Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods:

Population:

The JHS is a longitudinal population-based cohort study that recruited AA participants residing in Jackson, MS [1] from each of 4 recruitment pools: random, 17%; volunteer, 22%; currently enrolled in the Atherosclerosis Risk in Communities (ARIC) Study, 30%; and secondary family members, 31%. Recruitment was limited to non-institutionalized adult AAs 35-84 years old, except in the family cohort where subjects 21 to 34 years of age were eligible. The final cohort of 5,301 participants includes 6.59% of all AA Jackson metropolitan statistical area residents aged 35-84 [2]. Subjects answered predefined questionnaires and underwent phlebotomy, including plasma ET measurement, echocardiography, and spirometry at the time of first exam in 2000-2004. One hundred and one subjects were excluded from all analyses due to absence of plasma ET level measurement, while another 1,977 subjects were excluded due to absence of a tricuspid regurgitation (TR) jet. The cohort used for the current study therefore included participants that had measurable TR jet velocity on echocardiography and plasma ET levels (n=3,223) at their first study visit. The characteristics of the 1,977 excluded subjects with measured plasma ET levels but no TR jet as compared to the 3,223 study subjects are detailed in Supplemental Table S1. Subjects with no TR jet were significantly younger (53.5 ± 13.0 years versus 56.6 ± 12.6 years) and were more likely to be male, to have higher body mass index (BMI), to have diabetes, and to have a reduced left ventricle (LV) ejection fraction than study subjects with a TR jet, but had comparable plasma ET levels and similar longitudinal outcomes.

Exposure:

The main exposure was plasma ET level at the first (baseline) study visit. ET was measured in pg/ml by QuantiGlo Human ET-1 Immunoassay (R&D Systems, Inc., 614 McKinley Place NE, Minneapolis, MN). The range of ET levels in the JHS study subjects was 0.1pg/ml-9.6pg/ml. Log-transformed plasma ET levels (Log-ET) were used in the primary analyses. Additional analyses were performed with the exposure being a plasma ET value ≥ 1.7pg/ml (High ET). This value was set at the cut-off value for above the 75th percentile in the study cohort.

A complete description of the specimen collection procedures and quality control measures for the Jackson Heart Study is available online [3]. Blood for plasma ET levels was drawn at the baseline study visit from the antecubital fossa of supine subjects by trained technicians; specimens were processed and then frozen samples of plasma were shipped to the Central Laboratory at Fairview-University Medical Center in Minneapolis, MN for ET measurement[3]. The intra-assay coefficient of variation for this assay ranges from 2.6-3.4%; the inter-assay coefficient of variation ranges from 4.5-9.1%.[4] The minimum detectable dose of ET for this assay ranges from 0.023-0.102pg/ml (mean 0.064pg/ml).[4] Blood specimens were collected from October 2000 through March 2004; ET-1 testing was done July 2003-July 2004. There were zero freeze-thaw cycles of the samples prior to ET measurement.

Clinical Covariates:

Body mass index was categorized by AHA ideal cardiovascular health categorization (poor health: BMI≥30kg/m2; intermediate health: BMI ≥ 25, but < 30kg/m2; ideal health: BMI<25kg/m2)[5]. Physical activity was categorized according to AHA ideal cardiovascular health guidelines: poor physical activity: 0 minutes of moderate or vigorous physical activity per week; intermediate physical activity: less than 150 minutes of moderate physical activity, < 75 minutes

of vigorous physical activity, or less than 150 minutes of combined moderate and vigorous physical activity per week; and recommended physical activity: ≥ 150minutes of moderate, ≥ 75minutes of vigorous, or ≥ 150 minutes of combined moderate and vigorous physical activity per week [5,6].

Coronary heart disease was considered present if the subject reported a history of coronary heart disease, a prior abnormal stress test, prior coronary bypass graft, or prior coronary angioplasty, or if there was EKG evidence of a prior myocardial infarction (per Minnesota code). Diabetes was considered present if the hemoglobin A1C was ≥6.5%, if a fasting plasma glucose was ≥126mg/dl, or if use of diabetes medications was reported [7]. Systemic hypertension was considered present if the systolic blood pressure was ≥140mmHg or the diastolic blood pressure was ≥ 90mmHg or if the subject was using blood pressure lowering medications [8]. High cholesterol was defined as a total cholesterol ≥240mg/dl or use of statin medication. Pulse pressure was defined as the difference between systolic and diastolic blood pressures. Severe mitral or aortic valve disease was considered present if the qualitative echocardiographic assessment showed severe mitral regurgitation, mitral stenosis, aortic regurgitation, or aortic stenosis. Heart rate was measured on a baseline EKG. A history of heart failure was considered present if the patients responded to the question “Has a doctor ever said you had heart failure or congestive heart failure?” in the affirmative at the time of first annual telephone follow up. History of stroke was considered present if the subjects responded to the question “Have you been told by a physician you had a stroke?” in the affirmative at baseline study visit. Atrial fibrillation was considered present if the subject had atrial fibrillation on baseline EKG. Chronic lung disease was considered present if the subjects responded to the question “Has your doctor or health professional ever said you have chronic lung disease, such as bronchitis or emphysema?” in the affirmative at baseline study visit.

Medications taken at the first study visit were classified using the Medispan therapeutic classification system [9]. Subjects were categorized as taking anti-hypertensive medication if a beta blocker, calcium channel blocker, antihypertensive, or diuretic was taken during the past 2 weeks. Cigarette smoking was derived from interview and categorized as never smoker (one who reported having smoked less than 400 cigarettes in one's life), former smoker (smoked >400 cigarettes but not currently smoking), and current smoker.

Aldosterone levels were measured in ng/dL. Serum creatinine values in mg/dL were calibrated to the Cleveland Clinic equivalent.[10] The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease formula.[10]

Airway obstruction was considered present if the FEV_1/FVC ratio was less than 0.70. Restriction was considered present if the FEV1/FVC ratio was ≥ 0.70, but the FVC % predicted was less than 80%. Subjects not having obstruction or restriction were considered to have normal spirometry. Percent predicted values for FVC were derived from NHANES III data.[11]

Echocardiography parameters:

Detailed echocardiography procedures are available online[12]. Briefly, echocardiograms were recorded by trained sonographers and interpreted by experienced cardiologists in a standardized manner at the University of Mississippi Medical Center [12]. Standard echocardiographic views were obtained and measurements performed by the interpreting physician who was blinded to the participants' clinical data. The echocardiography data used for the current study included: PASP, calculated from the peak TR gradient plus 5mmHg; pulmonary acceleration time, in milliseconds; left atrial diameter index, in mm/m^2; the unitless ratio of mitral valve peak E wave velocity (in m/sec) to mitral valve peak A wave velocity (in m/sec); and semi-quantitative left ventricular ejection fraction, to nearest 5%. Left ventricular hypertrophy

was defined as a left ventricular mass index greater than 51g/(height in meters/100)$^{2.7}$. Valvular disease was qualitatively graded. PH was defined as a PASP greater than 40mmHg.

Statistical analysis

Distribution of plasma ET levels in the study population was assessed using descriptive statistics. ET levels were not normally distributed in the population, as has been noted previously [13] [14]. Therefore, ET levels were log-transformed to approximate normality (Log-ET). Regression analysis was performed to assess the relationship between Log-ET and baseline clinical characteristics. A cut-off for an elevated ET level was established as a level in the upper quartile (≥1.7pg/ml) of the study cohort, an approach that has been used previously [13]; this group of subjects was designated High ET. The remainder of the cohort, with an ET level <1.7pg/ml, was categorized as Low ET. The baseline characteristics of the whole study cohort were described, and differences in baseline characteristics between the High ET and Low ET groups were compared using the Mann-Whitney U test for continuous variables and Chi-square analysis for categorical variables.

The association between Log-ET and presence of PH was assessed using logistic regression. Models were adjusted for age group, gender, BMI category (normal, overweight, obese), pulse pressure (mmHg), hypertension, diabetes, coronary heart disease, severe mitral/aortic valvular heart disease, history of chronic lung disease, spirometry profile (normal, obstruction, restriction), and for a left ventricular ejection fraction less than 50%. The fully adjusted model of PH was adapted from Choudhary et al[15], the adaptations being use of BMI as a continuous variable, rather than BMI categories, and additional adjustment for reduced left ventricular ejection fraction. The adapted PH model (without ET) has an area under the receiver operating characteristic curve for correctly classifying elevated PASP>40mmHg in this JHS study

population of 0.805. Integrated discrimination improvement was assessed following addition of Log-ET to the pulmonary hypertension model. Sensitivity analyses were repeated using High ET as the main exposure in lieu of Log-ET. Similarly, repeated analyses were conducted using log-transformed PASP (to approximate normality for PASP distribution) as the outcome, in lieu of PH, using linear regression. Exploratory analyses were performed with addition of left atrial diameter index to the PH model.

For the longitudinal analyses, Cox proportional hazards modeling was used. The hazard ratio for all-cause mortality associated with Log-ET (main exposure) was determined in a univariate analysis; followed by a determination of the hazard ratio in a fully adjusted model of mortality adapted from Gu et al [16], controlling for age, gender, BMI, physical activity, smoking status, high cholesterol, diabetes, history of heart failure, history of coronary heart disease, hypertension, estimated glomerular filtration rate (eGFR), and history of stroke. The adaptations used in the mortality model were the use of eGFR in place of chronic kidney disease history; and addition of AHA categories for assessment of physical activity. This model (without ET) has an area under the receiver operating characteristic curve for correctly classifying mortality in this JHS population of 0.802. The median follow-up time for the mortality analysis was 7.75 years (range 0-9.94years). Left atrial diameter index, presence of PH, or the log-transformed PASP value were added as variables to the mortality models to assess if the relationship of ET with mortality was independent of presence of these variables. Sensitivity analyses were conducted using High ET and also quartiles of ET as the main exposure(s) in lieu of Log-ET. Kaplan-Meier survival curves for the High ET and Low ET groups were plotted. To account for age-dependent mortality risk, we also conducted mortality analyses using an age-based time scale, where the event age (or age at censoring) was derived from the baseline age plus the follow-up time/365.25. Mortality analysis was also performed in the excluded subjects

without measureable tricuspid regurgitation but with plasma ET levels to assess internal validity. Exploratory analyses were conducted phenotyping the population into 4 subgroups based on presence or absence of PH, and High or Low ET levels, and survival curves were drawn and compared for the four groups using log-rank test.

Next, the relationship of ET levels with adjudicated decompensated HF events requiring hospitalization was assessed. Cox proportional hazards modeling was used to determine the hazard ratio for decompensated HF events associated with Log-ET in a univariate analysis; followed by a fully adjusted model of heart failure (ARIC model) from Agarwal et al[17], adjusting for age, sex, coronary heart disease, diabetes mellitus, systolic blood pressure, blood pressure medication use, heart rate, smoking status and body mass index. Race was a part of the ARIC model but was dropped as a covariate because our population is exclusively composed of African Americans. Subjects who died before a HF event were censored. To confirm that censoring subjects who died (competing event) did not significantly alter the hazards of HF admission (main event), we repeated our analyses, estimating the sub-hazard ratios using the competing risks regression model, according to the method of Fine and Gray.[18] The median follow-up for HF events was 5.32 years (range 0-6 years). Heart failure analysis was also performed in the excluded subjects without measureable tricuspid regurgitation but with plasma ET levels.

Interaction testing was performed to assess potential modifiers of the relationship between LogET and study outcomes (pulmonary hypertension, mortality, and heart failure hospitalizations). Interaction terms were developed for the following variables: age categories[19]; sex, BMI categories[20]; hypertension[21]; diabetes[20], coronary heart disease[22]; smoking categories[23]; spirometry profiles[24]; left ventricular ejection fraction category (normal or

reduced)[25]; left ventricular hypertrophy[26]; left atrial diameter index[27]; estimated glomerular filtration rate[21]; and, for the mortality and heart failure outcomes, pulmonary hypertension. Logistic regression models (for pulmonary hypertension outcome) or Cox proportional hazards models (for the mortality and heart failure hospitalization outcomes) including Log ET, the given variable, and the interaction term were constructed to test the significance of the association of the interaction term with the dependent variable in the model. For categorical variables with more than two levels, the Wald test was used to test overall significance of the interaction. Exploratory subgroup analyses were performed on those variables with significant multiplicative interaction testing at a significance level of $p<0.05$. In subgroup analyses for PH, an adjusted logistic regression model adapted from the pulmonary hypertension model used in the main analysis was analyzed in the relevant subgroup. For the mortality and HF hospitalization outcomes, Cox proportional hazards models including relevant covariates were adapted from the main analyses for analyses in the relevant subgroups.

Missing data ranged from 0.06% for diabetes status and physical activity to 20.8% for total cholesterol. Missing data were imputed based on 5 sets of simulated values generated from non-missing variables using the multiple imputation method in Stata (StataCorp, College Station, TX) [28]. Analyses were performed on each of the 5 data sets completed with imputed values, and then combined using Rubin's combination rules to consolidate the individual estimates into a single set of estimates using the MI estimate command in Stata[29].

All analysis was performed using Stata/SE version 11.2 software (StataCorp LP, College Station, TX). A two-sided p value of less than 0.05 was considered significant.

eTable 1. Baseline Characteristics of the Study Cohort Compared to the Excluded Subjects

	Study Cohort (ET* level and Tricuspid Regurgitation) (n=3,223)	Excluded Subjects: ET level but no Tricuspid Regurgitation (n=1,977)	p-value
Mean age (years) ± SD	56.6 ± 12.6	53.5 ± 13.0	**<0.0001**
Age <45 years	20.20%	29.39%	**<0.001**
Age 45-54 years	23.67%	26.00%	
Age 55-64 years	29.10%	23.72%	
Age ≥ 65 years	27.02%	20.89%	
Male	32.6%	43.4%	**<0.001**
Mean BMI (kg/m^2) ± SD	31.4 ± 7.0	32.3 ± 7.5	**<0.0001**
BMI category			
Obese (BMI ≥ 30)	51.2%	56.7%	**<0.001**
Overweight (25≤BMI<30)	33.7%	29.7%	
Ideal (BMI<25)	15.1%	13.6%	
AHA Physical Activity Category			
Poor amount of physical activity reported	49.9%	48.2%	0.301
Intermediate amount of physical activity reported	31.6%	31.7%	
Ideal amount of physical activity reported	18.5%	20.2%	

Hemodynamics			
Mean heart rate (bpm) ± SD	63 ± 10	66 ± 11	**<0.0001**
Mean systolic blood pressure (mmHg) ± SD	126 ± 18	128 ± 19	**0.025**
Mean diastolic blood pressure (mmHg) ± SD	78 ± 10	80 ± 11	**<0.0001**
Mean pulse pressure (mmHg) ± SD	48 ± 16	48 ± 16	0.3376
Medical conditions			
Hypertension	61.1%	61.9%	0.553
Diabetes	19.4%	25.6%	**<0.001**
High cholesterol	31.4%	30.8%	0.647
Coronary Heart Disease	10.1%	10.1%	0.999
Severe Mitral/Aortic Valvular Disease	0.22%	0.15%	0.600
Heart failure	2.84%	3.03%	0.703
Stroke	4.37%	4.35%	0.966
Atrial fibrillation	0.47%	0.15%	0.062
Chronic Lung Disease	7.0%	7.5%	0.525
Medications			
Antihypertensives	62.2%	60.6%	0.304
Beta blockers	12.6%	11.8%	0.429
Calcium channel blockers	23.0%	23.0%	0.982
Diuretics	39.4%	39.9%	0.765

Smoking History			
Never Smoked	68.0%	67.7%	**0.003**
Former Smoker	19.9%	17.2%	
Current Smoker	12.1%	15.0%	
Spirometry Profile			
Normal	71.0%	68.8%	0.104
Obstruction	9.0%	8.6%	
Restriction	20.0%	22.6%	
Echocardiography characteristics			
Mean estimated pulmonary arterial systolic pressure (mmHg) ± SD	28 ± 7	NA	NA
Pulmonary hypertension (estimated pulmonary artery systolic pressure>40mmHg)	6.7%	NA	NA
Mean pulmonary acceleration time (msec) ± SD	126.9 ± 32.8	124.3 ± 27.7	0.120
Mean left atrial diameter index (mm/m^2) ± SD	18.0 ± 2.5	17.2 ± 2.3	**<0.0001**
Ratio of mitral valve peak E wave velocity (m/sec)/mitral valve peak A wave velocity (m/sec)	1.11 ± 0.37	1.09 ± 0.35	0.197
Mean left ventricular ejection fraction (%) ±	62 ± 8	61 ± 8	**<0.0001**

SD			
LVEF<50%	2.7%	3.9%	**0.024**
LV Hypertrophy (LV mass index > 51 g/(height in meters/100)$^{2.7}$	8.0%	6.6%	0.151
Laboratory values			
Mean aldosterone (ng/dL) ± SD	56.6 ± 12.6	53.5 ± 13.0	**<0.0001**
Mean serum creatinine calibrated to Cleveland Clinic equivalent (mg/dl) ± SD	1.0 ± 0.6	1.0 ± 0.5	**0.0001**
Mean eGFR† based on MDRD‡ formula, (ml/min/1.73m^2) ± SD	84.9 ± 18.3	86.9 ± 18.8	**0.0001**
Plasma endothelin-1			
Mean ET (pg/ml) ± SD	1.36 ± 0.64	1.35 ± 0.60	0.7757
Outcomes			
Died	8.97%	10.22%	0.134
Heart failure hospitalization	4.59%	4.15%	0.449

*ET = endothelin-1

† eGFR = estimated glomerular filtration rate

‡ MDRD = Modification of Diet in Renal Disease

BOLD = significant

eTable 2: Baseline characteristics of subjects with High plasma ET levels compared to subjects with Low plasma ET levels

	All (n=3223)	Low plasma ET* (<1.7pg/ml) (n=2448)	High plasma ET (≥1.7pg/ml) (n=775)	p-value
Mean age (years) ± SD	56.6 ± 12.6	55.6 ± 12.7	59.6 ± 11.9	**<0.0001**
Age <45 years	20.20%	26.21%	15.61%	**<0.001**
Age 45-54 years	23.67%	25.38%	21.93%	
Age 55-64 years	29.10%	26.03%	30.34%	
Age ≥ 65 years	27.02%	22.38%	32.12%	
Male	32.6%	32.0%	34.6%	0.179
Mean BMI (kg/m^2) ± SD	31.4 ± 7.0	31.3 ± 7.0	31.8 ± 7.3	0.0914
BMI category				
Obese (BMI ≥ 30)	51.2%	50.7%	52.6%	0.607
Overweight:(25≤BMI<30)	33.7%	33.9%	33.2%	
Ideal (BMI<25)	15.1%	15.4%	14.2%	
AHA Physical Activity Category				
Poor amount of physical activity reported	49.9%	49.1%	52.3%	0.302
Intermediate amount of physical activity reported	31.6%	32.0%	30.3%	
Ideal amount of physical activity reported	18.5%	18.9%	17.4%	
Hemodynamics				
Mean heart rate (bpm) ± SD	63 ± 10	63 ± 10	63 ± 11	0.8535

Mean systolic blood pressure (mmHg) ± SD	126 ± 18	126 ± 18	129 ± 19	**<0.0001**
Mean diastolic blood pressure (mmHg) ± SD	78 ± 10	78 ± 10	79 ± 11	0.1365
Mean pulse pressure (mmHg) ± SD	48 ± 16	47 ± 15	51 ± 17	**<0.0001**
Medical conditions				
Hypertension	61.1%	58.0%	71.0%	**<0.001**
Diabetes	19.4%	18.8%	21.3%	0.134
High cholesterol	31.4%	30.1%	35.5%	**0.011**
Coronary Heart Disease	10.1%	9.2%	13.0%	**0.002**
Severe Mitral/Aortic Valvular Disease	0.22%	0.12%	0.52%	**0.041**
Heart failure	2.84%	1.96%	5.59%	**<0.001**
Stroke	4.37%	3.92%	5.81%	**0.025**
Atrial fibrillation	0.47%	0.25%	1.16%	**0.001**
Chronic Lung Disease	7.0%	6.6%	8.2%	0.149
Medications				
Antihypertensives	62.2%	58.5%	73.3%	**<0.001**
Beta blockers	12.6%	11.1%	17.4%	**<0.001**
Calcium channel blockers	23.0%	20.6%	30.2%	**<0.001**
Diuretics	39.4%	37.1%	46.4%	**<0.001**
Smoking History				

Never Smoked	68.0%	70.2%	60.9%	**<0.001**
Former Smoker	19.9%	19.8%	20.0%	
Current Smoker	12.1%	10.0%	19.1%	
Spirometry Profile				
Normal	71.0%	73.1%	64.2%	**<0.001**
Obstruction	9.0%	8.4%	10.7%	
Restriction	20.0%	18.4%	25.1%	
Echocardiography characteristics				
Mean estimated pulmonary arterial systolic pressure (mmHg) ± SD	28 ± 7	27 ± 7	30 ± 8	**<0.0001**
Pulmonary hypertension (estimated pulmonary artery systolic pressure>40mmHg)	6.7%	5.3%	11.2%	**<0.001**
Mean pulmonary artery acceleration time (msec) ± SD	126.9 ± 32.8	128.0 ± 32.9	123.2 ± 32.4	**0.0004**
Mean left atrial diameter index (mm/m^2) ± SD	18.0 ± 2.5	17.9 ± 2.4	18.3 ± 2.7	**0.0036**
Ratio of mitral valve peak E wave velocity (m/sec)/mitral valve peak A wave velocity (m/sec)	1.11 ± 0.37	1.11 ± 0.35	1.10 ± 0.45	**0.0105**
Mean left ventricular ejection fraction (%) ± SD	62 ± 8	62 ± 7	62 ± 9	0.9834
LVEF<50%	2.7%	2.1%	4.7%	**<0.001**

LV Hypertrophy (LV mass index > 51 g/(height in meters/100)$^{2.7}$	8.0%	6.45%	13.3%	**<0.001**
Laboratory values				
Mean aldosterone (ng/dL) ± SD	5.6 ± 5.9	5.4 ± 4.5	6.4 ± 9.0	**0.0009**
Mean serum creatinine calibrated to Cleveland Clinic equivalent (mg/dl) ± SD	1.0 ± 0.6	1.0 ± 0.3	1.1 ± 1.1	**0.0187**
Mean eGFR† based on MDRD‡ formula, (ml/min/1.73m^2) ± SD	84.9 ± 18.3	85.8 ± 16.9	82.2 ± 21.8	**0.0011**
Plasma endothelin-1				
Mean ET (pg/ml) ± SD	1.36 ± 0.64	1.11 ± 0.30	2.18 ± 0.74	By definition

eTable 3: Cox Proportional Hazards Analysis of Mortality by Quartiles of ET* Level:

	Hazard ratio, unadjusted	95% CI	Hazard ratio, adjusted for mortality model†	95% CI	Hazard ratio, adjusted for mortality model and PH‡	95% CI
Quartile 1 (n=1680, ET = 0.1pg/ml-1.0pg/ml)	Referent	NA	Referent	NA	Referent	NA
Quartile 2 (n=1305, ET = 1.1-1.3pg/ml)	**1.67**	**1.18-2.37**	1.33	0.94-1.89	1.36	0.96-1.94
Quartile 3 (n=979, ET = 1.4-1.6pg/ml)	**1.50**	**1.02-2.21**	1.04	0.71-1.55	1.07	0.73-1.59
Quartile 4 (n=1236, ET= 1.7-9.6pg/ml)	**2.84**	**2.06-3.91**	**1.60**	**1.15-2.23**	**1.57**	**1.12-2.18**

*ET=endothelin-1

†Adjusted for age, gender, BMI, physical activity category (none, intermediate, ideal), smoking status (never, former, current), total cholesterol category (<200mg/dl versus ≥200mg/dl), diabetes (fasting plasma glucose ≥126mg/dl, hemoglobin A1C ≥ 6.5%, or use of diabetes medications), history of heart failure, history of coronary heart disease, hypertension (blood pressure ≥ 140/90mmHg or use of antihypertensive), estimated GFR, history of stroke.

‡PH=pulmonary hypertension

BOLD=significant

eTable 4: Cox Proportional Hazards Analysis of Mortality Using Age-Based Time Scale, By Log-Transformed Plasma ET Level (Log-ET) and By High ET

	Hazard ratio	95% CI	p value
Log-ET, univariate	**2.03**	1.52-2.70	<0.001
Log-ET, adjusted for mortality model†	**1.65**	1.24-2.21	0.001
Log-ET, adjusted for mortality model† and left atrial diameter index	**1.57**	1.18-2.09	0.002
Log-ET, adjusted for mortality model† and presence of PH‡	**1.58**	1.18-2.10	0.002
Log-ET, adjusted for mortality model† and log PASP	**1.57**	1.18-2.10	0.002
High ET, univariate	**1.64**	1.29-2.08	<0.001
High ET, adjusted for mortality model†	**1.38**	1.08-1.76	0.011
High ET, adjusted for mortality model† and left atrial diameter index	**1.34**	1.04-1.71	0.021
High ET, adjusted for mortality model† and present of PH‡	**1.33**	1.03-1.70	0.026
High ET, adjusted for mortality model† and log PASP	**1.34**	1.04-1.71	0.022

*ET=endothelin-1

† Adjusted for age, gender, BMI, physical activity category (none, intermediate, ideal), smoking status (never, former, current), total cholesterol category (<200mg/dl versus ≥200mg/dl), diabetes (fasting plasma glucose ≥126mg/dl, hemoglobin A1C ≥ 6.5%, or use of diabetes medications), history of heart failure, history of coronary heart disease, hypertension (blood pressure ≥ 140/90mmHg or use of antihypertensive), estimated GFR, history of stroke.

‡PH= pulmonary hypertension

BOLD=significant

eTable 5 Cox Proportional Hazards Analysis of Mortality Based on Subgroups With and Without PH, and With or Without High Plasma ET (High ET) Levels

	HR, Unadjusted (95% CI)	***P* Value**	**HR, Adjusted[a] (95% CI)**	***P* Value**
Subgroup 1: No PH, Low ET	1.00 (Referent)NA	NA	1.00 (Referent)NA	NA
Subgroup 2: No PH, High ET	**1.92** (1.47-2.51)	<.001	**1.59** (1.21 -2.07)	.001
Subgroup 3: PH, Low ET	**2.84** (1.86-4.34)	<.001	**1.90** (1.23-2.92)	.004
Subgroup 4: PH, High ET	**6.05** (4.07-9.01)	<.001	**3.77** (2.51 -5.67)	<.001

Abbreviations: CI, Confidence Interval; ET, endothelin-1; PH, pulmonary hypertension.
[a]Adjusted for age, sex, BMI.
BOLD = significant.

eTable 6. Cox Proportional Hazards Analysis of Heart Failure Hospitalization by Log-transformed ET (Log-ET) Level

	Hazard Ratio (95% CI)	***P* Value**
Log-ET, univariate analysis	**2.52** (1.73-3.66)	<.001
Log-ET, adjusted for ARIC model[a]	**1.57** (1.05-2.37)	.029
Log-ET, adjusted for ARIC model[a] and left atrial diameter index	1.35 (0.91-2.01)	.133
Log-ET, adjusted for ARIC model[a] and PH‖	1.35 (0.90-2.02)	.145
Log-ET, adjusted for ARIC model[a] and log transformed PASP	1.37 (0.91-2.05)	.127

Abbreviations: ARIC, Atherosclerosis Risk In Communities; CI, Confidence Interval; ET, endothelin-1; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension.

[a]Adjusted for the ARIC heart failure model, which includes age, gender, heart rate, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, BMI, and smoking status.

BOLD = significant.

eTable 7: Cox proportional hazards analysis of heart failure hospitalization by log transformed ET* (Log-ET) level, with death treated as a competing risk

	Hazard ratio	95% Confidence Interval	p value
Log ET, univariate analysis	**2.43**	**1.67-3.53**	**<0.001**
Log ET, adjusted for ARIC† model‡	**1.56**	**1.03-2.38**	**0.036**
Log ET, adjusted for ARIC model‡ and left atrial diameter index	1.33	0.89-1.99	0.158
Log ET, adjusted for ARIC model and PH	1.41	0.95-2.10	0.091
Log ET, adjusted for ARIC model‡ and log transformed PASP#	1.40	0.94-2.08	0.096

* ET = endothelin-1

† ARIC = Atherosclerosis Risk In Communities

‡ Adjusted for the ARIC heart failure model, which includes age, gender, heart rate, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, BMI, and smoking status.

‖ PH = pulmonary hypertension

PASP = pulmonary artery systolic pressure

BOLD = significant

eTable 8: Cox proportional hazards analysis of mortality by log-transformed plasma ET* level (Log-ET) and if high plasma ET (High ET) level (≥1.7pg/ml) for the study subjects with tricuspid regurgitation, excluded subjects with no tricuspid regurgitation, and all subjects

	Hazard ratio, Study Population (ET level and Tricuspid Regurgitation) (n=3,191)	95% Confidence Interval	Hazard ratio, Excluded Subjects: ET level but No Tricuspid Regurgitation (n=1,951)	95% Confidence Interval	Hazard ratio, All subjects with ET level (n=5,142)	95% Confidence Interval
Log-ET, univariate	**2.70**	**2.08-3.52**	**3.03**	**2.19-4.23**	**2.81**	**2.29-3.45**
Log-ET, adjusted for mortality model†	**1.69**	**1.27-2.25**	**1.76**	**1.24-2.51**	**1.73**	**1.39-2.16**
High ET, univariate analysis	**2.12**	**1.67–2.68**	**2.49**	**1.88-3.29**	**2.25**	**1.88-2.69**
High ET, adjusted for mortality model†	**1.42**	**1.11-1.81**	**1.69**	**1.26-2.27**	**1.52**	**1.26-1.84**

BOLD=significant

† Adjusted for age, gender, BMI, physical activity category (none, intermediate, ideal), smoking status (never, former, current), total cholesterol category (<200mg/dl versus ≥200mg/dl), diabetes (fasting plasma glucose ≥126mg/dl, hemoglobin A1C ≥ 6.5%, or use of diabetes medications), history of heart failure, history of coronary heart disease, hypertension (blood pressure ≥ 140/90mmHg or use of antihypertensive), estimated GFR, history of stroke.

eTable 9: Cox Proportional Hazards Analysis of Decompensated Heart Failure By Log Transformed Et (Log-ET) Level or If High Plasma ET* (High ET) Level (≥1.7pg/ml) in Study Population, Excluded Population Without Tricuspid Regurgitant Jet, and Total Population With ET Level

	Hazard ratio, Study Population (ET level and Tricuspid Regurgitation) (n=3,108)	95% Confidence Interval	Hazard ratio, Excluded Population: ET level but No Tricuspid Regurgitation (n=1,888)	95% Confidence Interval	Hazard Ratio, All subjects with ET level (n=4,996)	95% Confidence Interval
Log ET, univariate analysis	**2.52**	1.73-3.66	**3.96**	2.33-6.74	**2.92**	2.16-3.97
Log ET, adjusted for ARIC† model‡	**1.57**	1.05 – 2.37	**2.26**	1.29-3.94	**1.77**	1.28-2.47

* ET = endothelin-1

† ARIC = Atherosclerosis Risk In Communities

‡ Adjusted for the ARIC heart failure model, which includes age, gender, heart rate, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, BMI, and smoking status.

BOLD = significant

eTable 10. Interaction Terms and *P* Values for Their Relationship With the Study Outcomes (Pulmonary Hypertension; Mortality; and Heart Failure)

Interaction term	Outcome: Pulmonary Hypertension	Outcome: Mortality	Outcome: Heart Failure Hospitalization
	P value	P value	P value
LogET*Age categories	**<0.0001***	**<0.0001***	**<0.0001***
LogET*Male sex	0.428	0.104	0.937
LogET*BMI categories	**<0.0001***	**<0.0001***	**<0.0001***
LogET*Hypertension	0.465	0.739	0.890
LogET*Diabetes	0.188	0.067	0.065
LogET*Coronary Heart Disease	**0.016**	0.323	0.939
LogET*Smoking History Category	**<0.0001***	**<0.0001***	**<0.0001***
LogET*Spirometry Profile Category	**<0.0001***	**<0.0001***	**<0.0001***
LogET*LVEF<50%	0.172	0.257	0.948
LogET*LA Diameter	0.311	0.115	0.082

Index			
LogET*LV Hypertrophy	0.431	0.610	0.960
LogET*eGFR	0.757	0.891	0.149
LogET*Pulmonary hypertension	NA	0.607	0.483

***** by Wald test

BOLD=significant

eTable 11: Relationship of Log-Transformed Endothelin (Log-ET) with Outcomes in Relevant Subgroups Based on Interaction Testing

Subgroup	Outcome: Pulmonary Hypertension	Outcome: Mortality	Outcome: Heart Failure Hospitalization
	Adjusted* odds ratio for PH by Log-ET (95% Confidence Interval)	Adjusted† hazard ratio for mortality by Log-ET (95% Confidence Interval)	Adjusted‡ hazard ratio for heart failure hospitalization by Log-ET (95% Confidence Interval)
Age<45 years	3.75 (0.25-56.06)	NA	4.51 (0.55-37.13)
Age 45-54 years	0.60 (0.24-1.49)	**1.89 (0.71-5.01)**	2.93 (0.78-2.35)
Age 55-64 years	1.63 (0.88-3.02)	**2.11 (1.11-4.02)**	1.28 (0.60-2.76)
Age≥65 years	**2.44 (1.39-4.28)**	1.43 (0.82-2.24)	1.37 (0.79-2.35)
BMI categories			
Obese	1.49 (0.93-2.39)	1.12 (0.69-1.83)	1.37 (0.78-2.39)
Overweight	**2.61 (1.27-5.38)**	**2.17 (1.22-3.87)**	1.80 (0.82-3.95)
Ideal	NA#	2.19 (0.98-4.87)	1.77 (0.55-5.63)
Smoking History			
Never Smoked	**1.93 (1.22-3.06)**	**1.81 (1.16-2.82)**	1.17 (0.66-2.07)
Former Smoker	1.11 (0.47-2.60)	1.42 (0.73-2.77)	2.21 (0.99-4.90)
Current	2.40	1.54	2.41

Smoker	(0.79-7.31)	(0.65-3.65)	(0.73-8.00)
Spirometry Profile			
Normal spirometry	0.92 (0.55-1.55)	1.36 (0.80-2.28)	1.51 (0.80-2.83)
Obstruction	**2.32 (1.03-5.19)**	**2.97 (1.38-6.39)**	1.35 (0.55-3.33)
Restriction	**5.24 (2.28-12.04)**	1.84 (0.89-3.83)	1.99 (0.78-5.08)
Coronary Heart Disease Absent	1.32 (0.87-1.99)	NA	NA
Coronary Heart Disease Present	**6.00 (2.13-16.9)**	NA	NA

*Adjusted for age group (<45, 45-54, 55-64, ≥65), gender, BMI category (normal, overweight, obese), pulse pressure (mmHg), hypertension, diabetes, coronary heart disease, severe mitral/aortic valvular disease, chronic lung disease (history of), spirometry profile (normal, obstruction, restriction), LVEF < 50%. (Note: non-relevant variable(s) were dropped from the model during particular subgroup analyses; e.g coronary heart disease when coronary heart disease present subgroup was analyzed)

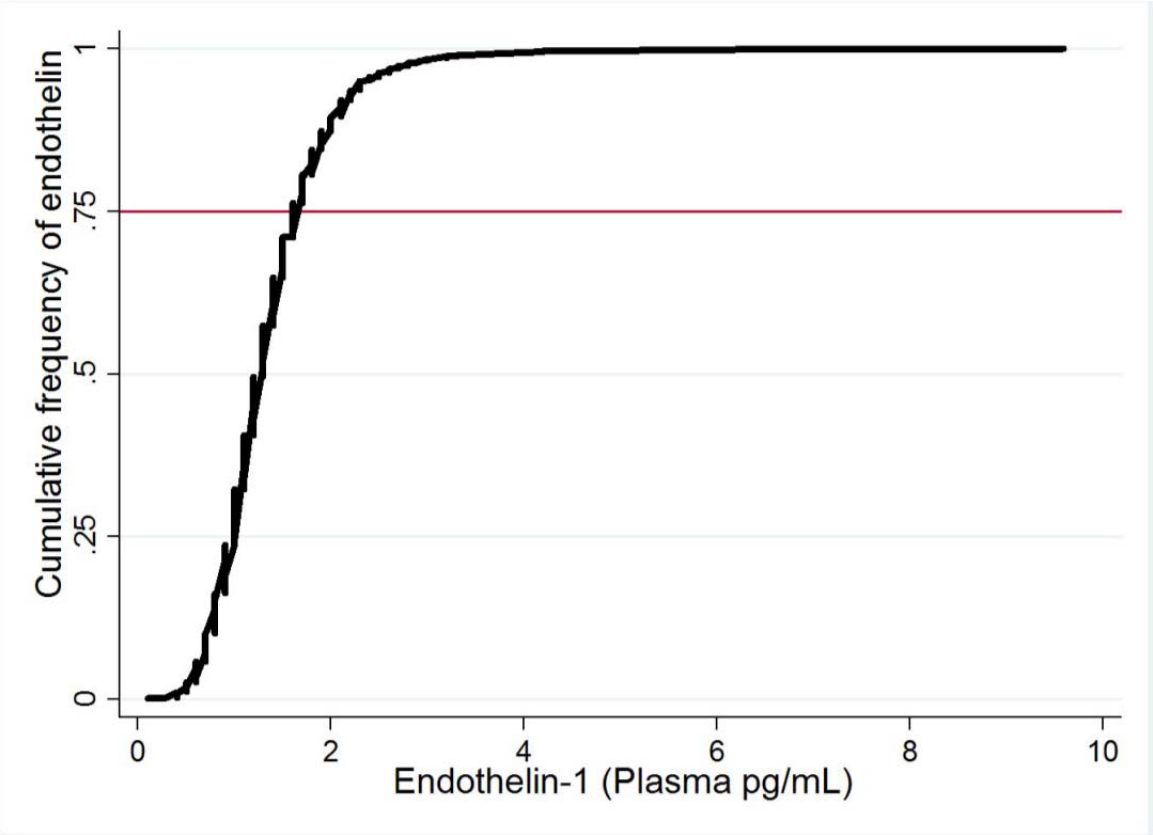
†Adjusted for age category, gender, BMI category (normal, overweight, obese), physical activity category (none, intermediate, ideal), smoking status (never, former, current), total cholesterol category (<200mg/dl versus ≥200mg/dl), diabetes (fasting plasma glucose ≥126mg/dl, hemoglobin A1C ≥ 6.5%, or use of diabetes medications), history of heart failure, history of coronary heart disease, hypertension (blood pressure ≥ 140/90mmHg or use of antihypertensive), estimated GFR, history of stroke. (Note: non-relevant variable(s) were dropped from the model during particular subgroup analyses; e.g other BMI categories when the obese subgroup was analyzed).

‡Adjusted for age, gender, heart rate, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, BMI, and smoking status (note non-relevant variable(s) were dropped from model during particular subgroup analyses as above).

Model failed (only 6 deaths in this age group)

#Model failed (only 23 subjects with PH in this group)

eFigure. Cumulative Frequency Plot of Plasma Endothelin-1 Levels



Endothelin-1 (ET) level at the 75th percentile (ET 1.6pg/mL) is indicated. ET level above the 75th percentile was taken as elevated for the population.

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