Heart failure

Introduction

- Heart failure is a clinical syndrome that evolves from either functional or structural changes to the ventricles that lead to filling or ejection abnormalities.
- Most common cause is impaired left ventricular myocardial function
- Disorders of the pericardium, myocardium, endocardium, heart valves or vessels can also cause heart failure.

Raj L et al. Postgrad Med J. 2016 ;92(1094):726-734.

Classification

- **Based on location of deficit:** predominantly left ventricular, right ventricular or biventricular
- **Depending on the time of onset:** acute or chronic.
- **Clinically based on the functional status of heart**: heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF).

Inamdar AA et al. J Clin Med. 2016 Jun 29;5(7).

Clinical classification: functional status of heart

Classification	EF (%)	Description
I. Heart failure with reduced ejection fraction (HF*r*EF)	≤40	Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HF*r*EF, and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart failure with preserved ejection fraction (HF*p*EF)	≥50	Also referred to as diastolic HF. Several different criteria have been used to further define HF*p*EF. The diagnosis of HF*p*EF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HF*p*EF, borderline	41 to 49	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HF*p*EF.
b. HF*p*EF, improved	>40	It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

EF indicates ejection fraction; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; and HF*r*EF, heart failure with reduced ejection fraction

Yancy CW et al. Circulation. 2013 ;128(16):1810-52

NYHA Classification of heart failure

- Class I: HF does not cause limitations to physical activity; ordinary physical activity does not cause symptoms.
- Class II: HF causes slight limitations to physical activity; the patients are comfortable at rest, but ordinary physical activity results in HF symptoms.
- Class III: HF causes marked limitations of physical activity; the patients are comfortable at rest, but less than ordinary activity causes symptoms of HF.
- Class IV: HF patients are unable to carry on any physical activity without HF symptoms or have symptoms when at rest.

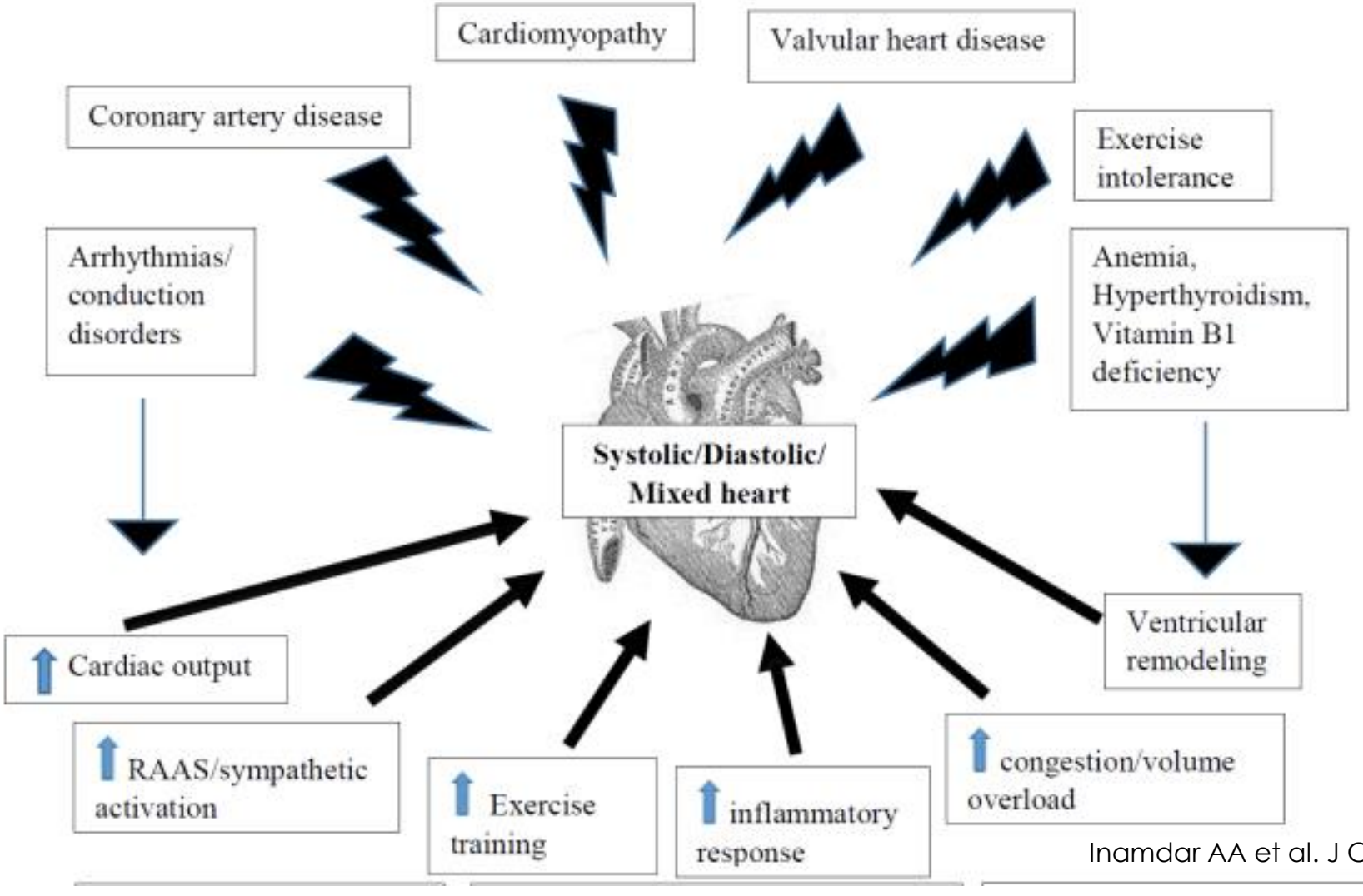
Inamdar AA et al. J Clin Med. 2016 Jun 29;5(7).

American Heart Association (ACC/AHA) staging of heart failure

- Stage A: High risk of heart failure, but no structural heart disease or symptoms of heart failure
- Stage B: Structural heart disease, but no symptoms of heart failure
- Stage C: Structural heart disease and symptoms of heart failure
- Stage D: Refractory heart failure requiring specialized interventions

Inamdar AA et al. J Clin Med. 2016 Jun 29;5(7).

Pathogenesis of heart failure



Inamdar AA et al. J Clin Med. 2016 ;5(7):1-28

Etiology of heart failure

DISEASED MYOCARDIUM		
Ischaemic heart disease	Myocardial scar	
	Myocardial stunning/hibernation	
	Epicardial coronary artery disease	
	Abnormal coronary microcirculation	
	Endothelial dysfunction	
Toxic damage	Recreational substance abuse	Alcohol, cocaine, amphetamine, anabolic steroids.
	Heavy metals	Copper, iron, lead, cobalt.
	Medications	Cytostatic drugs (e.g. anthracyclines), immunomodulating drugs (e.g. interferons monoclonal antibodies such as trastuzumab, cetuximab), antidepressant drugs, antiarrhythmics, non-steroidal anti-Inflammatory drugs, anaesthetics.
	Radiation	
Immune-mediated and inflammatory damage	Related to infection	Bacteria, spirochaetes, fungi, protozoa, parasites (Chagas disease), rickettsiae, viruses (HIV/AIDS).
	Not related to infection	Lymphocytic/giant cell myocarditis, autoimmune diseases (e.g. Graves' disease, rheumatoid arthritis, connective tissue disorders, mainly systemic lupus erythematosus), hypersensitivity and eosinophilic myocarditis (Churg–Strauss).
Infiltration	Related to malignancy	Direct infiltrations and metastases.
	Not related to malignancy	Amyloidosis, sarcoidosis, haemochromatosis (iron), glycogen storage diseases (e.g. Pompe disease), lysosomal storage diseases (e.g. Fabry disease).

Ponikowski P et al. European Heart Journal;2016.37(27):

Etiology of heart failure

DISEASED MYOCARDIUM		
Metabolic derangements	Hormonal	Thyroid diseases, parathyroid diseases, acromegaly, GH deficiency, hypercortisolaemia, Conn's disease, Addison disease, diabetes, metabolic syndrome, phaeochromocytoma, pathologies related to pregnancy and peripartum.
	Nutritional	Deficiencies in thiamine, L-carnitine, selenium, iron, phosphates, calcium, complex malnutrition (e.g. malignancy, AIDS, anorexia nervosa), obesity.
Genetic abnormalities	Diverse forms	HCM, DCM, LV non-compaction, ARVC, restrictive cardiomyopathy (for details see respective expert documents), muscular dystrophies and laminopathies.
ABNORMAL LOADING CONDITIONS		
Hypertension		
Valve and myocardium structural defects	Acquired	Mitral, aortic, tricuspid and pulmonary valve diseases.
	Congenital	Atrial and ventricular septum defects and others (for details see a respective expert document).
Pericardial and endomyocardial pathologies	Pericardial	Constrictive pericarditis Pericardial effusion
	Endomyocardial	HES, EMF, endocardial fibroelastosis.
High output states		Severe anaemia, sepsis, thyrotoxicosis, Paget's disease, arteriovenous fistula, pregnancy.
Volume overload		Renal failure, iatrogenic fluid overload.
ARRHYTHMIAS		
Tachyarrhythmias		Atrial, ventricular arrhythmias.
Bradyarrhythmias		Sinus node dysfunctions, conduction disorders.

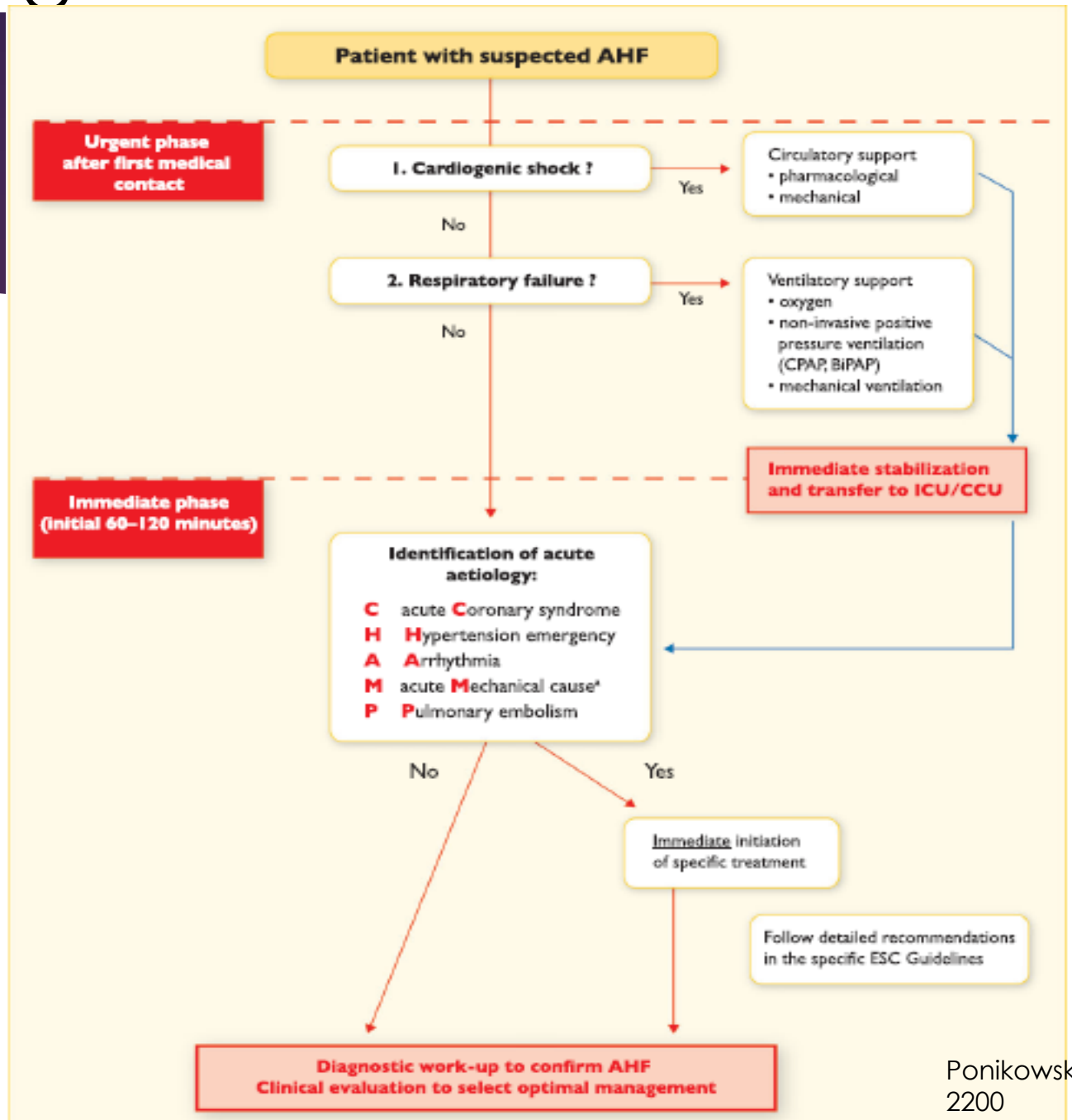
Ponikowski P et al. European Heart Journal;2016.37(27):

Symptoms and signs of acute heart failure

Symptoms	Signs
Typical	**More specific**
Breathlessness Orthopnoea Paroxysmal nocturnal dyspnoea Reduced exercise tolerance Fatigue, tiredness, increased time to recover after exercise Ankle swelling	Elevated jugular venous pressure Hepatojugular reflux Third heart sound (gallop rhythm) Laterally displaced apical impulse
Less typical	**Less specific**
Nocturnal cough Wheezing Bloated feeling Loss of appetite Confusion (especially in the elderly) Depression Palpitations Dizziness Syncope Bendopnea[53]	Weight gain (>2 kg/week) Weight loss (in advanced HF) Tissue wasting (cachexia) Cardiac murmur Peripheral oedema (ankle, sacral, scrotal) Pulmonary crepitations Reduced air entry and dullness to percussion at lung bases (pleural effusion) Tachycardia Irregular pulse Tachypnoea Cheyne Stokes respiration Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure

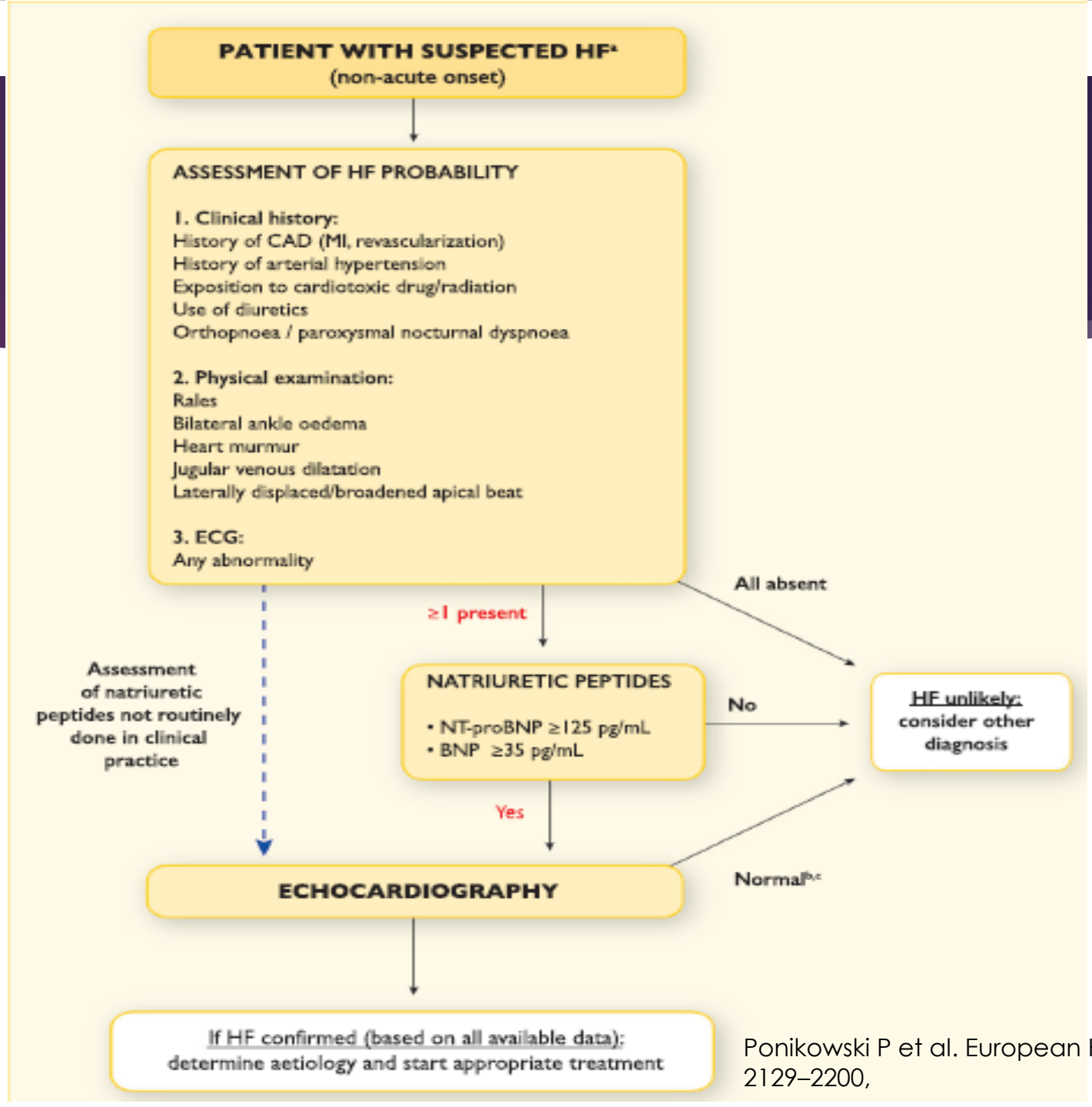
Ponikowski P et al. European Heart Journal;2016.37(27): 2129–2200,

Management of Acute heart failure



Ponikowski P et al. European Heart Journal;2016.37(27): 212
2200

Diagnostic algorithm for heart failure



Ponikowski P et al. European Heart Journal;2016.37(27): 2129–2200,

Investigations

- Complete blood count
- Serum electrolytes (sodium, potassium, etc.)
- Renal function test
- Liver function test
- Blood glucose (fasting plasma glucose and postprandial plasma glucose)
- Glycosylated hemoglobin (HbA1c)
- Lipid profile
- Thyroid function test
- Iron profile—serum iron, total iron-binding capacity, ferritin and folate

Mishra S et al. Indian Heart J. 2018 Jan - Feb;70(1):105-127

ECG findings

- Helps to understand the etiology of the disease e.g., presence of ST-segment deviation, T-wave inversion or pathologic Q-waves might indicate the presence of CAD
- Provides information about the prognosis of the disease
- Helps understand the indications for therapy, e.g., anticoagulation for AF, pacing for bradycardia etc.
- Indicates presence of ventricular tachyarrhythmia

CAD = coronary artery disease; AF = atrial fibrillation

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Chest X ray findings

- Enhanced cardiothoracic ratio
- Presence of pulmonary venous congestion or pulmonary edema
- Presence of pleural effusion
- Lung abnormalities
- LA and pulmonary artery enlargement
- Kerley B lines

LA = left atrial

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Echocardiography findings

- Enlargement of heart chambers
- LVEF
- Grade of diastolic dysfunction
- Presence and severity of mitral regurgitation and tricuspid regurgitation
- Functional mitral regurgitation
- Estimation of pulmonary artery pressure
- LA volume index
- Global longitudinal strain
- IVC diameter and collapsibility
- Pericardial effusion and pleural effusion
- Other structural abnormalities such as aneurysm, scar, thrombus, etc.
- LVEF = left ventricular ejection fraction;

LA = left atrial; IVC = inferior vena cava

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Biomarkers in heart failure

Myocardial Stress	Myocardial Injury	Matrix and Cellular Remodeling	Inflammation	Oxidative Stress	Neuro-Hormones	Vascular System	Cardio-Renal Syndrome
Natriuretic	Cardiac troponins	Osteopontin	C-reactive protein	Oxidized LDL	Nor-epinephrine	Homocysteine	Creatinine
peptides	High sensitivity cardiac troponins	Galectin-3	sST2	Myeloperoxidase	Renin	Adhesion molecules	Cystatin C
Mid-regional	Myosin light-chain kinase 1	sST2	Tumor necrosis factor	Urinary biopyrrins	Angiotensin-II	ICAM, P-selectin	NGAL
Pro-adrenomedullin	Heart-type fatty acid binding protein	GDF-15	FAS (APO-1)	Urinary and plasma isoprostanes	Co-peptin	Endothelin	Trace protein
Neuregulin	Pentraxin 3	MMPs	GDF-15	Plasma malondialdehyde	Endothelin	Adiponectin	
sST2		TIMPs	Pentraxin 3			C-type natriuretic peptide	
		Collagen propeptides	Adipokines				
			cytokines				
			Procalcitonin				
			Osteoprotegerin				

APO: apoptosis antigen; GDF: growth differentiation factor; ICAM: intercellular adhesion molecule; MMPs: matrix metalloproteinases; NGAL: neutrophil gelatinase-associated lipocalin; sST2: soluble ST2; TIMPs: matrix metalloproteinase tissue inhibitors

Ahmad T et al. Nat. Rev. Cardiol. 2012, 9, 347–359

Indications of biomarkers in heart failure

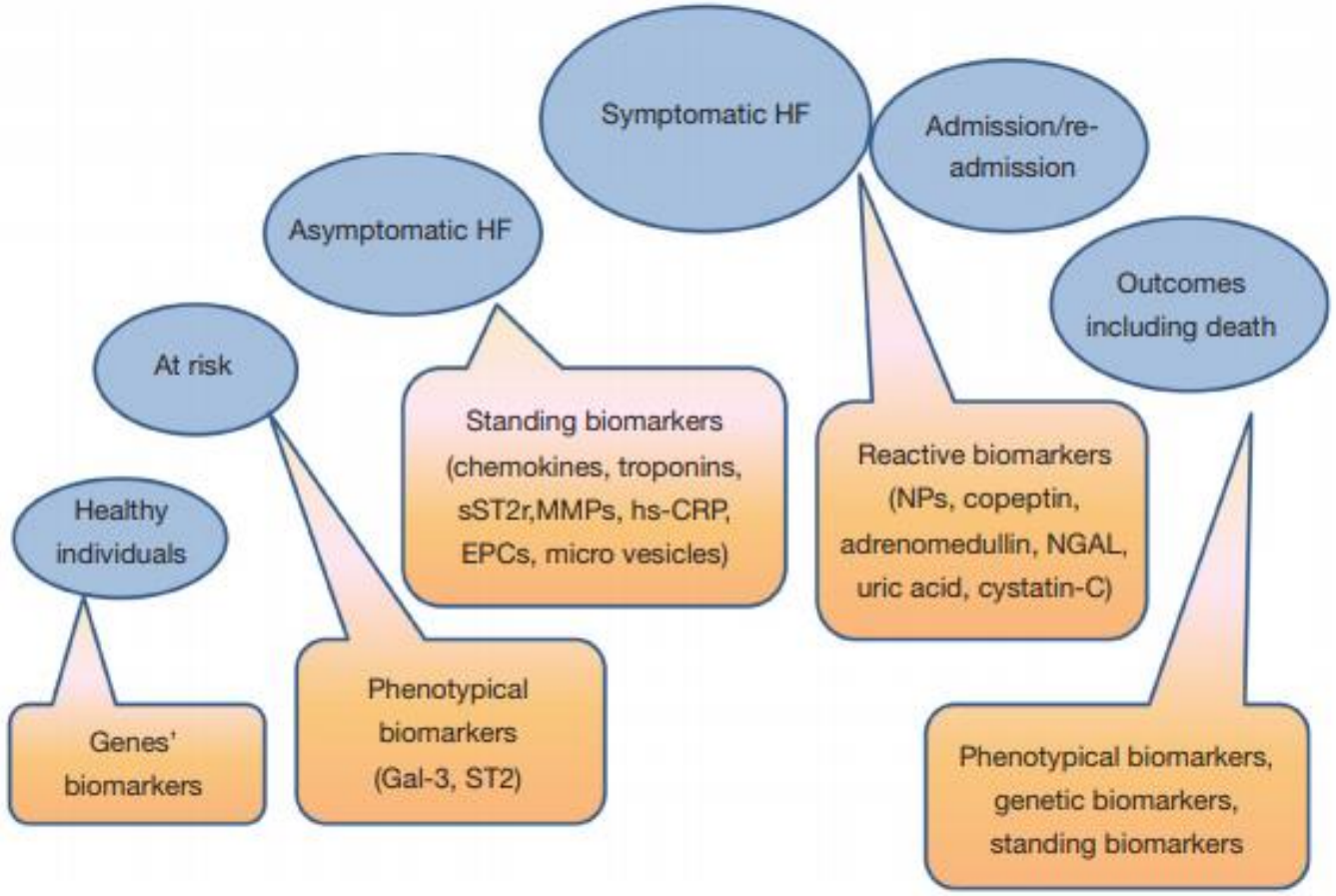
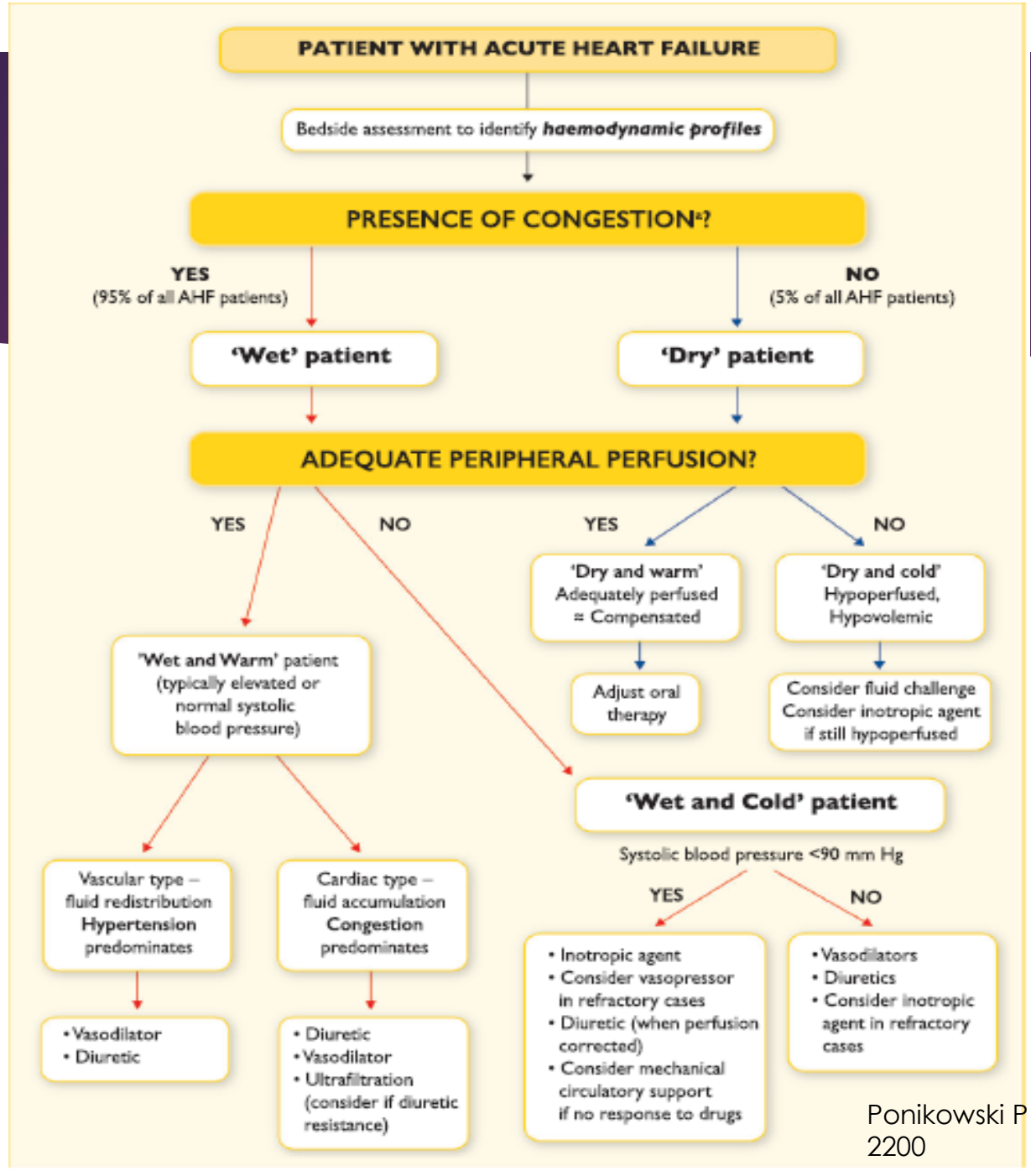


Figure Indications for biomarker use in heart failure (HF) management. ADHF, actually decompensated heart failure; pts, patients; Gal-3, galectin-3; NT-proBNP, NT-pro-brain natriuretic peptide; BNP, brain natriuretic peptide; TrT, troponin T; TrI, troponin I; sST2, soluble suppressor of tumorigenicity-2 receptor.

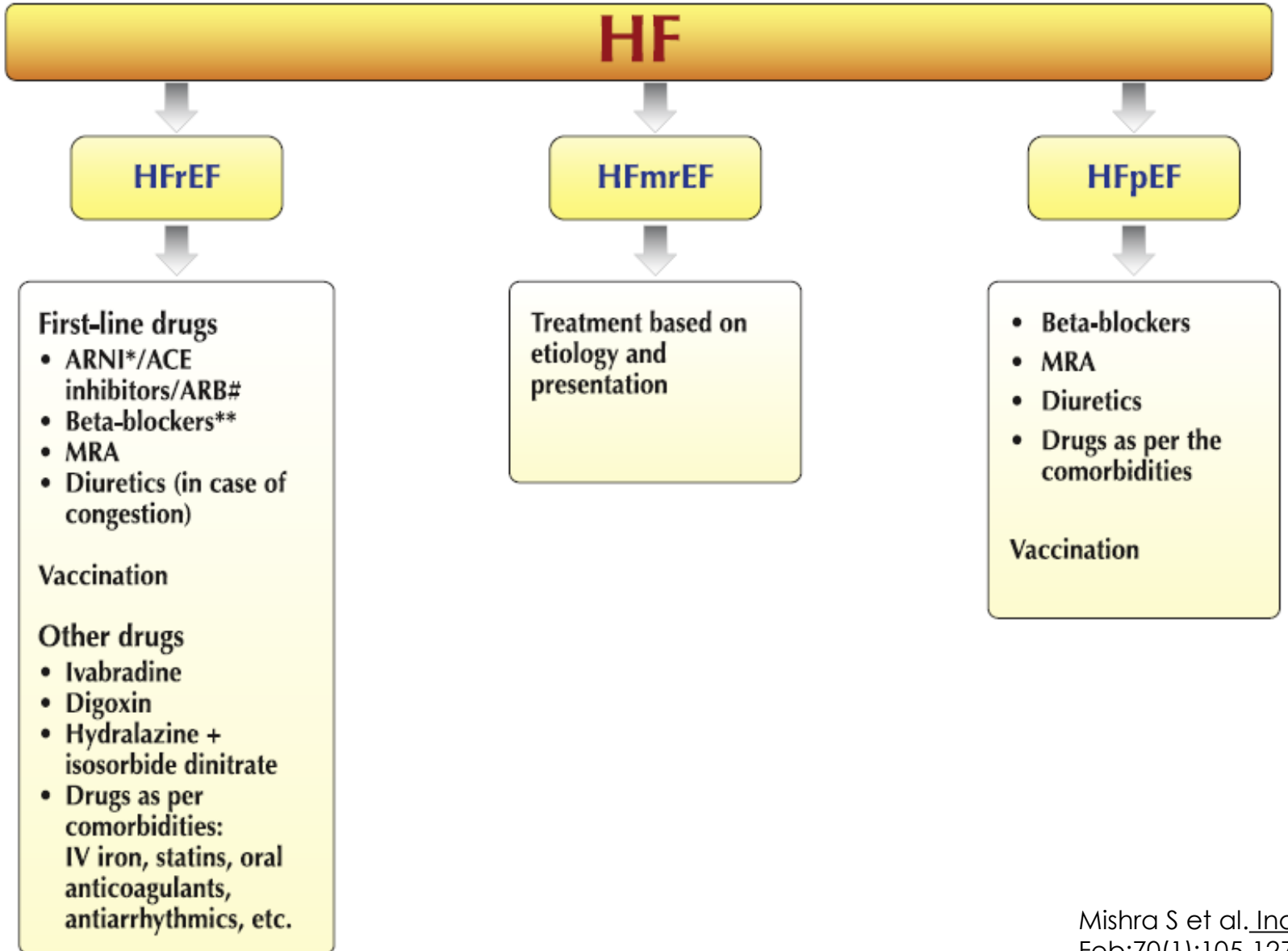
Berezin AE et al. J Lab Precis Med 2018;3:36:1-18.

Management of Acute heart failure based on Clinical profile



Ponikowski P et al. European Heart Journal;2016.37(27): 2129-2200

Management of patients with Heart failure



ARNI = angiotensin II receptor blocker neprilysin inhibitor;
MRA = mineralocorticoid receptor antagonist;
ACE = angiotensin converting enzyme,
ARB = angiotensin II receptor blocker

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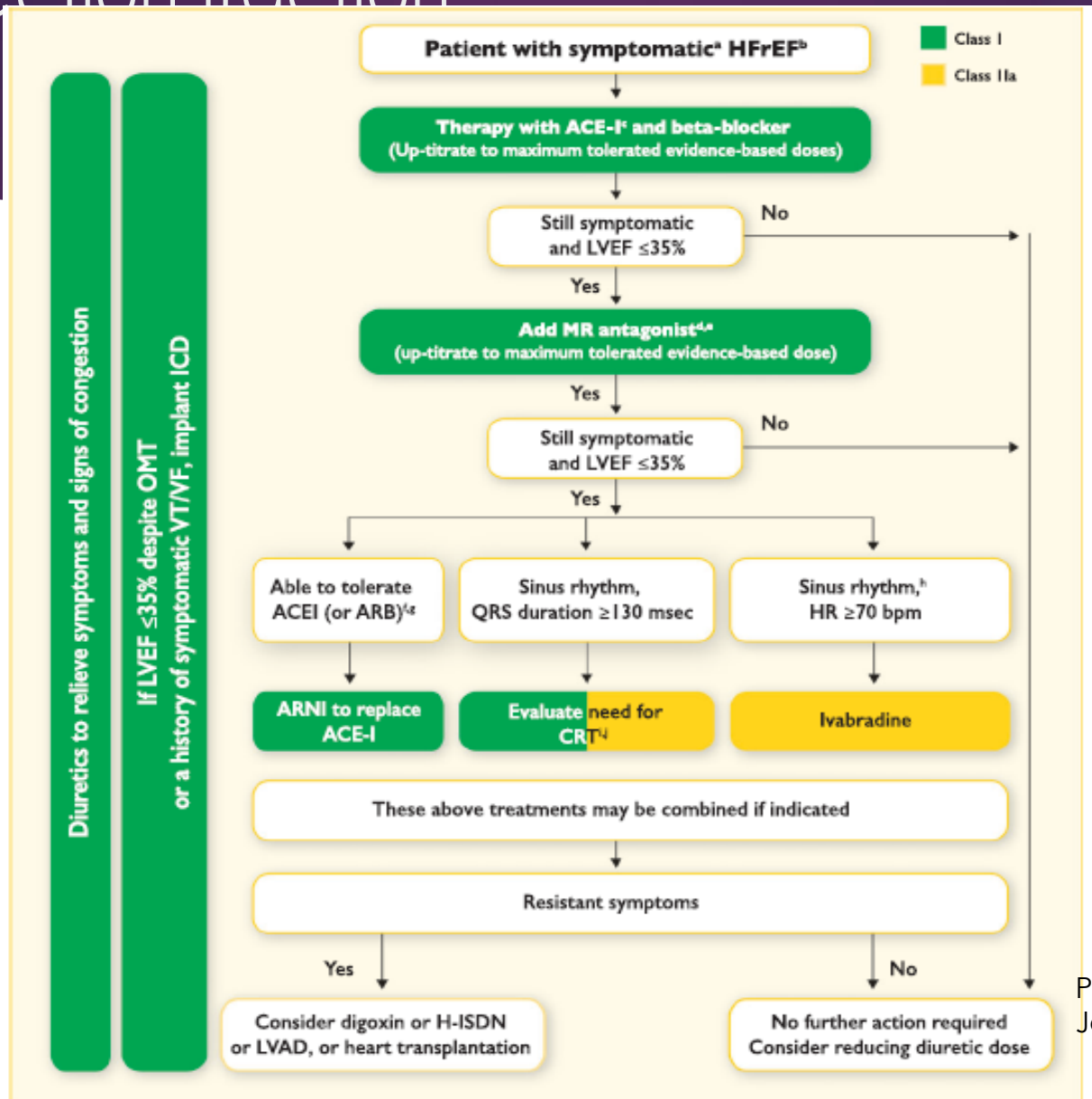
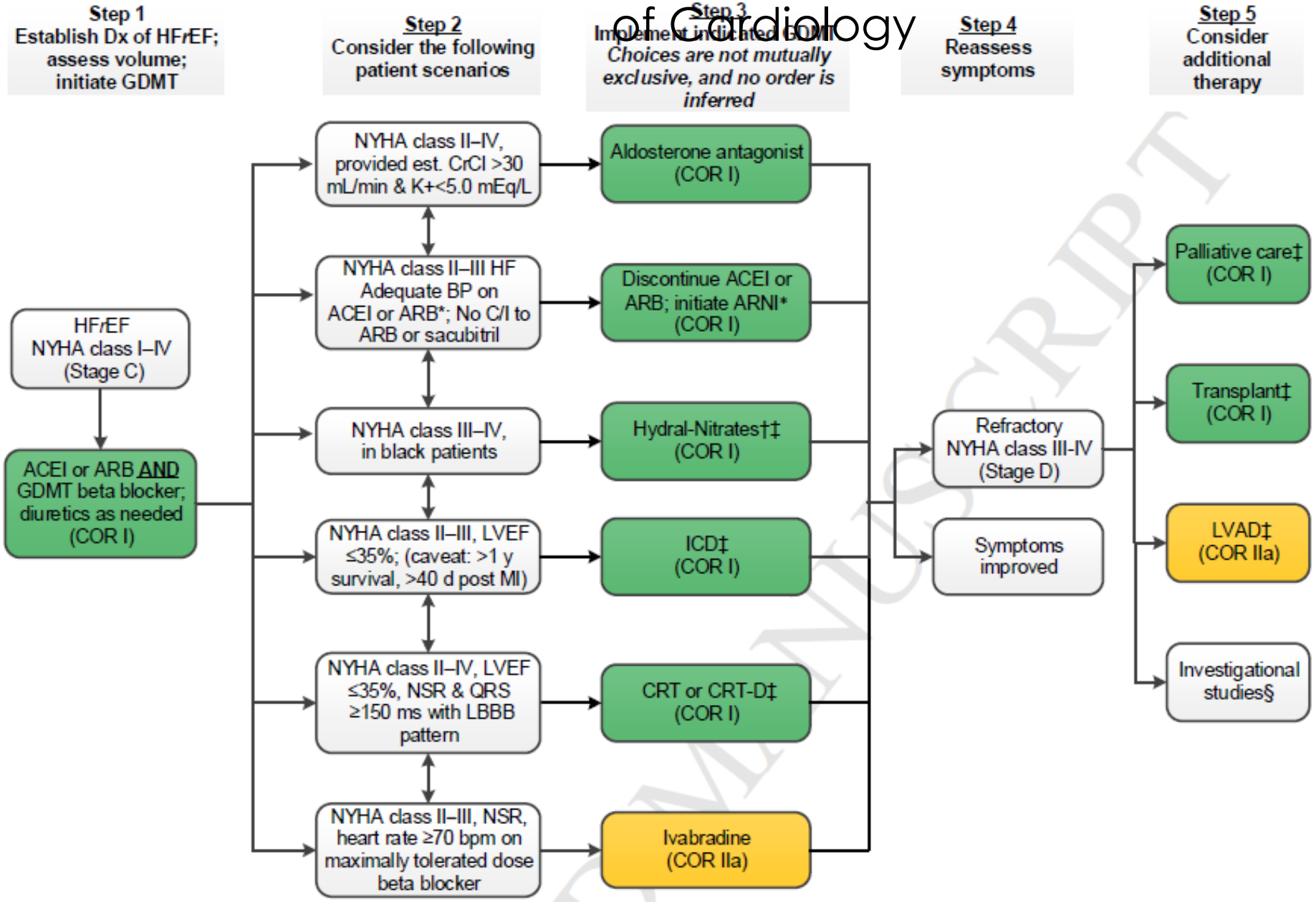
Therapeutic Algorithm for symptomatic HFrEF(heart failure with reduced ejection fraction



Ponikowski P et al. European Heart Journal;2016.37(27): 2129–2200

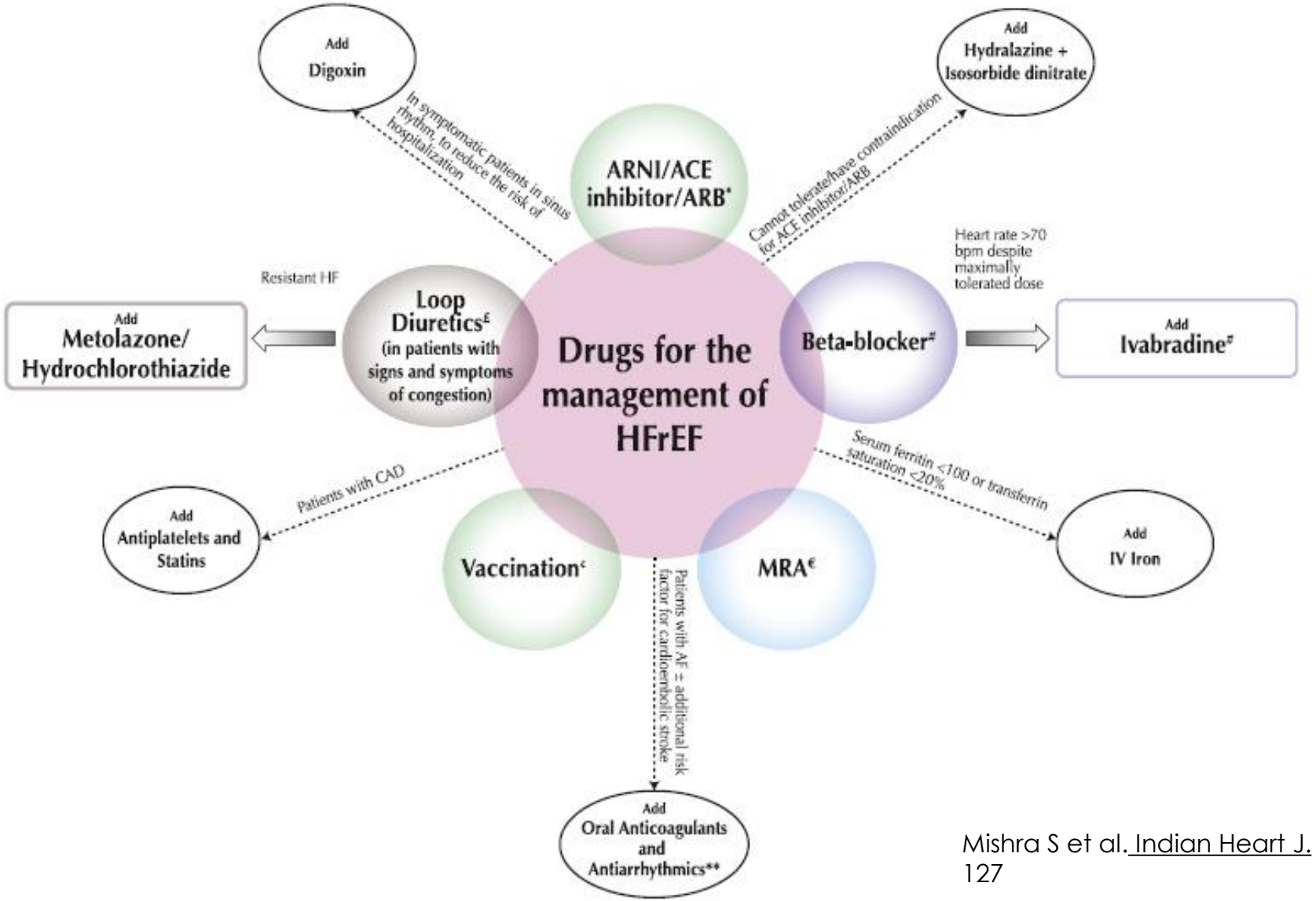
Management of Acute heart failure based on Class by American college of Cardiology



Yancy CW et al. J Am Coll Cardiol. 2017 Aug 8;70(6):776-803.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor-blocker; ARNI, angiotensin receptor-neprilysin inhibitor; C/I, contraindication; COR, Class of Recommendation; CrCl, creatinine clearance; CRT-D, cardiac resynchronization therapy–device; GDMT, guideline-directed management and therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ISDN/HYD, isosorbide dinitrate hydral-nitrates; LBBB, left bundle-branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSR,

Management of heart failure



HFrEF = heart failure with reduced ejection fraction; ARNI = angiotensin receptor neprilysin inhibitor; ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; MRA = mineralocorticoid receptor antagonist; IV = intravenous; AF = atrial fibrillation; CAD = coronary artery disease; HF = heart failure

Mishra S et al. Indian Heart J. 2018 Jan - Feb;70(1):105-127

Heart failure treatment with mechanism

Drug	Indications	Mechanism	Adverse effects	Precautions
ACE inhibitors	First-line therapy when LVEF <40%	Reduces vasoconstriction Reduces sodium reabsorption Reduces aldosterone	Hypotension Worsening renal function Hyperkalaemia Chronic cough Angioedema	Previous angioedema Other drugs that increase potassium
Angiotensin receptor antagonists (sartans)	If intolerant of ACE inhibitors	Reduces vasoconstriction Reduces sodium reabsorption Reduces aldosterone	Hypotension Worsening renal function Hyperkalaemia	Other drugs that increase potassium
Beta blockers	First-line therapy when LVEF <40%	Reduces sympathetic activity Has antiarrhythmic effects Reverses remodelling	Hypotension Bradycardia Fatigue Bronchospasm Impotence Worsening heart failure Masking hypoglycaemia	2nd and 3rd degree heart block Asthma Chronic obstructive pulmonary disease – exclude significant reversibility
Aldosterone antagonists	If symptomatic despite ACE inhibitor and beta blocker and LVEF <40%	Is a weak diuretic Reduces effects of aldosterone	Hyperkalaemia Worsening renal function Hypotension Gynaecomastia (spironolactone)	Other drugs that increase potassium

Hopper I et al.Aust Prescr 2017;40:128–36

Heart failure treatment with mechanism

Drug	Indications	Mechanism	Adverse effects	Precautions
Sacubitril with valsartan	Heart failure LVEF <35% In place of ACE inhibitor or angiotensin receptor antagonist	Causes vasodilation Reduces sympathetic activity Enhances diuresis	Angioedema Hypotension	Previous angioedema A 36-hour ACE inhibitor washout is an absolute requirement before starting
Diuretics	Relief of congestive symptoms	Reduces retention of sodium and water	Renal dysfunction Hypokalaemia Worsened gout	Other drugs that lower potassium
Ivabradine	Heart rate 77 beats/min or higher despite beta blocker, or intolerant to beta blocker Sinus rhythm	Reduces heart rate in sinus rhythm	Visual disturbances (phosphenes) Headache Bradycardia Atrial fibrillation	3rd degree atrioventricular block Sinoatrial block Stop if atrial fibrillation develops Prolonged QT syndrome
Digoxin	Heart failure in sinus rhythm with symptoms despite ACE inhibitor, beta blocker, aldosterone antagonist, diuretic. Atrial fibrillation	Is a weak positive inotrope Reduces heart rate Increases vagal tone	Bradycardia Digoxin toxicity	Narrow therapeutic range requires monitoring Interacting drugs Impaired renal function

LVEF left ventricular ejection fraction

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Drug and dosage by American college of cardiology in heart failure

Drug	Initial Daily Dose(s)	Maximum Doses(s)
ACE inhibitors		
Captopril	6.25 mg TID	50 mg TID
Enalapril	2.5 mg BID	10–20 mg BID
Fosinopril	5–10 mg QD	40 mg QD
Lisinopril	2.5–5 mg QD	20–40 mg QD
Perindopril	2 mg QD	8–16 mg QD
Quinapril	5 mg BID	20 mg BID
Ramipril	1.25–2.5 mg QD	10 mg QD
Trandolapril	1 mg QD	4 mg QD
ARBs		
Candesartan	4–8 mg QD	32 mg QD
Losartan	25–50 mg QD	50–150 mg QD
Valsartan	20–40 mg BID	160 mg BID
ARNI		
Sacubitril/ valsartan	49/51 mg BID (sacubitril/valsartan) (therapy may be initiated at 24/26 mg BID)	97/103 mg BID (sacubitril/valsartan)

Yancy CW et al. J Am Coll Cardiol. 2017 Aug 8;70(6):776-803.

Drug and dosage by American college of cardiology in heart failure

Drug	Initial Daily Dose(s)	Maximum Doses(s)
I_f channel inhibitor		
Ivabradine	5 mg BID	7.5 mg BID
Aldosterone antagonists		
Spironolactone	12.5–25 mg QD	25 mg QD or BID
Eplerenone	25 mg QD	50 mg QD
Beta blockers		
Bisoprolol	1.25 mg QD	10 mg QD
Carvedilol	3.125 mg BID	50 mg BID
Carvedilol CR	10 mg QD	80 mg QD
Metoprolol succinate extended release (metoprolol CR/XL)	12.5–25 mg QD	200 mg QD
Isosorbide dinitrate and hydralazine		
Fixed-dose combination	20 mg isosorbide dinitrate / 37.5 mg hydralazine TID	40 mg isosorbide dinitrate / 75 mg hydralazine TID
Isosorbide dinitrate and hydralazine	20–30 mg isosorbide dinitrate / 25–50 mg hydralazine TID or QD	40 mg isosorbide dinitrate TID with 100 mg hydralazine TID

Yancy CW et al. J Am Coll Cardiol. 2017 Aug 8;70(6):776-803.

Drugs to be avoided

- Non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors should be avoided as they cause salt and water retention and impair renal function.
- Non-dihydropyridine calcium channel blockers (verapamil and diltiazem) should be strictly avoided in heart failure with reduced ejection fraction due to their negative inotropic effect.
- Antiarrhythmic drugs (except beta blockers and amiodarone) and tricyclic antidepressants have pro-arrhythmic potential.

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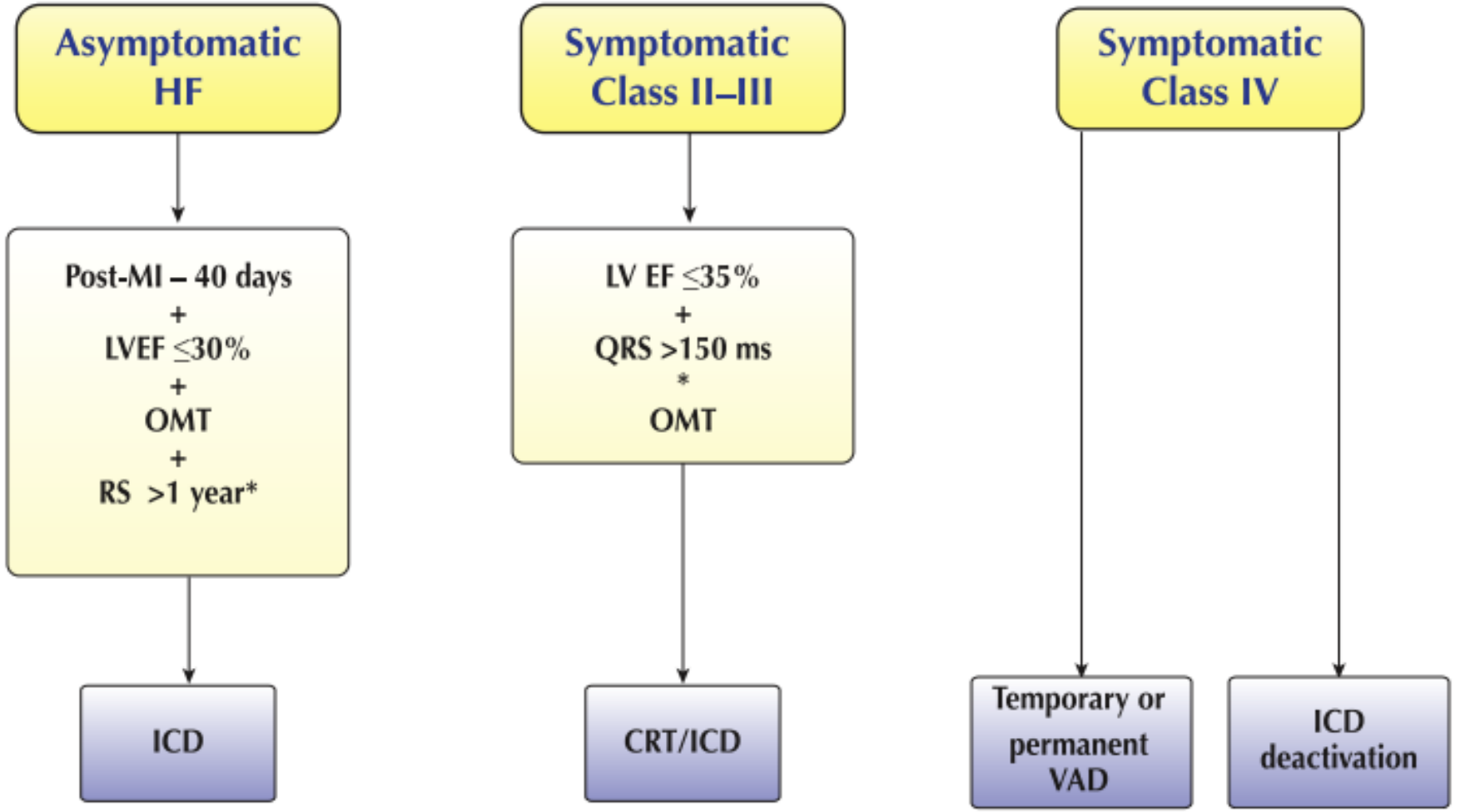
Drugs to be avoided

- Corticosteroids result in salt and water retention.
- Pioglitazone and some dipeptidyl peptidase 4 (DPP-4) inhibitors may increase the risk of heart failure.
- Non-potassium sparing diuretics can contribute to digoxin toxicity by causing hypokalaemia, and digoxin concentrations can be increased by amiodarone and spironolactone.
- Potential drug–drug interactions occur with various complementary therapies, including St John's wort, black cohosh and grapefruit juice. These should be avoided.

Hopper I et al.Aust Prescr 2017;40:128–36

Device therapy in Heart failure



*RS = Residual Survival 1 year
HF = heart failure;
MI = myocardial infarction,
LVEF = left ventricular ejection fraction, OMT = optimal medical therapy; ICD = implantable cardioverter defibrillators;
CRT = cardiac resynchronizatio

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Summary

- Despite the advancement in medicine, management of heart failure (HF), which usually presents as a disease syndrome, has been a challenge to healthcare providers.
- ACE inhibitors and beta blockers are the cornerstone of therapy for heart failure with reduced ejection fraction. Aldosterone antagonists are added if the patient is still symptomatic.
- Digoxin and diuretics may also be useful if symptoms persist.
- The combination of valsartan with sacubitril is an evolving alternative to ACE inhibitors in heart failure with reduced ejection fraction.
- Drug doses need to be titrated to maximally tolerated doses to obtain the most benefit on symptoms and survival.
- Future directions likely include more pharmacological therapies as well as gene therapy hoping to reduce fatalities and improve quality of life of these patients.