Journal of the American College of Cardiology Vol. 59, No. 3, 2012

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.06.076

CME

Pulmonary Pressures and Death in Heart Failure

A Community Study

Francesca Bursi, MD, MSc,*‡ Sheila M. McNallan, MPH,† Margaret M. Redfield, MD,* Vuyisile T. Nkomo, MD, MPH,* Carolyn S. P. Lam, MBBS,*§‖ Susan A. Weston, MS,† Ruoxiang Jiang, BS,† Véronique L. Roger, MD, MPH*†

Rochester, Minnesota; Modena, Italy; Singapore; and Boston, Massachusetts

JACC JOURNAL CME

This article has been selected as the month's *JACC* Journal CME activity.

Accreditation and Designation Statement

The American College of Cardiology Foundation (ACCF) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The ACCF designates this Journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Method of Participation and Receipt of CME Certificate

To obtain credit for *JACC* CME, you must:

1. Be an ACC member or *JACC* subscriber.
2. Carefully read and reflect upon the CME-designated article available online and in this issue of the journal.
3. Answer the post-test questions. At least 2 out of the 3 questions provided must be answered correctly to obtain CME credit.
4. Complete a brief evaluation.
5. Claim your CME credit and receive your certificate electronically by following the instructions given at the conclusion of the activity.

CME Objective for This Article: At the conclusion of this activity, the learner should be able to determine among community patients with heart failure, whether pulmonary artery systolic pressure assessed by Doppler echocardiography was associated with death and improved risk prediction over established factors, using the integrated discrimination improvement and net reclassification improvement.

CME Editor Disclosure: *JACC* CME Editor Ajit Raisinghani, MD, FACC, reports that he has no financial relationships or interests to disclose.

Author Disclosures: The authors have reported they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz)

CME Term of Approval:

Issue date: January 17, 2012
Expiration date: January 16, 2013

From the *Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; †Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota; ‡Policlinico University Hospital of Modena, Modena, Italy; §National University Health System, Singapore; and the ‖Boston University School of Medicine, Boston, Massachusetts. Supported by grants from the National Institutes of Health (R01 HL59205, R01 HL72435) and the Rochester Epidemiology Project from the National Institute on Aging (R01 AG034676). The authors have reported they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 12, 2010; revised manuscript received June 20, 2011, accepted June 28, 2011.

Pulmonary Pressures and Death in Heart Failure

A Community Study

Objectives The purpose of this study was to determine among community patients with heart failure (HF) whether pulmonary artery systolic pressure (PASP) assessed by Doppler echocardiography was associated with death and improved risk prediction over established factors, using the integrated discrimination improvement and net reclassification improvement.

Background Although several studies have focused on idiopathic pulmonary arterial hypertension, less is known about pulmonary hypertension among patients with HF, particularly about its prognostic value in the community.

Methods Between 2003 and 2010, Olmsted County residents with HF prospectively underwent assessment of ejection fraction, diastolic function, and PASP by Doppler echocardiography.

Results PASP was recorded in 1,049 of 1,153 patients (mean age 76 ± 13; 51% women). Median PASP was 48 mm Hg (25th to 75th percentile: 37.0 to 58.0). There were 489 deaths after a follow-up of 2.7 ± 1.9 years. There was a strong positive graded association between PASP and mortality. Increasing PASP was associated with an increased risk of death (hazard ratio [HR]: 1.45, 95% confidence interval [CI]: 1.13 to 1.85 for tertile 2; HR: 2.07, 95% CI: 1.62 to 2.64 for tertile 3 vs. tertile 1), independently of age, sex, comorbidities, ejection fraction, and diastolic function. Adding PASP to models including these clinical characteristics resulted in an increase in the c-statistic from 0.704 to 0.742 ($p = 0.007$), an integrated discrimination improvement gain of 4.2% ($p < 0.001$), and a net reclassification improvement of 14.1% ($p = 0.002$), indicating that PASP improved prediction of death over traditional prognostic factors. All results were similar for cardiovascular death.

Conclusions Among community patients with HF, PASP strongly predicts death and provides incremental and clinically relevant prognostic information independently of known predictors of outcomes. (J Am Coll Cardiol 2012;59: 222–31) © 2012 by the American College of Cardiology Foundation

Pulmonary hypertension (PH) is prevalent among patients with heart failure (HF), among both those with reduced and with preserved left ventricular ejection fraction (EF) (1–3), with HF being 1 of the most common causes of PH (4,5). Although there are substantial data on the rare idiopathic pulmonary arterial hypertension, less is known about the predictive value of pulmonary pressures in the more common PH associated with HF (4,6). Some studies indicate that PH portends a poor prognosis among patients with HF (1–3,7–11), but have notable limitations including retrospective design and limitation to prevalent cases and to subgroups of patients such as advanced HF and reduced or preserved EF. Further, chronic obstructive pulmonary disease (COPD) was often excluded, diastolic function was seldom assessed, and most studies included highly selected patients from echocardiographic or catheterization series or referrals to HF clinics. The only population-based study published thus far was limited to patients with preserved EF (3); therefore, the prevalence, clinical characteristics, and prognosis of PH among all community patients with HF remains uncertain. Further, publications focused chiefly on all-cause death, and information on the impact of PH on cardiovascular death is limited.

With the present population-based study, we addressed these gaps in knowledge by prospectively investigating all in-patients and out-patients presenting with HF in Olmsted County. We aimed to examine the prevalence and prognostic role of PH estimated by pulmonary artery systolic pressure (PASP) from Doppler echocardiography, which is currently considered the best screening method for PH (6). We tested whether the associations were independent of other predictors such as EF and diastolic function, and investigated whether PASP improved risk prediction over established prognostic factors using the c-statistic, integrated discrimination improvement (IDI) and net reclassification improvement (NRI).

See page 232

Methods

The Rochester Epidemiology Project. This study was conducted in Olmsted County, Minnesota, and the methods are analogous to our previously published study of systolic and diastolic HF (12). Population-based epidemiological research is feasible in Olmsted County because it is relatively isolated from other urban centers, and only a few providers (chiefly, Mayo Clinic and Olmsted Medical Center) deliver nearly all health care to local residents. Each provider uses a medical record that captures information for all encounters and can be easily retrieved. These records are indexed through the Rochester Epidemiology Project, resulting in the linkage of medical records from all sources of care (13).

Identification of patients. As previously described, natural language processing of the unstructured text of the electronic medical record was used to prospectively identify pa-

Abbreviations and Acronyms

BMI = body mass index
BNP = brain natriuretic peptide
CI = confidence interval
COPD = chronic obstructive pulmonary disease
EF = ejection fraction
HF = heart failure
HR = hazard ratio
IDI = integrated discrimination improvement
MI = myocardial infarction
NRI = net reclassification improvement
PASP = pulmonary artery systolic pressure
PH = pulmonary hypertension

tients presenting with clinical findings compatible with HF (12,14).

After real-time case identification, subjects were immediately contacted to participate in the prospective study that included Doppler echocardiography and venous blood draw for brain natriuretic peptide (BNP). If a clinical echocardiogram was not scheduled within 1 day of the enrollment, it was scheduled by the research team with experienced research sonographers performing the examinations under quality control similar to that in place for clinical examinations. Therefore, there was no difference between examinations performed under clinical or research auspices. The complete records of potential cases were manually reviewed to verify the diagnosis of HF using both clinical and Framingham criteria (15) and to collect clinical data. The feasibility and reliability of the Framingham criteria to ascertain HF in Olmsted County have been previously published (16).

Participants provided written consent, and the study was approved by the Mayo Clinic institutional review board.

Echocardiography Doppler. In Olmsted County, all echocardiograms are performed and interpreted in the Mayo Clinic Echocardiographic Laboratory. M-mode, 2-dimensional, Doppler, and Doppler tissue imaging were performed according to guidelines of the American Society of Echocardiography (17). Digital echocardiographic data containing a minimum of 3 consecutive beats (5 in atrial fibrillation) were acquired and transferred to a Mayo Clinic institutional server for storage and archiving. Left ventricular EF was measured by M-mode or 2-dimensional echocardiography using the Quinones formula from the parasternal views (18), by the quantitative 2-dimensional biplane volumetric Simpson method from 4- and 2-chamber views (17), and by the semiquantitative 2-dimensional visual estimate method from multiple echocardiographic views. All methods have been previously validated (18). The EF values were averaged when multiple measurements were performed. As recommended (19), preserved systolic function was defined as an EF $\geq$50%. Left ventricular end-diastolic diameter and interventricular septal and posterior wall thickness were measured by M-mode or 2-dimensional echocardiography from the parasternal views at end diastole as recommended by the American Society of Echocardiography, and they were used to calculate left ventricular mass, which was indexed to body surface area (17).

As PASP is equal to right ventricular systolic pressure in the absence of pulmonary stenosis, PASP was estimated using Doppler echocardiography by calculating the right ventricular to right atrial pressure gradient during systole, approximated by the modified Bernoulli equation as $4v^2$, where v is the velocity of the tricuspid regurgitation jet in m/s. Right atrial pressure, estimated on the basis of echocardiographic characteristics of the inferior vena cava and assigned a standardized value (20), was then added to the calculated gradient to give PASP (3). Although the agreement between echocardiographic estimates of PASP and invasively measured values on right-side heart catheterization is suboptimal (21), especially among patients with lung disease (22), these 2 methods are sufficiently correlated (20) to warrant the use of Doppler to screen for PH (21,23).

Diastolic function was assessed as previously published (12,24). It integrates Doppler measurements of the mitral inflow and Doppler tissue imaging of the mitral annulus (25), a sensitive and relatively load-independent measure of left ventricular relaxation (12,25,26). The algorithm relies on mitral inflow and Doppler tissue imaging, both methods that can be applied to large numbers of patients with high reproducibility (25). This approach enabled classifying diastolic function into 4 categories: normal, mild (impaired relaxation without evidence of increased filling pressures), moderate (impaired relaxation or pseudonormal with moderate elevation of filling pressures), and severe (advanced reduction in compliance) (12,25). Diastolic function was categorized as indeterminate in the presence of missing data.

Patient characteristics. The characteristics at the time of HF diagnosis were collected from the medical records. Subjects were classified as out-patient cases if not hospitalized within 7 days of the out-patient diagnosis. Clinicians' diagnoses were used to identify COPD, atrial fibrillation and flutter, hyperlipidemia, hypertension, and current smoking. Diabetes mellitus was defined according to the American Diabetes Association criteria (27). The hemoglobin value closest to HF diagnosis ($\pm$1 year) was used to define anemia (hemoglobin concentration $<$13.0 g/dl in men and $<$12.0 g/dl in women) (28). Body mass index (BMI [kg/m^2]) was calculated using height (first available out-patient value) and weight (last out-patient value before HF diagnosis).

Myocardial infarction (MI) was defined by published criteria (29), and comorbidity was measured by the Charlson index, excluding COPD (30). Estimated glomerular filtration rate was calculated using the last serum creatinine value before the diagnosis of HF or the first value post-HF diagnosis ($\pm$1 year), with the MDRD (Modification of Diet in Renal Disease) study equation (31).

Serum samples were stored at -70° C until laboratory testing was performed. The BNP was measured by a 2-site immunoenzymatic sandwich assay on the DxI 800 automated immunoassay system (Beckman Instruments, Chaska, Minnesota). Tests were performed in the Immunochemical Core Laboratory of Mayo Clinic, Rochester, Minnesota.

Follow-up for death relied on death certificates filed in Olmsted County, autopsy reports, obituary notices, and electronic files of death certificates obtained from the State of Minnesota Department of Vital and Health Statistics. Cardiovascular cause of death was based on codes from the 10th version of the International Classification of Diseases (ICD-10), while relying on the American Heart Association categories for cardiovascular deaths (I00 to I99) (32).

Statistical analysis. Data are presented as frequencies and percentages for categorical variables, mean ± SD for normally distributed continuous variables, or median (25th to 75th percentiles) for continuous variables with a skewed distribution. Trends in characteristics across groups were tested with Mantel-Haenszel chi-square for categorical variables and linear regression for continuous variables. Trends in skewed variables were analyzed after logarithmic transformation. PASP was categorized into tertiles and coded as a single 3-level variable.

Survival was analyzed with the Kaplan-Meier method according to PASP tertiles and was compared by the log-rank test. Cox proportional hazards regression was used to examine the association between PASP and all-cause death and cardiovascular (CV)-specific death, univariately and while controlling for baseline characteristics. Covariate data were missing in <1% of the patients. The proportional hazard assumption was tested using the Schoenfeld residuals and was found to be valid.

To determine whether PASP offered value in predicting 1-year mortality beyond traditional risk indicators, the incremental value of PASP was assessed using the c-statistic, IDI, and NRI. It is recognized that reporting a significant association between a predictor and outcome is not sufficient to demonstrate value in risk prediction (33). It is suggested that the c-statistic not be the sole determinant of clinical utility and that measures of risk discrimination (IDI) and reclassification (NRI) be used to evaluate the value of a risk indicator (33).

The IDI measures the change in the difference in the mean predicted probabilities of death between subjects dead and alive at 1 year after inclusion of PASP in the base model. Our base model included the covariates in our final Cox proportional hazards regression model (age, sex, incident HF status, comorbidity index, anemia, EF, diastolic function, and COPD). PASP was log-transformed and modeled continuously.

The NRI measures improvement in risk classification using event-specific reclassification tables. Logistic regression was used to determine the predicted probabilities for 1-year all-cause mortality for each patient using the base model. The probabilities were then ranked and categorized into tertiles (<13%, 13% to <23%, and ≥23%). Patients were reclassified according to the 1-year predicted probabilities of death after addition of PASP into the model. The NRI quantified the net improvement in risk reclassification (higher predicted probability of death in subjects dead at 1 year, lower predicted probability of death in subjects alive at 1 year). Similar methods were used to determine the NRI for 1-year CV-specific mortality. The tertile cutpoints for predicted probability of CV death were <6%, 6% to <12%, and ≥12%.

All statistical tests were 2-sided, and a p value of 0.05 was selected for the threshold of statistical significance. Analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Cary, North Carolina) and Splus statistical software, version 8 (TIBCO Software, Palo Alto, California).

Results

Patient identification and characteristics. Between September 4, 2003, and June 30, 2010, 8,460 Olmsted County residents were identified from the electronic medical record as potential candidates for inclusion. After manual record review, 1,938 patients with active HF (both incident and prevalent) were approached for participation. Among these, 1,300 consented (participation rate of 67.1%), and 1,153 underwent echocardiography at a median of 1 day (25th to 75th percentile: 0 to 3 days) within the diagnosis of HF. PASP could not be measured for 104 patients, resulting in a final study population of 1,049.

The mean age of study subjects was 76 ± 13 years; 1,016 (96.9%) met Framingham criteria for HF; and 51% were women. The burden of comorbidity was high in this population as 572 (54.5%) of the subjects presented with a modified Charlson comorbidity index of 3 or greater. Among the 1,049 study subjects, 282 (27%) were diagnosed in the out-patient setting, and 767 (73%) were in-patients; 538 (51%) were incident HF cases, and the remaining 511 (49%) were prevalent cases.

Pulmonary artery systolic pressure. The median PASP was 48 mm Hg (25th to 75th percentile: 37.0 to 58.0). When the upper limit of pulmonary pressure was defined as 35 mm Hg, only 21% of patients in this cohort had normal pulmonary pressures. Baseline characteristics were examined according to the tertiles of the distribution of PASP, defined as <41, 41 to 54, and >54 mm Hg (Table 1). Among patients with PASP <41 mm Hg, 64.4% had normal PASP (defined as ≤35 mm Hg).

Patients with higher PASP were more likely to be older, female, have anemia, atrial fibrillation, lower creatinine clearance and BMI, and higher New York Heart Association functional class and BNP level, while they were less likely to have hyperlipidemia (Table 1). Increasing PASP was associated with larger left atrial volume index, higher ratio of early transmitral flow velocity to early mitral annular (medial) diastolic velocity (E/e' ratio) and worse diastolic function; however, PASP was not associated with left ventricular mass index, EF, or left ventricular end-diastolic diameter (Table 2).

Mortality. After a mean follow-up of 2.7 ± 1.9 years, 489 patients died. There was a strong positive graded association

JACC Vol. 59, No. 3, 2012
January 17, 2012:222–31

Table 1 Clinical Characteristics of Patients With HF in Olmsted County

	No. Missing	Total (n = 1,049)	Tertile 1 PASP <41 mm Hg (n = 343)	Tertile 2 PASP 41–54 mm Hg (n = 370)	Tertile 3 PASP >54 mm Hg (n = 336)	p Value
Age, yrs	—	75.6 ± 13.3	73.4 ± 13.4	76.2 ± 13.0	77.1 ± 13.3	<0.001
Men	—	517 (49.3)	188 (54.8)	172 (46.5)	157 (46.7)	0.035
Cardiovascular risk factors						
Hypertension	—	897 (85.5)	294 (85.7)	311 (84.1)	292 (86.9)	0.664
Current smoker	—	97 (9.3)	37 (10.8)	32 (8.7)	28 (8.3)	0.269
Diabetes mellitus	—	347 (33.1)	113 (32.9)	110 (29.7)	124 (36.9)	0.278
Hyperlipidemia	—	783 (74.6)	274 (79.9)	269 (72.7)	240 (71.4)	0.011
BMI, kg/m^2	—	27.5 (24–32)	28.4 (25–32)	27.5 (24–31)	26.5 (23–31)	0.015
Comorbidities						
Prior MI	—	251 (23.9)	83 (24.2)	86 (23.2)	82 (24.4)	0.952
COPD	—	293 (27.9)	89 (26.0)	110 (29.7)	94 (28.0)	0.552
Estimated GFR, ml/min per 1.73 m^2	203	52.2 (38–64)	54.2 (44–67)	52.1 (39–64)	48.1 (34–59)	<0.001
Anemia	4	537 (51.4)	146 (42.7)	189 (51.4)	202 (60.3)	<0.001
Atrial fibrillation/flutter	1	379 (36.2)	98 (28.6)	155 (42)	126 (37.5)	0.015
Comorbidity index	—					0.096
0		156 (14.9)	58 (16.9)	52 (14.1)	46 (13.7)	
1–2		321 (30.6)	106 (30.9)	121 (32.7)	94 (28.0)	
≥3		572 (54.5)	179 (52.2)	197 (53.2)	196 (58.3)	
HF characteristics and severity indices						
NYHA functional class	—					0.001
I		63 (6.0)	29 (8.5)	16 (4.3)	18 (5.4)	
II or III		647 (61.7)	222 (64.7)	234 (63.2)	191 (56.9)	
IV		339 (32.3)	92 (26.8)	120 (32.4)	127 (37.8)	
BNP, pg/ml	154	426 (209–836)	306 (133–566)	417 (233–736)	675 (320–1,170)	<0.001

Values are mean ± SD, n (%), or median (25th to 75th percentile).

BMI = body mass index; BNP = brain natriuretic peptide; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; HF = heart failure; MI = myocardial infarction; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure.

between PASP and risk of all-cause death after HF ($p < 0.001$) (Fig. 1). One-year mortality estimates for patients in tertiles 1, 2, and 3 were 8%, 19%, and 28%, respectively. Compared to patients in the lowest PASP tertile, patients in the middle tertile had an unadjusted 72% increased risk of death (hazard ratio [HR]: 1.72, 95% confidence interval [CI]: 1.35 to 2.18) (Fig. 2), whereas patients in the highest tertile had >2.5 times increased risk of death (HR: 2.64, 95% CI: 2.09 to 3.33). Adjustment for age and sex and further adjustment for incident HF status, comorbidity index, anemia, EF, diastolic function, and COPD attenuated these results, although in the final multivariable model, patients in the middle PASP tertile still had a 45% increased risk of death (HR: 1.45, 95% CI: 1.13 to 1.85), whereas patients in the highest tertile were more than twice as likely to die compared to patients in the lowest tertile (HR: 2.07,

Table 2 Echocardiographic Characteristics of Patients With HF in Olmsted County

	No. Missing	Total (n = 1,049)	Tertile 1 PASP <41 mm Hg (n = 343)	Tertile 2 PASP 41–54 mm Hg (n = 370)	Tertile 3 PASP >54 mm Hg (n = 336)	p Value (Trend)
LV mass index, g/m^2	401	113 (91–137)	112 (90–136)	114 (92–135)	115 (91–140)	0.729
LVEDD, mm	46	51 (46–57)	50 (46–57)	51.3 (46–57)	51 (46–57)	0.697
LA volume index, ml/m^2	586	47 (38–58)	43 (34–54)	48 (38–61)	50.5 (41–59)	<0.001
E/e' ratio	152	18 (13–25)	15 (11–20)	18 (13–25)	20 (15–30)	<0.001
EF, %	2	47.6 ± 16.5	48.1 ± 15.5	47.3 ± 17.1	47.6 ± 16.9	0.654
Diastolic function						<0.001
Normal		72 (6.9)	25 (7.3)	29 (7.8)	18 (5.4)	
Mild		49 (4.7)	23 (6.7)	16 (4.3)	10 (3.0)	
Moderate		618 (58.9)	223 (65.0)	218 (58.9)	177 (52.7)	
Severe		183 (17.5)	42 (12.2)	64 (17.3)	77 (22.9)	
Indeterminate		127 (12.1)	30 (8.7)	43 (11.6)	54 (16.1)	

Values are median (25th to 75th quartile), mean ± SD, or n (%).

E/e' = ratio of early transmitral flow velocity to early mitral annular (medial) diastolic velocity; EF = ejection fraction; LA = left atrial; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; other abbreviations as in Table 1.

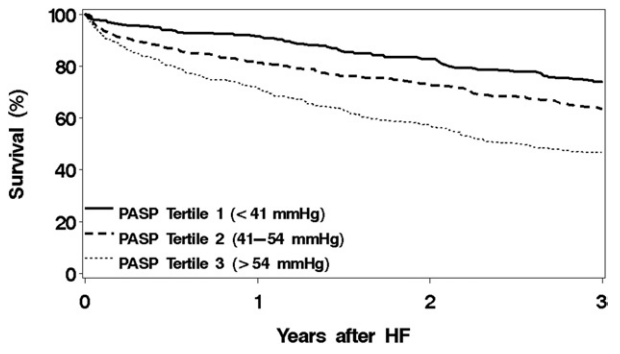

Figure 1 Overall Survival by PASP Tertiles Among HF Patients

Overall survival by pulmonary artery systolic pressure (PASP) tertiles among heart failure (HF) patients, n = 1,049 ($p < 0.001$). **Solid line** = PASP tertile 1 (<41 mm Hg); **dashed line** = PASP tertile 2 (41 to 54 mm Hg); and **dotted line** = PASP tertile 3 (>54 mm Hg).

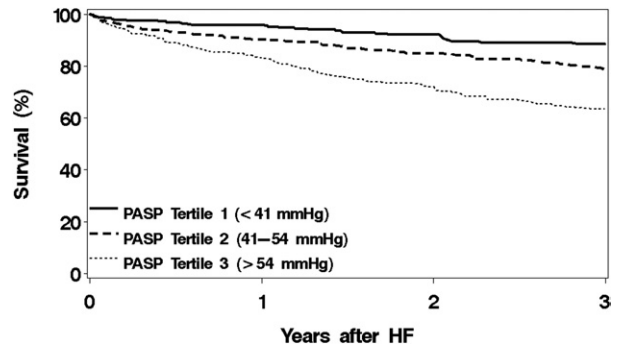

Figure 3 Survival From Cardiovascular Death by PASP Tertiles Among HF Patients

Survival from cardiovascular death by PASP tertiles among HF patients, n = 975 ($p < 0.001$). **Solid line** = PASP tertile 1 (<41 mm Hg); **dashed line** = PASP tertile 2 (41 to 54 mm Hg); and **dotted line** = PASP tertile 3 (>54 mm Hg). Abbreviations as in Figure 1.

95% CI: 1.62 to 2.64). The interaction between EF and PASP was not significant ($p = 0.357$), nor was the interaction between diastolic function and PASP ($p = 0.589$).

We could not obtain cause of death for 74 patients; thus, they were excluded from CV-specific death analyses. During follow-up, 218 patients died of CV death. There was a similar graded association between PASP and risk of CV-specific death. ($p < 0.001$) (Fig. 3). One-year mortality estimates for patients in tertiles 1, 2, and 3 were 4%, 10%, and 17%, respectively. Patients in the middle PASP tertile had an unadjusted twofold increased risk of CV death (HR: 2.22, 95% CI: 1.50 to 3.27) (Fig. 4) compared to patients in the lowest tertile, and patients in the highest tertile had nearly a 4-fold increased risk of CV death (HR: 3.79, 95% CI: 2.60 to 5.53). After adjustment for the same covariates as in the all-cause death analysis, patients in the middle tertile still had an 75% increased risk of CV death (HR: 1.75, 95% CI: 1.17 to 2.60) whereas patients in the highest tertile were 2.5 times as likely to die of CV death compared to patients in the lowest tertile (HR: 2.50, 95% CI: 1.69 to 3.71). There was not a significant interaction between EF

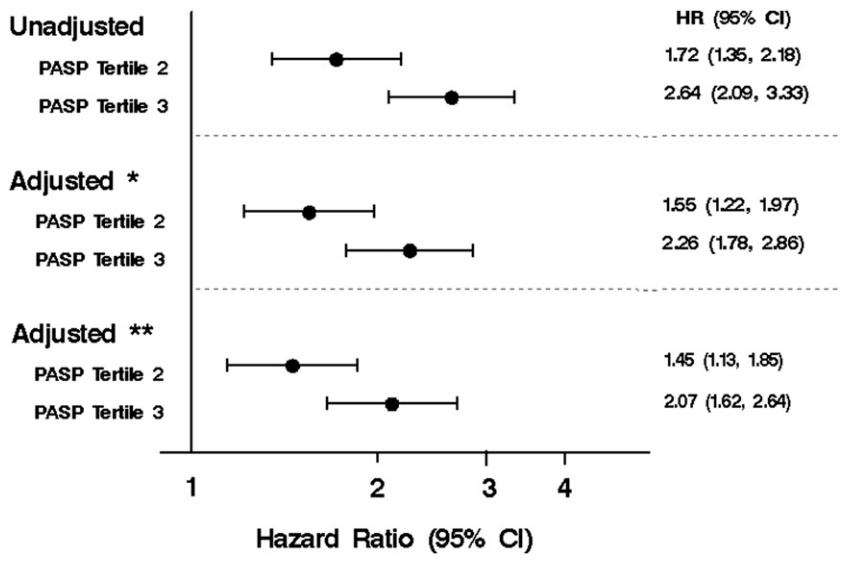

Figure 2 Association Between PASP Tertiles and All-Cause Mortality

The unadjusted and adjusted hazard ratios (HRs) for risk of all-cause mortality using Cox proportional hazards regression. *Adjusted for age and sex. **Adjusted for age, sex, incident HF status, comorbidity index, anemia, ejection fraction, diastolic function, and chronic obstructive pulmonary disease. CI = confidence interval; PASP = pulmonary artery systolic pressure.

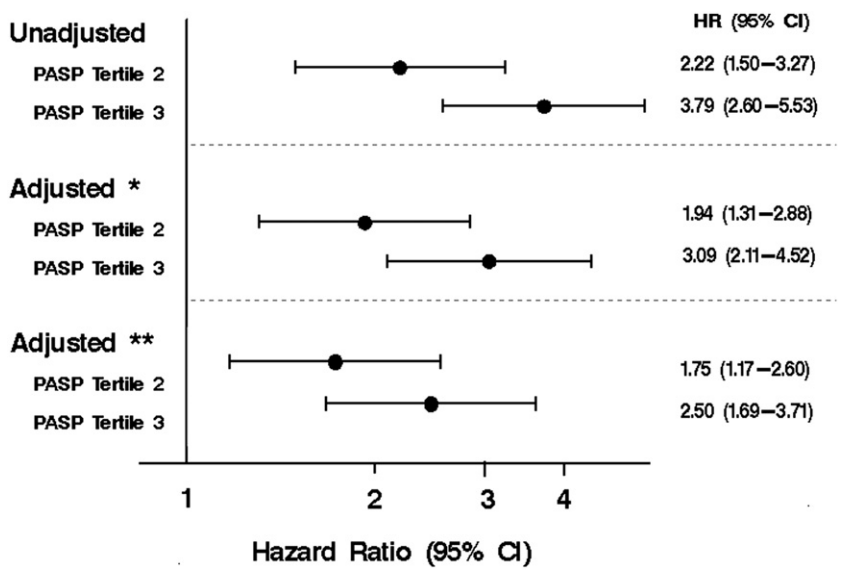

Figure 4 Association Between PASP Tertiles and CV Mortality

The unadjusted and adjusted HRs for risk of cardiovascular (CV) mortality using Cox proportional hazards regression. *Adjusted for age and sex. **Adjusted for age, sex, incident HF status, comorbidity index, anemia, ejection fraction, diastolic function, and chronic obstructive pulmonary disease. Abbreviations as in Figure 2.

and PASP (p = 0.079) or diastolic function and PASP (p = 0.201).

Impact of PASP on risk prediction. The addition of PASP to a prognostic model including age, sex, incident HF status, comorbidity index, anemia, EF, diastolic function, and COPD resulted in an increase in the c-statistic from 0.704 to 0.742 (p = 0.007), an IDI gain of 4.2% (p < 0.001), and an NRI of 14.1% (p = 0.002) (Table 3), indicating that PASP offered additional value in predicting 1-year all-cause mortality over traditional prognostic factors. Similar results were found when predicting 1-year CV mortality. After the addition of PASP, the c-statistic increased from 0.720 to 0.765 (p = 0.020), there was an IDI gain of 3.6% (p < 0.001), and an NRI of 13.5% (p = 0.025) (Table 4).

Sensitivity analyses. Several ancillary analyses were conducted to assess the robustness of our results. The distribution of PASP was similar when restricted to incident cases of HF, to patients meeting Framingham criteria, or to patients presenting in the out-patient setting.

Analyses in the subset of patients without COPD (n = 756; 72%) yielded similar results for all-cause and CV death, as did analyses in the subset of patients without atrial fibrillation (n = 669; 64%). Furthermore, results were similar when analyses were restricted to the subset of patients with an EF <45% (n = 424; 40%).

Table 3 Reclassification of Participants by 1-Year All-Cause Mortality Status Using Model With PASP

Model With Established Risk Factors*	Model With Established Risk Factors and PASP		
	<13% Risk	13%–<23% Risk	≥23% Risk
Participants dead at 1 yr (n = 190)			
<13% risk	14	8	3
13% to 23% risk	8	22	25
≥23% risk	5	14	91
Participants alive at 1 yr (n = 781)			
<13% risk	247	36	3
13% to 23% risk	103	121	47
≥23% risk	10	46	168

*Established risk factors include age, sex, incident heart failure status, comorbidity index, anemia, ejection fraction, diastolic function, and chronic obstructive pulmonary disease.
PASP = pulmonary artery systolic pressure.

Table 4 Reclassification of Participants by 1-Year Cardiovascular Mortality Status Using Model With PASP

Model With Established Risk Factors*	Model With Established Risk Factors and PASP		
	<6% Risk	6%–<12% Risk	≥12% Risk
Participants dead at 1 yr (n = 90)			
<6% risk	6	0	2
6% to 13% risk	7	9	12
≥13% risk	1	4	49
Participants alive at 1 yr (n = 781)			
<6% risk	256	34	2
6% to 13% risk	104	94	52
≥13% risk	10	62	167

*Established risk factors include age, sex, incident heart failure status, comorbidity index, anemia, ejection fraction, diastolic function, and chronic obstructive pulmonary disease.
PASP = pulmonary artery systolic pressure.

Adjustment for BMI, hypertension, hyperlipidemia, atrial fibrillation, New York Heart Association functional class, smoking status and estimated glomerular filtration rate yielded similar results, as did adjustment for BNP. Removing diastolic function from the final model and adjusting for E/e' ratio yielded similar results, as did further adjustment for BNP and left atrial volume.

Survival of patients without measurable PASP (9%) was not significantly different from that of patients with measurable PASP (log-rank p = 0.997).

Discussion

The present data indicate that pulmonary pressures can be readily assessed by Doppler echocardiography among patients with HF in the community and that pulmonary hypertension is overwhelmingly present in this setting. PASP was a strong and independent predictor of all-cause death and CV death independently of other known predictors, including diastolic function measures and BNP. Further, PASP improved risk prediction over established risk factors as assessed using novel risk prediction methodology.

Increased pulmonary pressures in HF. Although PASP increases with age (34) and patients with HF are mostly elderly, PASP is higher in HF patients than in the general population (34). The upper limit of normal for PASP is commonly defined as 35 mm Hg, while varying with age and BMI (35). Published studies used varying definitions of PH, which compromises our ability to compare even informally across studies and with our data (2,8,36,37). However, among studies that used similar definitions (3,9), the prevalence of PH ranged from 46% to 83%. The corresponding populations were, however, heterogeneous and selected populations (Table 5). In the present cohort, when PH was defined as PASP >35 mm Hg, PH was prevalent in the vast majority of subjects (79%).

In addition, EF was similar across the tertiles of PASP, and the effect of PH on outcome was similar both for patients with reduced and for patients with preserved EF. Therefore, PH was not associated with the severity of systolic dysfunction. Similar to previous reports (38), in the present study, PH was associated with left atrial volume index, diastolic function grade, and left ventricular filling pressures (E/e'), confirming that patients included had type II PH according to the World Health Organization classification, hence, secondary to left-side heart disease and due chiefly to elevation in left-sided pressures. Sensitivity analyses excluding patients with COPD showed the results were unchanged and confirm these findings.

PH in HF has been postulated to be the result of the combination of the passive effect of elevated left ventricular end-diastolic pressure backward on the pulmonary venous circulation and an active vasoreactive process of vasoconstriction and pulmonary arterial remodeling (3,4). Pathology studies have shown remodeling changes in the elastic fibers of the pulmonary arterial wall, intimal fibrosis, and medial hypertrophy of pulmonary muscular arteries, with changes that are similar to or greater than those seen in idiopathic pulmonary arterial hypertension (39).

In the present study, PASP remained a strong predictor of death and CV death even after adjusting for diastolic function or E/e'. The statistical independence between diastolic function and PASP supports the hypothesis that, beyond the effect of post-capillary increased venous congestion, there is a superimposed active pre-capillary component of PH and that this plays a role in prognosis. Therefore, PH appears to be not only a marker of worse HF, but also may have itself a direct deleterious effect.

Pulmonary pressures and outcomes. Although there are substantial data on pulmonary pressures in idiopathic pulmonary arterial hypertension, which is less common (5,6), much less is known about the more common PH in HF (6). Indeed, Table 5 summarizes selected published studies, which consist chiefly of convenience samples of patients referred to out-patient or in-patient clinics (2,9), to diagnostic testing such as echocardiography (8,11,36), or were subanalyses of clinical trials (7,37). These studies are thus

Table 5 Selected Studies Reporting on PASP in the Literature 2000 to 2010

First Author (Ref. #)	n	Year	Design	HF Definition	EF	% With Measured PASP
Damy (9)	1,380	2001–2008	Consecutive referrals to HF clinic	Clinical	26% preserved EF (>45%); 74% reduced EF	26% of patients with LVSD; 40% no LVSD
Adhyapak (36)	147	2004–2007	Consecutive HF patients with echocardiography series	Framingham criteria	Mean EF 39%	100%
Khush (37)	171	2000–2003	Substudy of ESCAPE trial	Clinical	Only EF ≤30%	100%
Kjaergaard (7)	1,022	2001–2004	Substudy of patients screened for trial (ECHOS)	Clinical	24% preserved EF (>50%) 71% reduced EF	38%
Grigioni (8)	196	1996–2003	Echocardiographic series	Clinical	Mean EF 27%	100%
Ghio (2)	377	1992–1998	Consecutive patients referred for HF management	Clinical	Only EF <35%	100%
Lam (3)	244	2003–2005	Community HF patients	Framingham criteria	Only EF ≥50%	83%
Shalaby (11)	270	2004–2005	Echocardiographic series of HF patients undergoing CRT	Clinical	Not measured	79%

CRT = cardiac resynchronization therapy; ECHOS = Echocardiography and Heart Outcome Study; ESCAPE = Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; LVSD = left ventricular systolic dysfunction; other abbreviations as in Tables 1 and 2.

subject to various degrees of selection bias, which hinders the inference that can be drawn from them. In addition, most published studies were limited to patients with severe HF (8,37) or to patients with reduced EF (2,8,37) or preserved EF (3) and often did not include the whole spectrum of HF. Indeed, the only community study on PH in HF, conducted by our group, was limited to subjects with preserved EF (3).

The present data address those gaps in knowledge, reflect the comprehensive experience of a community, and pertain to the complete spectrum of HF including in- and out-patients, systolic and diastolic HF, as well as incident and prevalent cases. In this setting of high clinical relevance, PH is a strong independent predictor of outcomes as there is a graded association between the severity of PH and death in a large community cohort, irrespective of whether the patient was admitted to the hospital or evaluated as an out-patient, in primary or in subspecialty care. The novel risk prediction methodology used herein provides information on the value of PH for risk discrimination and reclassification, 2 measures of the practical value of a risk indicator (33). As PASP is readily available from echocardiographic studies, which are recommended by professional guidelines for the evaluation of heart failure (40), it can be obtained with no additional burden to the patient and no additional cost to provide important incremental prognostic information.

Study limitations, strengths, and clinical implications. Potential limitations should be acknowledged to facilitate the interpretation of the results. We did not account for right ventricular size and function as this information was not universally available. The inferior vena cava size and collapse were used to estimate right atrial pressure in a semiquantitative method, and right atrial pressure was added to the transtricuspid gradient (41). The reproducibility and reliability of Doppler in measuring PASP are lower than for right-side heart catheterization (23); however, this study could have not been performed using invasive methods. We recognize that right-side heart catheterization is the standard to accurately diagnose PH and determine its severity as well as impact on right ventricular function. However, Doppler estimates of PASP have been shown to have adequate correlation with invasive measures (42); therefore, Doppler echocardiography is now considered the reference screening method to detect PH (6).

PASP could not be measured in 9% of the patients, a proportion that is much lower than what is usually reported (7,9). However, survival of patients without measurable PASP was not significantly different from that of patients with measurable PASP.

Strengths of this study include the community-based approach, which enhances its external validity, and the novel case-finding method, which enables rapid identification of all cases of HF (12). We captured the complete spectrum of HF by including incident and prevalent systolic and diastolic HF cases indentified during both in-patient and out-patient visits. Further, we relied on rigorous validated Doppler echocardiography techniques applied promptly after HF diagnosis.

In aggregate, these data support the concept that PH may be a central determinant in the outcome of HF and may, therefore, represent a potential therapeutic target. Further studies are warranted to test this hypothesis.

Conclusions

In a large community-based prospective cohort of subjects with HF, pulmonary pressures can be readily estimated by Doppler echocardiography. Pulmonary hypertension is a strong and independent predictor of mortality among patients with HF and provides incremental and clinically relevant prognostic information independently of known predictors of outcomes.

Acknowledgments

The authors thank Ellen Koepsell, RN, and Kay Traverse, RN, of the Mayo Clinic for their assistance with subject enrollment and data collection, and Kristie Shorter, Mayo Clinic, for secretarial assistance. They also thank the study sonographers Jo-Ellen Ehrsam, RDCS, Tammy Green, RDCS, and Mary E. Hagen, RN, RDCS, of the Mayo Clinic. These persons were not compensated for their contributions.

Reprint requests and correspondence: Dr. Véronique L. Roger, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: roger.veronique@mayo.edu.

REFERENCES

1. Abramson SV, Burke JF, Kelly JJ Jr., et al. Pulmonary hypertension predicts mortality and morbidity in patients with dilated cardiomyopathy. Ann Intern Med 1992;116:888–95.
2. Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 2001;37:183–8.
3. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol 2009;53:1119–26.
4. Guglin M, Khan H. Pulmonary hypertension in heart failure. J Card Fail 2010;16:461–74.
5. Hoeper MM, Barbera JA, Channick RN, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 2009;54 Suppl:S85–96.
6. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Heart J 2009;30:2493–537.
7. Kjaergaard J, Akkan D, Iversen KK, et al. Prognostic importance of pulmonary hypertension in patients with heart failure. Am J Cardiol 2007;99:1146–50.
8. Grigioni F, Potena L, Galie N, et al. Prognostic implications of serial assessments of pulmonary hypertension in severe chronic heart failure. J Heart Lung Transplant 2006;25:1241–6.

9. Damy T, Goode KM, Kallvikbacka-Bennett A, et al. Determinants and prognostic value of pulmonary arterial pressure in patients with chronic heart failure. Eur Heart J 2010;31:2280–90.
10. Butler J, Stankewicz MA, Wu J, et al. Pre-transplant reversible pulmonary hypertension predicts higher risk for mortality after cardiac transplantation. J Heart Lung Transplant 2005;24:170–7.
11. Shalaby A, Voigt A, El-Saed A, Saba S. Usefulness of pulmonary artery pressure by echocardiography to predict outcome in patients receiving cardiac resynchronization therapy heart failure. Am J Cardiol 2008;101:238–41.
12. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. JAMA 2006;296:2209–16.
13. Melton LJ III. History of the Rochester Epidemiology Project. Mayo Clin Proc 1996;71:266–74.
14. Pakhomov SV, Buntrock J, Chute CG. Prospective recruitment of patients with congestive heart failure using an ad-hoc binary classifier. J Biomed Inform 2005;38:145–53.
15. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22:6A–13A.
16. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. JAMA 2004;292:344–50.
17. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group. J Am Soc Echocardiogr 2005;18:1440–63.
18. Quinones MA, Waggoner AD, Reduto LA, et al. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. Circulation 1981;64:744–53.
19. Yturralde RF, Gaasch WH. Diagnostic criteria for diastolic heart failure. Prog Cardiovasc Dis 2005;47:314–9.
20. Ommen SR, Nishimura RA, Hurrell DG, Klarich KW. Assessment of right atrial pressure with 2-dimensional and Doppler echocardiography: a simultaneous catheterization and echocardiographic study. Mayo Clin Proc 2000;75:24–9.
21. Rich JD, Shah SJ, Swamy RS, Kamp A, Rich S. Inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension: implications for clinical practice. Chest 2011;139:988–93.
22. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 2003;167:735–40.
23. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126 Suppl:14S–34S.
24. Redfield MM, Jacobsen SJ, Burnett JC Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.
25. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788–94.
26. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527–33.
27. American Diabetes Association: clinical practice recommendations 1997. Diabetes Care 1997;20 Suppl 1:S1–70.
28. Izaks GJ, Westendorp RG, Knook DL. The definition of anemia in older persons. JAMA 1999;281:1714–7.
29. White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) study: methods and initial two years' experience. J Clin Epidemiol 1996;49:223–33.
30. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
31. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–54.
32. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation;121:e46–215.
33. Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72, discussion 207–12.
34. Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-associated increases in pulmonary artery systolic pressure in the general population. Circulation 2009;119:2663–70.
35. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. Circulation 2001;104:2797–802.
36. Adhyapak SM. Effect of right ventricular function and pulmonary pressures on heart failure prognosis. Prev Cardiol 2010;13:72–7.
37. Khush KK, Tasissa G, Butler J, McGlothlin D, De Marco T. Effect of pulmonary hypertension on clinical outcomes in advanced heart failure: analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) database. Am Heart J 2009;157:1026–34.
38. Neuman Y, Kotliroff A, Bental T, Siegel RJ, David D, Lishner M. Pulmonary artery pressure and diastolic dysfunction in normal left ventricular systolic function. Int J Cardiol 2008;127:174–8.
39. Delgado JF, Conde E, Sanchez V, et al. Pulmonary vascular remodeling in pulmonary hypertension due to chronic heart failure. Eur J Heart Fail 2005;7:1011–6.
40. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;53:e1–90.
41. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713.
42. Capomolla S, Febo O, Guazzotti G, et al. Invasive and non-invasive determinants of pulmonary hypertension in patients with chronic heart failure. J Heart Lung Transplant 2000;19:426–38.

Key Words: community ■ heart failure ■ mortality ■ pulmonary hypertension.