SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

Clinical characteristics

We collected the following data in all study participants: demographics, race/ethnicity, New York Heart Association (NYHA) functional class, comorbidities, medications, vital signs, body-mass index, and laboratory data, including serum sodium, blood urea nitrogen, creatinine, hemoglobin, and BNP. Estimated glomerular filtration rate (GFR) was calculated using the Modified Diet in Renal Disease equation.

Definitions of comorbidities

Hypertension was defined by systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg, physician-documented history of hypertension, or current use of antihypertensive medications. Diabetes mellitus (DM) was defined by the presence of physician-documented history of DM or the use of oral hypoglycemic agents or insulin for the treatment of hyperglycemia. Coronary artery disease (CAD) was defined by the presence of physician-documented history of CAD, known coronary stenosis > 50%, history of myocardial infarction, percutaneous intervention, coronary artery bypass grafting, or abnormal stress test results consistent with myocardial ischemia. Obesity was defined by a body mass index $\geq$ 30 kg/m^2. Chronic kidney disease was defined as an estimated glomerular filtration rate < 60 ml/min/1.73 m^2.

Echocardiography

All study participants underwent comprehensive 2-dimensional echocardiography with Doppler and tissue Doppler imaging (TDI) using commercially available ultrasound systems with harmonic imaging (Philips iE33 or 7500, Philips Medical Systems, Andover, MA; or Vivid 7, GE Healthcare, General Electric Corp., Waukesha, WI). Cardiac structure and function were quantified as recommended by the American Society of Echocardiography (ASE).[1-3]

LV end-diastolic and end-systolic volumes, and left atrial volume, were measured in the apical 4- and 2-chamber views using the biplane method of discs. LV ejection fraction was calculated as (LV end-diastolic volume – LV end-systolic volume)/LV end-diastolic volume. LV mass index was calculated using the linear method, as outlined in the ASE guidelines.[1] LV diastolic function was graded according to published criteria by using mitral inflow characteristics and tissue Doppler e' velocities.[4] Tissue Doppler e' and s' velocities were measured at the septal and lateral aspects of the mitral annulus. Sample volume size and placement were optimized for all pulse-wave Doppler and tissue Doppler measurements. All Doppler and tissue Doppler measurements were averaged over three beats (five beats for patients in atrial fibrillation).

Right heart parameters were measured on echocardiography according to published guidelines.[3] Specifically, we measured RV basal diameter, RV length, RV end-diastolic area, RV end-systolic area, RV wall thickness, and right atrial area. Tricuspid annular plane systolic excursion (TAPSE) was also calculated. Lastly, pulmonary artery systolic pressure was measured using the peak tricuspid regurgitation (TR) velocity (to estimate peak TR gradient) and adding that to the estimated right atrial pressure, which was based on size and collapsibility of the inferior vena cava.[3]

All echocardiographic measurements were made blinded to all other data by an experienced research sonographer using ProSolv 4.0 echocardiographic analysis software (FujiFilm; Indianapolis, IN) and verified by an experienced investigator with expertise in echocardiography. For the phenomapping analyses, we normalized echocardiographic variables describing chamber dimensions by regressing log-transformed echocardiographic parameters on log-transformed height and gender and using the residuals as phenotypic features.[5]

Non-invasive pressure-volume analysis

For the estimation of LV compliance, we calculated the end-diastolic pressure-volume relationship (EDPVR) using a single-beat method [6] with the equation: $LVEDP = \alpha(LVEDV)^{\beta}$, where LVEDP is the LV end-diastolic pressure and LVEDV is the LV end-diastolic volume. The EDPVR represents the non-linear relationship between ventricular pressure and volume at end diastole and can be estimated non-invasively. The parameters α and β are constants that allow point measurements of the non-linear EDPVR as reviewed elsewhere,[7] and were calculated for each individual based on their LVEDV and LVEDP (estimated by [11.96 + (lateral E/e' ratio)*0.596]).[8] These parameters were then used to calculate the LVEDV at an idealized LVEDP of 20 mmHg (EDV_{20}) for each patient.

To evaluate LV contractility, we estimated the end-systolic pressure volume relationship (ESPVR) as represented by the slope of ESPVR (end-systolic elastance [E_{es}]).[7] E_{es} is a load-independent measure of LV contractility, and can be estimated using a single-beat method.[9, 10] The relationship between end-systolic pressure (P_{es}) and end-systolic volume (ESV) was defined as: [$P_{es} = E_{es}(ESV - V_0)$]. Using 0.9*(systolic blood pressure) at the time of echocardiography as

an estimate of P_{es}, we estimated V_0, the volume-axis intercept, and then generated the estimated ESV at an idealized P_{es} of 120 mmHg (ESV_{120}) for each patient.

The effective arterial elastance (E_a), which is a measure of systemic arterial stiffness, was estimated using the equation: E_a = 0.9*SBP/stroke volume.[11] Stroke volume (SV) was estimated on echocardiography using the equation: SV = (LV outflow tract diameter/2)^2 × LV outflow tract velocity time integral. V-A coupling was defined as E_a/E_{es}.[7]

Invasive hemodynamics

In a subset of the study cohort (N=211), right heart and pulmonary arterial (PA) catheterization was performed from either the right internal jugular or right femoral vein approach using standard Seldinger technique under fluoroscopic guidance. Participants underwent recording of invasive hemodynamics (mean RA pressure; systolic, diastolic, and mean PA pressure [mPAP]; and PCWP) using a fluid-filled, 6F PA catheter (Edwards Lifesciences, Irvine, CA) and a properly zeroed pressure transducer. Pressure recordings were analyzed off-line using a WITT Hemodynamic Workstation (Philips Medical Systems, Andover, MA) at a 50 mm/s paper speed with adjustment of pressure (mmHg) scale as needed. All hemodynamic pressure measurements were made at end-expiration and in duplicate using a standardized measurement protocol, by a physician blinded to all clinical data. Cardiac output was calculated using the thermodilution method, and PVR was calculated as the transpulmonary gradient (mPAP – PCWP) divided by cardiac output.

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SUPPLEMENTAL TABLES

Supplementary Table S1. Pressure-Volume Analysis Parameters Stratified by Pheno-Group

Parameter	Group 1 (N=128)	Group 2 (N=120)	Group 3 (N=149)	P-value
End-systolic elastance (E_{es}), mmHg/ml	2.30±0.72	2.32±0.65	2.39±0.83	0.57
ESV_{120}, ml	37.2±15.0	35.5±14.6	41.1±22.6	0.036
Effective arterial elastance (E_a), mmHg/ml	1.40±0.45	1.43±0.43	1.54±0.53	0.041
EDV_{20}, ml	83.5±24.6	84.1±24.6	83.8±32.6	0.98
Stroke work, g·m	83.0±24.5	83.6±34.7	70.4±30.5	<0.001
Stroke work / end-diastolic volume ratio, g·m/ml	1.06±0.32	1.40±0.46	0.89±0.43	0.001
Preload-recruitable stroke work, g/cm^2	82.7±21.6	75.0±28.5	58.0±21.9	<0.001
Ventricular-arterial coupling (E_{es}/E_a)	1.66±0.18	1.65±0.19	1.58±0.23	0.001
Pulse pressure / stroke volume ratio, mmHg/ml	0.62±0.24	0.72±0.26	0.76±0.31	<0.001

ESV_{120} = end-systolic volume at an idealized end-systolic pressure of 120 mmHg (lower values = increased left ventricular stiffness; higher values = decreased left ventricular stiffness); EDV_{20} = end-diastolic volume at an idealized end-diastolic pressure of 20 mmHg (lower values = reduced left ventricular diastolic compliance)

Supplementary Table S2. Clinical and Laboratory Characteristics: Original vs. Validation Cohort

Clinical characteristic	Original cohort (N=397)	Validation cohort (N=107)	P-value
Age (years)	64.7±13.0	65.4±12.5	0.63
Female, n(%)	249(63)	63(59)	0.47
Race, n(%)			0.008
White	207(52)	68(64)	
Black	152(38)	24(22)	
Other	38(10)	15(14)	
NYHA functional class, n(%)			0.12
I	49(12)	8(8)	
II	157(40)	42(40)	
III	180(45)	49(46)	
IV	10(3)	7(7)	
Comorbidities, n(%)			
Coronary artery disease	187(47)	56(52)	0.34
Hypertension	304(77)	83(78)	0.83
Hyperlipidemia	213(54)	68(64)	0.07
Diabetes mellitus	125(31)	33(31)	0.90
Obesity	204(51)	57(53)	0.73
Chronic kidney disease	128(32)	35(33)	0.93
Atrial fibrillation	107(27)	31(29)	0.68
Chronic obstructive pulmonary disease	145(37)	22(21)	0.002
Obstructive sleep apnea	141(36)	42(39)	0.48
Vital signs and laboratory data			
Heart rate (bpm)	70.8±13.8	72.5±14.2	0.27
Systolic blood pressure (mmHg)	124.7±20.0	129.4±21.0	0.03
Diastolic blood pressure (mmHg)	70.1±11.8	72.8±10.1	0.03
Pulse pressure (mmHg)	54.6±17.2	56.6±18.8	0.29
Body mass index (kg/m^2)	32.1±9.1	33.5±10.4	0.17
Serum sodium (mEq/L)	138.4±2.9	138.2±2.8	0.47
Blood urea nitrogen (mg/dl)	24.5±16.4	24.2±13.6	0.90
Serum creatinine (mg/dl)	1.6±1.5	1.6±1.4	0.83
Estimated GFR ($ml/min/1.73m^2$)	58.3±27.4	64.8±30.7	0.04
Fasting glucose (mg/dl)	119.5±55.0	117.1±43.3	0.68
Hemoglobin (g/dl)	11.9±1.8	12.3±2.3	0.03
B-type natriuretic peptide (pg/ml)	234 (86-530)	171 (64-382)	0.20
Medications, n(%)			
ACE-inhibitor or ARB	217(55)	45(44)	0.05
β-blocker	268(68)	67(65)	0.64
Calcium channel blocker	120(30)	34(33)	0.59
Nitrate	57(14)	14(14)	0.84
Loop diuretic	231(58)	62(60)	0.71
Thiazide diuretic	92(23)	7(7)	<0.001
Statin	193(49)	51(50)	0.87
Aspirin	185(47)	56(54)	0.16

Supplementary Table S3. Echocardiographic Characteristics: Original vs. Validation Cohort

Parameter	Original cohort (N=397)	Validation cohort (N=107)	P-value
LV end-diastolic volume, ml	83.4±27.2	89.0±27.6	0.06
LV end-systolic volume, ml	33.5±15.2	35.2±14.5	0.29
LV mass index, g/m^2	103.7±37.7	98.7±31.1	0.21
Left atrial volume index, ml/m^2	34.3±14.3	36.3±13.5	0.18
LV ejection fraction, %	60.9±6.5	61.6±6.1	0.37
Stroke volume, ml	84.3±29.2	79.7±23.6	0.13
Cardiac index, L/min/m^2	3.1±1.2	2.9±0.9	0.18
Pulmonary artery systolic pressure, mmHg	44.0±15.5	48.1±18.9	0.04
Right atrial pressure, mmHg	7.7±4.1	8.2±3.9	0.28
E velocity, cm/s	105.7±36.9	109.5±39.7	0.35
A velocity, cm/s	85.4±30.4	79.0±39.3	0.08
E/A ratio	1.4±0.7	1.7±1.0	<0.001
Lateral e' velocity, cm/s	9.3±3.9	9.5±3.4	0.78
Septal e' velocity, cm/s	7.1±2.7	6.9±2.5	0.50
E/e' (septal)	17.0±9.3	18.6±12.3	0.15
E/e' (lateral)	13.4±8.0	13.3±8.0	0.92
Diastolic dysfunction grade, n (%)			0.23
Normal diastolic function	32(8)	13(12)	
Grade I (mild) diastolic dysfunction	43(11)	7(7)	
Grade II (moderate) diastolic dysfunction	159(40)	37(35)	
Grade III (severe) diastolic dysfunction	137(35)	45(42)	
Indeterminate diastolic function	26(7)	5(5)	
RV basal diameter, cm	3.9±0.7	4.1±0.8	0.08
RV end-diastolic area index, cm/m^2	13.9±3.8	13.3±4.6	0.17
RV end-systolic area index, cm/m^2	8.0±2.8	8.3±3.5	0.51
RV wall thickness, cm	0.5±0.1	0.5±0.1	0.008
RV fractional area change	0.43±0.07	0.39±0.07	<0.001
TAPSE, cm	2.0±0.6	1.9±0.4	0.07

Supplementary Table S4. Association of Pheno-Groups with Adverse Outcomes in the Validation Cohort

	Group 1 (N=37)	Group 2 (N=29)	Group 3 (N=41)	P-value
Outcome, n(%)				
CV hospitalization	7 (19)	7 (24)	17 (41)	0.072
HF hospitalization	3 (8)	5 (17)	12 (29)	0.056
Death	0 (0)	1 (3)	7 (17)	0.007
Combined endpoint	7 (19)	7 (24)	24 (59)	<0.001
Hazard ratio (95% CI) for the composite outcome of HF or CV hospitalization, or death				
Unadjusted	1.0	1.1 (0.4-3.1)	3.6 (1.6-8.4)**	—
Model 1	1.0	1.3 (0.4-3.6)	4.0 (1.5-11.0)**	—
Model 2	1.0	1.4 (0.5-3.8)	3.3 (1.1-9.5)*	—

*<0.05; **≤0.01; ***≤0.001

Model 1 = Pheno-groups + BNP; Model 2 = Pheno-groups + BNP + MAGGIC risk score

The MAGGIC risk score includes the following variables: age, ejection fraction, creatinine, diabetes, chronic obstructive pulmonary disease, systolic blood pressure, body-mass index, heart rate, New York Heart Association class, ACE-inhibitor use, beta-blocker use, heart failure duration, and current smoker.

Supplementary Table S5. Performance Characteristics of Support Vector Machine (SVM) Models in the Prediction of Binary Cardiovascular Outcomes

Outcome	Kernel	AUROC	Mean Precision	Mean Sensitivity	Mean Specificity
Combined	sigmoid	0.759	0.675	0.666	0.591
CV hospitalization	sigmoid	0.723	0.637	0.643	0.579
HF hospitalization	sigmoid	0.704	0.636	0.631	0.572
Death	radial	0.718	0.609	0.640	0.577

CV=cardiovascular; HF=heart failure; AUROC = area under the receiver operator characteristic curve

SUPPLEMENTAL FIGURES

FIGURE LEGENDS

Supplementry Figure S1.

Title: Frequency of Missing Data

Caption: Variables with the highest percentage of missing data are those that are not present in the setting of atrial fibrillation (e.g., PR interval, tissue Doppler a' velocity, transmitral A velocity) or those that are not present or difficult to obtain in some patients on echocardiography (e.g., pulmonary artery systolic pressure, right atrial pressure, right ventricular wall thickness). Abbreviations: BMI = body-mass index; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; DBP = diastolic blood pressure; Ea = effective arterial elastance; EDV20 = end-diastolic volume at an idealized pressure of 20 mmHg, a measure of end-diastolic elastance; Ees = end-systolic elastance; EF = ejection fraction; GFR = glomerular filtration rate; HCO3 = bicarbonate; IVRT = isovolumic relaxation time; LAV = left atrial volume; LV/RV ratio = ratio of maximal left ventricular to right ventricular dimension in the apical 4-chamber view; LVEDD = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVESD = left ventricular end-systolic dimension; LVESV = left ventricular end-systolic volume; LV mass = left ventricular mass; PASP = pulmonary artery systolic pressure; PP/SV = pulse pressure/stroke volume; PRSW = preload-recruitable stroke work; PWT = posterior wall thickness; RA = right atrial; RDW = red cell distribution width; RV = rigth ventricular; RVEDA = right venricular end-diastolic area; RVESA = right ventricular end-systolic area; RVFAC = right ventricular fractional area change; SBP = systolic blood pressure/end-systolic volume; SWT = septal wall thickness; TAPSE = tricuspid annular plane systolic excursion; V-A = ventricular-arterial; WBC = white blood cell count.

Supplementary Figure S1. Frequency of Missing Data