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Baseline characteristics of patients with heart failure and preserved ejection fraction at admission with acute heart failure in Saudi Arabia



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Abstract Heart failure and preserved ejection fraction (HFpEF) is defined as heart failure symptoms and signs with a normal or near-normal ejection fraction (EF) with evidence of diastolic dysfunction. The few Middle Eastern studies that have been conducted were designed to compare patients with heart failure reduced ejection fraction (HFrEF) and HFpEF.

The aim of this study was to study Saudi patients with HFpEF who presented with acute heart failure, and define their clinical characteristics and the signs and symptoms of heart failure, echocardiographic findings and medications at admission and at hospital discharge.

Methods: This is a prospective observational study in which patients were included following an acute heart failure presentation with N-terminal pro-BNP (NT-proBNP) > 300 ng/L and left ventricular ejection fraction (LVEF) > 50%. They were admitted to the coronary care unit of King Saud Medical City from the period of March 2015 to September 2015.

Results: 114 patients were enrolled in the study and assessed at acute admission. Of these, 4% died on day one of admission.

The mean \pm SD age of 109 included patients was 59 ± 8 years and 55% were women. Hypertension (64%), dyslipidemia (76%), atrial tachyarrhythmia (38%), prior heart failure (33%) and anemia (35%), median NT-proBNP was 2490 ± 125 ng/l at admission. Mean (LVEF) was 61 ± 3 , mean LV mass index was 118 ± 11 , mean E/e' was 12.2 ± 2 , and left atrial volume index was 47 ± 7 mL/m². Mean global left ventricular strain was -13.5 ± 1.5 . At discharge the majority of patients were still symptomatic with high NT-proBNP 542 ± 266 .

Conclusions: Patients with HFpEF were old with slight female dominance, a high rate of hypertension, diabetes, dyslipidemia and much comorbidity. LVEF was preserved despite depressed left ventricular longitudinal and diastolic functions with high filling pressure. At discharge the patients were still symptomatic calling for further research to reach the best strategy for proper management.

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1. Introduction

Heart failure (HF) is a complex medical syndrome with high rates of mortality and morbidity across the world, and has a significant negative impact on quality of life, healthcare costs, and longevity despite recent improvements of its treatment.^{1,2} The incidence of HF is approximately 1–2% of the adult population, with the prevalence rising up to 10% among persons 70 years of age or older.^{3–5}

In the recent years, heart failure with preserved ejection fraction (HFpEF) has been increasingly recognized as a pathophysiological entity.⁶ The proportion of patients with heart failure with HFpEF is about 50% of the general heart failure population.^{7–9} In epidemiological surveys, the prognosis of HFpEF is nearly as poor as for heart failure with reduced ejection fraction (HFrEF).^{10–13}

Although heart failure with preserved ejection fraction (HFpEF) is defined as heart failure symptoms and signs with a normal or near-normal EF with evidence of diastolic dysfunction^{14,15} current guidelines highlight the importance of additional objective criteria to signs and symptoms and preserved or normal ejection fraction for the diagnosis of HFpEF.^{16–18} These criteria include normal left ventricular volume, increased left atrial volume, left ventricular hypertrophy and/or diastolic dysfunction and natriuretic peptides.¹⁹

HFpEF patients' demographics, comorbid conditions, prognosis, and response to therapies differ from those with heart failure reduced ejection fraction (HFrEF).¹⁸

However several studies have been conducted in western countries differentiating features of epidemiology, treatment, and outcomes among patients with preserved and reduced EF.^{20–22} Scarce data are available in the middle-east populations in general and Saudi patients in particular, who have different etiology, ethnic, cultural backgrounds and risk factors from those patients in the west.^{14,23,24} The few Middle Eastern Studies that have been conducted were designed either to detect the prevalence and etiology of HFpEF or to compare the prevalence, demography and comorbidity of patients with HFrEF and HFpEF,^{12,15,23–26} so, the aim of this study was to study Saudi patients with HFpEF who presented with acute heart failure, and define their clinical characteristics and the signs and symptoms of heart failure, echocardiographic findings and medications at admission and at hospital discharge.

2. Methods

This is a prospective observational study in which all patients presented with acute heart failure with ejection fraction >50% were included in the study. They were admitted to the coronary care unit (CCU) of King Saud Medical City from the period of March 2015 to September 2015.

The study was approved by the local ethics committee.

Inclusion criteria was acute presentation to the hospital with clinical signs and symptoms of HF, according to the Framingham criteria.²⁷ NT-pro B type natriuretic peptide (NT-pro-BNP) > 300 pg/mL and left ventricular ejection fraction (LVEF) > 50% by echocardiography performed within the first 72 h.

2.1. Exclusion criteria

All conditions known to be associated with diastolic dysfunction such as infiltrative heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy and constrictive pericarditis, cor-pulmonale, severe mitral stenosis and mechanical lesions need urgent open heart surgery as acute mitral regurg had been excluded as well.

All inclusion criteria (clinical HF, EF, and peptide criteria) were established within 72 h of presentation. Enrollment occurred during this time or shortly thereafter, after the presence of any of the exclusion criteria has been ruled out.

Clinical data, including the medical history, cardiovascular risk factors, and associate comorbidities, were collected from the patients' files.

The patients were followed up during their hospital stay and complementary data were collected including chest radiography, electrocardiography (ECG), echocardiography, Doppler, and laboratory tests.

The symptoms of patients were graded according to NYHA classification.²⁸

Blood samples were collected for analysis of (NT-pro-BNP) on day 1 of admission and was repeated before discharge, and complete laboratory investigations were performed as well.

A 12-lead surface ECG was recorded at 50 mm/s speed. Interpretation was performed by a skilled investigator, and left ventricular hypertrophy (LVH) was considered according to Sokolow index.²⁹

Echocardiography was performed using Vivid 7 (GE Healthcare, Horten, Norway).

Two independent investigators analyzed the recordings blinded to clinical data.

We calculated LV diameters by M-mode and LV EF by Simpson's biplane method. Right ventricular (RV) function was assessed by tricuspid annular plane systolic excursion (TAPSE) and tricuspid lateral annular systolic velocity (S') by pulsed tissue Doppler. Peak pulmonary arterial systolic pressure (PASP) was estimated as the sum of peak RV-right atrial gradient from the tricuspid valve regurgitant jet and right atrial pressure on the basis of size and collapse of inferior vena cava. The LV mass was estimated using the Penn formula and normalized by the body surface area. Echocardiographic LV hypertrophy was defined as an LV mass index > 134 g/m² for men and 110 g/m² for women.³⁰

LV longitudinal strains were analyzed by speckle tracking echocardiography, with frame rate \geq 50 s. From apical four-chamber, two-chamber, and long-axis view, peak longitudinal strains from each of the 16 LV segments, either negative or positive, were averaged automatically to LV global longitudinal strain (GLS).³¹

Diastolic function parameters were measured as follows: peak early diastolic filling (E) and late diastolic filling (A) velocities, E/A ratio, E deceleration time, early diastolic septal mitral annular velocity (e') (averaged from three cardiac cycles), and E/e' as an index of LV filling pressure. Left atrial volume index was calculated from apical four-and two-chamber views, using area – length formula. Diastolic dysfunction was classified into four grades according to 2009 ASE guidelines.³²

Previous and current medications were reported from studying the patients' files.

Table 1 Clinical characters, ECG and X-ray findings of the patients during acute presentation and on discharge.

	Acute presentation	At discharge
Age in years	59 ± 8, 39–78	
Mean ± SD, range		
Women	55%	
BMI mean ± SD, range	27 ± 3, 23–36	
HTN	64%	
Smoking	26%	
DM	64%	
Dyslipidemia	76%	
IHD	16%	
VHD	8%	
Kidney disease	20%	
Prior stroke	6%	
Prior HF admission	33%	
COPD	25%	
Dyspnea NYHA class		
1		23%
2		65%
3		12%
4	100%	
S3	64%	
S4	87	
LL edema	54%	20%
Hepatomegaly	31%	30%
Congested neck veins	80%	21%
Rales	100%	11%
FH	11%	
Anemia	35%	
SBPmmHg, mean ± SD, range	180 ± 29, 100–220	162 ± 25, 110–150
DBP mmHg mean ± SD, range	80 ± 10, 60–110	81 ± 11, 67–76
HR b/m mean ± SD, range	120 ± 9, 110–130	80 ± 6, 68–90
O2 SAT mean ± SD	90 ± 4	98 ± 2
LVH	21%	21%
LBBB	2%	2%
RBBB	6%	5%
Ventricular arrhythmia	1%	0.05%
Atrial arrhythmia	38%	19%
NT-pro-BNP pg/ml, mean ± SD, range	2490 ± 125, 600–2900	542 ± 266, 478–700
Pulmonary edema on X-ray	65%	11%

BMI = body mass index, HTN = hypertension, DM = diabetes mellitus, IHD = ischemic heart disease, VHD = valvular heart disease, HF = heart failure, COPD = chronic obstructive pulmonary disease, LL = lower limbs, NYHA = New York heart association, FH = family history of heart disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, LVH = left ventricular hypertrophy, LBBB = left bundle branch block, RBBB = right bundle branch block, NT-pro-BNP = N-terminal pro brain natriuretic peptide.

2.2. Statistical analysis

All analyses were performed using EXCEL data sheet, Microsoft office 2011. Continuous variables were presented as means ± standard deviations (SDs). Categorical variables are presented as counts and percentages, Student's *T* test was used to compare variables at admission and discharge, and a *p* value < 0.05 is considered significant.

3. Results

A total of 586 patients with clinical evidence of heart failure were admitted during the enrollment period.

152 patients were found to have HFpEF, 38 of them were excluded as follows: 22 of them had severe aortic stenosis, 7

had prosthetic valve dysfunction, 4 had hypertrophic obstructive cardiomyopathy (HOCM), 2 had restrictive cardiomyopathy (RCM), 2 had cor-pulmonale and 1 had constrictive pericarditis.

114 patients were enrolled in the study and assessed on acute admission. Of these, 5 patients (4%) died on day one of admission so 109 patients were admitted to hospital for heart failure management and were followed up during the period of admission which ranged from 2 to 7 days with the average of 5 days.

3.1. Characteristics at acute admission

The mean age was 59 ± 8, 102/109 (94%) of the patients were older than 55 years, they were more often females as they

Table 2 Laboratory findings of the patients during admission.

Parameter	Mean \pm SD	Range
HbA1c %	7 \pm 1	5.7–10
Total cholesterol mmol/L	5.5 \pm 0.8	3.9–7.2
Triglycerides mmol/L	2.5 \pm 1.3	1.3–5.8
HDL mmol/L	1.28 \pm 0.29	0.75–1.76
LDL mmol/L	5.1 \pm 0.7	3.8–6.5
HbG gm%	12.5 \pm 1.6	9.9–14
TSH uU/ml	3.5 \pm 0.9	2.5–6.8
Serum creatinine mg%	1.18 \pm 0.5	1–2.2

HbA1c = hemoglobin A1c, HDL = high density lipoprotein, LDL = low density lipoprotein, HbG = hemoglobin, TSH = thyroid stimulating hormone.

Table 3 Echocardiographic criteria of the patients during admission.

Parameter	Mean \pm SD	Range
LAD cm	4 \pm 0.4	3.2–4.6
LAVI mL/m ²	47 \pm 7	37–68
ESD CM	3.8 \pm 2	2.8–4.1
EDD CM	5.6 \pm 3.8	4.4–5.8
ESVI mL/m ²	52.6 \pm 6	20–65
EDVI mL/m ²	105 \pm 8	84–110
EF%	61 \pm 3	53–64
FS%	32 \pm 2.5	27–36
<i>e</i> cm/s	7 \pm 3	5–12
<i>E/A</i>	1.6 \pm 0.7	0.6–3.3
<i>E</i> deceleration time ms	206 \pm 76	200–302
<i>E/e</i>	12.2 \pm 2	10–22
IVS cm	1 \pm 0.1	0.8–1.3
LV mass index gm/m ²	118 \pm 17	90–178
RWMA	6%	
ESPP mmHg	40 \pm 5	32–50
TAPSE cm	1.5 \pm 0.3	1.1–2.2
LV S cm/s	8 \pm 0.7	7–12
RV S cm/s	10 \pm 0.7	12–18
LV GLS%	–13.5 \pm 1.5	–10 to –17

LAD = left atrial dimension, LAVI = left atrial volume index, ESD = end systolic dimension, EDD = end diastolic dimension, ESVI = end systolic volume index, EDVI = end diastolic volume index, EF = ejection fraction, FS = fractional shortening, IVS = inter-ventricular septum, LV = left ventricle, RV = right ventricle, RWMA = regional wall motion abnormality, ESPP = estimated systolic pulmonary pressure, TAPSE = tricuspid annular plane systolic excursion, GLS = global longitudinal strain.

constituted 55% of the patients (61/109), 55/61 (91%) of them were postmenopausal, and 2/61 (3%) were using oral contraceptive pills. 56/109 (51%) were overweight while 23/109 (21%) were obese. They have high prevalence of dyslipidemia, hypertension and diabetes. Coronary heart disease (CAD) was less prevalent among the patients 17/109 (16%). Few patients have valvular heart disease; 9/109 (8%) patients in total, 5 of them have aortic sclerosis with mild aortic stenosis, and 3 have moderate to severe mitral regurg due to mitral annular calcification (MAC) with no significant trans-mitral gradient and one patient with mitral valve replacement. Some of the patients

Table 4 Medications used by the patients at acute admission and at discharge.

Medications	At admission total 36 patients	At discharge total 109 patients
BB %	33	66
ACEI % or ARBs	23	74
DIU %	67	100
Spironolactone %	11	0
NO3 %	8	8
Digitalis %	1.2	0.5
Warfarin %	5	5
Statins %	54	70
Amiodarone %	2	2
NOAC %	1	7
ASA %	69	69
CCB %	14	23

BB = beta blockers, ACEI = angiotensin converting enzyme inhibitor, ARBS = angiotensin receptor blockers, DIU = diuretics, NO3 = nitrates, NOAC = new oral anticoagulants, ASA = acetyl salicylic acid, CCB = calcium channel blockers.

showed comorbidity as chronic obstructive pulmonary disease (COPD), renal diseases, anemia and prior stroke. Baseline criteria are listed in Table 1. 11/21 (52%) of the renal patients were treated with regular dialysis and 3/109 (3%) of the patients were diagnosed with hypothyroidism on hormone replacement.

On acute presentation all patients were presented with dyspnea New York Heart Association (NYHA) class IV. 36/109 (33%) of them have prior admission to the hospital with heart failure diagnosis while 94/109 (87%) have history suggesting heart failure before the exacerbation of acute heart failure. All patients had rales while most of them showed congested neck veins 87/109 (80%), 66/109 (60%) of the patients had severe hypertension; SBP > 180 mmHg and 90/109 (82%) were tachycardic; HR > 100 b/m. Clinical signs and symptoms are shown in Table 1. 41/109 (38%) of patients showed atrial arrhythmia, 34/41(85%) who constituted to 31% of all patients (109) had atrial fibrillation on acute presentation and only 22/109 (21%) showed increased left ventricular (LV) voltage criteria. ECG criteria are shown in Table 1.

N-terminal pro-Brain natriuretic peptide (NT-proBNP) was significantly high on acute admission in 96% of patients. 37/109 (34%) of the patients had HbA1c > 7%, 20/109 (19%) showed hemoglobin < 12 gm% in men and < 11 gm% in women, 19/109 (17%) had serum creatinine > 1.1 mg%, 10/109 (10%) had total cholesterol > 5.2 mmol/l and 2/109 (1.8%) had serum TSH > 6 uU/ml%.

Laboratory findings during hospital stay are shown in Table 2.

None of the patients suffered from acute coronary syndrome at acute admission.

3.2. Echocardiographic measurements

Ejection fraction was > 50% in all patients.

Left ventricular fractional shortening was > 30% for most patients (69/109; 63%). Left ventricular *s'* was > 7 cm/s for

59/109 (53%). Left ventricular global longitudinal strain (GLS) was $< -16\%$ for 78/109 (71%). A total of 80/109 patients (73%) showed no significant left ventricular enlargement as left ventricular end-diastolic volume ≤ 97 mL/m². 81/109 (73%) had concentric LVH.

Left atrial dimension (LAD) was > 4 cm in 45/109 (41%), left atrial volume index (LAVI) was > 40 mL/m² in 59/109 (55%), LV mass index (LVMI) > 122 gm/m² in women and > 149 in men in 55/109 (51%) of all patients, E/e' ratio was > 15 in 24/109 (22%), $E/e > 12$ was in 67/109 (61%), e' wave was < 11 cm/s for 98/109 (89%) patients while estimated systolic pulmonary pressure (ESPP) was > 35 mmHg in 72/109 (66%) of the patients, and only 11 of 109 (10%) had RV s less than 12 cm/s. 43/109 (40%) of patients had grade 1 diastolic dysfunction, 59/109 (54%) had grade 2 and 7/109 (6%) had grade 3 diastolic dysfunction. Echo criteria are listed in Table 3.

3.3. Medication

36/109 (33%) of patients were receiving medications prior to admission, and the most commonly prescribed medications were aspirin followed by diuretics 69%, 67% simultaneously.

On discharge all patients received medications; diuretics was for all, 74% received either ACEI or ARBs, 12% were receiving spironolactone on admission and were discontinued on discharge, statin use increased from 54% to 70%, and also NOAC use increased from 1% to 7% for stroke prevention in atrial fibrillation (SPAF).

5/109 (5%) received warfarin, 4 patients for SPAF and one patient for mitral valve (MV) replacement Table 4.

On admission 87% were chronic users for non-steroidal anti-inflammatory drugs (NSAI), 53% for proton pump inhibitors (PPI), 20% for iron supplements, 3% for thyroxin, and 10% for renal support medications.

On discharge NSAI prescription decreased to 33%, and PPI increased to 67%.

3.4. On discharge

Most patients were still symptomatic (65%) in NYHA class 2, few patients were still having fine basal rales and less patients had AF 20/109 (19%) and significantly less NT-pro-BNP level $p = 0.0002$ Table 1.

4. Discussion

This study prospectively included a population of HFpEF patients as strictly defined by validated Framingham criteria, preserved ejection fraction and elevated natriuretic peptides, and they were studied at admission with AHF and during hospital admission till discharge. They were elderly (59 ± 8), and showed a high proportion of female gender 55%, dyslipidemia, diabetes, hypertension and high mean weight. They suffered from multiple comorbidities such as chronic obstructive pulmonary disease (COPD), chronic renal failure and anemia; atrial fibrillation was the most common arrhythmia found in our patients and only few patients had a history of coronary artery disease (CAD).

Most of the researches studying HFpEF patients in western countries^{33,34} had older population, but this is not true in

Table 5 Baseline criteria of patients included in the current study, in Dubai,²⁵ in PREVEND³⁴ and in KaRen³³ studies.

	This study	Dubai ²⁵	PREVEND ³⁴	KaRen ³³
Total number	109	106	125	539
Age	59 \pm 8	67 \pm 15	63 + 9	77 \pm 9
Females	55	59	52	56
BMI > 25	71	63	32 > 30 ^a	
HTN	64	77	75	78
DM	64	63	12	30
Dyslipidemia	76	22	42	
Smoking	26	22	25	
Prior HF	33	83	New onset	40
AF	31	33	5	44
CAD	16	46	19	29
Anemia	35	79		37
Hospital stay	5	6		5
COPD	25	26		14
Mortality	4	6		2.4

DM = diabetes mellitus, HTN = hypertension, AF = atrial fibrillation, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease.

^a 32% of the patients had BMI > 30.

researches done in the gulf because of the early occurrence of more prevalent diabetes mellitus.^{14,26}

Women constituted the main bulk of the patients of HFpEF^{33,34,37} and this is probably due to the fact that gender affects cardiac remodeling. When confronted with pressure overload, the LV hypertrophies more and dilates less in women than in men.³⁵ A reduced rate of myocyte loss in women and transcriptional regulation by estrogens of genes implicated in cardiac hypertrophy may contribute to persistent gender related differences in cardiac remodeling.³⁶

25% of our patients had COPD and asthma comparable to another research done in the gulf (Dubai trial)²⁵ but was less often reported in KaRen study³³ and this may be due to lower smoking rate.

The investigators of the PREVEND trial³⁴ found out that 19% of their patients had CAD which agrees with our findings in contrast to the patients of KaRen³³ and Dubai²⁵ trials who had history of more CAD, and this may be because of the shorter inclusion period (6 months) in our study and the fact that all the patients were recruited from one single hospital.

Our patients showed more prevalent dyslipidemia as compared to all other studies^{25,33,34}, most probably because they were more obese and diabetics.

Atrial fibrillation was a frequent finding in our study, consistent with other studies^{33,20,37}, as it is a common cause of HF precipitation in HFpEF³⁸ Table 5.

33% of the patients were previously diagnosed with heart failure, comparable to 40% in KaRen³³ which is much lower than in registries such as ADHERE²⁰, CHARM-Preserved³⁹ and Dubai²⁵ possibly because of the shorter inclusion period and the fact that all the patients were recruited from one single hospital.

It seems that anemia is prevalent in HFpEF patients as proved by our study and previous studies^{33,40} and it is associated with increased mortality.⁴¹

Few of our patients showed chronic kidney disease comparable to previous studies.^{33,48} Chronic renal dysfunction is

frequently associated with diastolic HF and has been shown to independently increase mortality.⁴²

At presentation, most of the patients presented with severe hypertension due to the stress associated with AHF but during hospital stay SBP readings were comparable to the previous studies.^{25–33}

Aspirin was utilized more frequently in patients at acute admission possibly for primary prevention as fewer patients were diagnosed with coronary artery disease.

Diuretics were more frequently prescribed at discharge for symptoms control, statins prescription increased for primary prevention as well as the prescription of ACEI or ARBs at discharge given the fact that most of the patients were diabetics and had increased left ventricular mass.^{43,44}

Spirolactone prescription decreased as there is evidence that spironolactone has no more benefit in the treatment of HFpEF.⁴⁵

CCBs prescription increased at discharge as they constituted the second or third line of treatment of uncontrolled hypertension after diuretics and ACEI.⁴⁶ At discharge beta-blockers, diuretics, and blockers of the renin angiotensin system were prescribed in similar proportions to previous reports.⁴⁷

At discharge the majority of patients were still symptomatic, with evidence of pulmonary and systemic congestion suggesting insufficient treatment of congestion at the acute admission in spite of a mean hospital stay of 5 days and relatively high usage of diuretics. More evidence for insufficient therapy is the fact the NT-proBNP level remained high even at discharge. It is natural to assume that one of the reasons for this insufficient improvement is a lack of guideline-indicated treatments besides diuretics and drugs for hypertension.

4.1. Echocardiographic characteristics

All patients had LVEF > 50%. Although they had normal systolic indices, LV global strain was abnormal in the majority of patients indicating a sort of subclinical systolic dysfunction.⁵⁰

Most patients had LVH and an increase in left ventricular mass and these are very common findings in such population of patients as they are older, more often women, and have a high prevalence of hypertension, and a large number of comorbidities, each of which increase the risk for developing concentric remodeling.⁵¹

They showed normal LV internal dimensions and volumes. They also had diastolic dysfunction, high filling pressure and increased LA volume index, and the majority of our patients showed variable degrees of pulmonary hypertension, and mild depression of RV longitudinal function. These findings are comparable to the findings in other studies.^{33,11}

Although all of our patients had variable degrees of diastolic dysfunction 45% had normal LA volume index and that was shown in I-PRESERVE,⁴⁹ as well. LA size results from both the extent and duration of increased LV diastolic pressure so there was no atrial remodeling in these patients possibly because the disease was early or the left ventricular end diastolic pressure (LVEDP) was not high enough.

5. Limitations

- (1) This study is limited to the assessment of HFpEF patients during acute admission with no long term follow-up.
- (2) Patients were recruited only from one big hospital.
- (3) The study may not represent the Saudi population because other non-Saudi residents were included (only few).
- (4) Not all parameters of diastolic function assessment were measured, and only the most validated ones were used.

6. Conclusion

Patients with HFpEF were old (but younger than western patients) with slight female dominance, a high rate of hypertension, diabetes, dyslipidemia and much comorbidity. LVEF was preserved despite depressed left ventricular longitudinal and diastolic functions with high filling pressure. Patients discharged from the hospital after acute admission were still symptomatic due to lack of guidelines for the treatment of HFpEF which calls for more research.

Conflict of interest

There is no conflict of interest.

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