SUPPLEMENTAL MATERIAL

Supplemental Methods

Other Measurements

A self-reported questionnaire was used to determine age, sex, race, and medical history. Height and weight were measured, leading to the calculation of body mass index (kg/m2). Blood pressure, both systolic and diastolic, along with heart rate was measured in the supine position after five minutes of rest.

We measured serum Troponin T, N-terminal pro-B-type natriuretic peptide (NT-pro BNP), high density lipoprotein (HDL), low density lipoprotein (LDL), and creatinine from fasting blood samples drawn at the initial visit. The estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet and Renal Disease (MDRD) formula[1].

Standard 12-lead electrocardiogram (ECG) was performed on all subjects upon enrollment and during the 5-year follow up visit. The rhythm was adjudicated by two independent, blinded physicians. A third adjudicator was used to arbitrate any disagreements.

LV volumes were measured using the biplane method of disks from standard apical 2- and 4-chamber views at end-diastole (LV end-diastolic volume) and end-systole (LV end-systolic volume). The LVEF was determined by subtracting the LV end-systolic volume from the LV end-diastolic volume and dividing that by the LV end-diastolic volume. The truncated-ellipse method was used to determine the LV mass[2].

Three categories of LV diastolic dysfunction were determined based on mitral inflow and pulmonary venous flow. Pulsed-wave (PW) Doppler was performed in the apical 4-chamber view to measure the peak E (early diastolic) and A (late diastolic) velocities. PW Doppler of pulmonary venous flow was also measured. The three categories of LV diastolic dysfunction were as follows: 1) impaired relaxation with

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an E/A ratio of 0.75 or less and systolic dominant pulmonary venous flow; 2) pseudonormal with an E/A ratio more than 0.75 and less than 1.5 and diastolic dominant pulmonary venous flow; and 3) restrictive with an E/A ratio of at least 1.5 and diastolic dominant pulmonary venous flow[3]. Based on a prior study from the same cohort, rates of cardiovascular outcomes differ based on these three categories of LV diastolic dysfunction[4]. Since only 5% of the study population had restrictive filling, the pseudonormal and restrictive categories were combined for this analysis.

All subjects underwent a baseline exercise treadmill test using the standard Bruce protocol with continuous 12-lead ECG monitoring during exercise and echocardiography before and after exercise. Inducible ischemia was defined as the presence of at least one new wall motion abnormality at peak exercise.

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SUPPLEMENTAL REFERENCES

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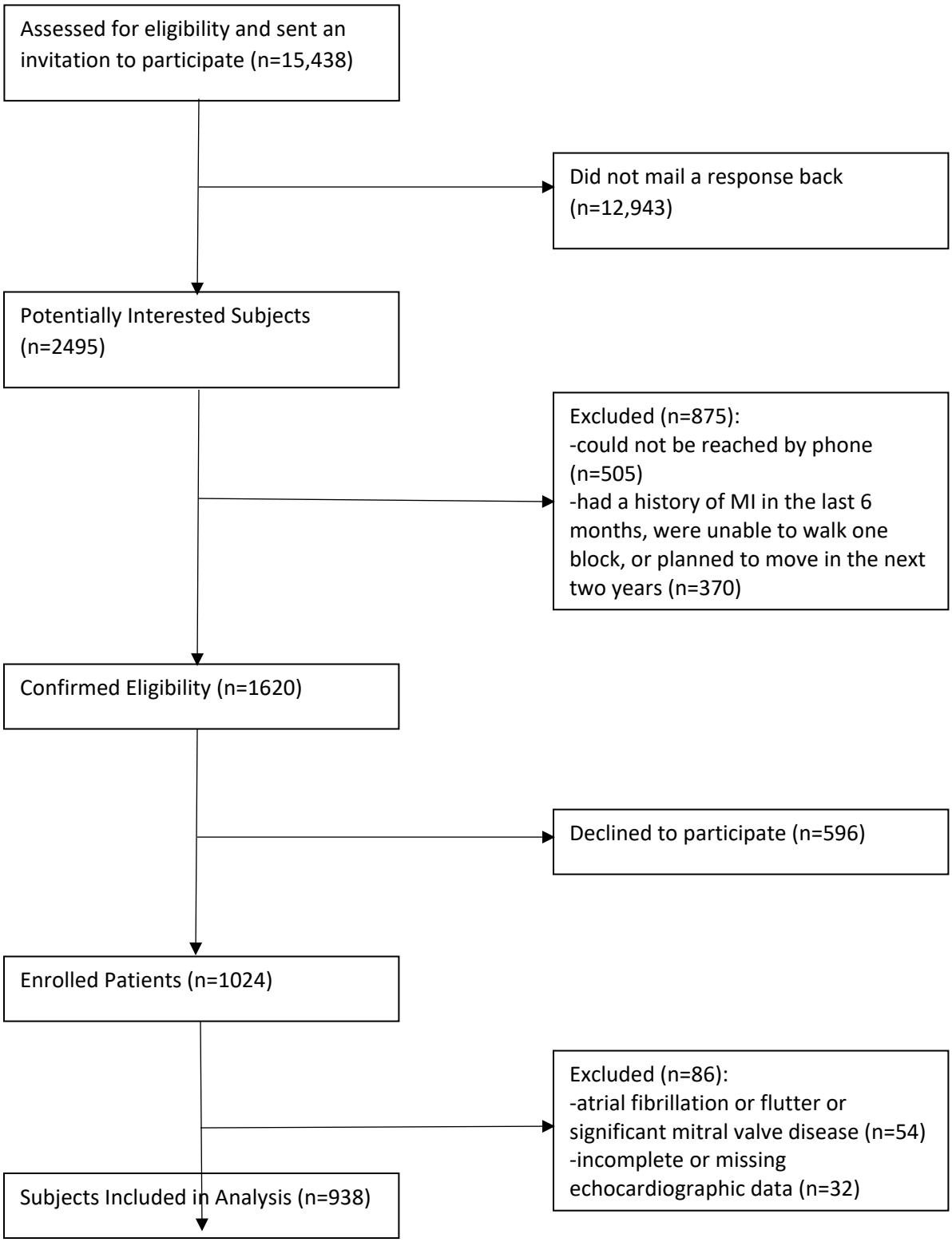
Supplemental Figure 1. CONSORT Diagram



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Supplemental Table 1. C statistics for Cox proportional hazards models with LAEDVI and LAESVI entered as continuous variables (per 1 ml/m^2 increase)

Outcome	Model A*	Model B: Model A with LAEDVI added		Model C: Model A with LAESVI added		p-value Model B vs. C
	C statistic (95% CI)	C statistic (95% CI)	p-value vs. Model A	C statistic (95% CI)	p-value vs. Model A	
Heart failure hospitalization	0.82 (0.78-0.87)	0.84 (0.80-0.88)	0.03	0.84 (0.80-0.88)	0.06	0.64
Composite CV Outcome	0.75 (0.71-0.79)	0.76 (0.72-0.79)	0.15	0.75 (0.72-0.79)	0.11	0.58
All-Cause Mortality	0.72 (0.69-0.76)	0.73 (0.69-0.76)	0.47	0.72 (0.69-0.76)	0.44	0.94
	Model D†	**Model E: Model D with LAEDVI added**		**Model F: Model D with LAESVI added**		**p-value Model E vs. F**
	C statistic (95% CI)	**C statistic (95% CI)**	**p-value vs. Model D**	**C statistic (95% CI)**	**p-value vs. Model D**	
Heart failure hospitalization	0.83 (0.79-0.88)	0.85 (0.81-0.89)	0.04	0.85 (0.81-0.89)	0.12	0.58
Composite CV Outcome	0.77 (0.73-0.80)	0.77 (0.73-0.81)	0.21	0.77 (0.73-0.81)	0.21	0.89
All-Cause Mortality	0.73 (0.70-0.76)	0.73 (0.70-0.77)	0.47	0.73 (0.70-0.77)	0.30	0.82

*Model A includes age, sex, race, prior revascularization, heart failure, medication use (beta blockers, angiotensin inhibitors, diuretics, and antiarrhythmic drugs), systolic blood pressure, heart rate, low density lipoprotein, estimated glomerular filtration rate, inducible ischemia, and NT-proBNP

†Model D includes age, sex, race, prior revascularization, heart failure, medication use (beta blockers, angiotensin inhibitors, diuretics, and antiarrhythmic drugs), systolic blood pressure, heart rate, low density lipoprotein, estimated glomerular filtration rate, inducible ischemia, NT-proBNP, LV end-diastolic and end-systolic volume indices, diastolic function, LV ejection fraction, and LV mass index

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Supplemental Table 2. Fine-Gray model of Cumulative Incidence Function for HF Hospitalizations

	Left atrial end-diastolic volume index (Quartile IV vs. I)			Left atrial end-systolic volume index (Quartile IV vs. I)	
	SHR (95% CI)	p-value		SHR (95% CI)	p-value
Unadjusted	5.74 (3.20-10.33)	<0.01		5.12 (2.83-9.27)	<0.01
Model 1	5.20 (2.88-9.38)	<0.01		4.56 (2.49-8.36)	<0.01
Model 2	3.67 (1.90-7.08)	<0.01		3.56 (1.78-7.11)	<0.01
Model 3	3.90 (1.87-8.12)	<0.01		3.30 (1.51-7.20)	=0.003
Model 4	3.16 (1.50-6.67)	=0.003		3.17 (1.40-7.18)	=0.006
Model 5	2.46 (1.05-5.75)	=0.038		2.73 (1.12-6.68)	=0.028

SHR – Sub-distribution hazard ratio

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