HeFSSA Practitioners Program 2018
"Back to basics on heart failure treatment?"

- Co-morbidity in heart failure
- Arrhythmias in heart failure
- Special investigations in heart failure
- Heart failure with preserved EF, what is new?"

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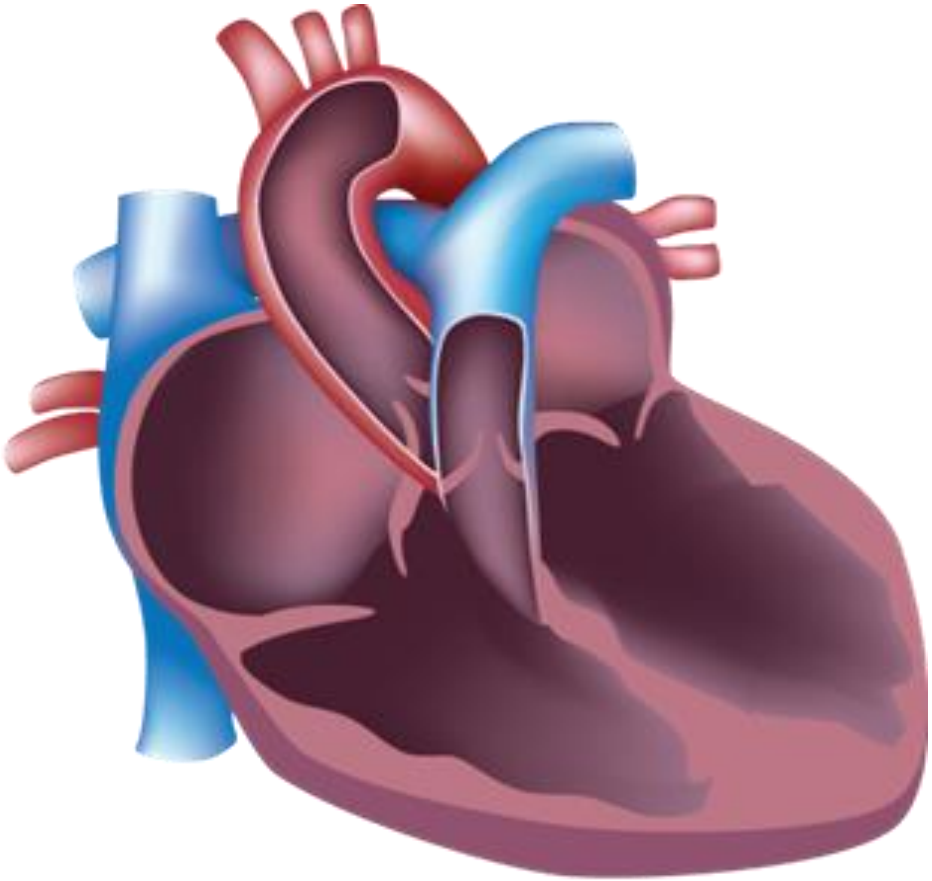
COMORBIDITY IN CHRONIC HEART FAILURE (HFrEF)



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BACKGROUND: HEART FAILURE

DEFINITION OF HEART FAILURE

Type of HF		HFrEF	HFmrEF	PFpEF
CRITERIA	1	Symptoms ± Signs	Symptoms ± Signs	Symptoms ± Signs
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1.Elevated levels of natriuretic peptides. 2.At least one additional criterion: a.relevant structural heart disease (LVF and/or LAE); b.diastolic dysfunction (for details see Section 4.3.2.).	1.Elevated levels of natriuretic peptides. 2.At least one additional criterion: a.relevant structural heart disease (LVF and/or LAE); b.diastolic dysfunction (for details see Section 4.3.2.).

Eur Heart J. 2016;37(27):2129-200.

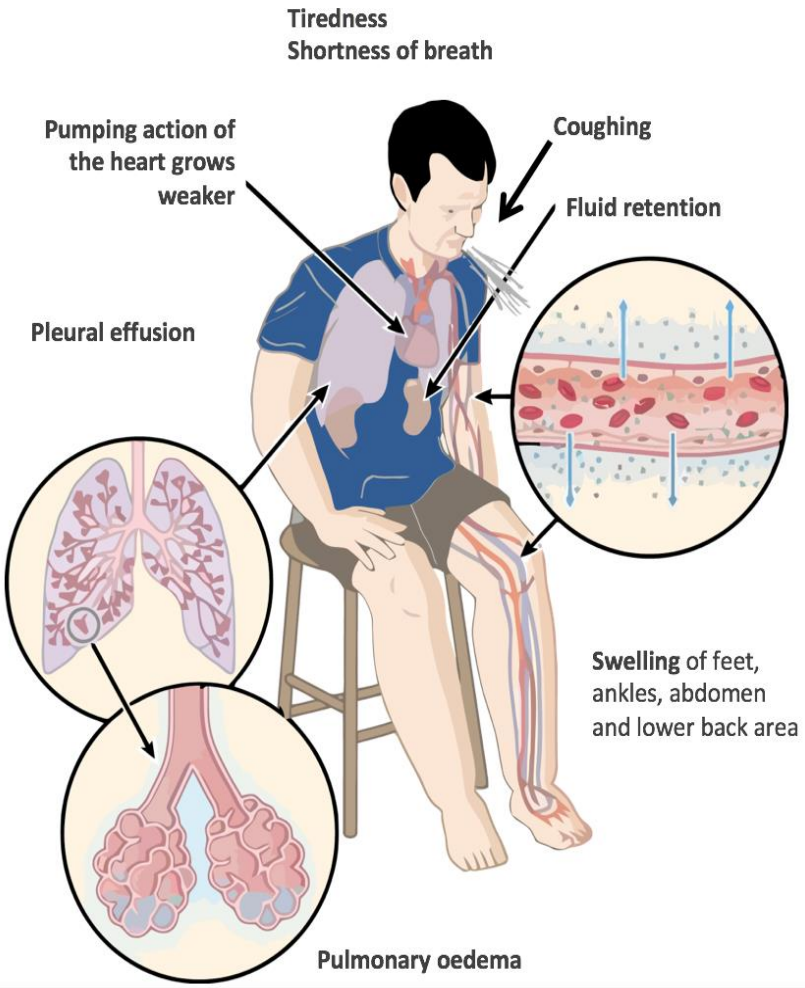
TYPICAL SIGNS AND SYMPTOMS

Main symptoms

- Breathlessness
- Orthopnea
- Paroxysmal Nocturnal Dyspnea
- Reduced exercise tolerance
- Fatigue
- Ankle swelling

Main signs

- Elevated jugular venous pressure
- Hepato-jugular reflux
- Third heart sound
- Laterally displaced apical impulse
- Cardiac murmur



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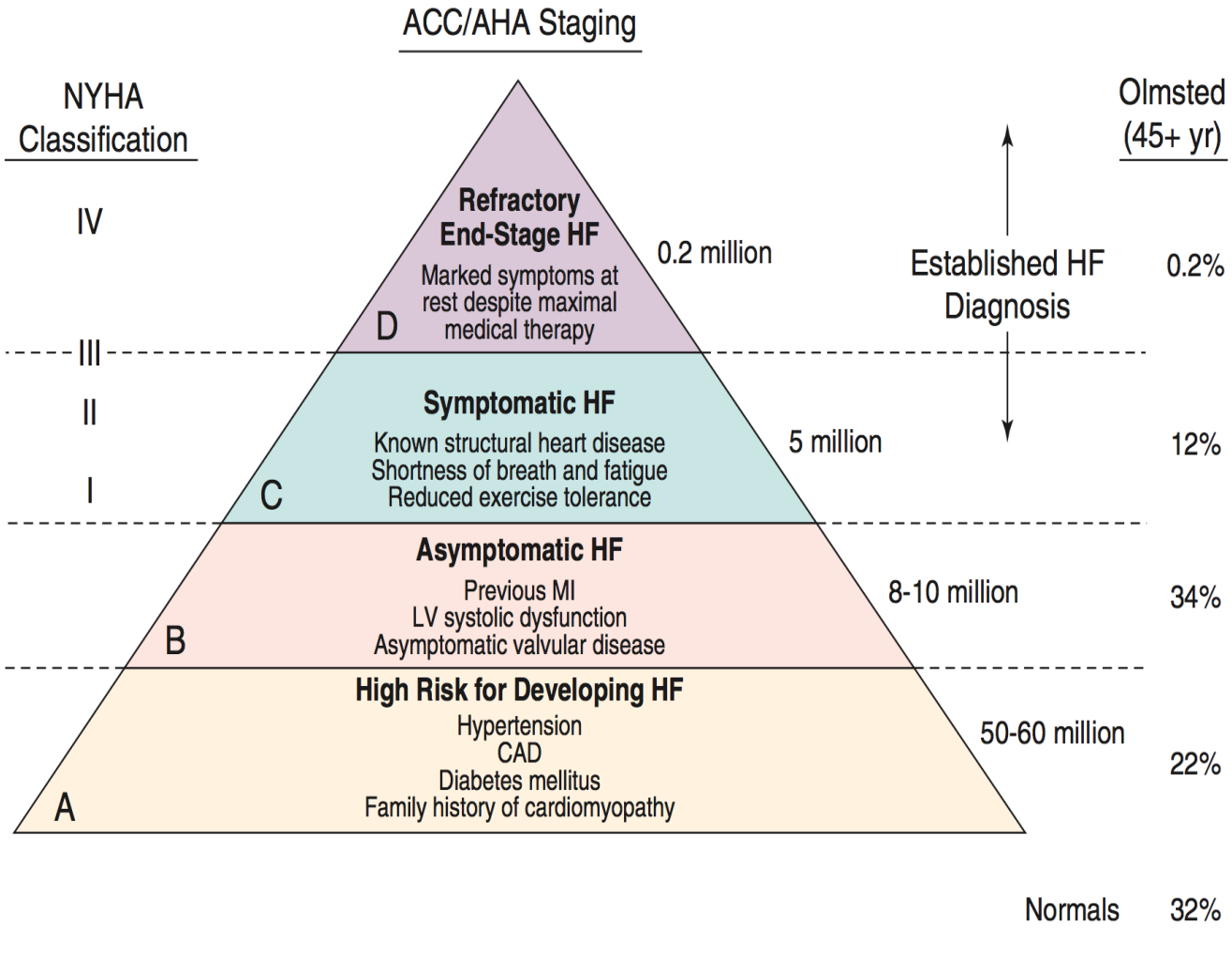
McMurray et al. Eur Heart J 2012;33:1787–847

EPIDEMIOLOGY OF HEART FAILURE



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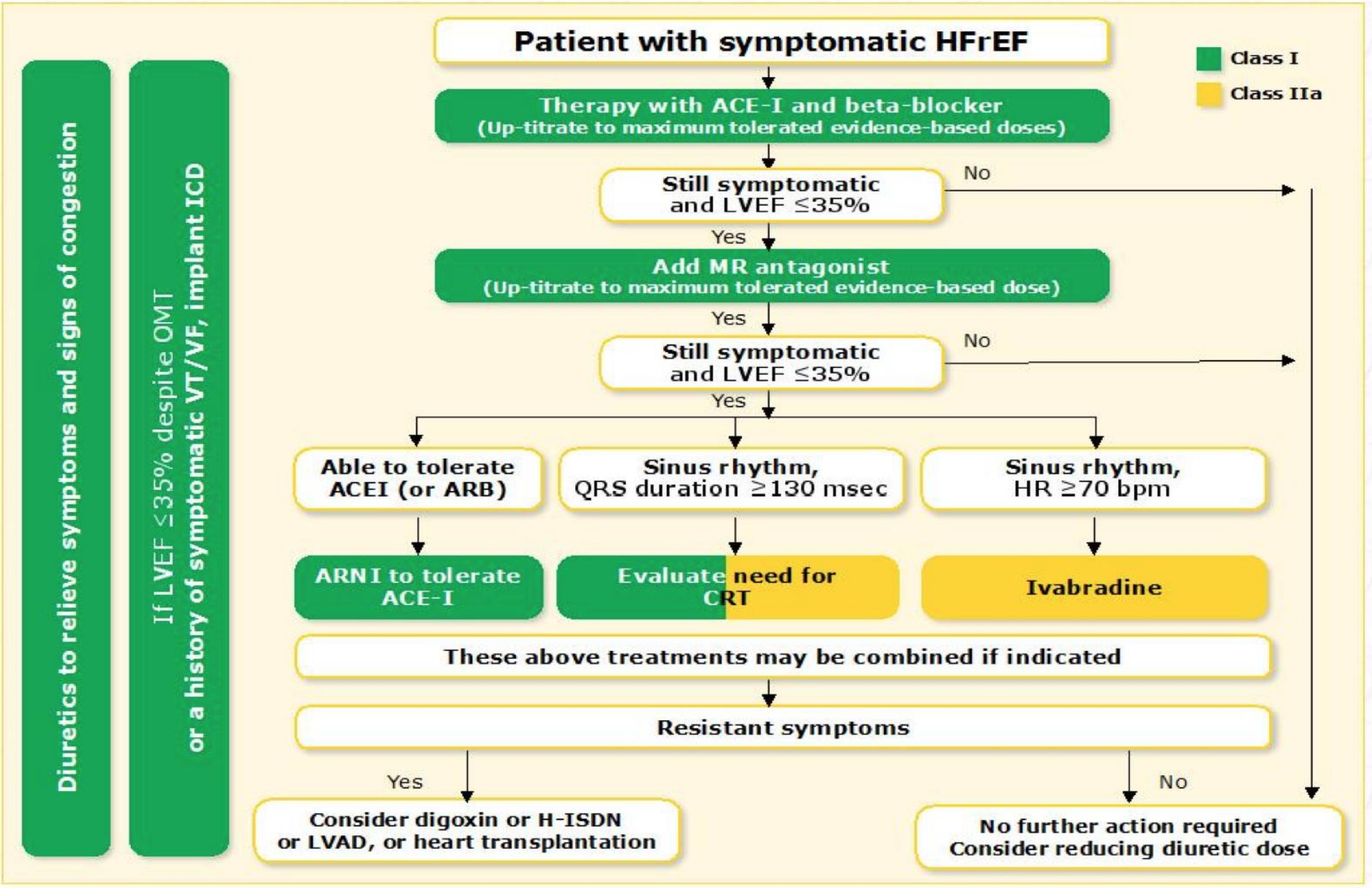
MEDICAL THERAPY



COMORBIDITY IN CHRONIC HEART FAILURE (HFrEF)

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AGING HEART FAILURE POPULATION

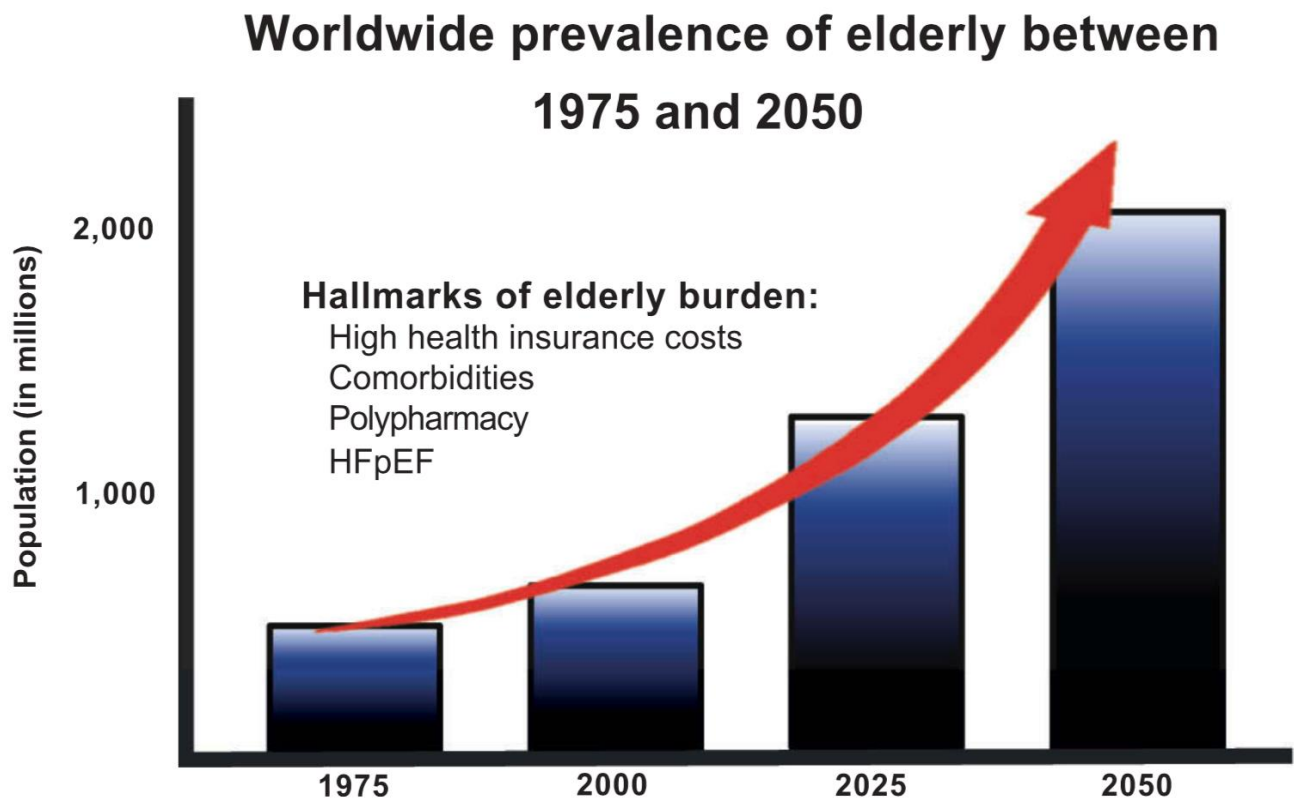
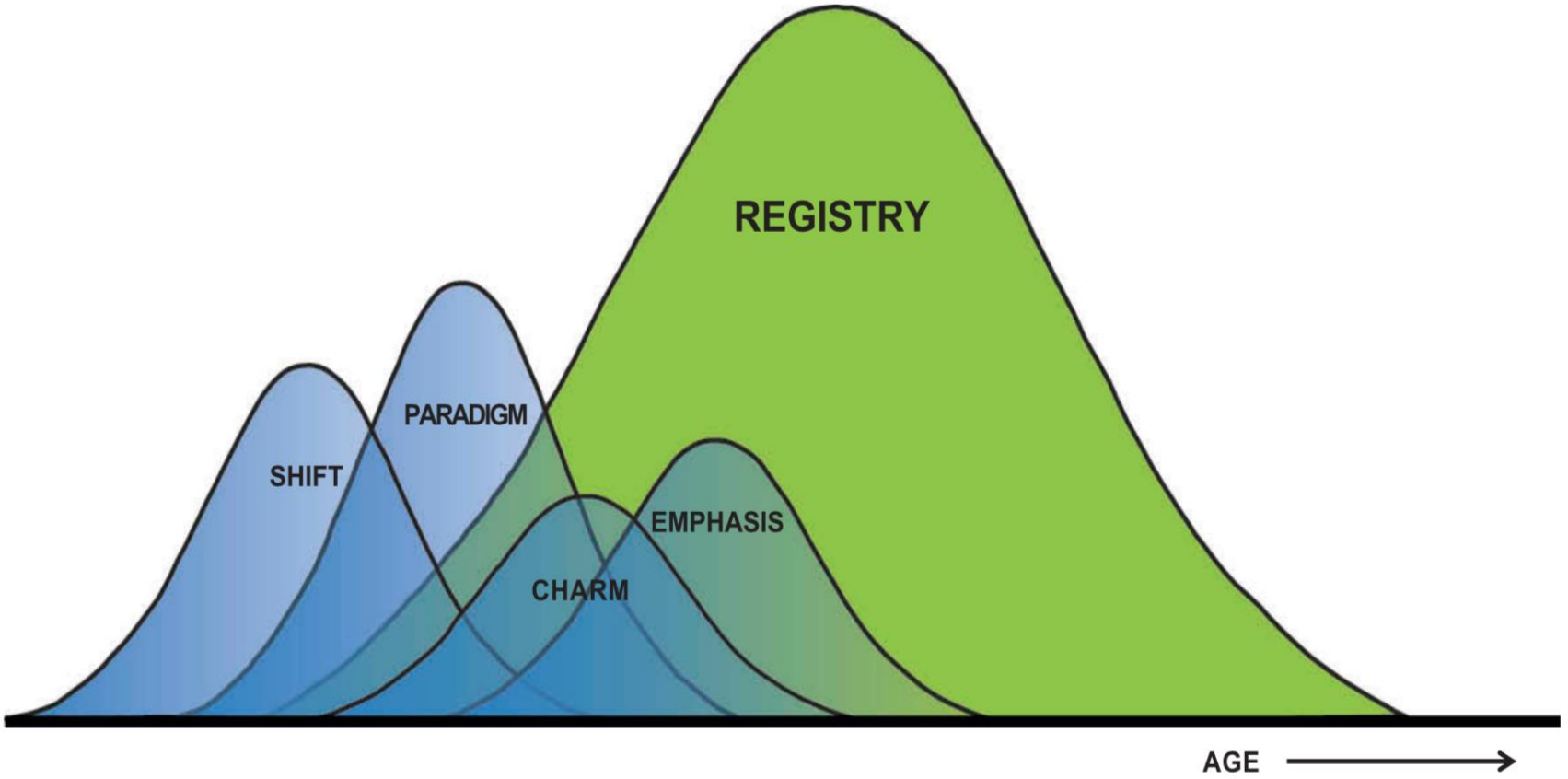


Figure 1. The increasing prevalence of the elderly population entails inherent problems.

Expert Opin Pharmacother. 2017;18(7):645-55.

AGING HEART FAILURE POPULATION



Expert Opin Pharmacother. 2017;18(7):645-55.

EPIDEMIOLOGY

Heart Fail Rev (2014)19:163-172

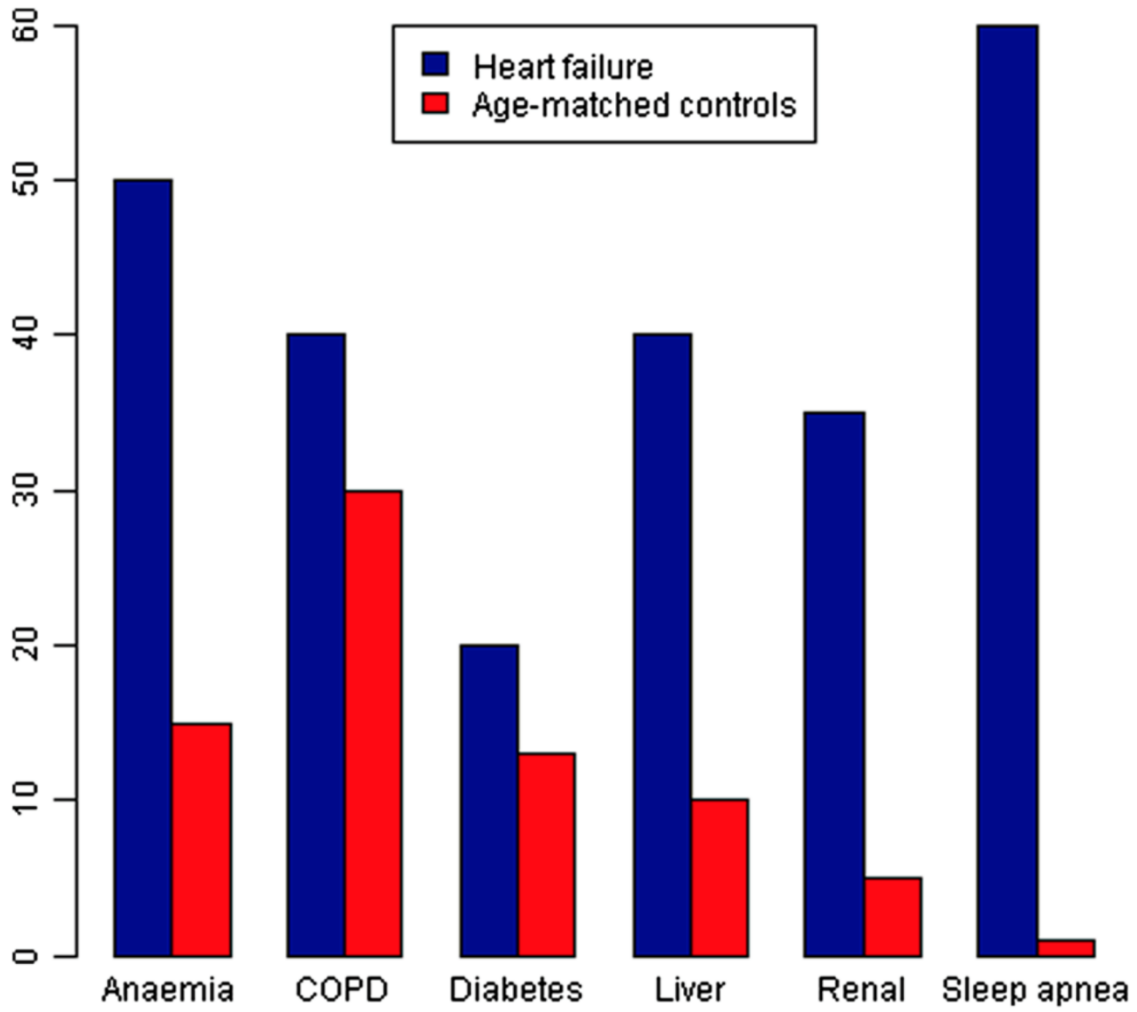


Fig. 1 Prevalence of co-morbidities in heart failure—prevalence of co-morbidities in patients with heart failure (*blue*) compared to age-matched controls

EPIDEMIOLOGY

	Prevalence (%)	Related with mortality	MeSH-search (*N* articles)
Anaemia	37	Yes	1,010
Cerebral dysfunction	28–58	Yes	407
Cognitive dysfunction	50–60	Yes	116
COPD	10–50	Yes	449
Depression	22	Yes	577
Diabetes	6–44	Yes	2,100
Erectile dysfunction	85	–	36
Gout/hyperuricemia	–	Yes	34
Hypertension	60–70	Yes	4,734
Iron deficiency	50–60	Yes	168
Kidney dysfunction	Up to 55	Yes	1,610
Liver dysfunction	30–60	Yes	521
Sleep apnoea	60	Yes	641
Stroke	5	Yes	720

Heart Fail Rev (2014)19: 163-172

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IMPORTANCE OF CO - MORBIDITIES IN PATIENTS WITH HEART FAILURE

1. Interfere with the diagnostic process of HF (e.g. COPD as a potentially confounding cause of dyspnoea).
2. Aggravate HF symptoms and further impair quality of life.
3. Contribute to the burden of hospitalizations and mortality, as the main cause of readmissions at 1 and 3 months.
4. May affect the use of treatments for HF (e.g. renin–angiotensin system inhibitors contra-indicated in some patients with severe renal dysfunction or beta-blockers relatively contra-indicated in asthma).
5. Evidence base for HF treatment is more limited as co-morbidities were mostly an exclusion criterion in trials; efficacy and safety of interventions is therefore often lacking in the presence of co-morbidities.
6. Drugs used to treat co-morbidities may cause worsening HF (e.g. NSAIDs given for arthritis, some anti-cancer drugs).
7. Interaction between drugs used to treat HF and those used to treat co-morbidities, resulting in lower efficacy, poorer safety, and the occurrence of side effects (e.g. beta-blockers for HFrEF and beta-agonists for COPD and asthma).

Causes of elevated concentrations of Natriuretic Peptides

Cardiac	Heart failure	**Non-cardiac**	Advanced age
	Acute coronary syndromes		Ischaemic stroke
	Pulmonary embolism		Subarachnoid haemorrhage
	Myocarditis		Renal dysfunction
	Left ventricular hypertrophy		Liver dysfunction (mainly liver cirrhosis with ascites)
	Hypertrophic or restrictive cardiomyopathy		Paraneoplastic syndrome
	Valvular heart disease		Chronic obstructive pulmonary disease
	Congenital heart disease		Severe infections (including pneumonia and sepsis)
	Atrial and ventricular tachyarrhythmias		Severe burns
	Heart contusion		Anaemia
	Cardioversion, ICD shock		Severe metabolic and hormone abnormalities (e.g. thyro-toxicosis, diabetic ketosis)
	Surgical procedures involving the heart		
	Pulmonary hypertension		

Markers of Worse Prognosis In Patients With HEART FAILURE

Demographic data	Older age, male sex, low socio-economic status.
Severity of heart failure	Advanced NYHA Class, longer HF duration, reduced peak oxygen consumption, high VE-VCO_2 slope, Cheyne–Stoke ventilation, short 6-minute walking distance, reduced muscle strength, poor quality of life.
Clinical status	High resting heart rate, low blood pressure, clinical features of fluid overload (both pulmonary congestion and peripheral oedema, jugular venous dilatation, hepatomegaly), clinical features of peripheral hypoperfusion, body wasting, frailty.
Myocardial remodeling and severity of heart dysfunction	Low LVEF, LV dilatation, severe diastolic LV dysfunction, high LV filling pressure, mitral regurgitation, aortic stenosis, LV hypertrophy, left atrial dilatation, RV dysfunction, pulmonary hypertension, dyssynchrony, vast area of hypo/akinesis, wide QRS complex, presumed inflammation or infiltration on CMR, inducible ischaemia and poor viability on imaging.
Biomarkers of neurohormonal activation	Low sodium, high natriuretic peptides, high plasma renin activity, high aldosterone and catecholamines, high endothelin-1, high adrenomedullin, high vasopressin.
Other biomarkers	Markers of renal function, inflammationatory markers, cardiac stress markers, cardiac damage markers, metabolic markers, collagen markers, markers of organ damage/dysfunction.
Genetic testing (see section 5.10.1)	Certain mutations in inherited cardiomyopathies associated with high-risk of sudden cardiac death or rapid HF progression.
Cardiovascular co-morbidities	Atrial fibrillation, ventricular arrhythmia, non-revascularizable coronary artery disease, previous stroke/TIA, peripheral arterial disease.
Non-cardiovascular co-morbidities	Diabetes, anaemia, iron deficiency, COPD, renal failure, liver dysfunction, sleep apnoea, cognitive impairment, depression.
Non-adherence	Non-adherence with recommended HF treatment.
Clinical events	HF hospitalization, aborted cardiac arrest, ICD shocks.

HYPERTENSION AND HEART FAILURE

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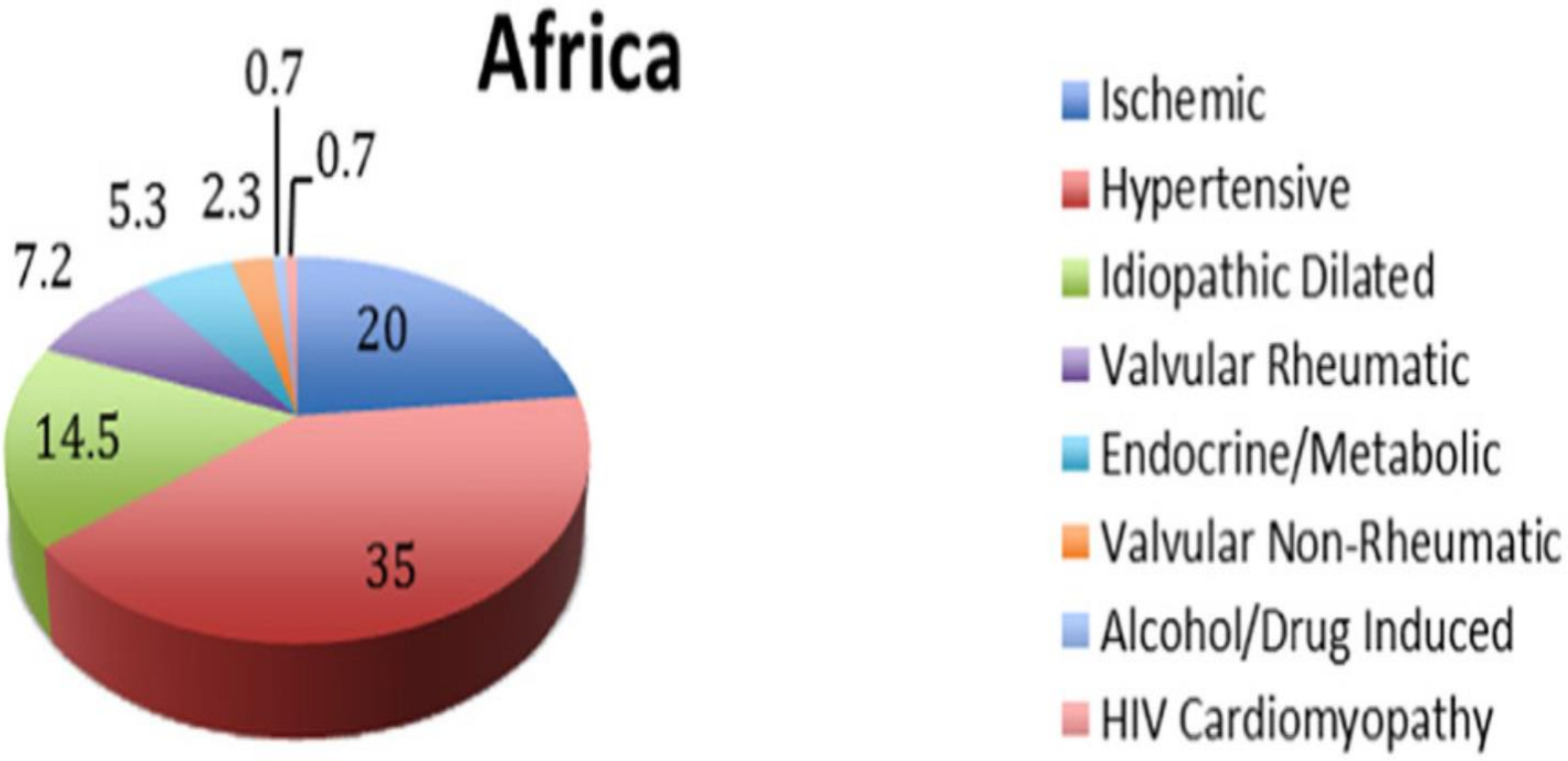
HFrEF AETIOLOGY



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Dokainish H, et al. Heart Failure in Africa, Asia, the Middle East and South America: The INTER-CHF study. Int J Cardiol. 2016;204:133-41.

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Prevalence & Pathophysiology: HPT and HF

- Higher baseline systolic, diastolic and pulse pressure levels associated with increased adverse events.
- NB Optimal BP control
- BP targets in HPT Guidelines apply
- Uncontrolled HPT in HFrEF is very rare – in patients optimally treated for HF
- AHF i.v. nitrates recommended to lower BP

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Clin Res Cardiol. 2015;104(12):1088-96.

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CATEGORIES OF BP IN ADULTS

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.

JAMA. 2017;318(21):2083-4.

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THERAPEUTIC OPTIONS: HPT and HF

Recommendations	Class	Level
Step 1		
ACE-I (or ARB) a beta-blocker or an MRA (or a combination) is recommended to reduce blood pressure as first-, second- and third line-therapy, respectively, because of their associated benefits in HFrEF (reducing the risk of death and HF hospitalization). They are also safe in HFpEF.	I	A
Step 2		
A thiazide diuretic (or if the patient is being treated with a thiazide diuretic, switching to a loop diuretic) is recommended to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker and an MRA.	I	C
Step 3		
Amlodipine or hydralazine is recommended to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker, an MRA and a diuretic.	I	A

THERAPEUTIC OPTIONS: HPT and HF

Recommendations	Class	Level
Step 3 *(cont'd)*		
Felodipine should be considered to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker, an MRA and a diuretic.	IIa	B
Moxonidine is not recommended to reduce blood pressure because of safety concerns in HFrEF patients (increased mortality).	III	B
Alpha-adrenoceptor antagonists are not recommended to reduce blood pressure because of safety concerns in HFrEF patients (neurohormonal activation, fluid retension, worsening HF).	III	A
Diltiazem and verapamil are not recommended to reduce blood pressure in patients with HFrEF because of their negative inotropic action and risk of worsening HF.	III	C

DIABETES AND HEART FAILURE

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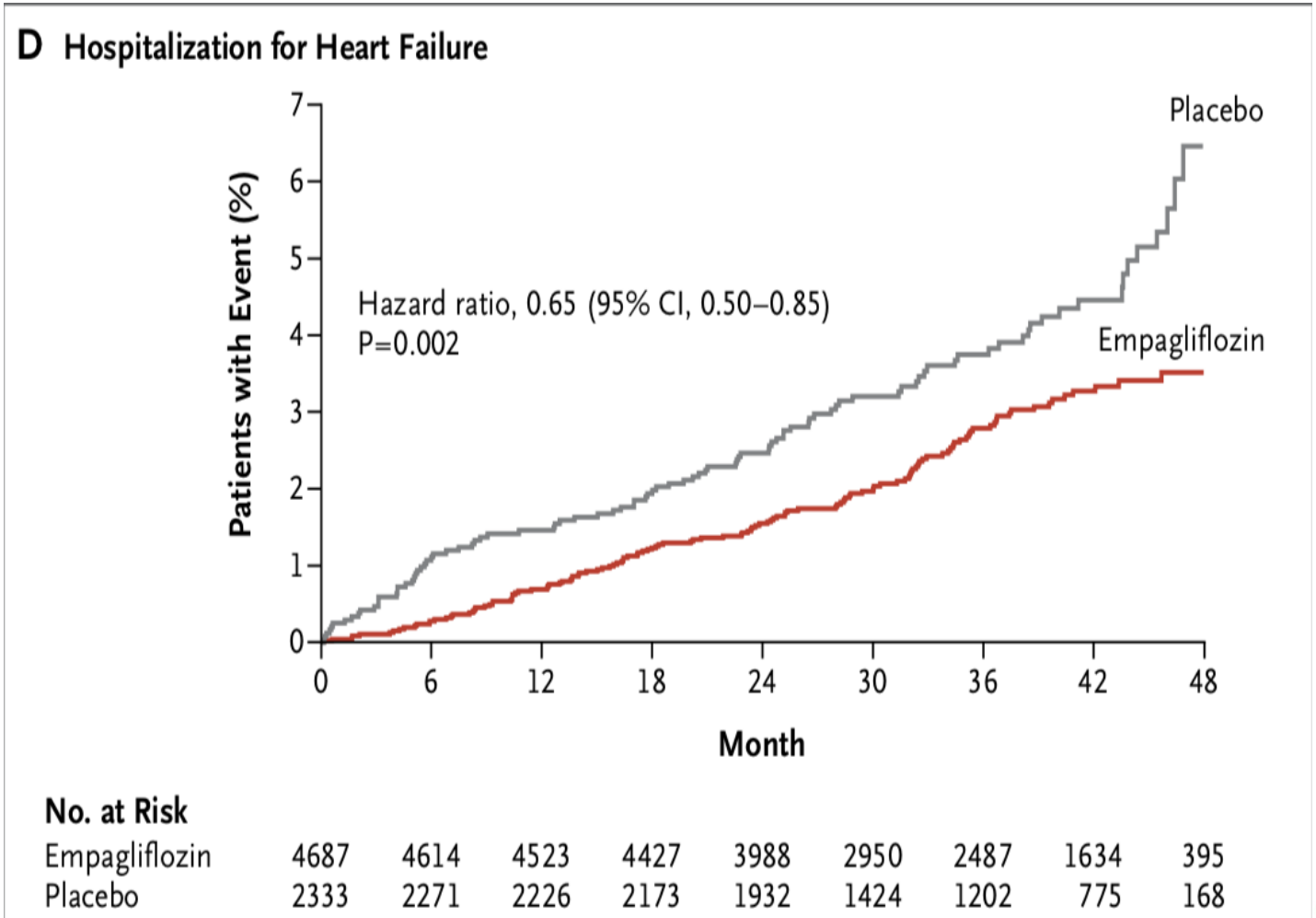
Prevalence & Pathophysiology: DM and HF

- Diabetes is associated with increased incidence of Heart Failure
- 1% increase in HBA1c associated with an 8% increased risk of HF
- Diabetes associated with poor prognosis in HF regardless of LVEF
- RR of CVS death or HF hospitalisation conferred by diabetes – greater in HFpEF vs HFrEF

Circulation. 2001;103(22):2668-73.

THERAPEUTIC OPTIONS: Diabetes and HF



n engl j med 373;22

THERAPEUTIC OPTIONS: DIABETES and HF

Recommendations	Class	Level
Diabetes		
Metformin should be considered as a first-line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated.	IIa	C
Diabetes		
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B

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IRON DEFICIENCY AND HEART FAILURE

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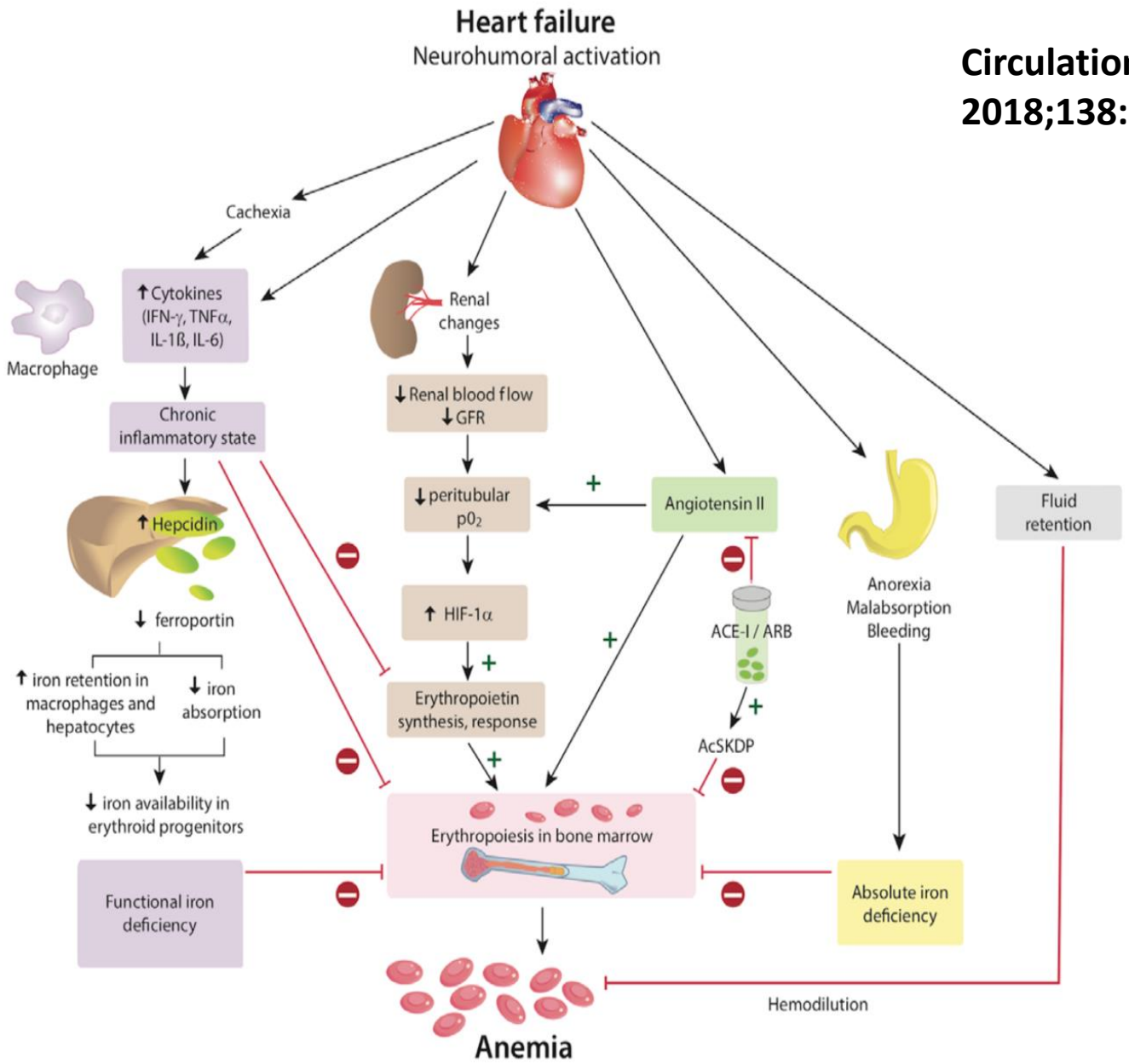
Prevalence & Pathophysiology: ID and HF

- ID is common in HF
- ID associated with worse prognosis
- Patients with ID need to be screened for reversible or treatable causes.
- Treatment with Ferric Carboxymaltose improves:
  - Symptoms
  - Exercise capacity
  - Quality of Life
  - Reduction in hospitalisations for worsening HF

Eur Heart J. 2016;37(27):2129-200.

Pathogenesis of Anaemia in Heart Failure



Circulation. 2018;138:80–98

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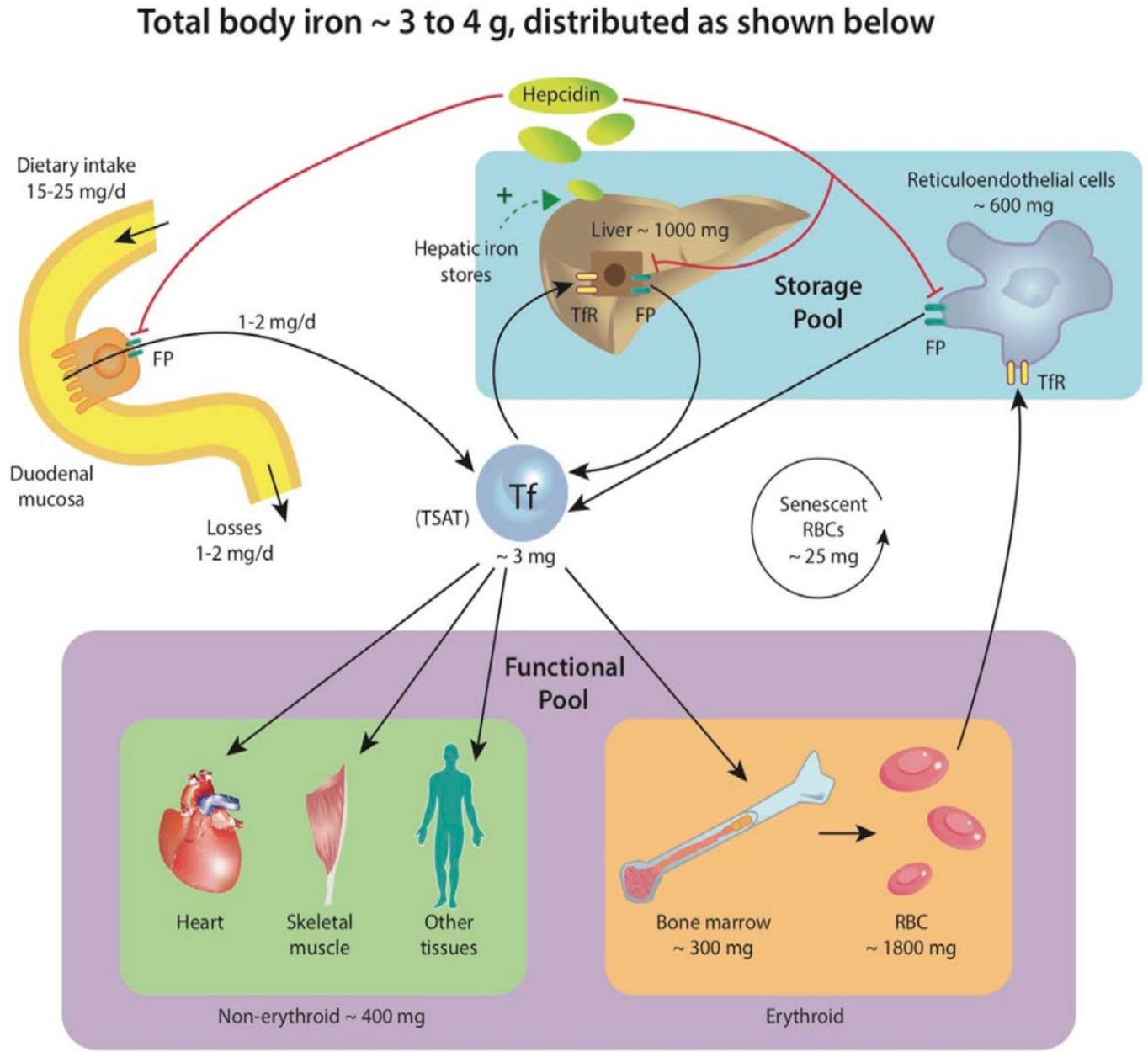
Normal Iron Metabolism and Homeostasis



Circulation. 2018;138:80–98

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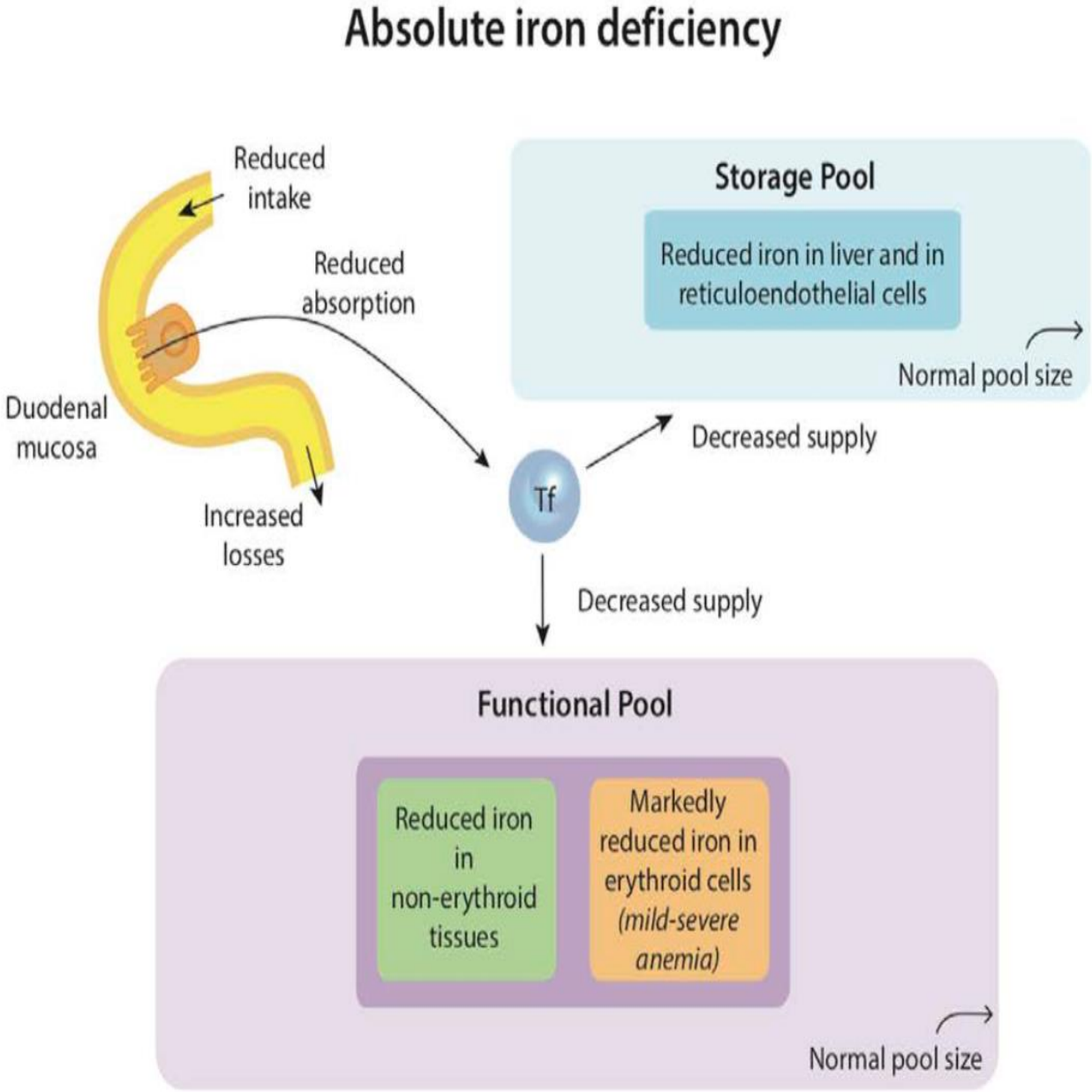
Absolute Iron Deficiency



Circulation. 2018;138:80–98

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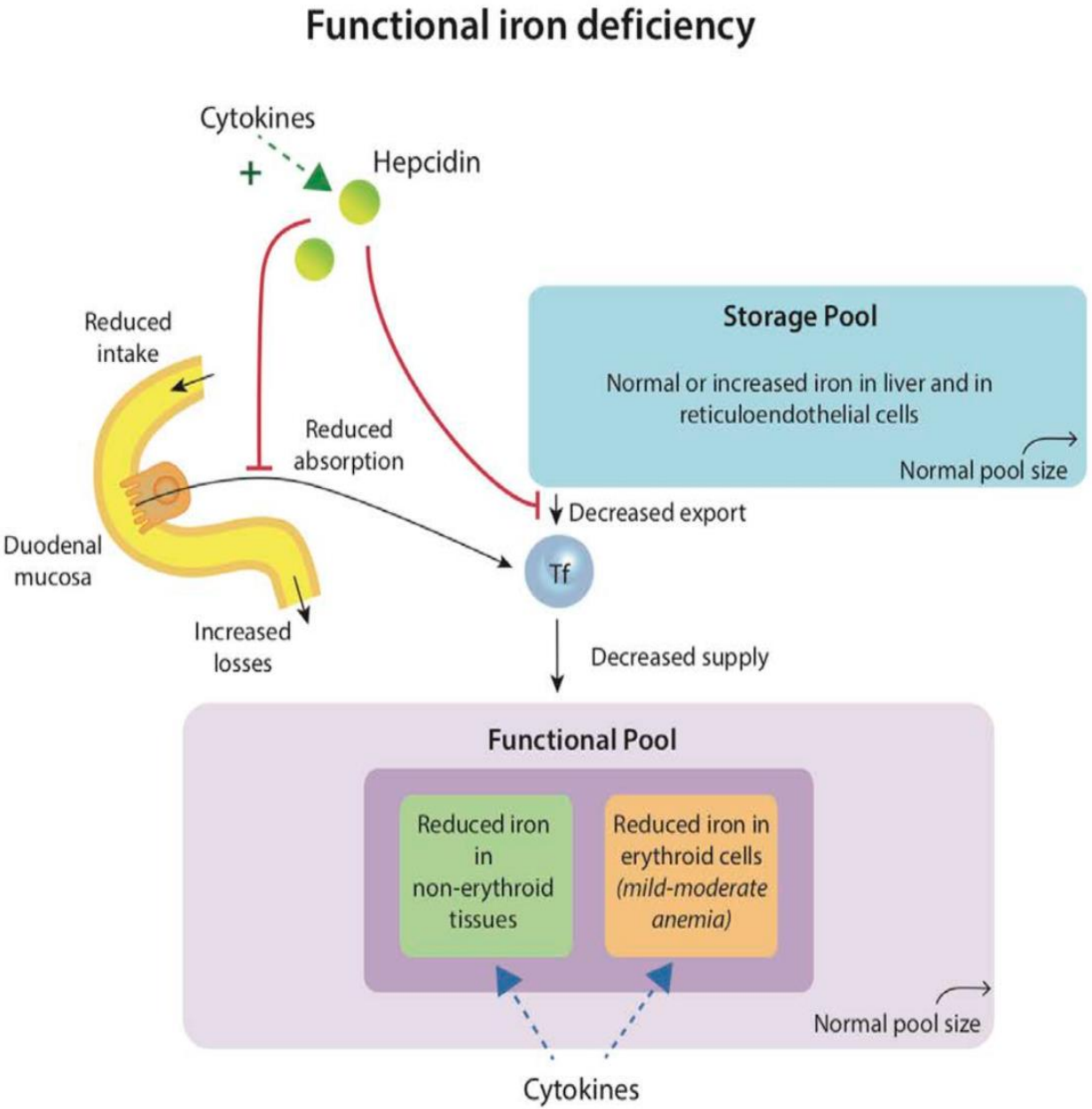
Functional Iron Deficiency



Circulation. 2018;138:80–98

Laboratory tests available for the diagnosis of ID

Parameter	Normal Range*	Absolute Iron Depletion Without Anemia	Absolute ID With Anemia	Functional ID Without or With Anemia	Sensitivity, %†	Specificity, %†
Bone marrow iron stores	Normal	Absent from both erythroid progenitors and reticuloendothelial cells	Absent from both erythroid progenitors and reticuloendothelial cells	Low in erythroid progenitors, normal in reticuloendothelial cells	Gold standard	
Hemoglobin, g/dL	M: 13.5–17.5; F: 12.0–15.5	N	↓/↓↓	N /↓	Poor	Poor
Mean red cell volume, fL	M: 81–95; F: 82–98	N /↓	↓/↓↓	N /↓	Poor	88.3
Ferritin, µg/L	M: 24–336; F: 11–307	≈20	<15–30	N /↑	35–48	75–100
Serum iron, µg/dL‡	M: 50–150; F: 35–145	↓	↓	↓	Poor	Poor
Total iron binding capacity, µg/dL, or transferrin, mg/dL	250–400; 200–360	N	↑	N /↓	Poor	Poor
TSAT, %‡	≈15–50	≈30	<15	N /↓	59–88	63–78
sTfR, mg/L§‖	1.8–4.6	↑	↑↑	↓	70–81	59–71
sTfR:log(ferritin) ratio‖	≤1.03[66]	↑	↑↑	↑	81	83
Hepcidin, ng/mL‖[67]	M: 29–254; F: 17–286	N	↓	↑	50–92.5	85–90
ZPP, µmol ZPP/mol heme‖[68]	<70	↑	↑	↑	38	87
Hypochromic RBC, %	<2.5	N /↑	↑	N /↑	64–78	77–78
CHr, pg	≈28–35	N /↓	↓	N /↓	53–78	53–100

THERAPEUTIC OPTIONS: ID and HF

Iron Preparation	Maximal Single Dose in Adults*	Administration in Adults*	Indications*	Most Common Adverse Effects	Evaluated in Heart Failure†
Ferric carboxymaltose	750 mg. Can be repeated at least 7 d later for a maximal total dose of 1500 mg per course. Courses can be repeated if ID recurs.	Slow intravenous push at 100 mg/min or diluted in normal saline and infused over at least 15 min.	Treatment of ID anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron or those who have non–dialysis-dependent chronic kidney disease.	Nausea, hypertension, flushing, hypophosphatemia, and dizziness. Warnings: hypersensitivity reactions, hypertension.	Yes
Iron sucrose	100–400 mg, depending on clinical setting. Limited experience with 500 mg. Doses can be repeated at various intervals, depending on setting. Courses can be repeated if ID recurs.	Slow intravenous injection of 100–200 mg over 2–5 min. Infusion schedules vary depending on dose and setting.	Treatment of ID anemia in patients with chronic kidney disease.	Diarrhea, nausea, vomiting, headache, dizziness, hypotension, pruritus, pain in extremity, arthralgia, back pain, muscle cramp, injection site reactions, chest pain, and peripheral edema. Warnings: hypersensitivity reactions, hypotension, iron overload.	Yes
Sodium ferric gluconate	125 mg (adults). 1.5 mg/kg (pediatric patients).	Adults: slow intravenous injection at 12.5 mg/min or diluted in normal saline and infused over 1 h per dialysis. Pediatric patients: dose diluted in normal saline and infused over 1 h per dialysis.	Treatment of ID anemia in adult patients and in pediatric patients ≥6 y of age with chronic kidney disease receiving hemodialysis who are receiving supplemental erythropoietin therapy.	Nausea, vomiting and/or diarrhea, injection site reaction, hypotension, cramps, hypertension, dizziness, dyspnea, chest pain, leg cramps and pain. In patients 6–15 y of age: hypotension, headache, hypertension, tachycardia, and vomiting. Warnings: hypersensitivity, hypotension, iron overload, benzyl alcohol toxicity.	No

THERAPEUTIC OPTIONS: ID and HF

Iron Preparation	Maximal Single Dose in Adults*	Administration in Adults*	Indications*	Most Common Adverse Effects	Evaluated in Heart Failure†
Ferumoxytol	510 mg. Second 510-mg dose 3–8 d later.	Diluted in normal saline or 5% dextrose and infused over at least 15 min.	Treatment of ID anemia in adults with chronic kidney disease.	Diarrhea, nausea, dizziness, hypotension, and constipation. Black Box warning: fatal and serious hypersensitivity reactions, including anaphylaxis.	No
Iron dextran	100 mg daily. Total dose calculated on the basis of body iron deficit.	Slow intravenous injection not to exceed 50 mg/min.	Treatment of ID anemia when oral administration is unsatisfactory or impossible.	Most common side effects not separately listed in the label. Black Box warning: fatal and serious hypersensitivity reactions, including anaphylaxis.	No
Iron isomaltoside‡	20 mg iron/kg. Cumulative dose based on Ganzoni formula.	Intravenous injection not to exceed 250 mg iron/min; dose ≤500 mg 3 times a week; diluted in normal saline. Intravenous infusion: diluted in normal saline and infused over 15 min (dose ≤1000 mg) or 30 min (dose >1000 mg).	Treatment of ID when oral iron preparations are ineffective or cannot be used or when there is a clinical need to deliver iron rapidly. Not recommended for age <18 y.	Nausea, injection site reactions. Special warnings and precautions: hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Administer with caution/avoid in patients with liver dysfunction or acute/chronic infection. Hypotension if infused too rapidly. Injection site irritation or discoloration with leakage.	No

THERAPEUTIC OPTIONS: ID and HF

Recommendations	Class [a]	Level [b]
Iron deficiency		
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A

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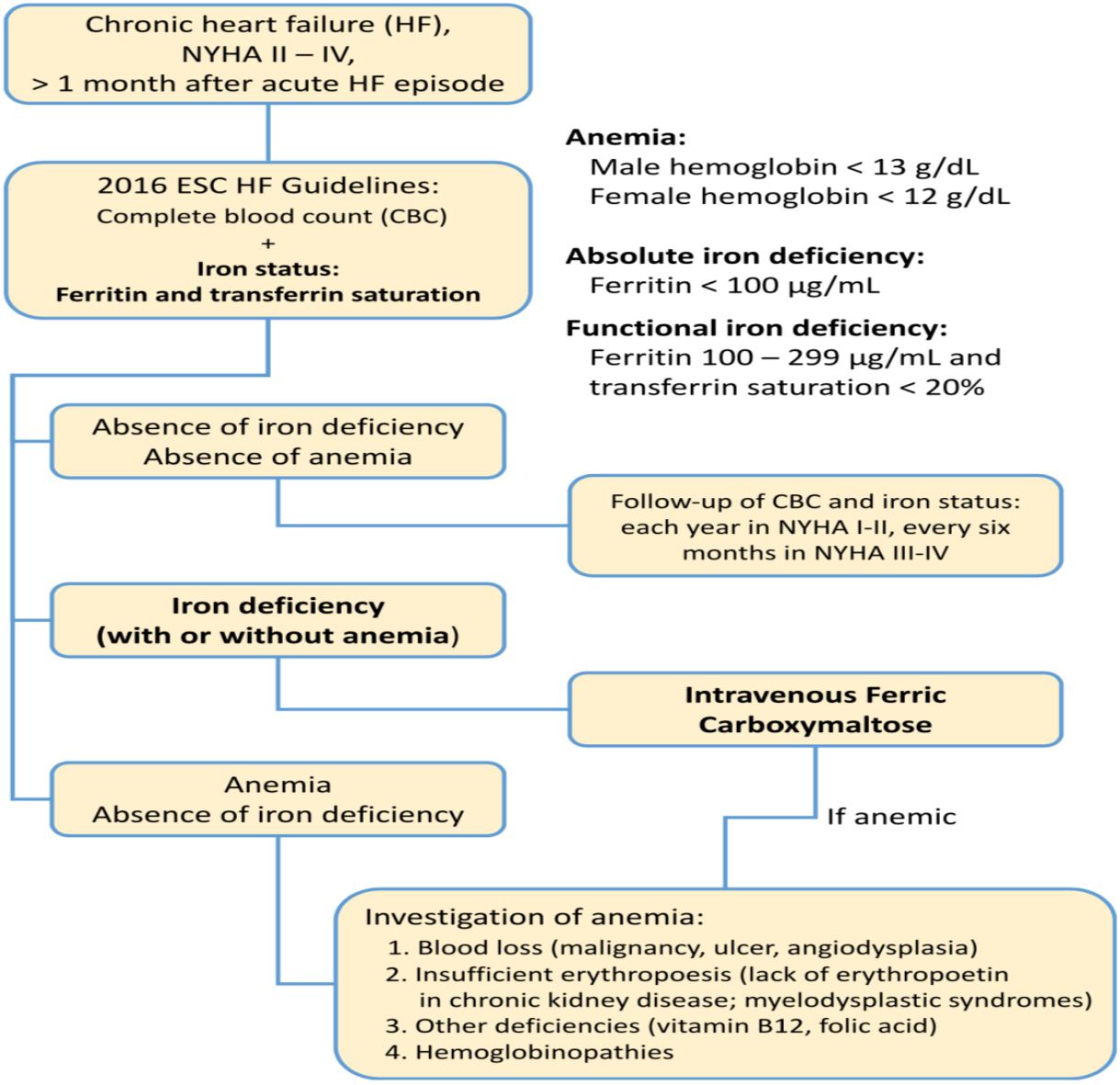
Eur Heart J. 2016;37(27):2129-200.

Treatment Algorithm for ID and HF



Curr Heart Fail Rep (2017) 14:223–234

COPD AND HEART FAILURE

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Prevalence & Pathophysiology: COPD and HF

- Prevalence of COPD in HF ranges up to 50%
- Seven times higher than age matched controls
- Challenging spirometry interpretation in HFpEF
- COPD associated with worse functional state and prognosis in HFrEF

Heart Fail Rev (2014)19:163-172

Prevalence & Pathophysiology: COPD and HF

- Diagnosis of COPD & asthma difficult in HF
- Overlap of symptoms & signs
- Smoking and inflammation are common risk factors in both conditions

Eur Heart J. 2016;37 (27):2129-200.

THERAPEUTIC OPTIONS: COPD and HF

- B-Blockers relatively contraindicated in asthma
- B-Blockers absolute CI in COPD
- B1 selective adrenoceptor antagonists preferred (Bisoprolol, Metoprolol succinate or Nebivolol)
- Oral corticosteroids cause sodium and water retention – may lead to worsening HF
- Pulmonary HPT – may complicate COPD causing features of RHF
- CPAP improves outcomes in acute respiratory failure due to hypercapnic exacerbation of COPD or HF in acute pulmonary oedema

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THERAPEUTIC OPTIONS: COPD and HF

- Beta-agonist may be harmful in HF patients
- New long-acting beta2-agonist (Indacaterol) more effective & safer CVS profile
- Long acting anticholinergic bronchodilator (tiotropium) equally effective
- Tiotropium preferred long-acting bronchodilator in patients with COPD and Heart Failure
- Theophylline is not recommended in patients with Heart Failure

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European Journal of Heart Failure (2016) 18, 744–758

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THANK YOU

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