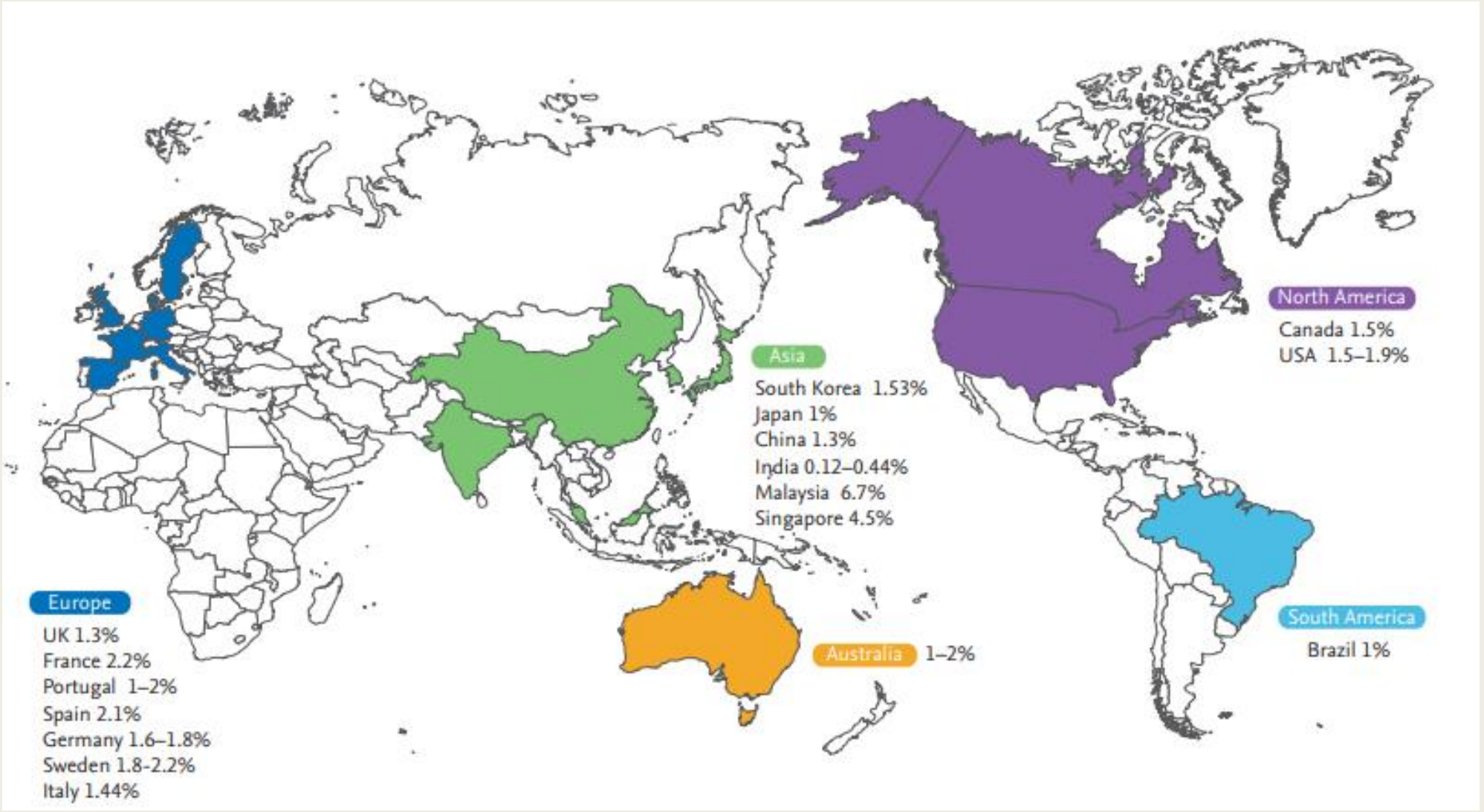
ROLE OF ARB IN HEART FAILURE

Introduction

- Heart failure is a leading and increasing cause of morbidity and mortality worldwide.
- The prevalence of heart failure is increasing worldwide because of an increasing incidence due to ageing, poorly controlled risk factors like hypertension, diabetes, and obesity.
- Delaying or preventing heart failure has become increasingly important in patients who are prone to heart failure.
- The prevention of worsening chronic heart failure and hospitalisations for acute decompensation is also of great importance

Choi HM et al. Korean J Intern Med 2019;34:11-43.
Rossignol P et al. Lancet 2019; 393: 1034–44.

Global Epidemiology of heart failure



Choi HM et al. Korean J Intern Med 2019;34:11-43.

Epidemiology in India

- The prevalence rate of HF in India is estimated to be 1% of the overall population.
- Re -hospitalization rates have increased over the years posing a major burden on public health.
- Heart failure in India has a post admission mortality of 20%–30%.
- Medication adherence ranges from 25% to 50 %.

Seth S et al. J Pract Cardiovasc Sci 2017;3:133-8.
Munusamy Vet al. J Clin Prev Cardiol 2019;8:56-63

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.

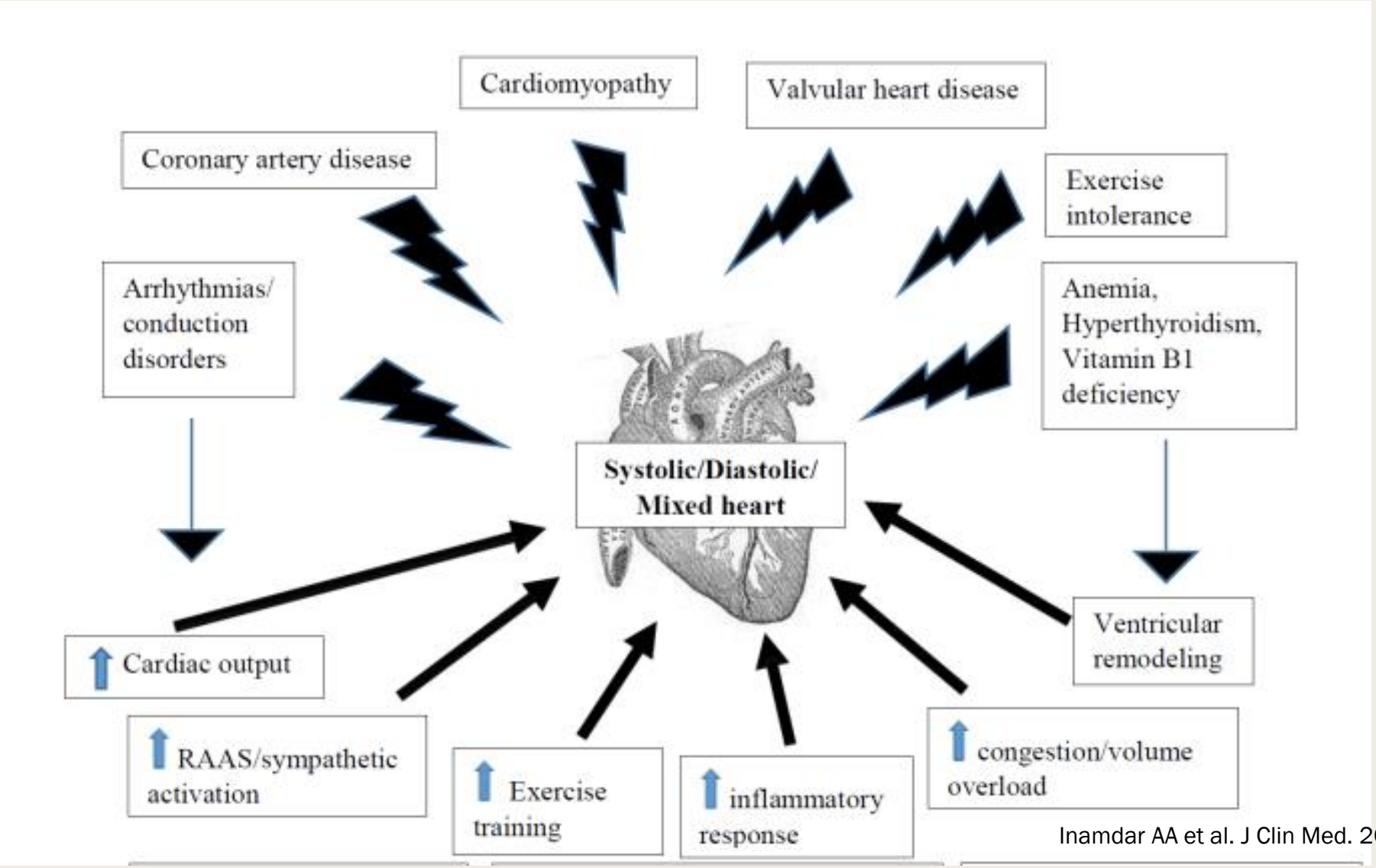
Inamdar AA et al. J Clin Med. 2016 Jun 29;5(7).

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

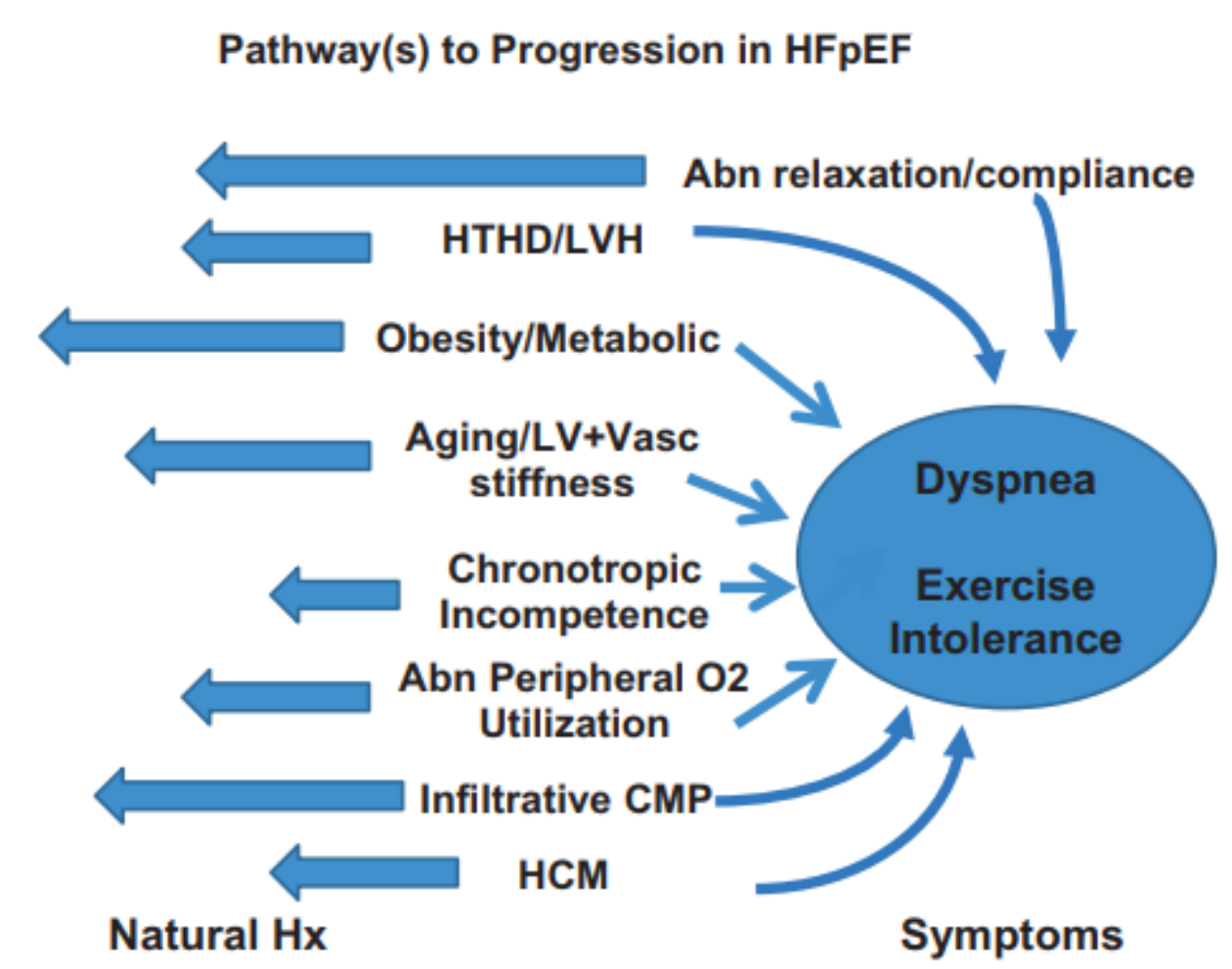
Inamdar AA et al. J Clin Med. 2016 Jun 29;5(7).

Pathogenesis of heart failure



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

Progression of heart failure



Abn indicates abnormal;
ACEi, angiotensin-converting enzyme inhibitors;
ARB, angiotensin receptor blockers; CMP, cardiomyopathy;
CV, cardiovascular;
HCM, hypertrophic cardiomyopathy;
HD, heart disease;
HFpEF, heart failure with preserved ejection fraction;
HFrEF, heart failure with reduced ejection fraction;
HTHD, hypertensive heart disease; Hx, history;
LVH, left ventricular hypertrophy; MRA, mineralocorticoid antagonist;
Vasc, vascular

Udelson JE et al . Circulation. 2016;133:2671-2686

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): 2129–

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.

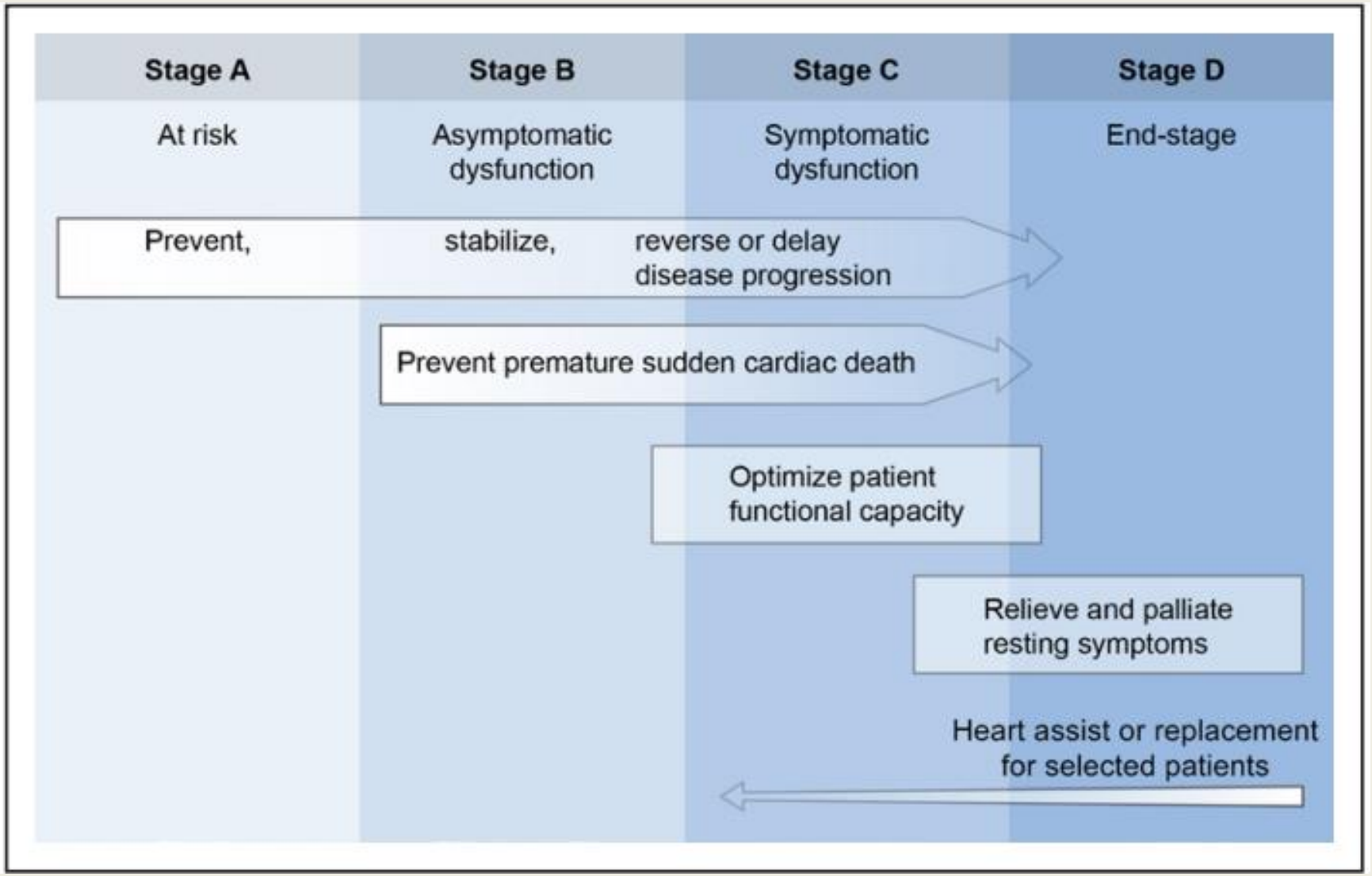
Ponikowski P et al. European Heart Journal;2016.37(27): 2129–2200,

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

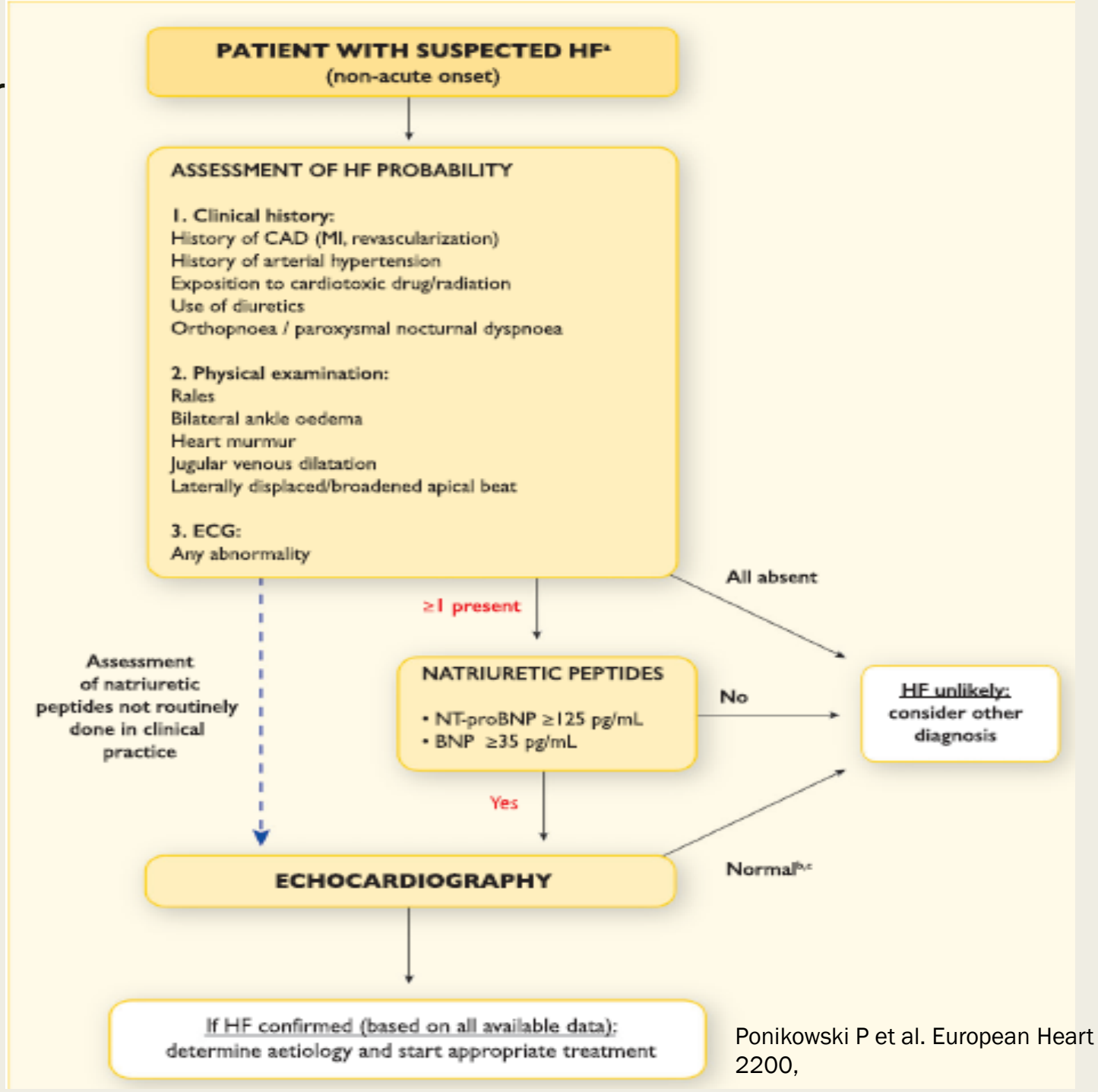
Ponikowski P et al. European Heart Journal;2016.37(27): 2129–2200,

Goals of therapy according to progression by ACC/AHA -stages of heart failure



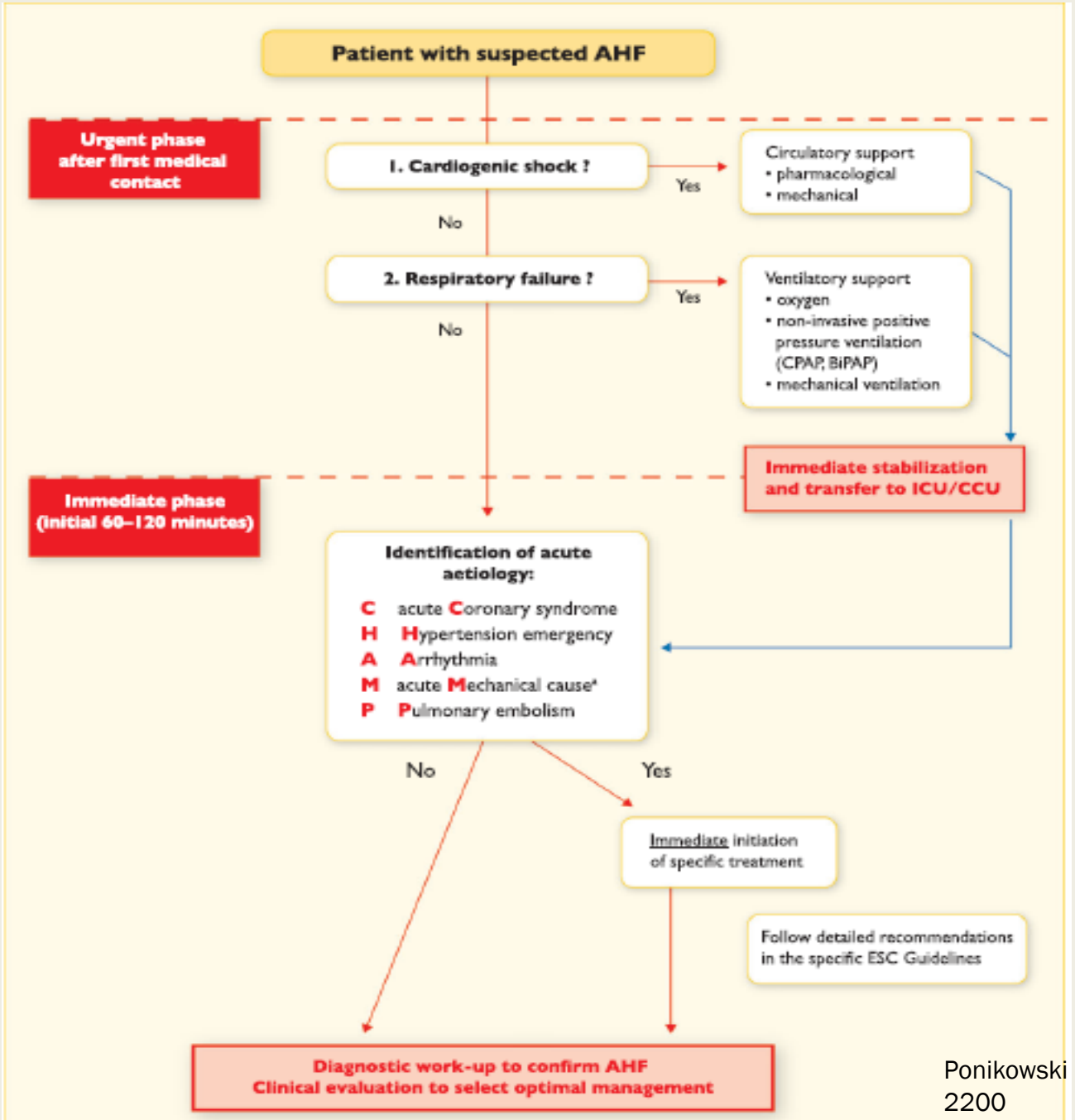
Udelson JE et al . Circulation. 2016;133:2671-2686

Diagnostic algorithm for heart failure



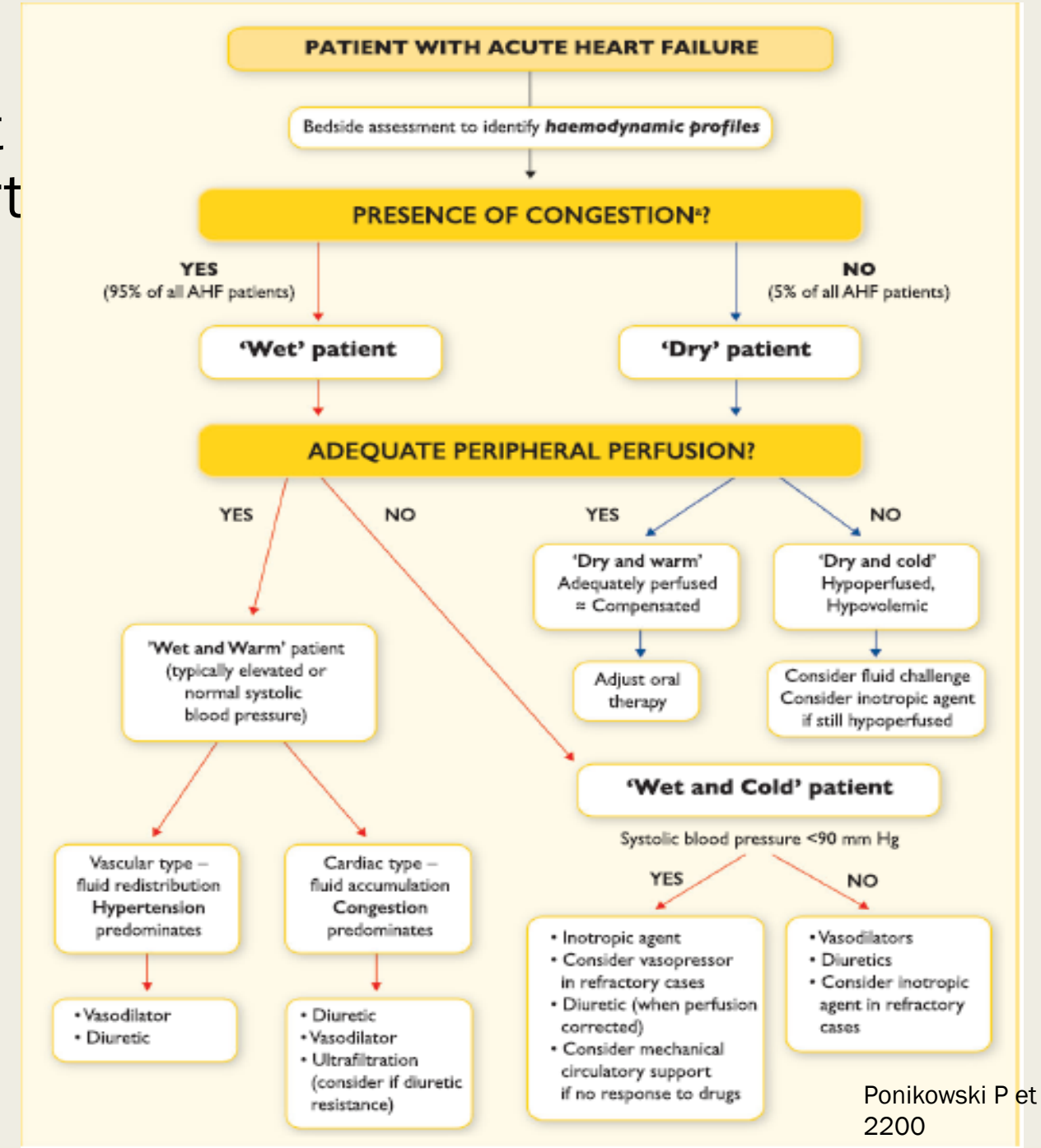
Ponikowski P et al. European Heart Journal;2016.37(27): 2129–2200,

Management of Acute heart failure



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

Management of Acute heart failure based on Clinical profile



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

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

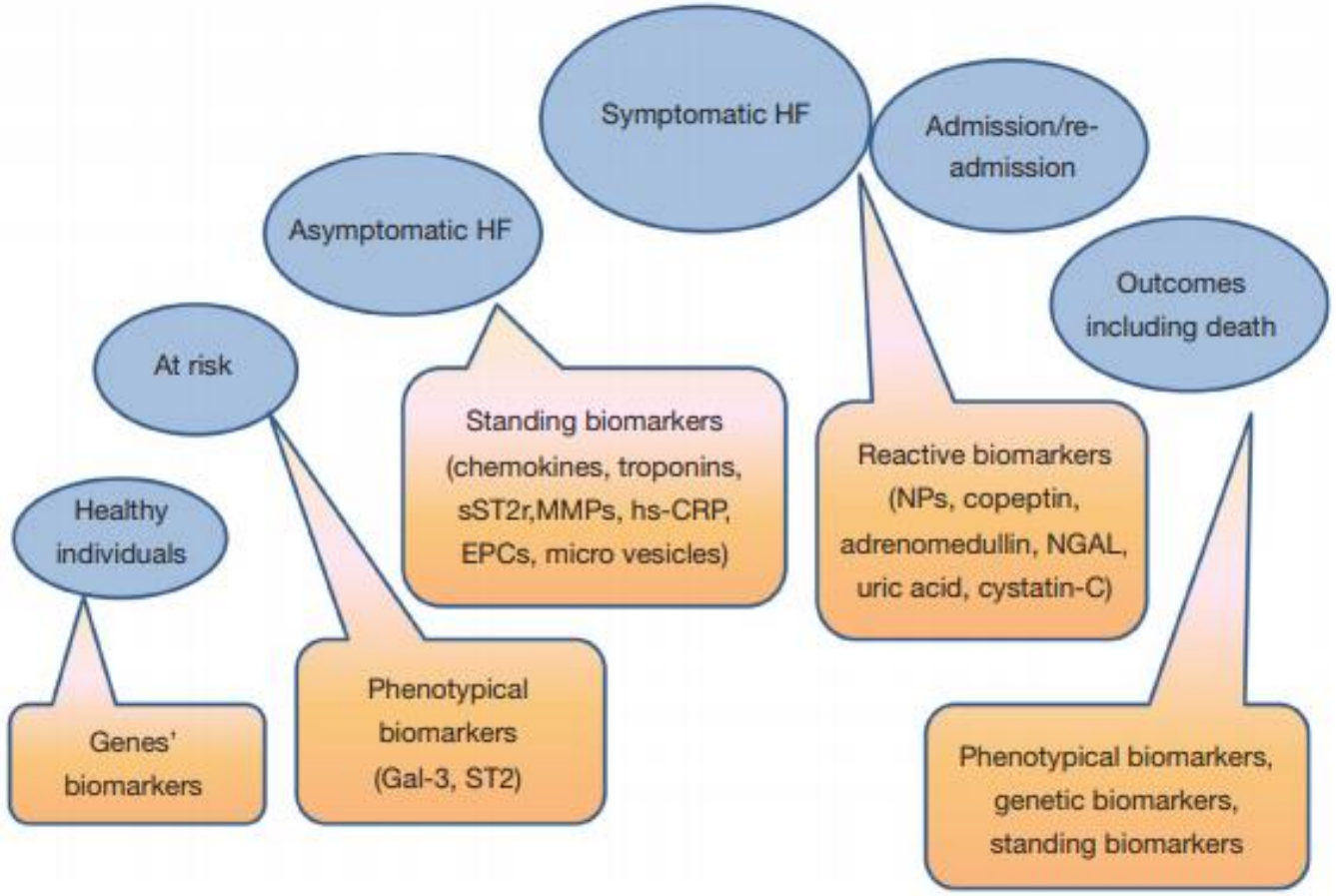


Figure Indications for biomarker use in heart failure (HF) management. ADHF, actually decompensated heart failure; pts, patients; Gal-3, galectin-3; NT-proBNP, NT-pro-brain natriuretic peptide; BNP, brain natriuretic peptide; TrT, troponin T; TrI, troponin I; sST2, soluble suppressor of tumorigenicity-2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

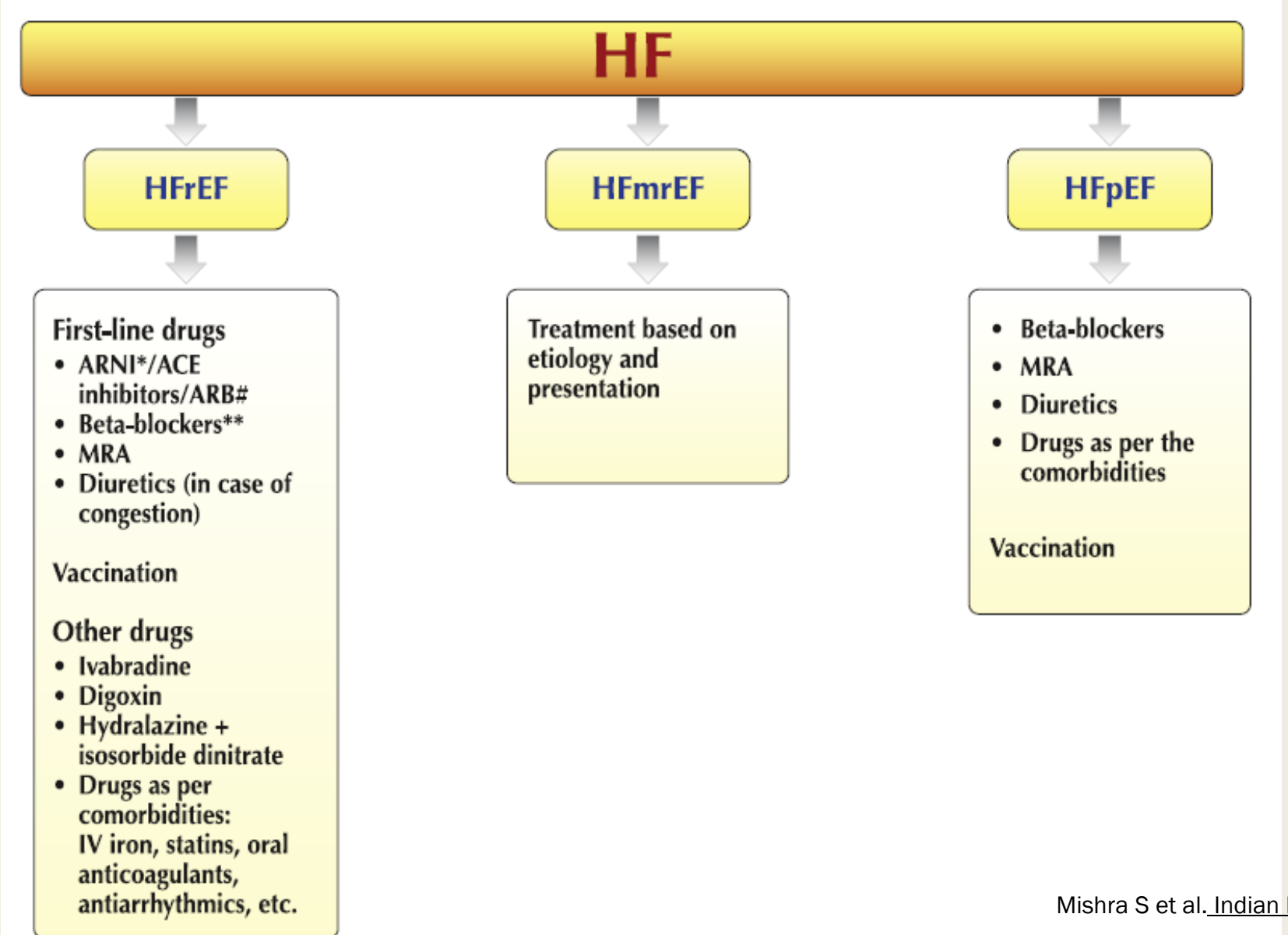
Berezin AE et al. J Lab Precis Med 2018;3:36:1-18.

Predictors of poor prognosis in systolic heart failure patients

Prognosis Markers	Description
Patient characteristics	Older age, male sex and low socio-economic status
Worsening symptoms	High resting heart rate, pulmonary congestion, peripheral edema, , jugular venous dilatation, and hepatomegaly
Severity of LV dysfunction	Depressed LVEG, LV dilatation, severe LV dysfunction, mitral regurgitation, aortic stenosis and left atrial dilatation.
Increased biomarker levels	Increased natriuretic peptides (B-type natriuretic peptide [BNP] and/or N-terminal proBNP [NT-proBNP]).
Cardiovascular comorbidities	Atrial fibrillation (AF), ventricular arrhythmia, coronary artery disease, previous stroke or transient ischemic attack, myocardial infarction and arterial hypotension.
Others	Non-adherence with recommended treatment and clinical events such as HF hospitalization, aborted cardiac arrest and ICD shocks.

Albakri A. Trends in Res. 2018;1(4): 1-2

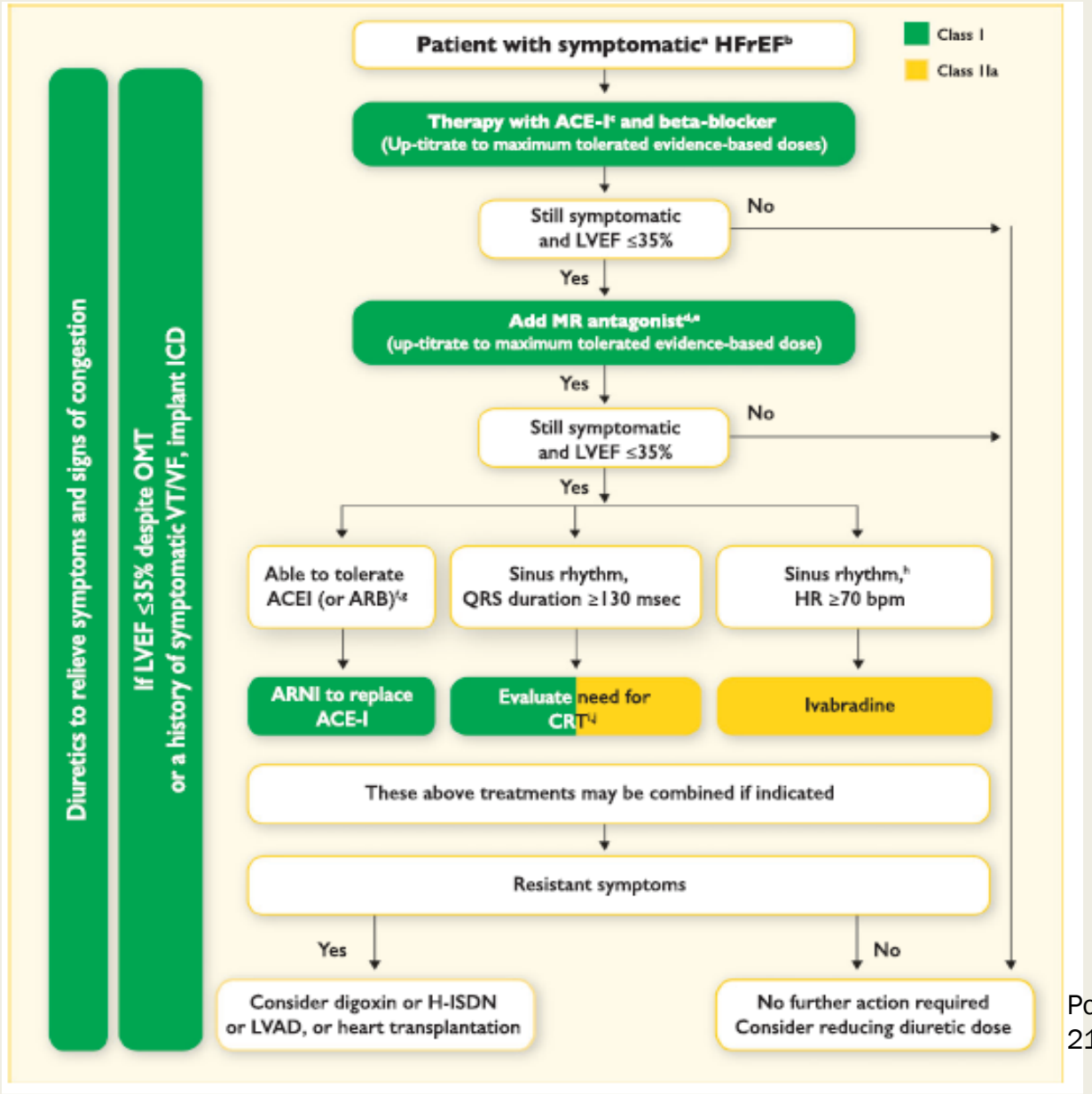
Management of patients with Heart failure



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

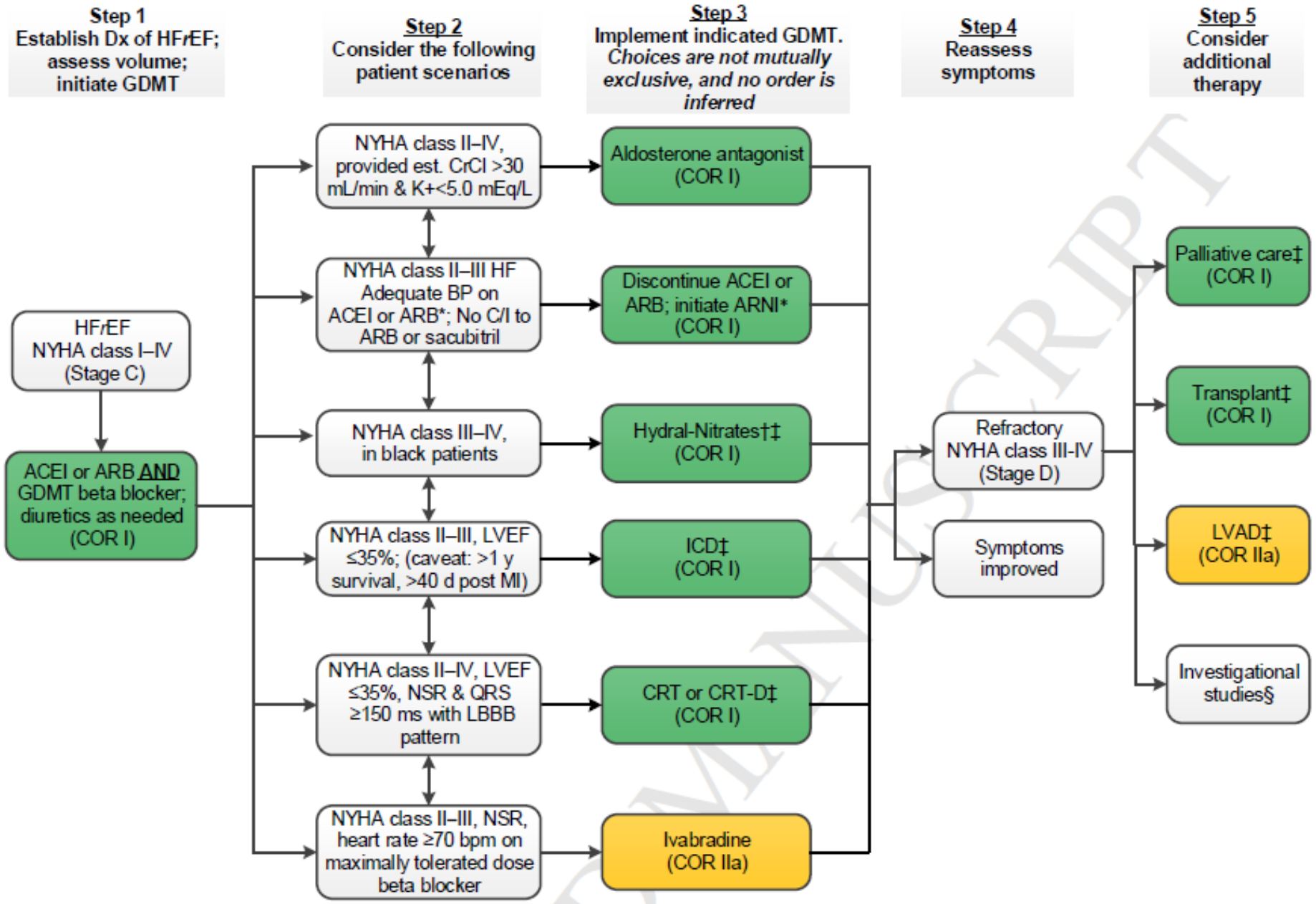
Mishra S et al. Indian Heart J. 2018 Jan - Feb;70(1):105-127

Therapeutic Algorithm for symptomatic HFrEF(heart failure with reduced ejection fraction from European Society of Cardiology



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, normal sinus rhythm; and NYHA, New York Heart Association.

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

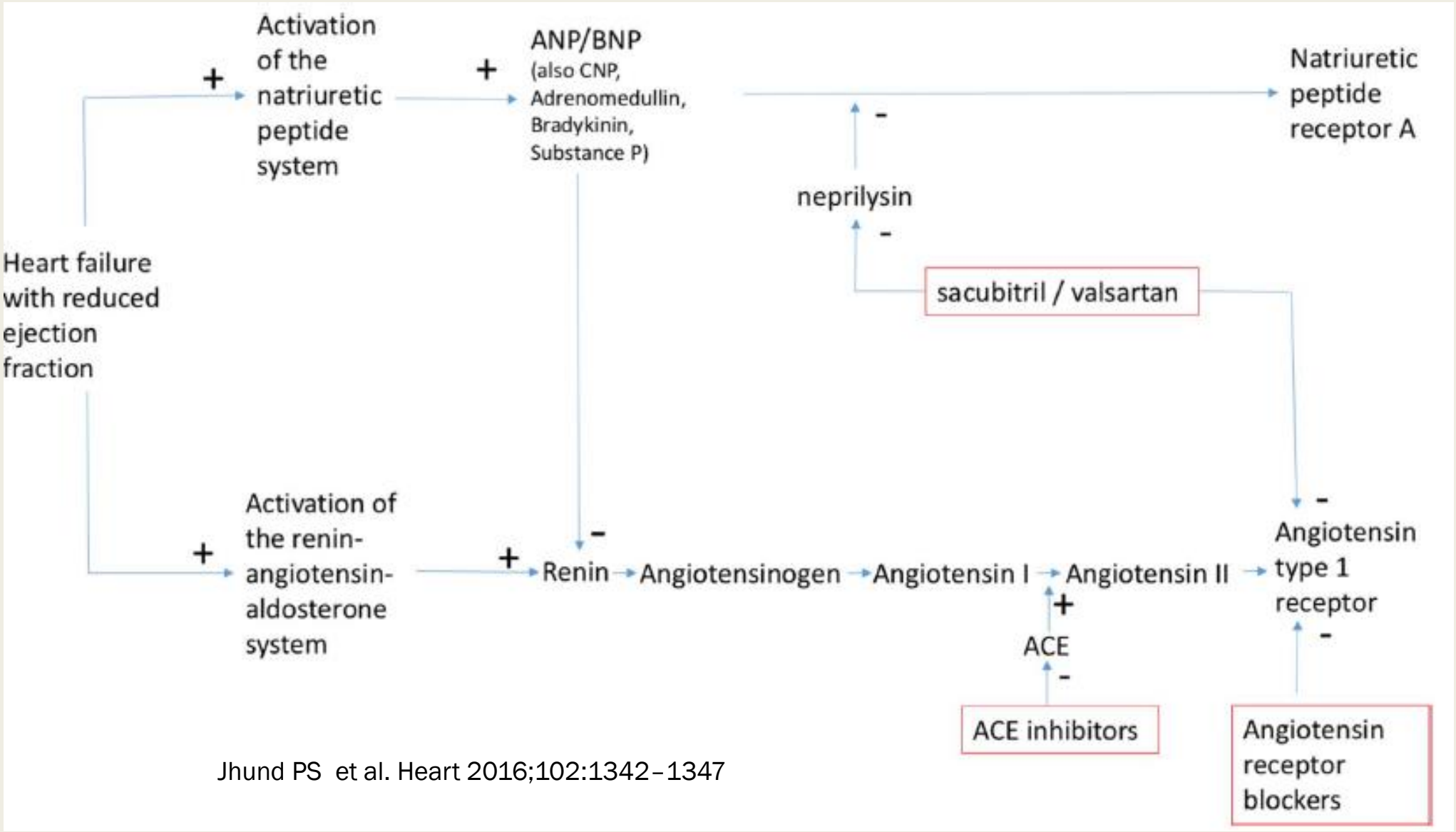
Heart failure treatment with mechanism

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

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

Pathways blocked by ACE inhibitors, angiotensin receptor blockers and neprilysin inhibitors



Jhund PS et al. Heart 2016;102:1342–1347

Renin -angiotensin aldosterone system (RAAS) in heart failure

- Neurohormonal activation primarily mediated through Renin -angiotensin aldosterone system (RAAS) plays a major role in the pathogenesis and progression of heart failure.
- Activation RAAS system in turn increased production of angiotensin II (ATII) leads to hemodynamic dysfunction, renal dysfunction, inflammation, and cardiac remodeling
- Detrimental neurohormonal activation involving the RAAS and sympathetic nervous system is a key target for HF therapy.
- Renin-angiotensin system blockade by an angiotensin-converting enzyme (ACE) inhibitor, **or** angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI), is a key component of treating patients with HFrEF

Givertz MM et al. Pharmacologic therapy of heart failure with reduced ejection fraction: Mechanisms of action UptoDate. 2019; updated Nov 11 2019

Role of ACE inhibitor in heart failure

- Inhibition of the adverse effects of circulating angiotensin and/or aldosterone on target organs.
- Modulation of the tissue renin-angiotensin that cause pathological myocardial remodeling .
- Reduction in central sympathetic outflow and enhancement of sympathoinhibitory responses to baroreceptor stimulation
- Decreased LV afterload contributing to improved systolic function and/or decreased hypertrophy and diastolic dysfunction.
- However it blocks both AT1 and AT 2 receptors, angiotensin II suppression is not complete and reduced degradation of kinins lead to side effects like cough.

Givertz MM et al. Pharmacologic therapy of heart failure with reduced ejection fraction: Mechanisms of action UptoDate. 2019; updated Nov 11 2019

Role of Angiotensin receptor blockers

- ARB causes Suppression of RAAS system with selectively blocking AT 1 receptor.
- ARB unlike ACE inhibitor does not block AT2 receptor that mediates vasodilation and decreased cell growth, hence has a beneficial effect.
- ARB does not interfere with kinin metabolism unlike ACE inhibitor, Cough and angioedema is not seen with ARBs. Hence has a better tolerability profile.

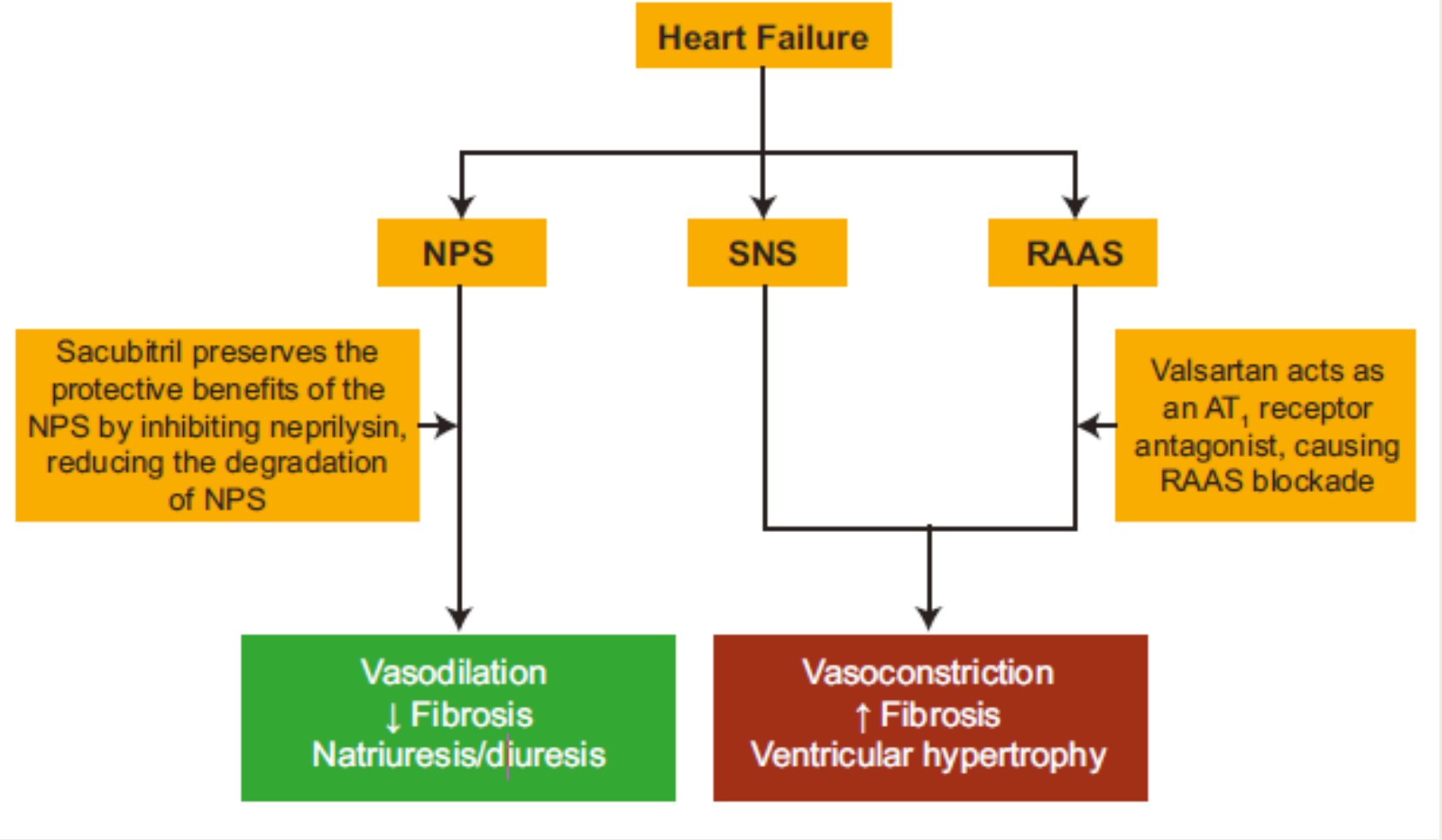
Givertz MM et al. Pharmacologic therapy of heart failure with reduced ejection fraction: Mechanisms of action UptoDate. 2019; updated Nov 11 2019

Role of Angiotensin receptor-neprilysin inhibitor (ARNI) in heart failure

- Drug combination blocks the harmful effects of renin-angiotensin-aldosterone system (RAAS) activation ,raises endogenous natriuretic peptides that are degraded by neprilysin.
- Natriuretic peptides persist longer and promote vasodilation, diuresis, and natriuresis, as well as prevent cardiac hypertrophy.
- Neprilysin catalyzes the degradation of natriuretic peptides. Natriuretic peptides are produced in response to volume overload and cardiac dysfunction, and exert a beneficial response in HF
- Combination prevents vasoconstriction and decreases both aldosterone secretion and renal reabsorption of sodium.
- Eg: Sacubitril + Valsartan

Hayman S et al. Cardiac failure review. 2016 May;2(1):47.

Mechanism of action of Sacubitril + Valsartan



AT1- Angiotensin type 1,
NP- natriuretic peptide,
NPS- natriuretic peptide system,
RAAS -renin–angiotensin–aldosterone system,
SNS - sympathetic nervous system

Sauer AJ et al. Heart Fail Rev.2019; 24 :167–176

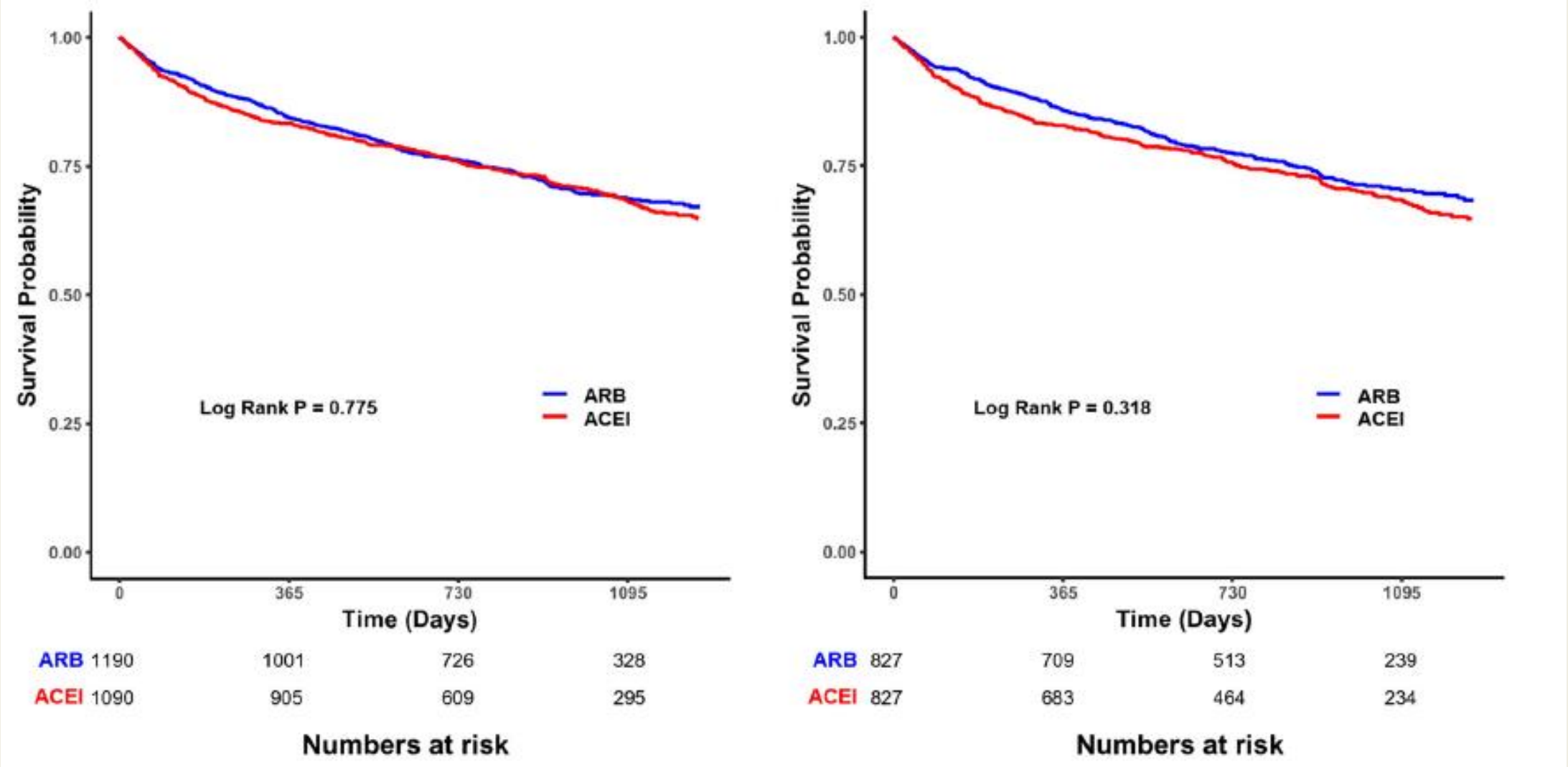
CLINICAL TRIALS ON ANGIOTENSIN RECEPTOR BLOCKERS

Effects of angiotensin receptor blocker at discharge in patients with heart failure with reduced ejection fraction: Korean Acute Heart Failure (KorAHF) registry

- Methods: 3005 patients with heart failure with reduced ejection fraction (HFrEF_ (<40%), and divided into Angiotensin receptor blocker (ARB) (n = 1190), ACE inhibitor(n = 1090), and no RASB (Renin Angiotensin system blocker (n = 725) groups.
- HFrEF with Left Ventricular Ejection Fraction <40%
- The primary end point of the present study was the occurrence of all-cause death during follow-up.
- Results: All-cause death was significantly lower in the ARB group than in the no RASB group (ARB vs. no RASB, 538 pairs, HR 0.69, 95% CI 0.56–0.83, p < 0.001).
- The ARB group had a significantly lower discontinuation rate than the ACEI group (20.8% vs. 33.6%, p < 0.001).

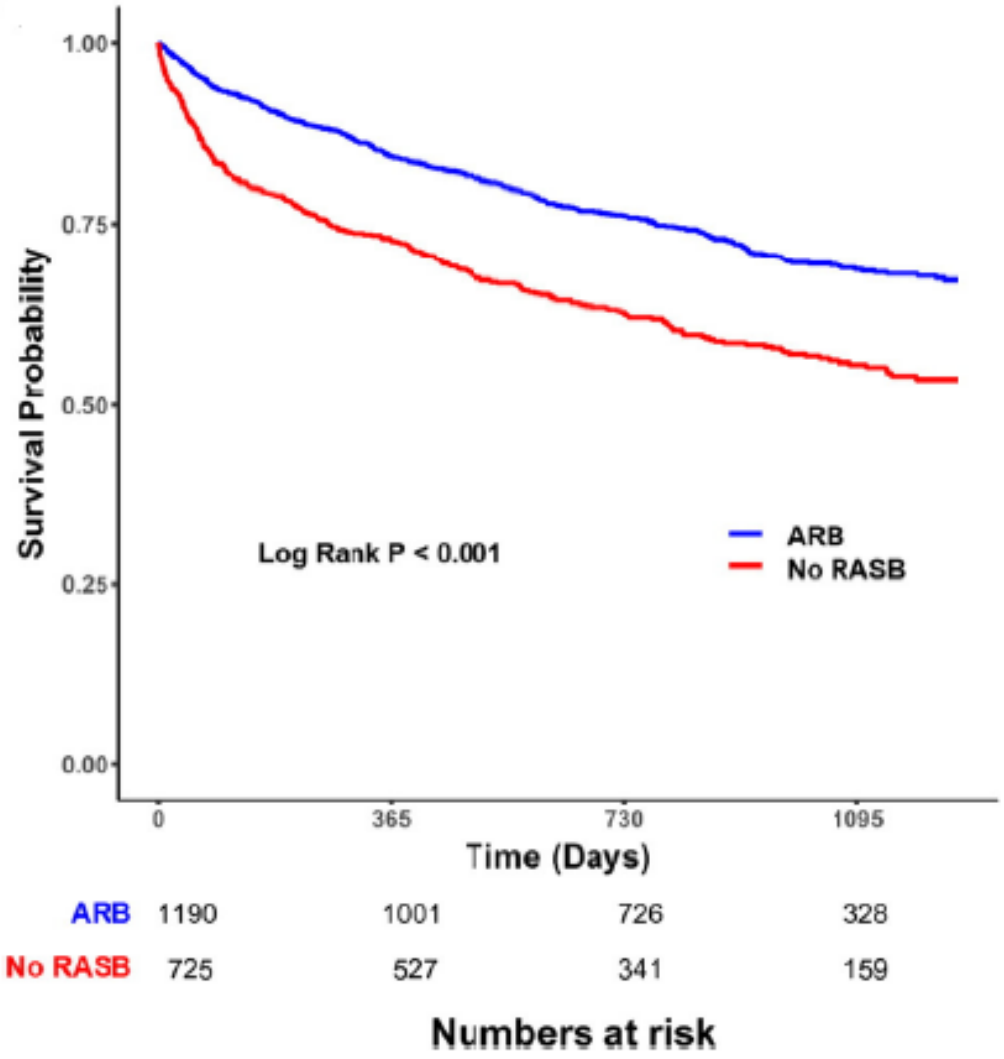
Choi KH et al. Int J Cardiol. 2018;257:168–176.

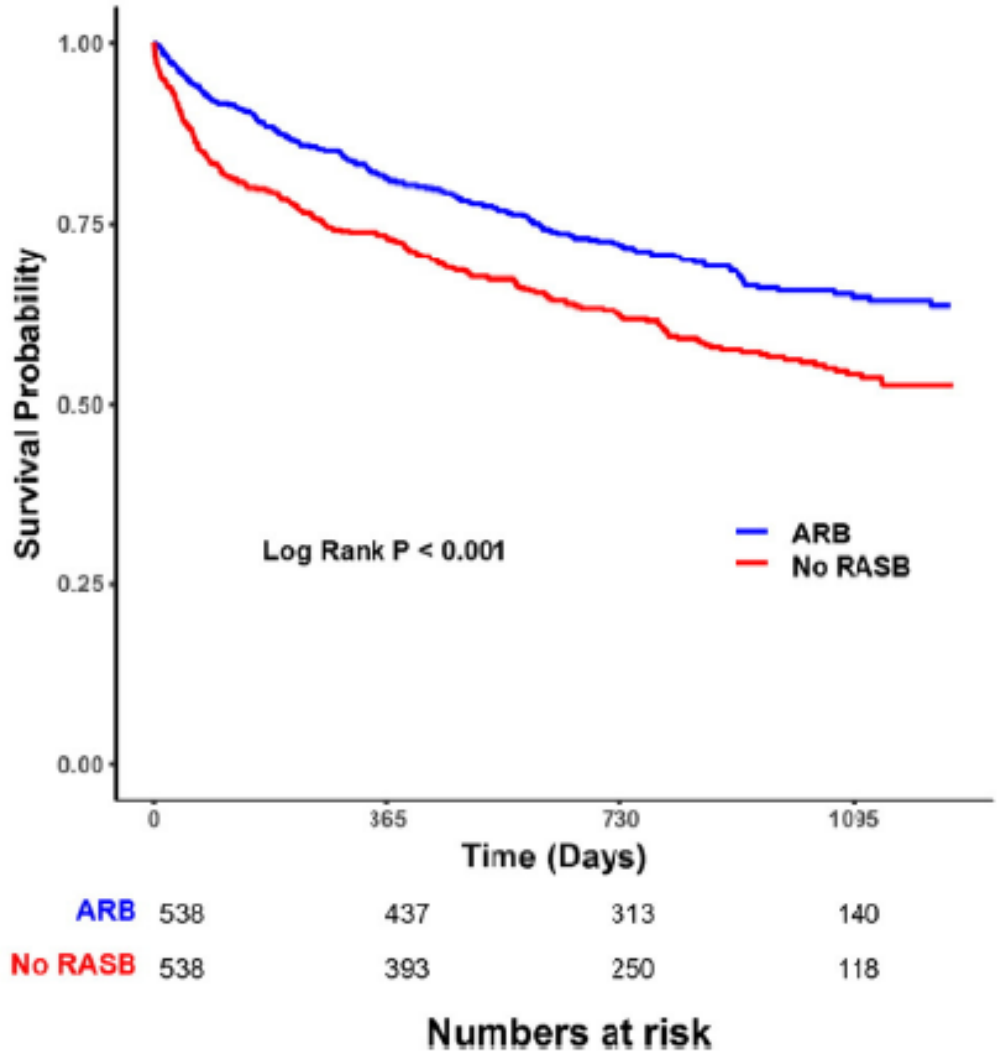
Results -Comparison for all-cause mortality in Acute Heart Failure with HFrEF in ARB compared to ACE inhibitor



Choi KH et al. Int J Cardiol. 2018;257:168–176.

Results of Comparison for all-cause mortality in Acute Heart Failure with HFrEF in ARB compared to No ARB





Choi KH et al. Int J Cardiol. 2018;257:168–176.

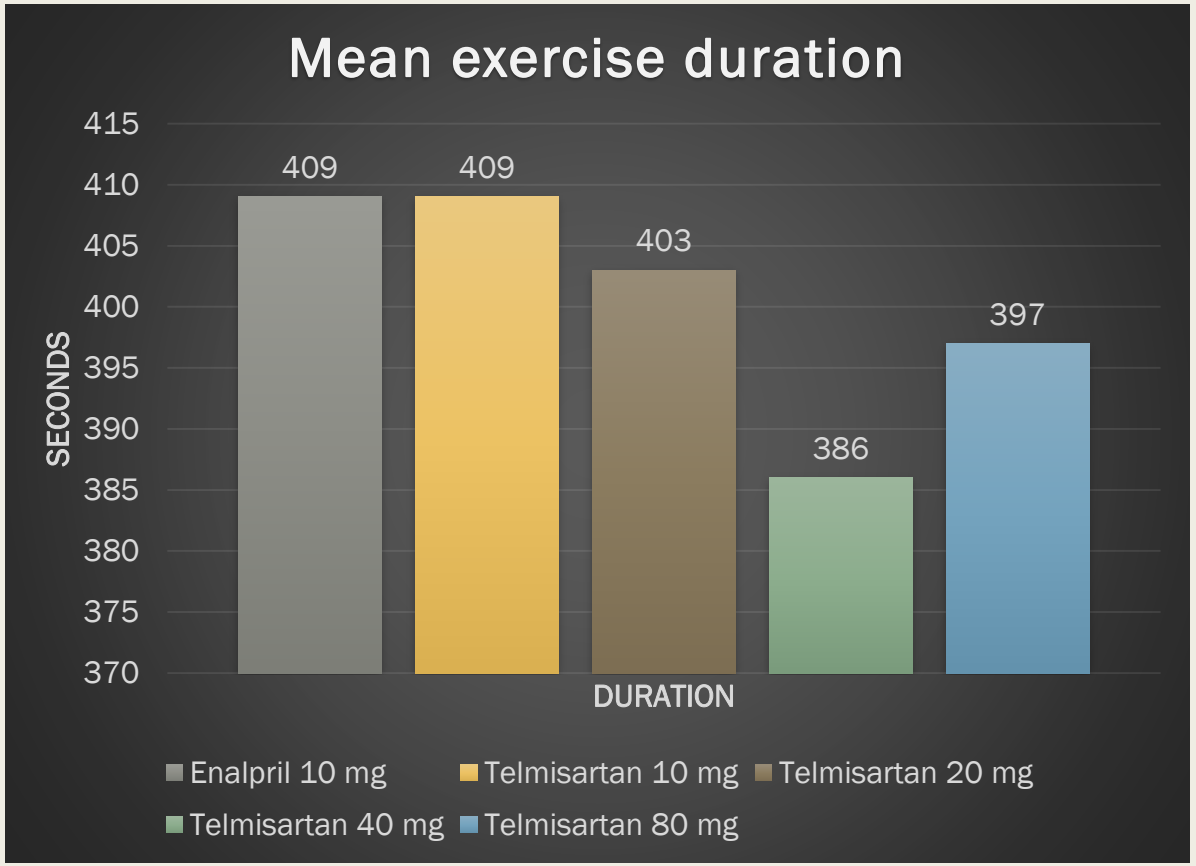
Effects of the replacement of the enalapril by the Telmisartan in patients with congestive heart failure (REPLACE - The replacement of angiotensin converting enzyme inhibition investigators)

- Aim: To compare the effects on maximal exercise tolerance of 12 weeks of Telmisartan (10/20/40/80 mg once daily), enalapril, in patients with stable, mild-to-moderate congestive heart failure (NYHA Class II and III and left ventricular ejection fraction <40%).
- Methods: Multicenter, double-blind, parallel-group trial in 378 patients, randomized to once-daily treatment with telmisartan 10, 20, 40 mg, 80 mg, or continuation of enalapril 10 mg twice daily for 12 weeks
- Primary efficacy parameter: change from baseline to final visit in bicycle exercise duration. Secondary efficacy parameters included left ventricular ejection fraction, quality-of-life parameters, arterial blood pressures, neurohormonal changes and NYHA classification.

Dunselman Phet al. Int J Cardiol. 2001;77(2-3):131–140.

Effects of the replacement of the enalapril by the Telmisartan in patients with congestive heart failure (REPLACE - The replacement of angiotensin converting enzyme inhibition investigators)

- Results: Exercise tolerance improved in Telmisartan 20,40, 80 mg without deterioration in exercise capacity or clinical status.
- <u>Conclusion:</u> **In mild-to-moderate congestive heart failure, enalapril could be replaced by telmisartan for a period of 12 weeks without deterioration in exercise capacity or clinical status.**



Dunselman Phet al. Int J Cardiol. 2001;77(2-3):131–140.

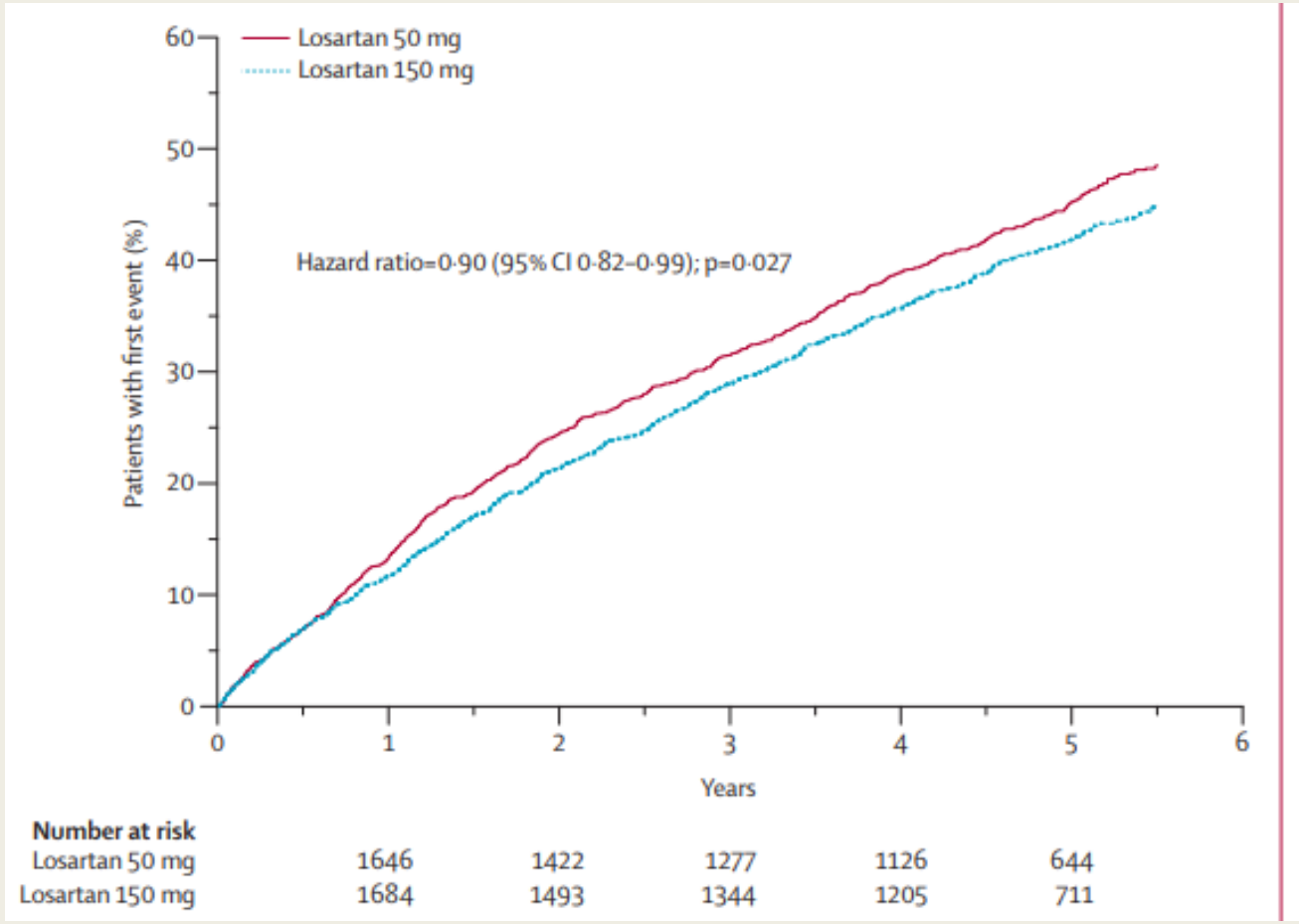
Low dose 50 mg vs high dose 150 mg Losartan in the treatment of heart failure

- Aim: To compare the effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure.
- Methods: 3846 patients with heart failure of New York Heart Association class II–IV, left-ventricular ejection fraction 40% or less, and intolerance to angiotensin-converting-enzyme (ACE) inhibitors were randomly assigned to losartan 150 mg (n=1927) or 50 mg daily (n=1919).
- The primary endpoint was a composite of death or admission for heart failure. Admission for heart failure was defi ned as a minimum of 24 h inpatient admission.
- The major secondary endpoint was a composite endpoint of death or cardiovascular admission.

Konstam MA et al. Lancet 2009; 374: 1840–48.

Low dose 50 mg vs high dose 150 mg Losartan in the treatment of heart failure

- Results: Losartan 150 mg daily significantly reduced the mortality rate or admission, compared to losartan 50 mg daily in patients with heart failure ($p<0.001$)
- **Conclusion: Uptitration of Losartan is beneficial in reducing the risk of hospital admission and mortality in heart failure patients.**



Konstam MA et al. Lancet 2009; 374: 1840–48.

CLINICAL TRIALS ON **ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITORS**

Comparing the effect of Sacubitril Valsartan with Enalapril in the treatment of heart failure (PARADIGM HF) trial

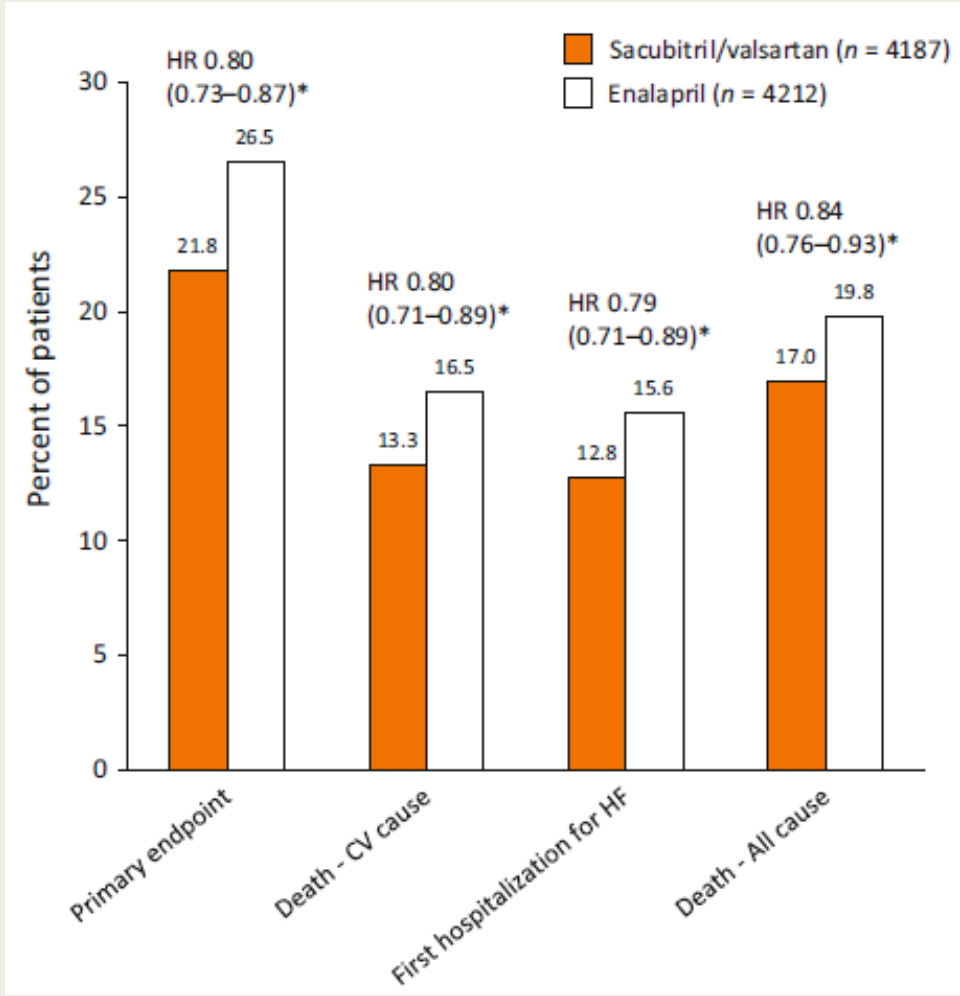
- Aim : To assess the cardiovascular outcomes of Sacubitril Valsartan and Enalapril in heart failure with a reduced ejection fraction.
- Methods: Randomised double-blind trial with 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less.
- Patients received either Sacubitril Valsartan (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy.
- The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

McMurray JJ et al. N Engl J Med. 2014;371(11):993–1004.

Comparing the effect of Sacubitril Valsartan with Enalapril in the treatment of heart failure (PARADIGM HF) trial

- Results: As compared with enalapril, Sacubitril Valsartan reduced the risk of hospitalization for heart failure by 21% (P 0.001).
- Death from cardiovascular causes or hospitalization for heart failure were lesser in Sacubitril Valsartan group
- The Sacubitril Valsartan group had higher episodes ofhypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

<u>Conclusion</u> : Sacubitril Valsartan improves cardiovascular outcomes better than Enalapril in heart failure patients



McMurray JJ et al. N Engl J Med. 2014;371(11):993–1004.

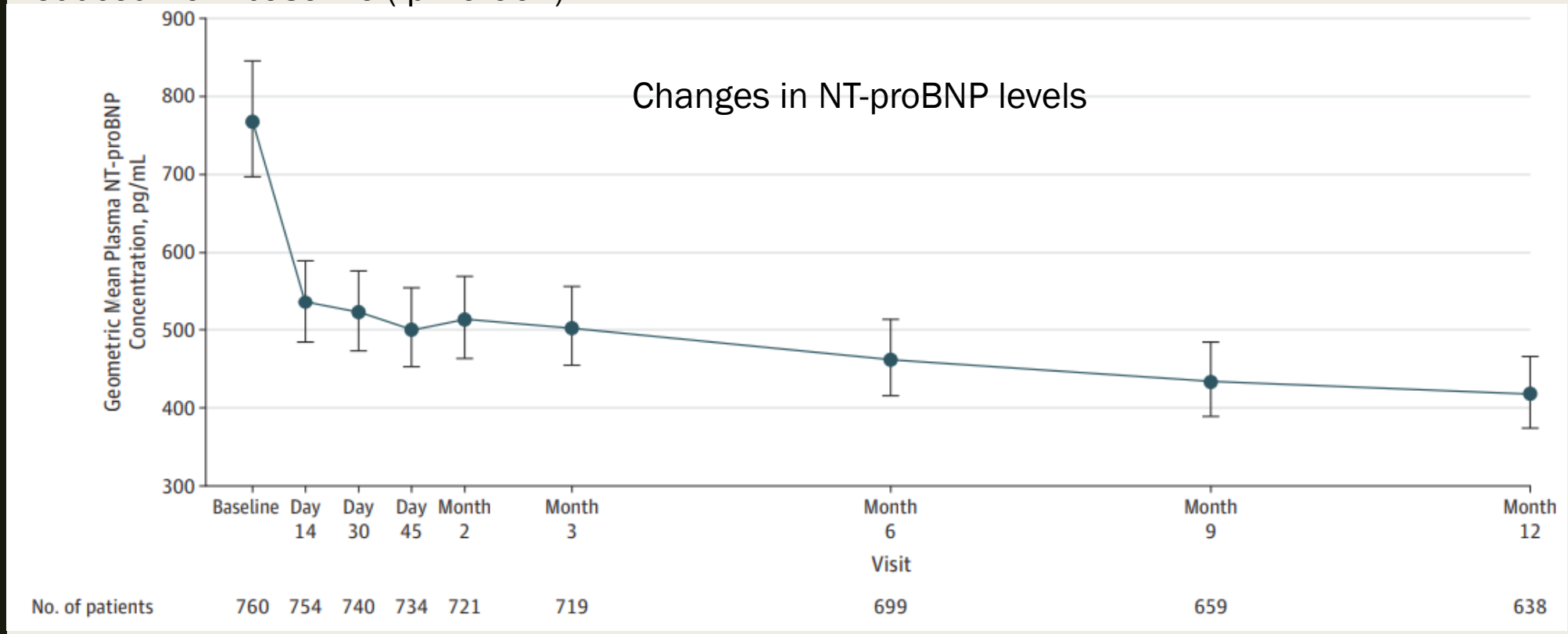
Effect of Sacubitril Valsartan on NT-pro BNP levels and it association with cardiac remodeling (PROVE HF) trial

- Aim: NT-pro BNP levels correlation with changes in measures of cardiac volume and function in patients with HFrEF treated with sacubitril-valsartan.
- Methods: Prospective, 12-month, single-group, open-label study of patients with HFrEF. 794 patients were included in the study., were assigned to Sacubitril Valsartan
- The initial dose of sacubitril-valsartan was 24/26 mg twice daily in 81.7 percent of participants. By study end, 65.0 percent of participants achieved the goal dose of 97/103 mg twice daily, whereas the dose was 49/51mg twice daily in 21.2 percent and 24/26mg twice daily in 13.9 percent.
- Primary outcomes: Changes in NT-pro BNP levels and assessing cardiac remodeling parameters.

Januzzi JL et al. JAMA. 2019;322(11):1–11.

Effect of Sacubitril Valsartan on NT-pro BNP levels and it association with cardiac function

Results: changes in log2–NT-proBNP concentrations and cardiac remodelling parameters like left ventricular (LV) EF, LV end-diastolic volume index (LVEDVI), LV end-systolic volume index (LVESVI), left atrial volume index (LAVI), and ratio of early transmitral Doppler velocity/early diastolic annular velocity (E/e′) at 12 months significantly reduced from baseline.(p <0.001)



Januzzi JL et al. JAMA. 2019;322(11):1–11.

Conclusion: Sacubitril Valsartan significantly reduced NT-proBNP levels and resulted in significant reverse cardiac remodelling in patients with heart failure with Reduced Ejection Fraction

Sacubitril/Valsartan compared with enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction (EVALUATE HF) trial

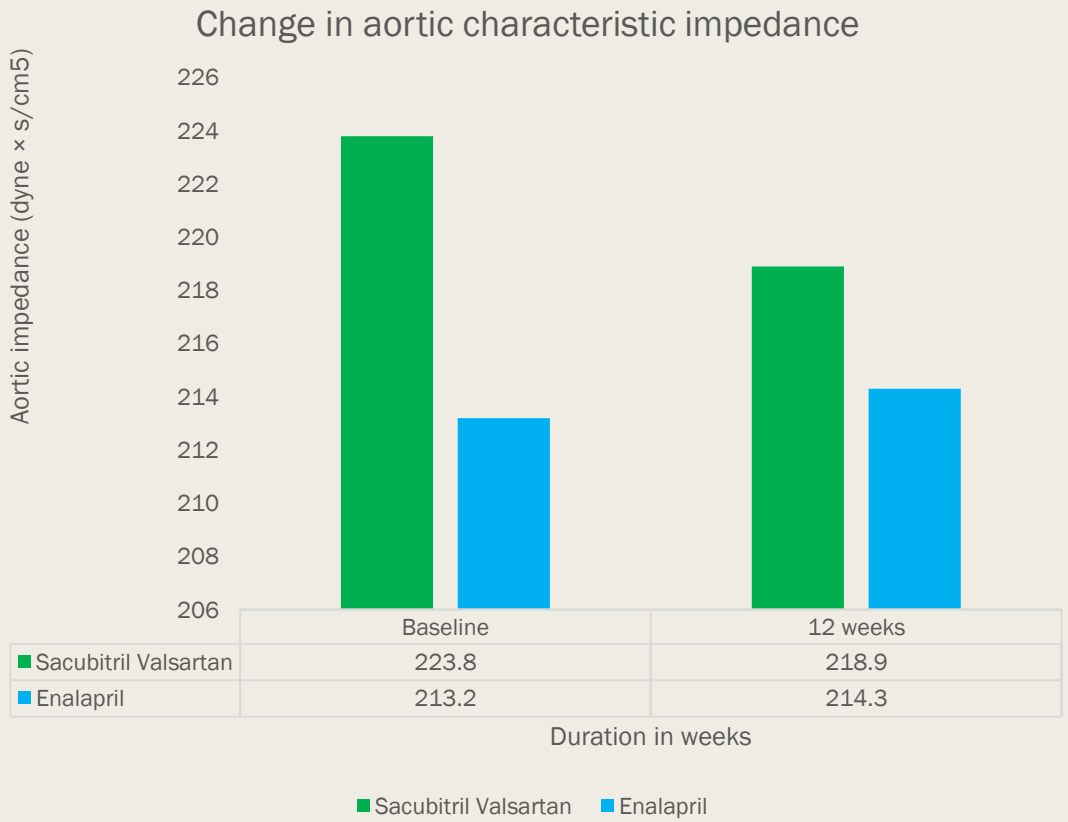
- Aim: To determine whether treatment with sacubitril-valsartan improves central aortic stiffness and cardiac remodeling compared with enalapril in of HFrEF patients.
- Methods: Randomized, double-blind clinical trial with 464 participants with heart failure and ejection fraction of 40% or less.
- Randomized in 1:1 ratio to sacubitril-valsartan (n = 231; target dosage, 97/103 mg twice daily) vs enalapril (n = 233; target dosage, 10 mg twice daily) for 12 weeks.
- Primary outcome was change from baseline to week 12 in aortic characteristic impedance (Zc), a measure of central aortic stiffness
- Secondary outcomes included change from baseline to week 12 in N-terminal pro–B-type natriuretic peptide, cardiac remodeling parameters.

Desai A et al. *JAMA*. 2019;322(11):1–10.

Sacubitril/Valsartan compared with enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction (EVALUATE HF) trial

- Results: Improvement in Aortic impedance was seen with Sacubitril/Valsartan which was not statistically significant compared to increase in aortic impedance with Enalapril. P =0 .001.

<u>Conclusion:</u> Sacubitril/Valsartan reduced the Aortic stiffness better than Enalapril



Desai A et al. *JAMA*. 2019;322(11):1–10.

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 or Angiotensin receptor blockers is first line in the treatment of patients with heart failire.
- Latest studies have shown that ARB's has a better efficacy, tolerability profile and lesser withdrawal rates compared to ACE inhibitors in heart failure.
- Angiotensin-receptor-neprilysin-inhibitor is beneficial in heart failure with better reduction in cardiac biomarkers and extended benefits in cardiac remodeling.
- 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.