Heart Failure Preserved Ejection Fraction

Dr Alastair Gray

Consultant cardiologist SHSCT

Disclosures 1/2

- Speaker Honoraria/Advisory Board:
 - FIRE1
 - Airmed
 - Medtronic
 - Biotronik
 - NICE



Diagnosis and Management of Heart Failure with Preserved Ejection Fraction in Primary Care

Medscape # UK X Guidelines
Primary Care Hacks

Authors: Dr Patricia Campbell, Consultant Cardiologist and Clinical Lead for Heart Failure, Northern treand; Dr Eimear Darcy, GP Partner, Grange Family Practice, Omagh; Dr Kevin Fernando, Portfolio GP, East Lothian, and Content Advisor, Medscape alche and UK (email: kfernando@webmd.net)

Heart failure is a significant global public health crisis



>37M people with HF worldwide¹

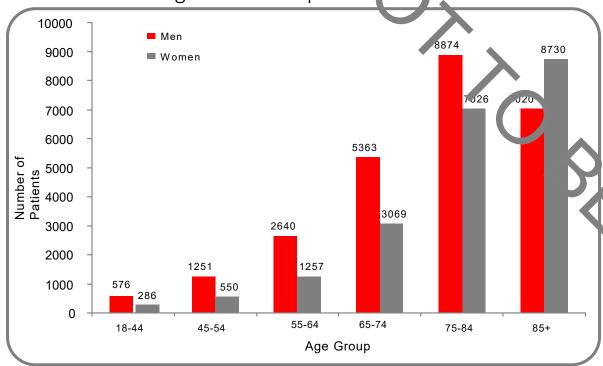
of entire healthcare expenditure due to hospitalisations for HF²

1 in 5 people over the age of 40 will develop HF³



Ageing populations and comorbidities impact on prevalence





Medical History	HFrEF(%)	HFpEF(%)
IHD	46	37
Atrial fibrillation (from ECG)	41	51
Valve disease	27	33
Hypertension	52	61
piabetes	34	34
СОРД	18	20
Asthma	9	9

Mean age - 77.8 years Median age - 80 years Mean age men - 75.9 years Mean age women - 80.2 years



₩

Most common reasons for non- HF referrals

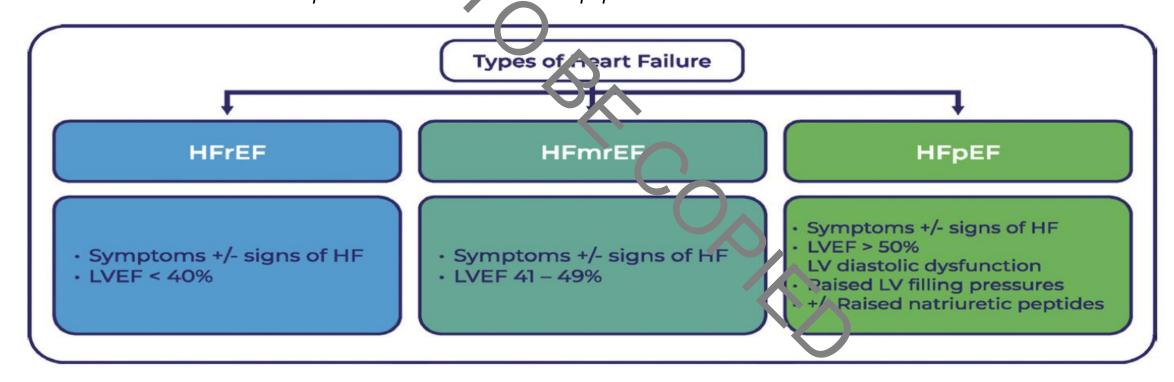
- Elevated Nt-proBNP in the setting of advancing age
- Elevated Nt-proBNP in the setting of renal disease
- Elevated Nt-proBNP in the setting of acute infection
- Oedema secondary to
 - Venous stasis / dependent oedema
 - Renal disease
 - Chronic lymphoedema
 - Medication
- Shortness of breath in absence of other HF signs and normal BNP



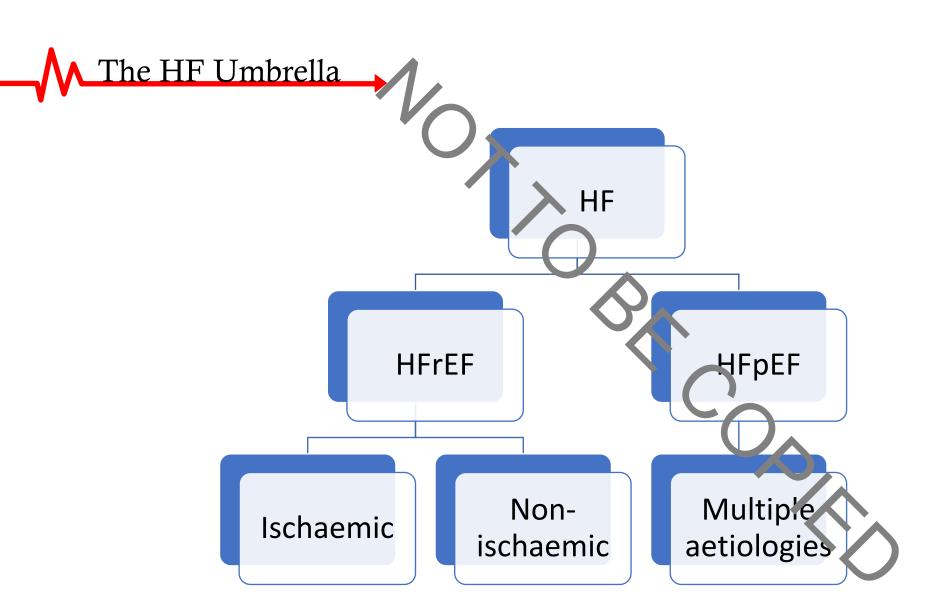
What is heart failure?

Definition

"Signs and symptoms accompanied by structural or functional cardiac defects resulting in altered filling pressures – at rest or on exertion and reduced cardiac output and/or elevater natriuretic peptides"









HF Preserved Ejection Fraction

Accounts for at least 50% HF

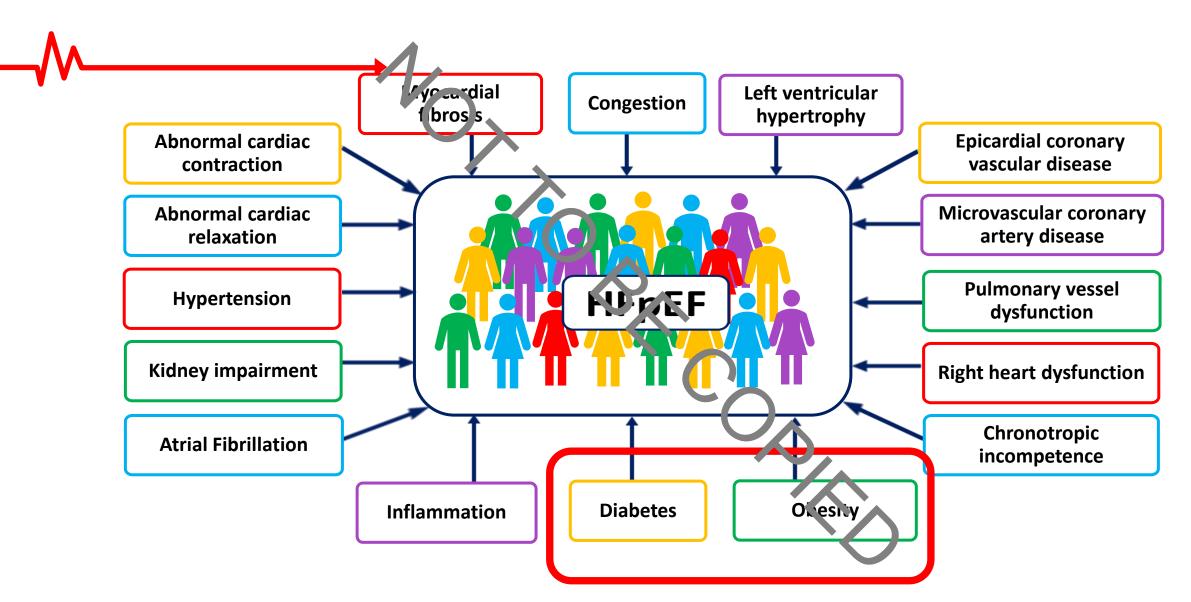
High mortality and hospitalization rates

Multiple risk factors / shared pathologies

Often multiple co-morbidities

Unifying feature is raised LVEDP, impaired relaxation and increased stiffness







67y female

HTN x 25 years (lercanidipine, perindopril)

Obesity BMI 37

T2DM HbA1C 117 (metformin, linagliptin)

CKD GFR 48



67y female



SOBOE, swollen legs

BP 158/99

HR 90 sinus

Soft pan systolic murmur

Peripheral volume overload



∧ 67y female

Non-anaemic Hb 131

Normal WBC, inflammatory markers

GFR 41, Na 130, K 4.7

Normal thyroid function

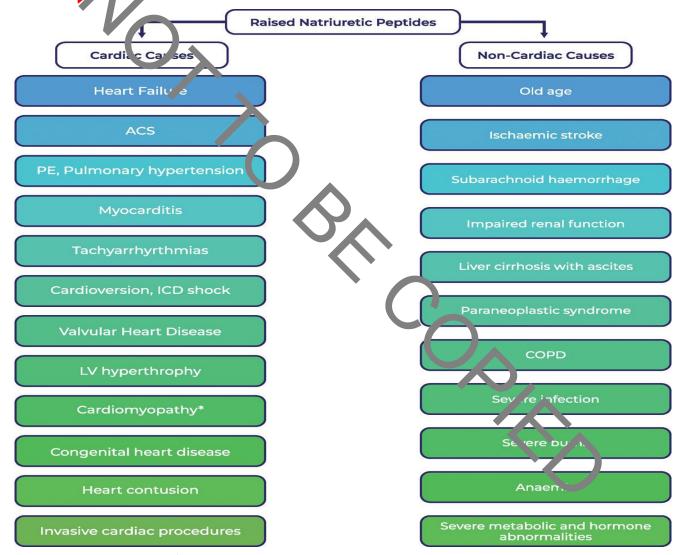
Ferritin 130, Tsat 19%

CXR upper lobe venous diversion, small bilateral pleural effusions



NTproBNP 1108pg/ml

<u> ∧ Nt-ProBNP – high negative predictive value</u>





_______Ejection Fraction

Only part of assessment of cardiac performance

2D imaging of complex 3D structure - multiple technical and interpretative factors

Who looks at the Stroke volume CO = HR x SV

Useful to be supplemented with Tissue Doppler, Strain etc.







Echo summary:

Preserved LV systolic function.

Mild LVH with diastolic dysfunction.

Mild-moderate TR.

High probability of pulmonary hypertension with estimated RVSP of 58mmHg.



"Pulmonary Hypertension"



Referral sent for review in specialist centre





Do we have enough to say she has HFpEF

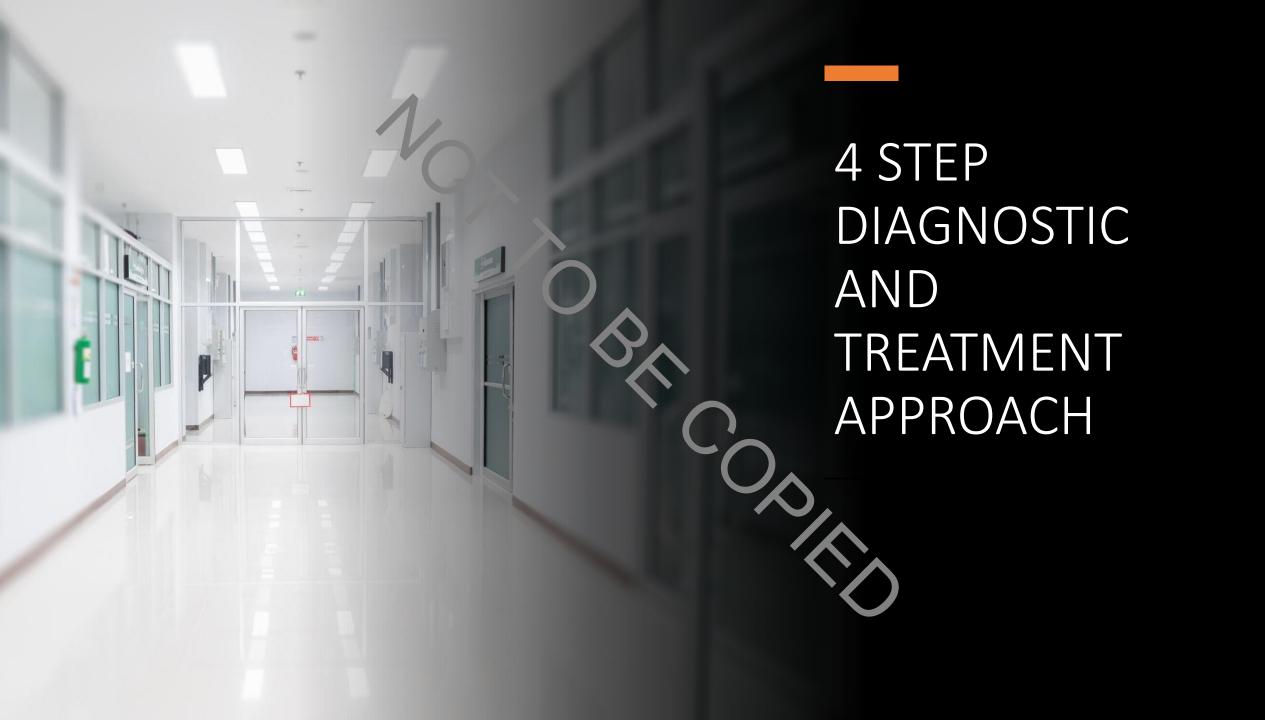


HFpEF, simply put, is when a person has a diagnosis of heart failure and their LVEF is 50% or higher



"Those with symptoms and signs of HF,
with evidence of structural and/or functional cardiac abnormalities
and/or raised natriuretic pertions (NPs),
and with an LVEF ≥50%, have HFpEF"







	Clinical Variable	Values	Points
ш	Heavy	Body mass index > 30 kg/m ²	2
H ₂	Hypertens ve	2 or more antihypertensive medicines	1
F	Atrial Fibrillation	Paroxysmal or Persistent	3
Р	Pulmonary Hypertension	Pulmonary Artery Systolic Pressure > 35	1
Е	Elder	Age > CJ years	1
F	Filling Pressure	Doppler Echoc ardio graphic E/e' > 9	1
	H ₂ FF	PEF score	Sum (0-9)
Total P	oints 0 1	2 3 4 5 6 7	8 9
Probab	ility of HFpEF 0.2 0.	3 0.4 0.5 0.6 0.7 0.8 0.9 0.95	

H2FPEFF score

The HFA-PEFF Algorithm for the Diagnosis of HFpEF

P Initial Workup (Step 1 (P): Pretest Assessment) HFAPEFF score 6

Symptoms and/or Signs of HF Comorbidities / Risk factors

- · ECG
- Standard Echocardiography Natriuretic Peptides
- Ergometry / 6 min walking test or Cardiopulmonary Exercise Testing

Diagnostic Workup
(Step 2 (E): Echocardiographic and Natriuretic Peptide Score)

Comprehensive Echocardiography
Natriuretic Peptides, if not measured in Ste

Advanced Workup
(Step 3 (F1): Functional testing in Case of Uncertainty)

- Diastolic Stress Test: Exercise Stress Echoca
- Invasive Haemodynamic Measurements

Aetiological Workup (Step 4 (F2): Final Aetiology)

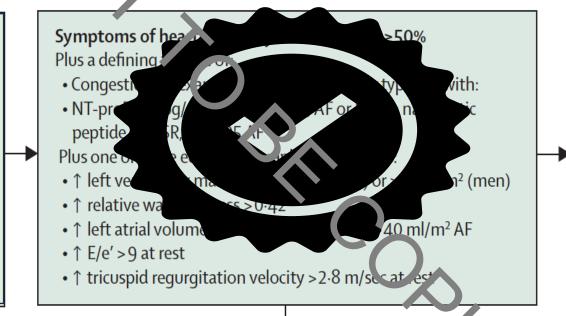
- Cardiovascular Magnetic Resonance
- Cardiac or Non-Cardiac Biopsies
- Scintigraphy / CT / PET
- Genetic testing
- Specific Laboratory Tests

F₂

B Pieske DOI 10.1093/eurheartj/ehz641

STEP 1

80% diagnosed at this stage



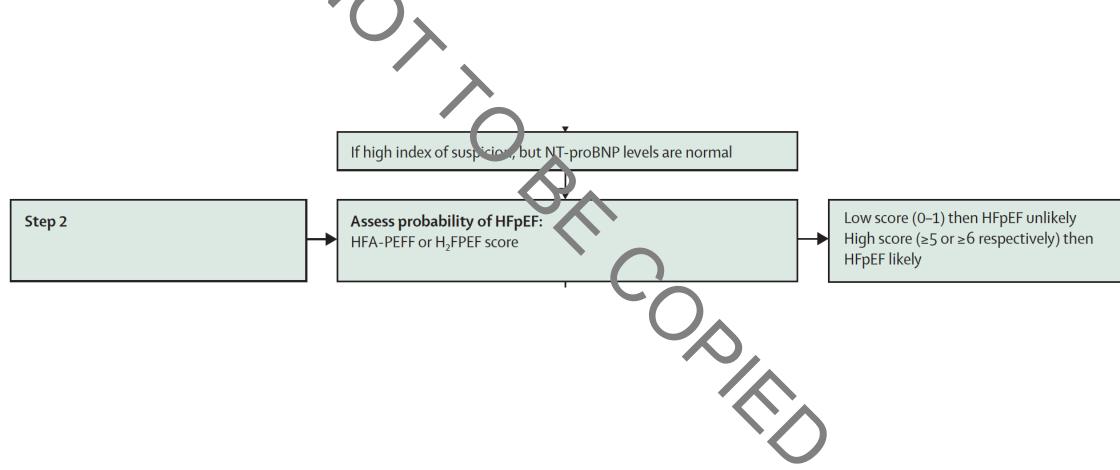
CONESTION –

RADIOLOGICALLY AND
PERIPHERALLY

BNP ELEVATION
LVH
EF>50%
TRV > 2.8M/S

SIGNS - BIOMARKER - PRESERVED LV FUNCTION

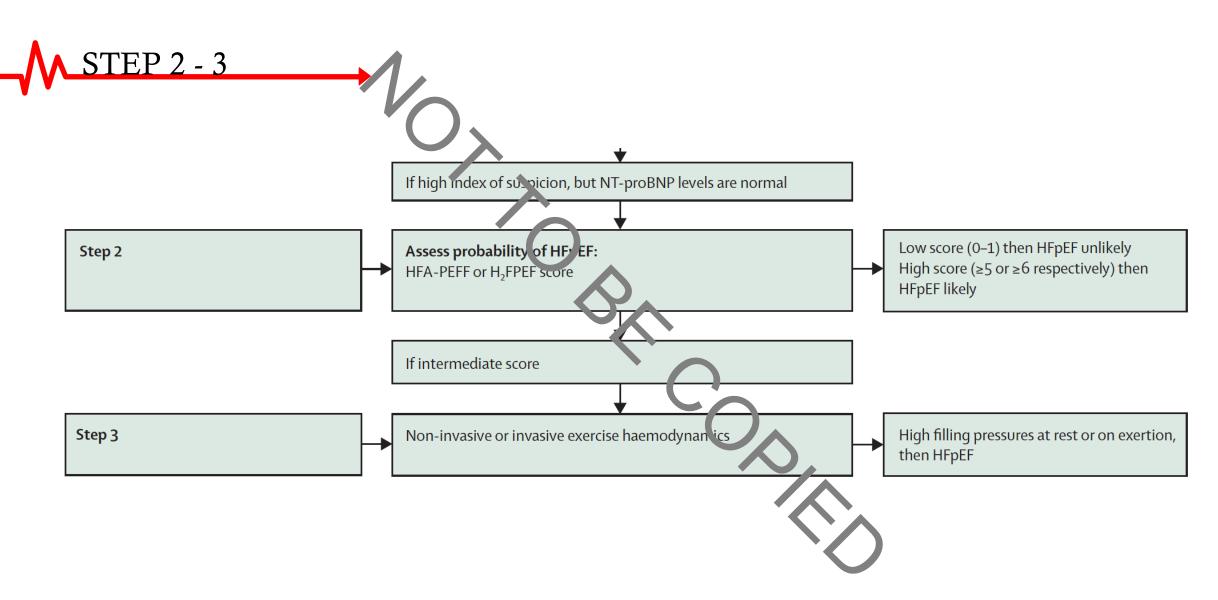
Imagine her NTproBNP was 110 instead of 1108?



M HFAPEFF SCORE

	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major	septal e' < 7 cm/s or lateral e' < 10 cm/s or Average E/e' ≥ 15 or TR velocity > 2.8 m/s (PASP > 35 mmHg)	LAVI > 34 ml/m² or LVMI ≥ 149/222 g/m-(m/w) and RWT > 0,42 #	NT-proBNP > 220 pg/ml or BNP > 80 pg/ml	NT-proBNP > 660 pg/ml or BNP > 240 pg/ml
Minor	Average E/e' 9 -14 or GLS < 16 %	LAVI 29-34 ml/m ² or LVMI > 115/95 g/m ² (m/w) or RWT > 0,42 or LV wall thickness <u>></u> 12 mm	NT-proBNP 125-220 pg/ml or BN 2 35-80 pg/ml	NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml
Мајо	or Criteria: 2 points	≥ 5 points: HFpEF		
Mino	or Criteria: 1 point	2-4 points: Diastolic Stress	Test or Invasive Haemody	mic Measurements



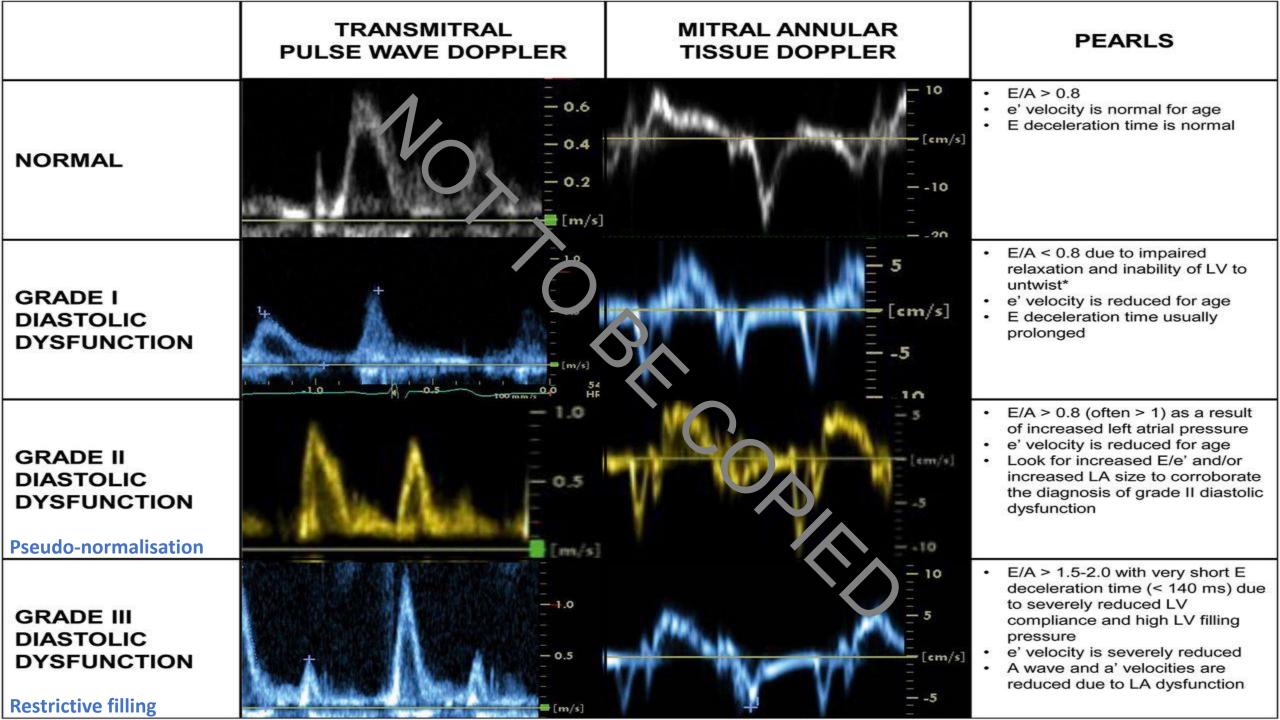


HEART FAILURE

SOUNDS SIMPLE!

POOR ECHO WINDOWS
ARRYTHMIA
COMPLEX VARIABLES
MULTIPLE CO-MORDITIES
NORMAL RESTING PARAMETERS





Web Table 4.3 Normal and abnormal values of echocardiographic indices of diastolic function of left ventricle at rest according to age categories, differentiated for gender. Values are presented as means (± standard deviations) (the cut-offs of these parameters have been derived from the following references). 65,70,72,80-86

Parameter	Normal diastolic fi retion					Diastolic dysfunction			
	20-40 years		40-60 years		≥60 years		Impaired	Pseudo-normal	Restrictive
	Male	Female	Male	Female	Male	Female	relaxation	filling	filling
MV-inflow									
MV-E (m/s)	0.79 ± 0.14	0.84 ± 0.17	0.72 ± 0.16	0.77 ± 0.17	0.67 ± 0.15	0.72 ± 0.17			
MV-A (m/s)	0.50 ± 0.13	0.51 ± 0.12	0.61 ± 0.1	9.63 ± 0.14	0.73 ± 0.16	0.76 ± 0.16			
DecT (m/s)	179.8 ± 46.4	176.7 ± 40.1	186.6 ± 52.8	188 (± 39.8	217.5 ± 69.7	201.5 ± 55.7	>220	140-220	<140
E/A ratio (m/s)	1.69 ± 0.52	1.72 ± 0.52	1.22 ± 0.31	1.25 0 3	0.96 ± 0.27	0.99 ± 0.31	<1.0	1.0-2.0	>2.0
lvrt (m/s)							>110	60-100	<60
Tissue Doppler									
e' septal (cm/s)	11.9 ± 2.7	12.3 ± 2.3	9.8 ± 2.6	9.7 ± 2.5	1.3 : 1.2.2	7.9 ± 2.3	<8	<8	<8
e' lateral (cm/s)	16.2 ± 3.6	16.6 ± 3.2	12.6 ± 3.0	12.4 ± 3.0	9.5 ± 2.4	9.7 ± 3.2	<10	<10	<10
e' mean sept-lat (cm/s)	14.0 ± 2.9	14.5 ± 2.4	11.2 ± 2.4	11.1 ± 2.5	8.5 ± 1.9	8/1 ± 2.6			
E/e' septal	6.9 ± 1.7	6.9 ± 1.6	7.8 ± 2.4	8.2 ± 2.2	9.8 ± 3.0	9/ 1- 2.6			
E/e' lateral	5.0 ± 1.3	5.2 ± 1.3	6.1 ± 2.2	6.5 ± 2.3	7.6 ± 2.1	7.9 ± 2.2			
E/e' mean sep-lat	5.8 ± 1.4	5.9 ± 1.3	6.7 ± 2.1	7.2 ± 2.0	8.4 ± 2.2	8.6 ± 2.2		≥13	≥13

DecT = deceleration time of MV-E; e' = early diastolic tissue velocity; E/e' = a ratio between early mitral inflow velocity and mitral annular early diastolic velocity; IVRT = a isovolumetric relaxation time; IVRT = a is IVRT = a in IVRT = a is IVRT = a is IVRT = a in IVRT = a



SO NOW WHAT?

DO WE NEED TO LOOK FORTHER / UNDERTAKE MORE TESTS
DO THEY NEED ROUTINE FOLLOW UP
WHAT ARE THE TREATMENT OFTIONS





Aetiology workup

Ischaemia

toxins

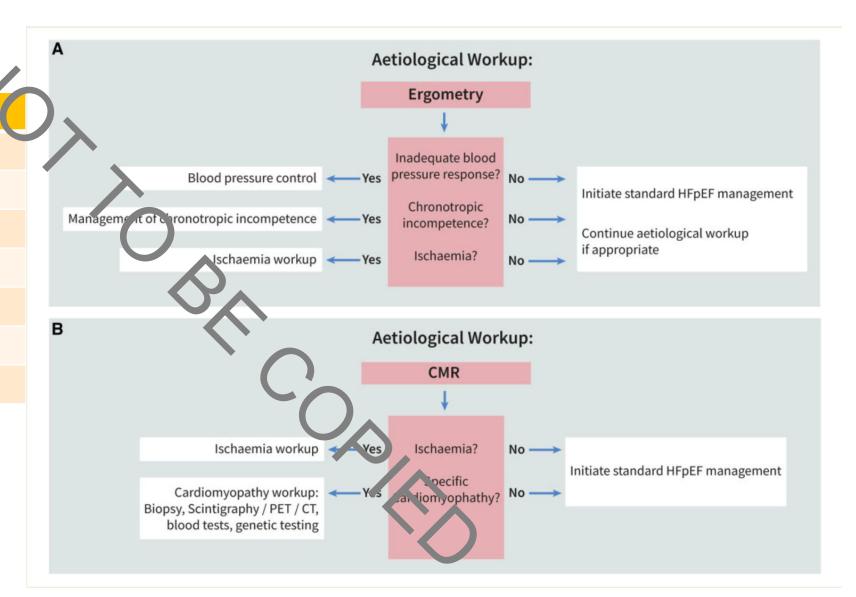
infiltration

Hypertension

High output disorders

Metabolic disorders

Immune/inflammatory





Clinical hints — symptoms of potential TTR



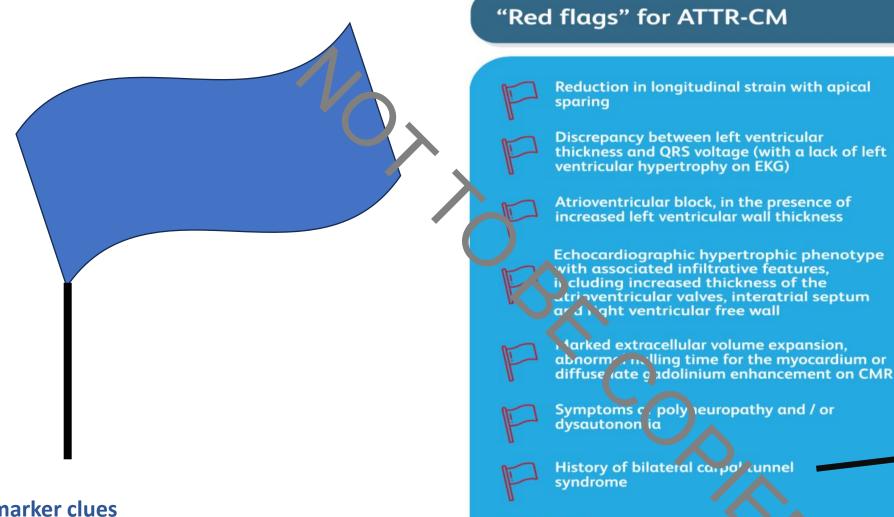
Biceps rupture and spinal stenosis relatively unique to ATTR vs AL

CTS association with amyloid remains unclear 1.2%-37%

varying with ethnicity age

filateral involvement

Michelle M. Kittleson et al. *JACC* 2023; 81:1076-1126.



Biomarker clues

- persistent troponin elevation
- BNP disproportionately raised compared to HF degree

"Red flags" that further support the possibility of an underlying ATTR-CM. ATTR-CM transthyretin amyloid cardiomyopathy; CMR = cardiac magnetic resonance imaging;

Mild increase in troponin well on speated

occasions

EKG = electrocardiogram.

May occur 10 years before onset of cardiomyopathy





Web Table 9.1 Phase II and III clinical trials performed in patients with heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction

Trial	Intervention	Major inclusion criteria	Mean follow-up	Primary endpoints
PEP-CHF ³²⁰	Perindopril vs placebo.	LV w/n notion index ≥1.4 (corresponding to LVEF ≥4.0%), symptomatic HF treated with diuretic, diastolic dynamic ion in echocardiography, age ≥70 y.	2.1 y	No difference in combined all-cause mortality or cardiovascular hospitalization (36% vs 37%, P =0.35).
I-PRESERVE 318	Irbesartan vs placebo.	LVEF ≥45%, NYH A III-IV with corroborative evidence, or NYHA II wan HP pospitalization in recent 6 months, age ≥60 //.	4.1 y	No difference in combined all-cause mortality or HF hospitalization (24% vs 25%, P =0.54).
CHARM- Preserved ³¹⁹	Candesartan vs placebo.	LVEF >40%, NYHA II-IV, history of cardiac hospitalization.	3.0 y	Trend towards a reduction in combined cardiovascular mortality or HF hospitalization by 11% (22% vs 24%, unadjusted $P = 0.12$, adjusted $P = 0.051$).
Aldo-DHF ³³⁰	Spironolactone vs placebo.	LVEF ≥50%, NYHA II—III, peak VO ≤25 mL/min/kg, diastolic dysfunction on echocary lography or atrial fibrillation, age ≥50 y.	1.0 y	Reduction in E/e' by -1.5 ($P < 0.001$) No change in peak VO ₂ ($P = 0.81$).
TOPCAT ³¹⁰	Spironolactone vs placebo.	LVEF ≥45%, ≥1 HF sign, ≥1 HF symptom HF hospitalization within recent 12 month, or BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL are ≥50 y.	3.3 y	No difference in combined cardiovascular death, aborted cardiac arrest, or HF hospitalization (19% vs 20% , $P = 0.14$).
SENIORS ¹⁷³	Nebivolol vs placebo.	HF confirmed as HF hospitalization in recent 12 months and/or LVEF ≤35% in recent 6 months, age ≥70 y, 36% with LVEF >35%.	1.8 y	Reduction in combined all-cause mortality or cardiovascular hospitalization by 14% (31% vs 35%, P =0.04).
DIG-PEF ³²³	Digoxin vs placebo.	HF with LVEF >45%, sinus rhythm.	У	No difference in combined HF mortality or HF hospitalization (21% vs 24%, P = 0.14)
PARAMOUNT ³⁰⁹	Sacubitril/ valsartan vs valsartan.	HF with LVEF ≥45%, NYHA II-III, NT-proBNP >400 pg/mL.	10,	Reduction in NT-proBNP: ratio of change sacubitril/ valsartan 0.77, 95% CI 0.64-0.92 (P =0.005).
RELAX ³¹¹	Sildenafil vs placebo.	HF with LVEF ≥45%, NYHA II-IV, peak VO ₂ <60% of reference values, NT-proBNP >400 pg/mL or high LV filling pressures.	24 w	No change in peak VO ₂ (P =0.90).

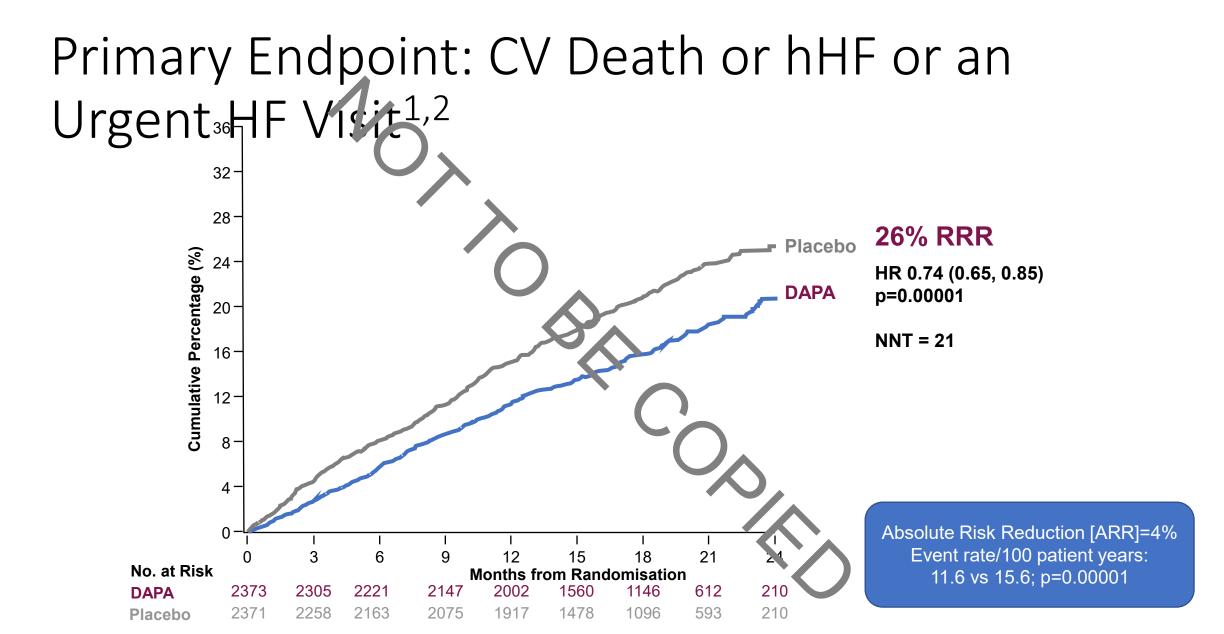
Aldo-DHF = Aldosterone Receptor Blockade in Diastolic Heart Failure; BNP = B-type natriuretic peptide; CHARM-Paulerved = Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality; DIG-PEF = ancillary Digitalis Investigation Group trial; HF = heart failure; I-PRESERVE = Irbesartan in Heart Failure with Preserved Ejection Fraction Study, LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PARAMOUNT = LCZ696 Compared to Valsartan in Patients With Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction; Peak VO₂ = peak oxygen uptake; PEP-CHF = Perindopril in Elderly People with Chronic Heart Failure; RELAX = Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure; SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisations in Seniors with Heart Failure; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; w = week; y = year.



	Left ventricular ejection fraction	Left vent cular hypertrophy	Left atrium enlargement	Elevated filling pressures	Natriuretic peptide level (pg/mL)
EMPEROR- Preserved (2021) ³	>40%	Septal or posterior want thickness ≥1.1 cm; left ventricular mass index ≥95 g/m² (women) and ≥115 g/m² (men)	Width ≥4·0 cm; length ≥5·0 cm; area ≥20·0 cm²; /olume ≥55 mL or volume index ≥34 mL/m²	E/e' (mean septal and lateral) ≥13; e' (mean septal and lateral) <9 cm/s	NT-proBNP >300 (no atrial fibrillation) or >900 (with atrial fibrillation)
DELIVER (2022) ⁴	>40%	Septal or posterior wall thickness ≥1·1 cm	Width (character) ≥3.8 cm, lengt (≥5.0 cm; volume ≥55 mL or volume index ≥29 mL/m ²	NA	NT-proBNP ≥300 (no atrial fibrillation or flutter) or ≥600 (with atrial fibrillation or flutter)

e'=early diastolic mitral annulus velocity. E/e'=early diastolic mitral inflow velocity to early diastolic nitral annulus velocity. HFpEF=heart failure with preserved ejection fraction. NA=not applicable. NT-proBNP=N-terminal pro-B type natriuretic peptide. SGLT2i=SGLT2 inhibitor.

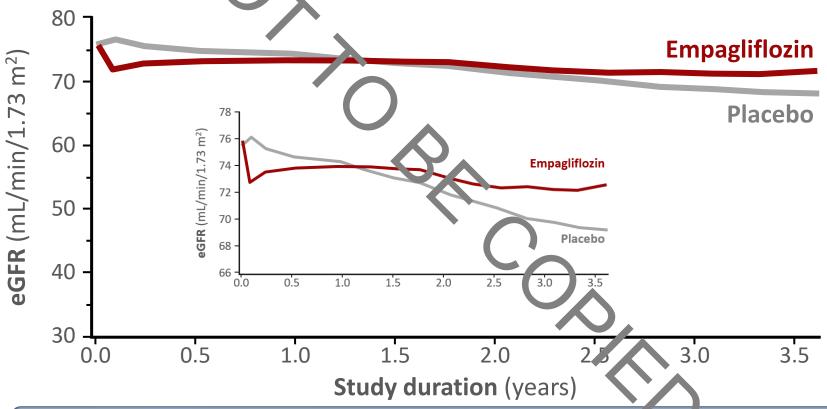
Table: HFpEF definitions in recent clinical trials of SGLT2 inhibitors



DAPA = dapagliflozin; HF = heart failure; hHF = hospitalisation for heart failure; HR = hazard ratio; NNT = number needed to treat.

Renal function over time

Empagliflozin slowed deterioration in renal function as measured by eGFR levels, compared with place 10, on top of standard of care

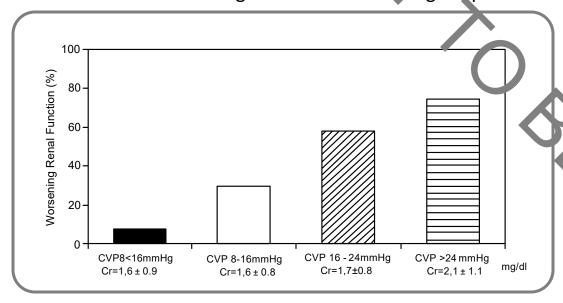


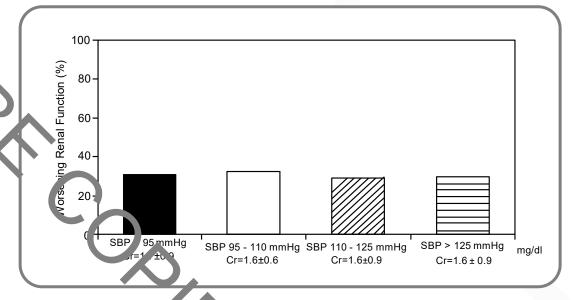
There was a 39% relative reduction (6.1% ARR) in the risk of incident or worsening nephropathy with empagliflozin vs placebo

Worsening Renal Function in decompensated HF is driven by congestion not hypotension



Prevalence of worsening renal function driving hospitalisation according to categories of admission







Joint heart failure-renal position statement

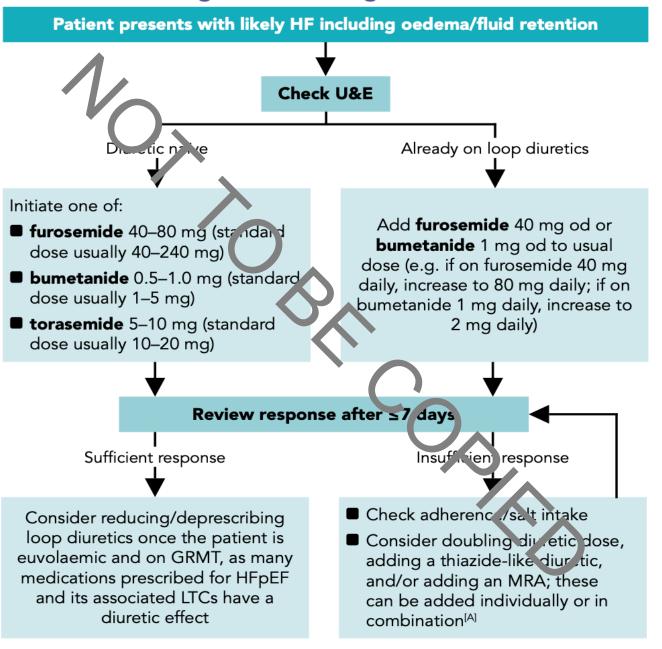


ACEI/ARB/MRA/sacubitril valsartan are disease modifying drugs in patients with heart failure with reduced ejection fraction which improve patient outcomes. The risk of stopping or reducing dose is, in general, likely to be greater detriment to a patient's prognesis than a modest increase in serum creatinine, or mild hyperkalae mia.





Management of Congestion 9,14,22,35



Complementary and additive 1,2

SGLT2 may be administered with...

Existing HF therapy

Any combination of ACEi, ARBs, ARNI, BB, MRA and devices

Diuretics

Note: in patients with volume depletion, recommend correcting prior to initiation of dapagliflozin

Common CV medications

Including antiplatelets and statins

Common T2T me lications

Including metformin, DP74i and GLP1-RA

Also including SU and insulin – increased risk of hypoglycemia when dapagliflozin is combined with insulin and SUs; may need to adjust dose of these agents

Consult the Summary of Product Characteristics for full details

*In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10mg.

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor—neprilysin inhibitor; BB, beta blocker; CV, cardiovascular; DPP4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide 1 receptor agonist; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SU, sulfonylurea; T2D, type 2 diabetes.

References: 1. Forxiga 10mg film-coated tablets. Summary of Product Characteristics. November 2020. 2. McMurray JJV, et al. N Engl J Med. 2019;381:1995-2008.

SGLT2 inhibitor (Class I)



Dapagliflozin 10mg o.d.

OR

Empagliflozin 10mg o.d.

Diuretics for fluid retention (Class I)

Loop (Furosemide, Burnetanide, Torasemide)

+/- Thiazide (Bendroflun ethialide, Chlorthalidone, Hydrochlo, this zide, Indapamide, Metolazone

+/- MRA (Spironolactone, Eplerenone)

Screening for, treatment of aetiologies, CV and non-CV comorbidities (Class I)



CV

AF: anticoagulate, rate ± rhythm control

CAD: antiplatelet, lipid-lowering, revascularise

Valvular heart disease

HTN: ACEi/ARB, Calcium Channel Blockers, diuretics

Stroke

Non-CV

DM: SGLT2i; [avoid saxagliptin & TZD]

Obesity: GLP-1RA, exercise, caloric restriction

Ci'D: SGLT2i, ACEi/ARB, finerenone

Jung disease/sleep disorder: OSA screen/treat Also: thyroid disorders, frailty / cachexia / sarcopenia, iron deficiency & anaemia, electrolyte disorders, gout & arthritis, erectile dysfunction, depression, cancer, infection

Treatment

1/0,

Dapagliflozin 10mg OD

Avoidance of beta-blockers

Bumetanide 2mg bid

Increase ACEi

Spironolactone 25mg od

Cardiac rehabilitation

Change linagliptin for GLP1RA



Conclusion /

HSpEF diagnosis often more complicated than LV systolic dysfunction

Use simple steps outlined to aid stepwise approach to diagnosis

SC (T2

Treat congestion

Treat co-morbidities

Call on HF cardiologist for advice if unsure

REMEMBER – RELAXATION IS IMPORTANT – BUT ENERGY DEPENDENT!



