SUPPLEMENTAL MATERIAL

Supplemental methods:

Identification of HF cohort and definition of HFpEF:

All Olmsted County residents with a first diagnosis of HF (incident HF) between January 1, 1983 and December 31, 2010 were identified by medical record documentation of code 428 (heart failure), from the international Classification of Diseases – Ninth Revision – Clinical Modification (ICD-9-CM), as part of our on-going Olmsted County HF community study. The medical records of a random sample of individuals with ICD-9-CM code 428 were reviewed by nurse abstractors and HF diagnosis validated against the modified Framingham criteria[1, 2, 3]. Patients who had underwent echocardiography within 2 months of HF diagnosis, with a left ventricular ejection fraction (LVEF) ≥0.5 (n=939), were determined to have HFpEF and formed the final study cohort.

Data collection:

Height (m), weight (kg, prior and closest to HF diagnosis), body mass index (BMI) and body surface area (BSA) were collected. Heart rate, systolic (SBP), and diastolic blood pressure (DBP) readings (average of 3 on usual medications) were taken from a visit closest in time to HF diagnosis. Hypertension was defined by: ≥2 ambulatory BP recordings (SBP≥140mmHg and/or DBP≥90mmHg) preceding HF diagnosis, a physician diagnosis, or prescribed antihypertensive medication. Diabetes was determined based on American Diabetes Association (ADA) criteria [4]; previous myocardial infarction, thyroid disease, chronic obstructive pulmonary disease (COPD), and cerebrovascular disease (previous stroke or transient ischemic attack) from physician diagnoses. Medication at HF diagnosis, prior to HF treatment, was abstracted electronically.

Serum creatinine, plasma brain natriuretic peptide (BNP) and thyroid stimulating hormone (TSH) within 2 months of HF diagnosis were obtained from the Mayo Laboratory Information System. Glomerular filtration rate was estimated using the Modified Diet in Renal Disease Study equation (eGFR)[5]. Plasma BNP was assessed by an automated 2-site immunoenzymatic sandwich assay (Beckman Coulter DXI 800, Chaska, MN; normal range <200pg/mL).

EF, reported by either transthoracic or transesophageal echo, was based on validated M-mode, quantitative or semi-quantitative (2D) methods. Where multiple values were available, the closest in time to HF diagnosis was selected. Where a range of EF was reported the lower limit was taken as a conservative estimate. LV end-diastolic and end-systolic dimensions were measured by standardized 2D techniques[6]. Diastolic function assessment included: a) early diastolic mitral inflow E wave deceleration time (pulsed wave, PW, Doppler), b) estimated pulmonary artery systolic pressure (PASP, from peak tricuspid regurgitation velocity), and c) the ratio of early diastolic mitral inflow velocity on PW Doppler to early diastolic (medial) mitral annular velocity on tissue Doppler imaging (E/e'), assessed as continuous variables. Left atrial volume was calculated using the area-length method or ellipsoid formula as directed by the sonographer, and indexed to body surface area (left atrial volume index; LAVI). Valvular disease was defined as the presence of any valve prosthesis or more than moderate valvular stenosis or regurgitation.

Supplemental Table 1. Baseline characteristics for patients with and without echocardiographic EF assessment at baseline.

Variable	EF unavailable (n=872)	EF<0.5 (n=1041)	EF ≥ 0.5 (n=939)	p-value
Age, years*	78.7±11.6†	72.7± 14.1	76.5±12.5	<0.01
Female sex, n (%)	531 (60.9)	451 (43.3)	573 (61.0)	<0.01
BMI, kg/m^2*	28.6±6.8†	28.7 ±7.0	29.7±7.6	0.01
Previous MI, n (%)	172 (19.8)†	276 (26.6)	131 (14.0)	<0.01
Hypertension, n (%)	540 (62.4)†	628 (60.7)	627 (67.1)	0.01
Diabetes, n (%)	199 (22.8)	266 (25.6)	237 (25.3)	0.33
COPD, n (%)	190 (22.4)	163 (15.9)	176 (19.1)	<0.01
Cerebrovascular disease, n (%)	196 (23.2)	219 (21.6)	194 (21.0)	0.52

*Mean (SD)

†p<0.05 vs. confirmed HFpEF cohort (EF≥0.5)

EF, ejection fraction; BMI, body mass index; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease.

Supplemental Table 2. Multivariable Cox proportional hazards regression for prediction of incident atrial fibrillation in HFpEF.

	Model 1		Model 2		Model 3		Model 4	
Variable	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
Age (per 10y)	1.28 (1.12-1.48)	0.0003	1.26 (1.09-1.47)	0.001	1.24 (0.95-1.68)	0.11	1.22 (0.96-1.61)	0.11
Female sex	0.79 (0.56-1.12)	0.18	0.75 (0.53-1.07)	0.12	1.16 (0.54-2.59)	0.71	1.14 (0.46-1.75)	0.70
Hypertension	1.41 (1.00-2.02)	0.050	1.36 (0.95-1.96)	0.097	3.64 (1.06-22.88)	0.038	1.12 (0.54-2.48)	0.77
Statin	0.61 (0.38-0.93)	0.021	0.60 (0.38-0.92)	0.019	0.71 (0.35-1.43)	0.35	0.61 (0.32-1.13)	0.11
eGFR (per 10ml/min/1.73m^2)			0.91 (0.83-0.99)	0.032	0.89 (0.75-1.05)	0.18	0.96 (0.82-1.11)	0.58
LAVI (per 10ml/m^2)					1.28 (0.96-1.69)	0.095		
E/e'							1.47 (1.00-2.12)	0.052

LAVI and E/e' were moderately correlated with one another (Spearman's ρ 0.3, p=0.0005), therefore not included in the same model.

E/e', ratio of early diastolic mitral inflow velocity (pulsed wave Doppler) to early diastolic (medial) mitral annular velocity (tissue Doppler); eGFR, estimated glomerular filtration rate; LAVI, left atrial volume index.

Supplemental Table 3. Cox proportional hazards regression for prediction of incident atrial fibrillation in HFpEF (Statin models).

Statin model	**N**	**HR (95%CI)**	**p-value**
Unadjusted	450	0.59 (0.37-0.90)	0.01
Adjusted for age	450	0.63 (0.39-0.96)	0.03
Adjusted for age and LDL*	233	0.54 (0.32-0.89)	0.02
Adjusted for age and diagnosis of hyperlipidemia	447	0.59 (0.36-0.92)	0.02

* LDL±1year HFpEF diagnosis

HR, hazard ratio; LDL, low density lipoprotein.

Supplemental Table 4. Atrial fibrillation (by category) and risk of death in HFpEF.

Variable	No AF (Referent)	Prior AF	Concurrent AF	Incident AF
Unadjusted	1.00	1.62 (1.34-1.97)**	1.38 (1.12-1.69)*	2.75 (2.17-3.49)**
Age and sex adjusted	1.00	1.40 (1.16-1.70)**	1.18 (0.96-1.45)	2.45 (1.93-3.11)**
Model 1†	1.00	1.33 (1.09-1.62)*	1.14 (0.92-1.41)	2.20 (1.72-2.81)**
Model 2‡	1.00	1.36 (1.12-1.66)*	1.17 (0.95-1.45)	2.22 (1.73-2.84)**

Data are reported as HR (95%CI)

**p<0.001 *p<0.05

†Model 1 covariates include: age, sex, BMI, estimated GFR, hypertension, COPD, ACEI or ARB use, BB use, statin.

‡Model 2 covariates include: Model 1 covariates and AAD use.

Supplemental Material References

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