAP

Table 4. Estimated Right Atrial Pressure, Transtricuspid Gradient, and Outcomes

Outcome	Univariable HR (95% CI)	*P* Value	Multivariable* HR (95% CI)	*P* Value
Primary endpoint (major clinical event)†				
Estimated right atrial pressure				
5 mm Hg	1.00 (reference)	—	1.00 (reference)	—
10 mm Hg	1.87 (0.65 to 5.38)	0.24	1.83 (0.58 to 5.72)	0.30
15 mm Hg	3.53 (1.17 to 10.6)	0.025	3.03 (0.93 to 9.87)	0.065
20 mm Hg	6.84 (2.02 to 23.2)	0.002	5.36 (1.43 to 20.0)	0.013
Tricuspid gradient, per 10 mm Hg	1.29 (1.10 to 1.50)	0.001	1.26 (1.06 to 1.49)	0.009
Secondary endpoint (major clinical event or HF hospitalization)				
Estimated right atrial pressure				
5 mm Hg	1.00 (reference)		1.00 (reference)	
10 mm Hg	0.93 (0.56 to 1.55)	0.78	0.84 (0.50 to 1.43)	0.52
15 mm Hg	1.42 (0.82 to 2.48)	0.21	1.12 (0.63 to 1.98)	0.69
20 mm Hg	3.30 (1.68 to 6.47)	0.001	2.35 (1.15 to 4.78)	0.019
Tricuspid gradient, per 10 mm Hg	1.14 (1.02 to 1.28)	0.021	1.14 (1.02 to 1.28)	0.38

ACE indicates angiotensin-converting enzyme; CI, confidence interval; HR, hazard ratio.

*Adjusted for clinical characteristics: age, gender, race, ischemic etiology, systolic blood pressure, sodium, blood urea nitrogen, left ventricular ejection fraction, hemoglobin, medications (β-blocker, ACE inhibitor or angiotensin receptor blocker, aldosterone antagonist), cardioverter defibrillator, and cardiac resynchronization therapy.

†Death, left ventricular assist device implantation, or urgent (UNOS IA) heart transplantation.

Table 5. Eligibility, Event Rates, and Number of Patients Needed to Detect a 25% Relative Risk Reduction in a Hypothetical Clinical Trial Targeting Pulmonary Hypertension in Heart Failure Outpatients With 1-Year Outcomes

Definition of PH	% Eligible	1-Year Event Rate	RRR	N to Enroll*	N to Screen†
Endpoint: death, left ventricular assist device implantation, or urgent heart transplantation					
PASP ≥35 mm Hg	52.2%	9.8%	25%	4140	7930
PASP ≥40 mm Hg	37.2%	11.7%	25%	3620	9730
PASP ≥45 mm Hg	26.4%	13.7%	25%	3020	11440
PASP ≥48 mm Hg	17.3%	15.5%	25%	2550	14740
PASP ≥55 mm Hg	11.3%	17.0%	25%	2260	20000
Endpoint: death, left ventricular assist device implantation, urgent heart transplantation, or HF hospitalization					
PASP ≥35 mm Hg	52.2%	32.4%	25%	1020	1950
PASP ≥40 mm Hg	37.2%	34.9%	25%	920	2470
PASP ≥45 mm Hg	26.4%	40.1%	25%	750	2840
PASP ≥48 mm Hg	17.3%	43.0%	25%	660	3820
PASP ≥55 mm Hg	11.3%	43.0%	25%	660	5840

HF indicates heart failure; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension; RRR, relative risk reduction.
*Assuming a 5% dropout.
†Assuming other criteria are met—eligibility pending on echocardiographic pulmonary artery systolic pressure screening only. Power set to 80% at the 2-sided α=0.05.

(20 mm Hg) category was still significantly associated with this endpoint in multivariable models.

Effect of Pulmonary Hypertension Definition on 1-Year Outcomes

At 1 year, 29 patients (7.0%) had reached the primary endpoint and 105 (25.3%) had reached the secondary endpoint. Table 5 presents the estimated proportion of patients, event rates, and numbers of patients needed to screen and enroll to detect a 25% RRR at 1 year for the primary and secondary endpoint using various PH eligibility definitions based on PASP.

Agreement Between Clinical and Research Readings of Estimated PASP

In 42 randomly selected echocardiograms, the mean difference (bias) in PASP values between independent readings for research purposes and clinical reports was 0.8 mm Hg. The 95% limits of agreement were −7.1 to 8.8 mm Hg (Figure S2). Lin's concordance coefficient between the 2 measurements was 0.93 (95% CI: 0.88, 0.96).

Discussion

In this HF cohort of stable outpatients (stage C HF), elevated PASP at baseline was strongly associated with increased risk for a major clinical event (death, ventricular assist device implantation, or urgent heart transplantation) and for the composite of a major event or HF hospitalization, independent of other clinical predictors of HF outcomes. Patients with elevated PASP had higher HF and all-cause hospitalization rates. In exploratory analyses, we observed that a cut-off point of 48 mm Hg for PASP was associated with the highest adjusted hazard ratio. A PASP of ≥48 mm Hg was associated with a 3-fold higher risk for major clinical events and a 2-fold higher rate of HF admissions. Importantly, these findings were consistent across gender- and race-based subgroups. Reduced right ventricular function compounded the risk associated with elevated PASP. Although we observed a trend for more pronounced risk with elevated PASP among patients with preserved LVEF, our study did not have the necessary power to confirm this finding in multivariable analyses.

Most studies to date have reported an association of PH with mortality in specific HF populations, including patients with newly diagnosed cardiomyopathy,[3] suspected HF,[8,33] acute HF,[9,20,34] advanced HF,[4,34] preserved LVEF,[6] and patients referred for heart transplantation[2] or cardiac resynchronization therapy.[5] Importantly, previous data have predominantly focused on the association of PH with outcomes in advanced HF using invasive methods, whereas data on PASP in the general stage C HF population using echocardiography are limited.[6,11,12] Moreover, previous echocardiographic studies reported the risk associated with elevated PASP using either varying predefined categorical definitions[1,5,8,11,12] or continuous PASP.[6,20] This diversity of definitions renders the comparison of risks and estimation of potential treatment

benefits for any given level of PH impossible. Therefore, we reported the association of echocardiographic PASP with outcomes in an outpatient, chronic, stage C HF patient population on optimal medical therapy using a comprehensive approach. In line with a recent report from the Olmsted Country, MN cohort,[12] our data demonstrate the clinical relevance of secondary PH detected by echocardiography in less symptomatic HF patients typically seen in outpatient clinics. Echocardiography is widely available, has lower cost than RHC, and carries practically no risk. Taken together, these data support the utility of echocardiography for patient selection in clinical trials targeting PH in HF patients.

Our exploratory analyses using various binary definitions of PH demonstrate the effect of varying PASP levels to define secondary PH for research purposes on (1) the prevalence of echocardiographically determined PH and (2) the numbers needed to detect potential treatment effects. In this regard, the median PASP and prevalence of PH in our study is consistent with those reported in a large outpatient cohort undergoing prospective echocardiography,[8] but lower than those in similar cohorts of patients retrospectively selected on the basis of PASP availability.[11,35] The latter approach induces obvious selection bias toward higher PASP distribution because only those patients with strong tricuspid regurgitation signals would be included unless measurement was explicitly attempted as part of a protocol. Of note, the prevalence of PH is conceivably higher in studies including admitted patients[6,12] or done in the acute setting.[20] In contrast to reports from general care populations,[8,11] we observed that PASP was estimable with echocardiography in a large proportion (≈90%) of our patients with HF, similar to other reports from HF programs.[6,12] Considering that selection of HF patients for clinical trials targeting PH will most probably occur in the context of centers with expertise in HF, including experience and standardization in echocardiographic assessment, echocardiography is most likely a feasible method for detection of elevated PASP and tracking of treatment effect on PASP in patients with Stage C HF. The recent mechanistic studies by Guazzi and colleagues evaluating the effects of a phosphodiesterase-5 inhibitor in patients with HF selected on the basis of elevated PASP by echocardiography provide proof-of-principle data.[36,37]

The relative risk for adverse events associated with elevated PASP in our study was higher than that observed in recent echocardiographic studies including both in- and outpatients[6,12] or exclusively done on patients with acute HF.[20] We attribute this difference to the already substantially higher overall risk in those studies (≥20% mortality at 1 year), compared to our cohort (7% mortality at 1 year). Interestingly, in a study of stable cardiac resynchronization therapy recipients with relatively low mortality (≈10% at 1 year),[5] the risk associated with elevated PASP was similar to that observed in our study. Although the composite of death plus HF hospitalization is an attractive endpoint in HF clinical trials because of the higher event rate and the resulting gains in power, our data call for attention to a trade-off associated with this endpoint. The risk associated with elevated PASP for the secondary, composite endpoint was diluted compared to the primary endpoint. A similar trend was reported in an early study by Abramson and colleagues.[1] In contrast to mortality, HF hospitalization is an outcome affected by many other factors beyond disease biology, especially in patients with Stage C HF.[38] This is highlighted by the fact that clinical risk prediction models in patients with HF perform much better for mortality than hospitalizations.[38] Hence, the treatment effect by therapies targeting PH might be diminished when the composite endpoint is selected.

Deriving and using binary cut-off points for biologically continuous predictors in cohort studies has inherent limitations.[39] However, although dichotomizing continuous predictors is a suboptimal approach from a statistical modeling perspective, we still need categorical definitions to include patients in clinical trials and cohort studies. In this aspect, our study provides risk estimates for PASP both as continuous and as a categorical variable. The PASP cut-off that optimized prediction of major clinical events in our cohort was 48 mm Hg. This cut-off also yielded the higher hazard ratios for 1-year outcomes, which is a reasonable time frame for many HF clinical trials. Echocardiograms were not performed prospectively in our study. Also, the number of primary outcome events was relatively small. Therefore, we do not contend that we have identified the optimal PASP cut-off point for secondary PH definition. It is important also to note that there is no universally accepted scheme for assigning RAP values based on IVC diameter and collapsibility in patients with stage C heart failure. We used a scheme studied in patients with advanced (stage D) HF, and thus there is a possibility that our RAP estimates are biased. However, our findings lend support to echocardiographic cut-offs between 45 and 50 mm Hg for a practical definition of PH, as a reasonable compromise between selection of a high-risk population and eligibility.

Our study has several limitations. First, echocardiograms were not performed specifically for the purposes of this study. As a result, tissue Doppler-based measures of right ventricular function, including tricuspid annular systolic velocity and myocardial performance index, were not consistently available in our study. However, acquisition follows a standardized protocol in our institution. Also, we read the echocardiograms independently for the purposes of the current study to reduce interpretation bias. Second, the number of major clinical events was relatively small and did not allow us to reliably evaluate the effect of PASP on outcomes in patients with

preserved LVEF. Also, our multivariable models included a large number of covariates relative to events, leading to wide confidence intervals. However, our estimates were stable in the various model iterations. Third, PASP in patients with HF has a dynamic component dependent on volume status. To reduce variability related to this component, we only considered data derived from patients in stable condition without recent hospitalizations or changes in medical treatment. Fourth, severely reduced right ventricular systolic function may lead to underestimation of PASP.[40] However, we observed an approximately linear association of PASP with adverse events in our study. Taken together with the nature of our study population, which included only stable, ambulatory patients on medical treatment, contamination by falsely low PASP is probably minimal in this study. Fifth, the PASP cut-off points that optimized prediction in our study were not validated externally. Finally, our patients are cared for in a referral HF clinic, and thus there is potential for selection bias. However, there is no reason to believe that similar degrees of PASP elevation confer lower risk in a community-based sample. In a tertile-based analysis in our data (not shown), the risk for all-cause mortality in the upper versus the lower tertile of PASP was similar to that reported in a community-based study.[12]

In conclusion, our data suggest that echocardiography is a feasible and practical noninvasive alternative to identify stable patients with HF and elevated PASP. Importantly, these patients are at substantially increased risk for adverse events. Therefore, echocardiographically determined PASP can be used to select patients for clinical trials with novel agents targeting pathophysiological pathways of secondary PH in HF. Further studies are needed to assess the role of serial changes in PASP over time using echocardiography.

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Disclosures

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