Heart Failure

Hanna K. AL-Makhamreh, MD FACC

Associate Professor of Cardiology

University Of Jordan

Edited by: Ruaa Hdeib

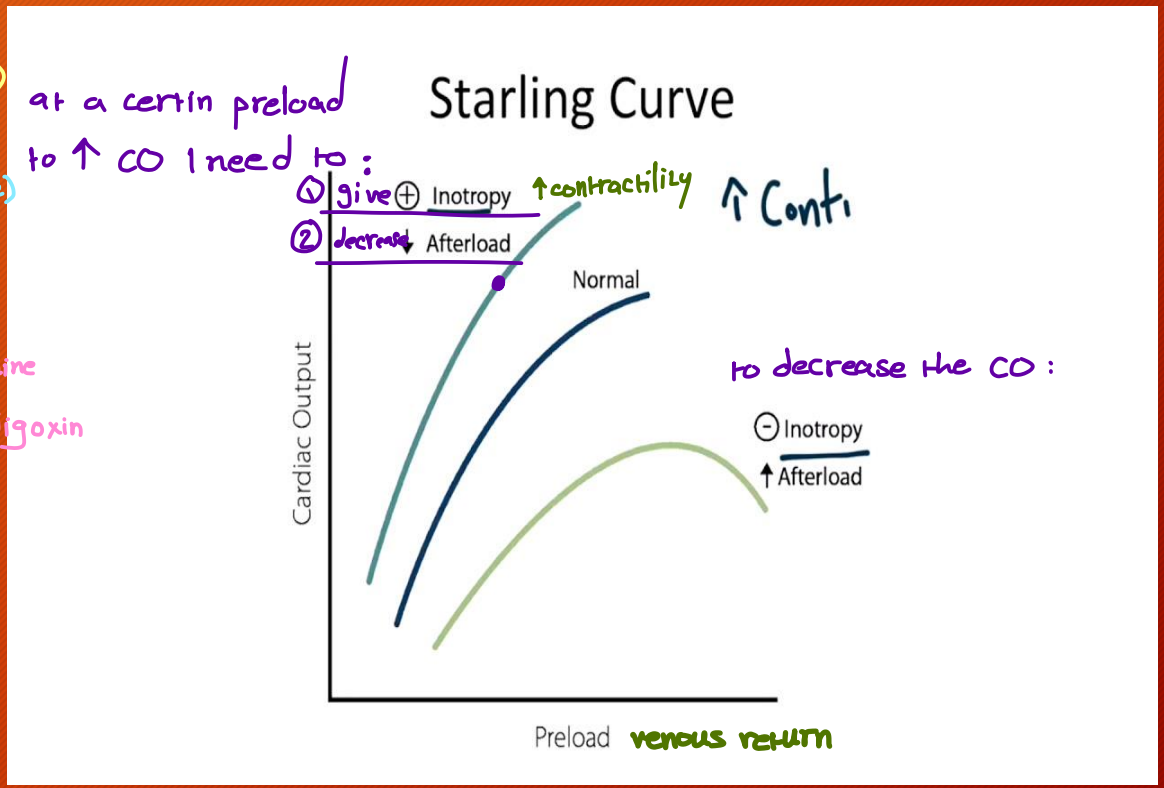
Physiology (Frank-Starling) curve

3 moderators. Preload, afterload, ionotropy

- Preload reduction
  - Diuretics
  - venodilators (nitrates)

→ Afterload reducers:

- Vasodilators (Na nitroprusside)
  - ACEI • Hydralazine
- Inotropes
  - Acutely we use debutamine
  - Chronically we use digoxin



↑ preload → ↑ CO

Pressure-Volume loop

D: relaxed ventricle, starts filling with blood, increase volume, pressure is nearly constant.
Mitral valve is open

A: systole, starts with isovolomic contraction (constant volume with increasing pressure)
Mitral valve is closed

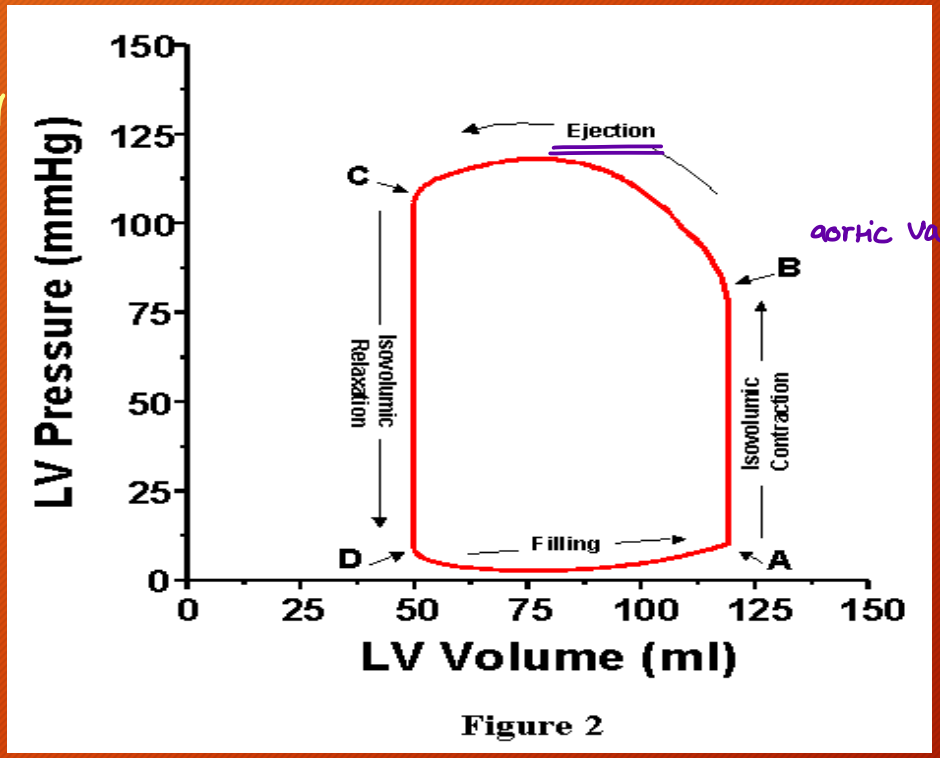


Figure 2

aortic valve opens

C: end systole, the ventricle relax, isovolomic relaxation (volume doesnot change, but pressure is dropping significantly)

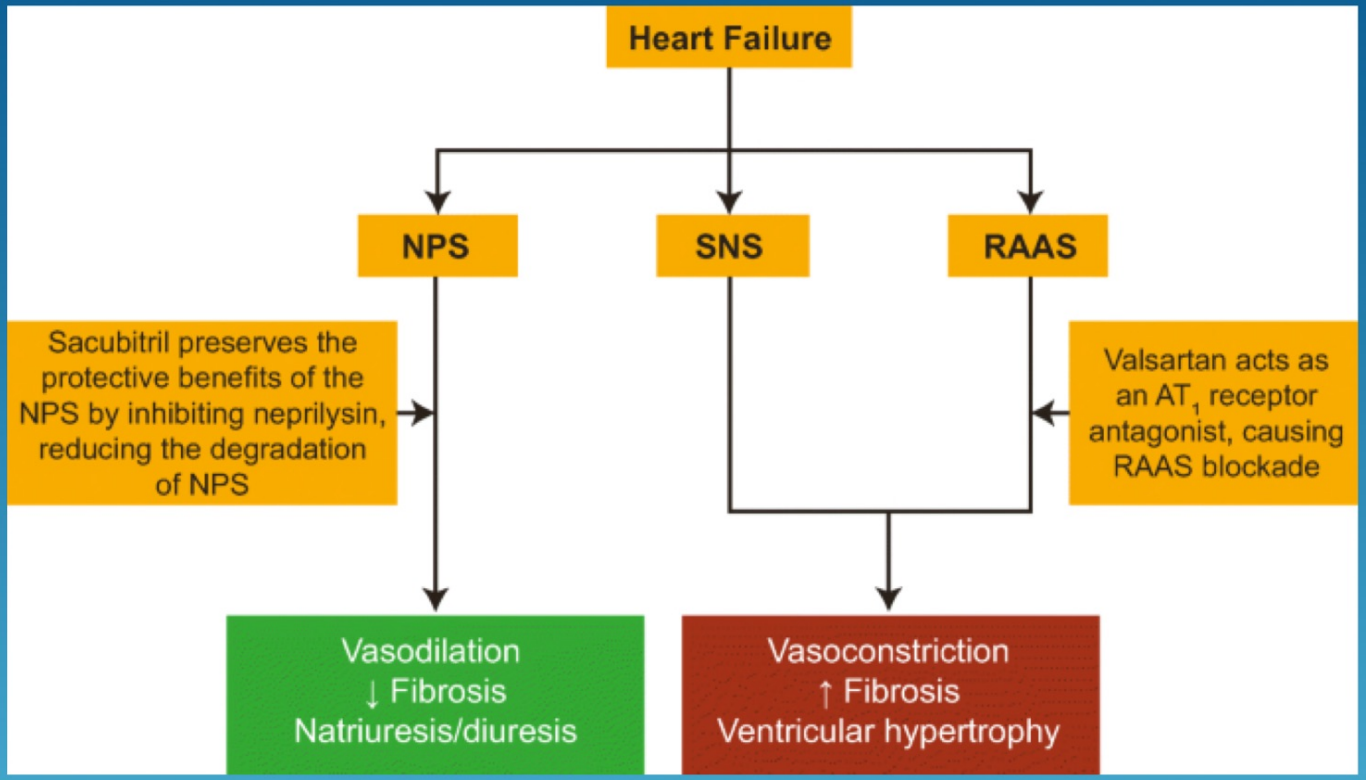
Mitral valve not open yet / Aortic valve is closed

Pathophysiology

- Initial Compensation for impaired myocyte contractility: in HF for example
  - Frank-Starling mechanism ↑ dilation to accept more afterload
  - Neurohumoral activation increase in Epinephrin, Norepinephrin, RAAS, symp.
  - ↑ intravascular volume due to increase in Aldosterone [and any other hormone causes water & Na+ retention]

▶ If HF continues without therapy:

- Eventual decompensation
  - ventricular remodeling
  - myocyte death/apoptosis this causes geometric changes in ventricle which causes dilatation so valvular regurge
  - valvular regurgitation



PATHOPHYSIOLOGY OF HF

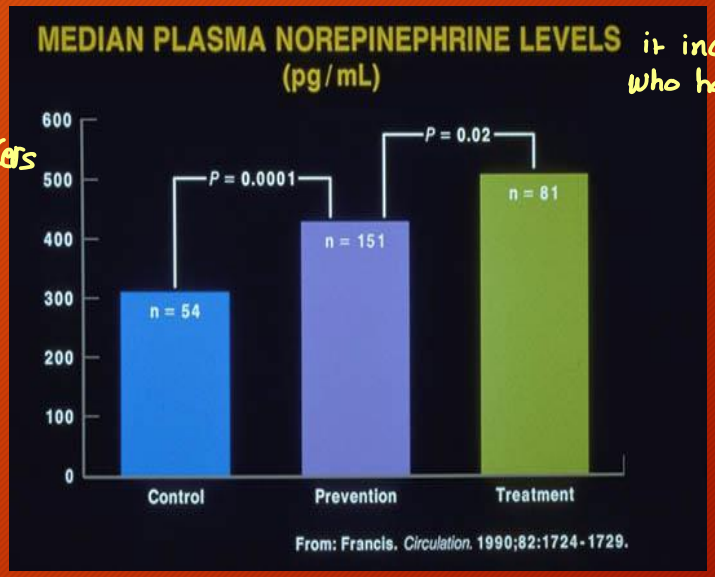
Pathophysiology: Neurohumoral

* 3 mechanisems involved as corner stone in HF as etiology in propagation of HF & as targets for therapy :

① Adrenergic nervous system → so we use β blockers

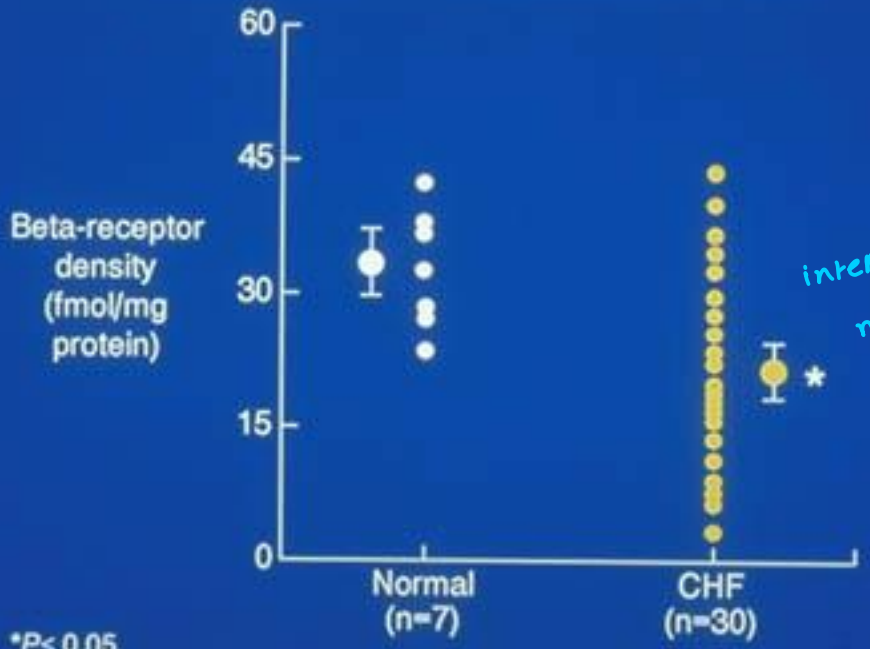
② Renin-angiotensin-aldosterone system

③ Natriuretic peptides



it increases in patients who have HF on therapy

Beta-Receptor Density in Healthy Individuals and Patients with CHF

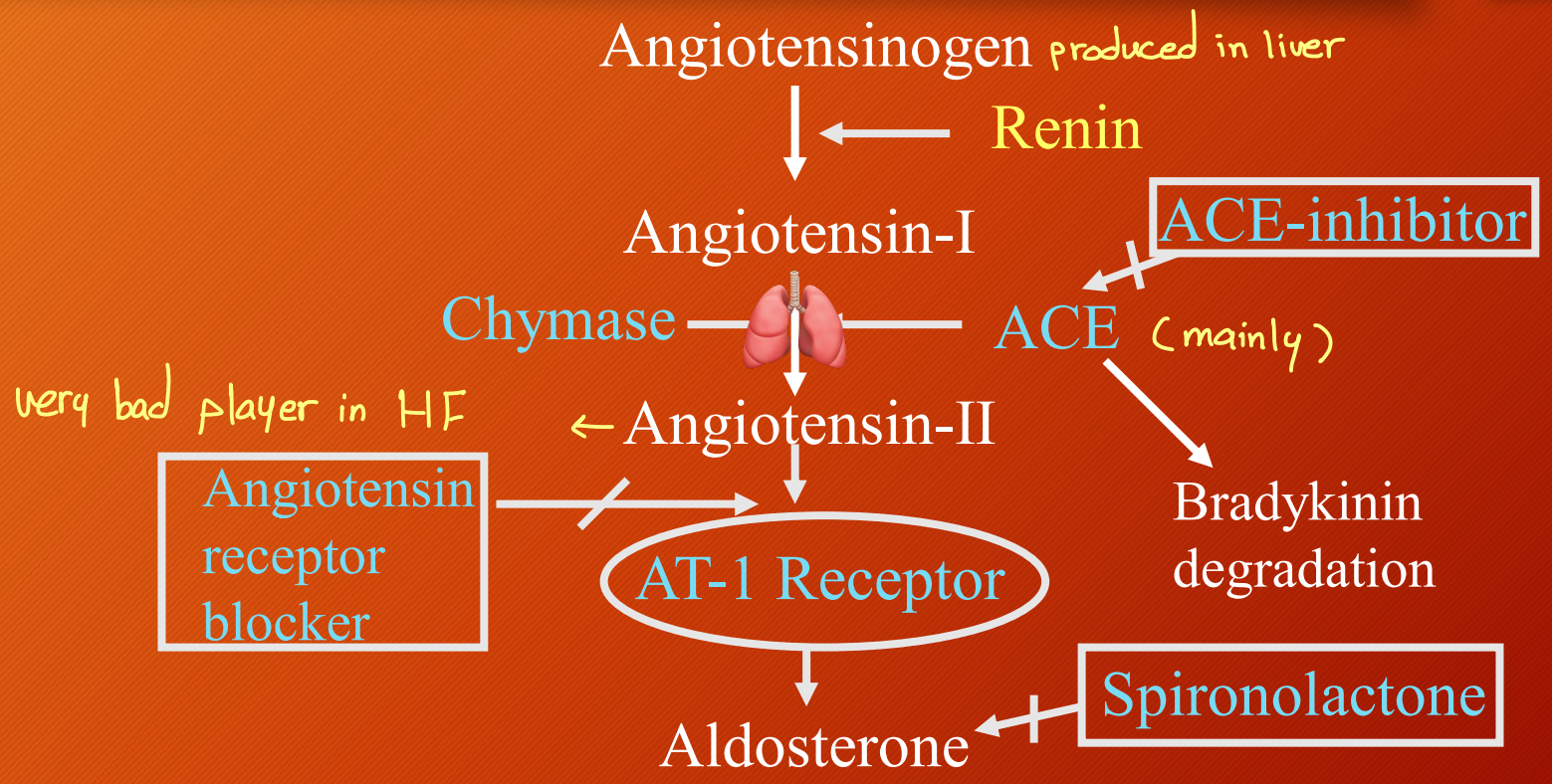


intensively much more sympathetic

*$P < 0.05$.

Mancini et al: *Am J Cardiol* 1989; 63:307–312.

Renin-Angiotensin-Aldosterone Pathways

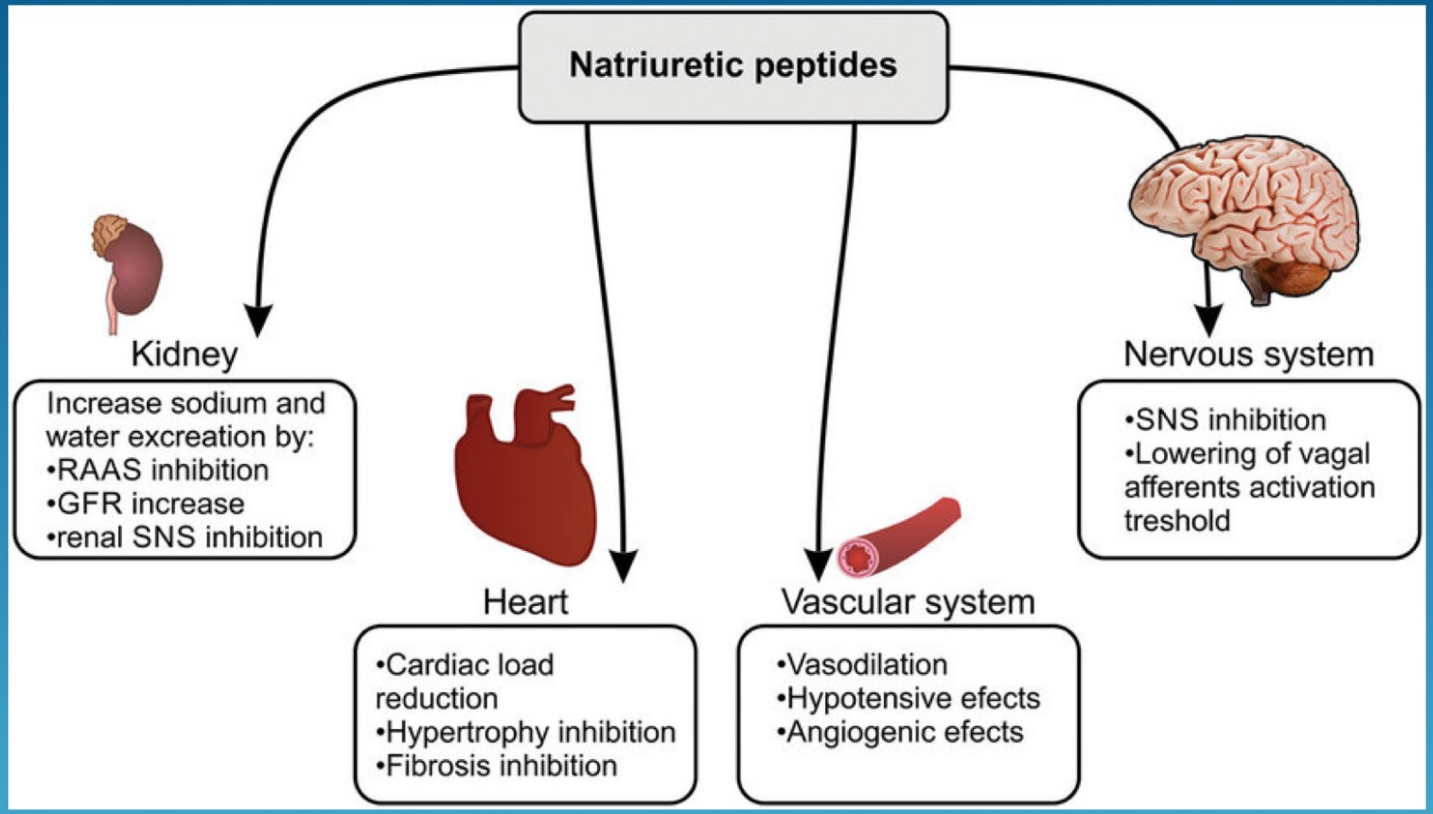


↳ Formation of Ang II & Aldosterone in HF patients is associated with worse outcome & apoptosis

Angiotensin-II Effects

very bad drawbacks:

- Vasoconstriction
- Aldosterone production
- Myocyte hypertrophy
- Fibroblast proliferation
- Collagen deposition
- Apoptosis
- Pro-thrombotic
- Pro-oxidant
- Adrenergic stimulation
- Endothelial dysfunction


Natriuretic peptides
Kidney
Increase sodium and water excreation by:
•RAAS inhibition
•GFR increase
•renal SNS inhibition
Heart
•Cardiac load reduction
•Hypertrophy inhibition
•Fibrosis inhibition
Vascular system
•Vasodilation
•Hypotensive efects
•Angiogenic efects
Nervous system
•SNS inhibition
•Lowering of vagal afferents activation treshold

NP

The Kidney and the Heart Failure

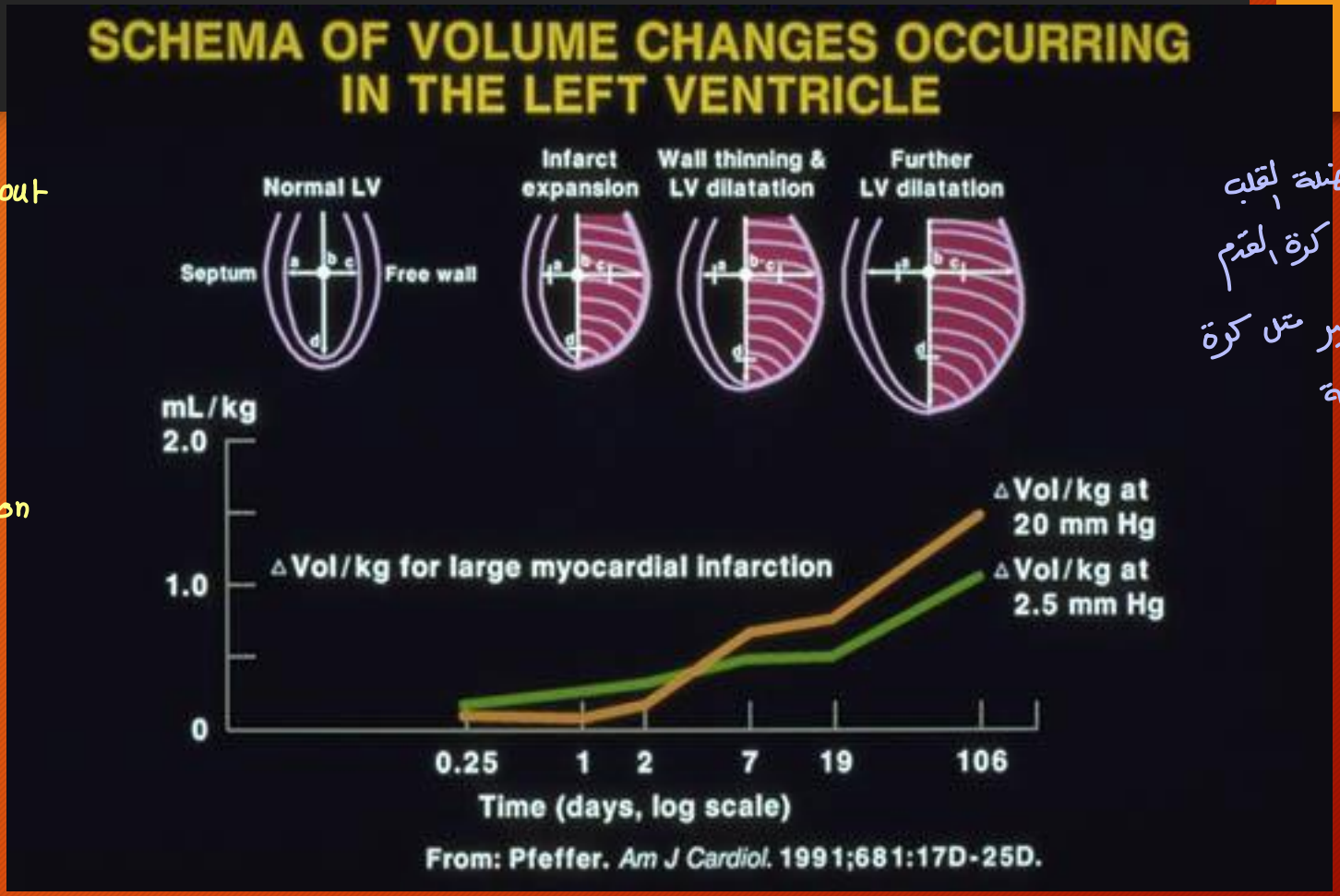
HF → ↓CO → ↓GFR → ↑ renin · activation of renin angiotensin system → ↑ sodium reabsorption
↑ water retention

- Reduced renal blood flow
- Reduced glomerular filtration rate
- Increased renin production
- Increased tubular sodium reabsorption
- Increased free water retention (vasopressin)

Ventricular Remodeling in Heart Failure

Fibrosis

Ventricular Remodeling following MI



If left without treatment: infarct size propagate & increase ↳ regurgitation of mitral & tricuspid & worsening of the HF

بتغير شكل عضلة القلب بدل ما هو متل كرة القدم الأمريكية بصير متل كرة القدم العادية

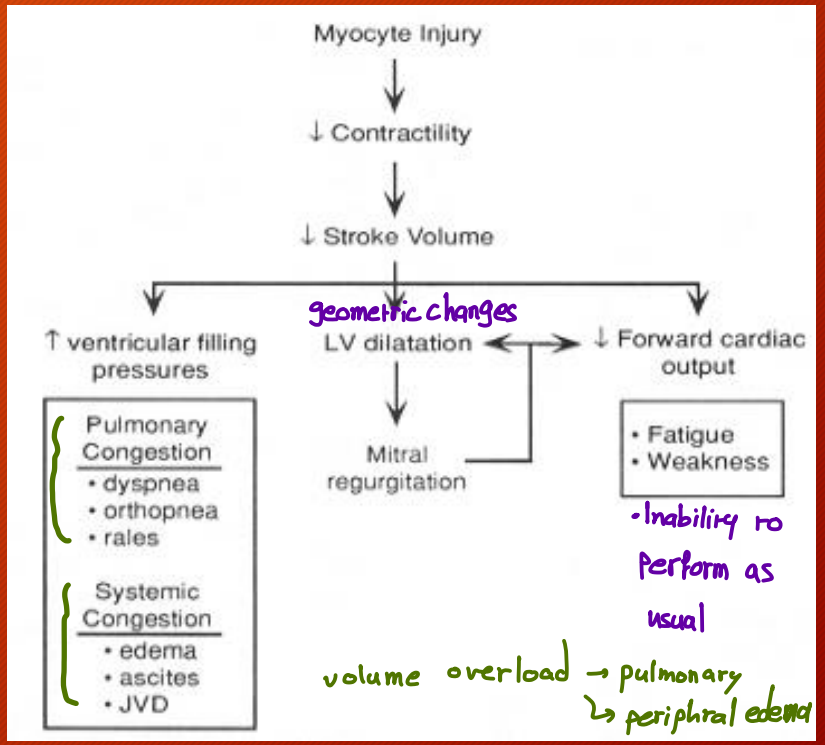
Clinical Findings

Biventricular Congestive Heart Failure

-Low forward Cardiac Output
  -fatigue, lightheadedness, hypotension

-Pulmonary Congestion
  -Dyspnea,
  -orthopnea, & PND

-Systemic Congestion
  -Edema
  -Ascites
  -Weight gain



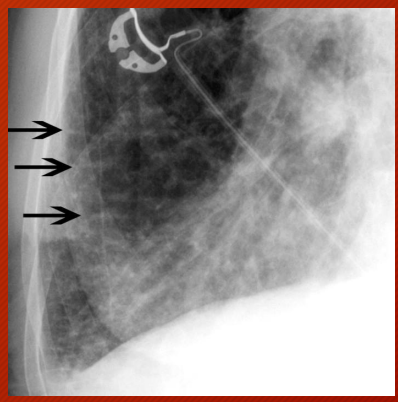
Physical Exam

- Decreased C.O.
  - Tachycardia
  - ↓ BP and pulse pressure
  - cool extremities (vasoconstriction)
  - Pulsus Alternans (end-stage)
- Pulmonary venous congestion:
  - rales
  - pleural effusions
- Cardiac: PE
  - laterally displaced PMI heart is displaced laterally
  - S3 (acutely)
  - mitral regurgitation murmur
- Systemic congestion
  - ↑ JVD
  - hepatosplenomegaly
  - ascites
  - peripheral edema

Diagnostic Studies

↳ **CXR** -enlarged cardiac silhouette, vascular redistribution interstitial edema, pleural effusions

We see: Cardiomegaly, vascular redistribution, Kerley B lines



↳ **EKG** –normal → can show anything: you look for ischemia as the underlying etiology, you look for arrhythmias which can be associated with heart failure espicialy Atrial fibrillation tachycardia, atrial and ventricular enlargement, LBBB, RBBB, Q-waves

↳ Blood Tests the regular blood tests + Brain natriuretic peptide (ANA,RF, Fe^{2+}, TFT's,ferritin,)

↳ **Echocardiography** (the cornerstone to diffrentiate btw systolic & diastolic HF) + also it may give you an idea about the etiology of the HF if the etiology is mitral regurge, amyloidosis

The main test to define the HF type and it's etiology

LV size, wall thickness function valve dz, pressures

↳ **Cardiac Catheterization** 70% of systolic HF is due to coronary artery disease so you have to image the coronaries

you look for:

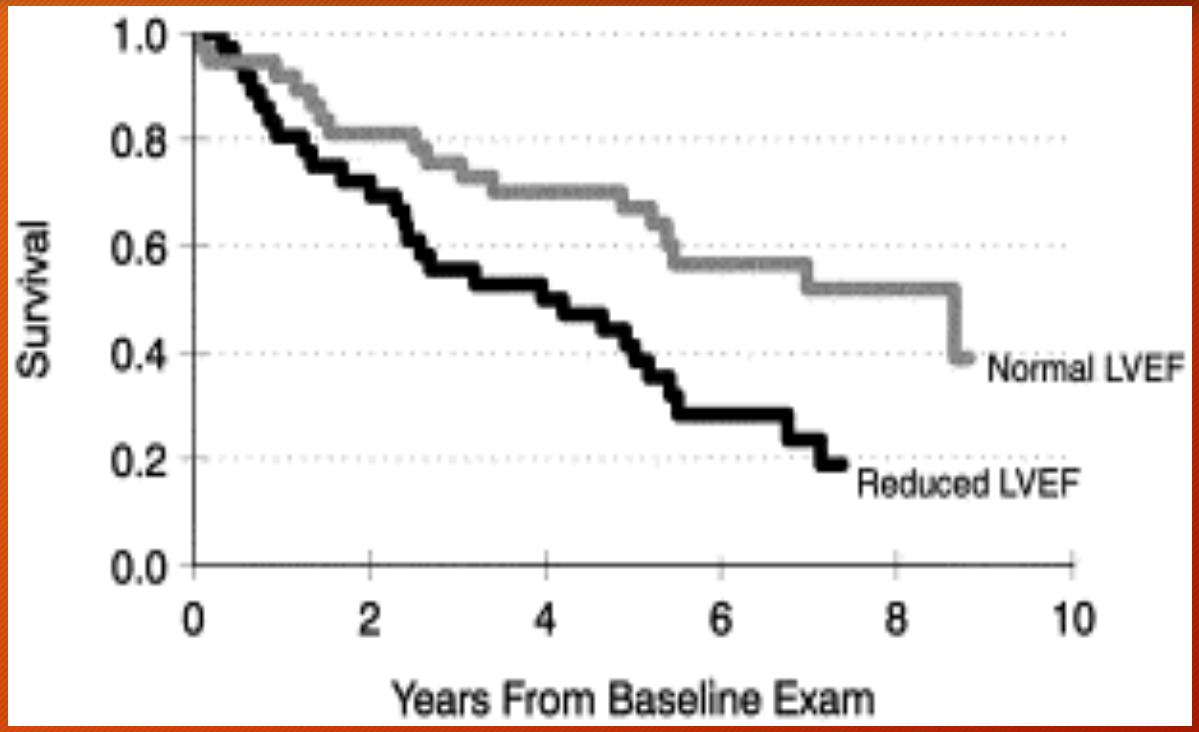
① hemodynamics ↳ certain hemodynamic parameters to find out weither the patient is compensated or decompens- - ated.

② LVEF

③ angiography ↳ and for diagnostic purposes.

↳ **Endomyocardial Biopsy** in certain situations to find out the cause of HF

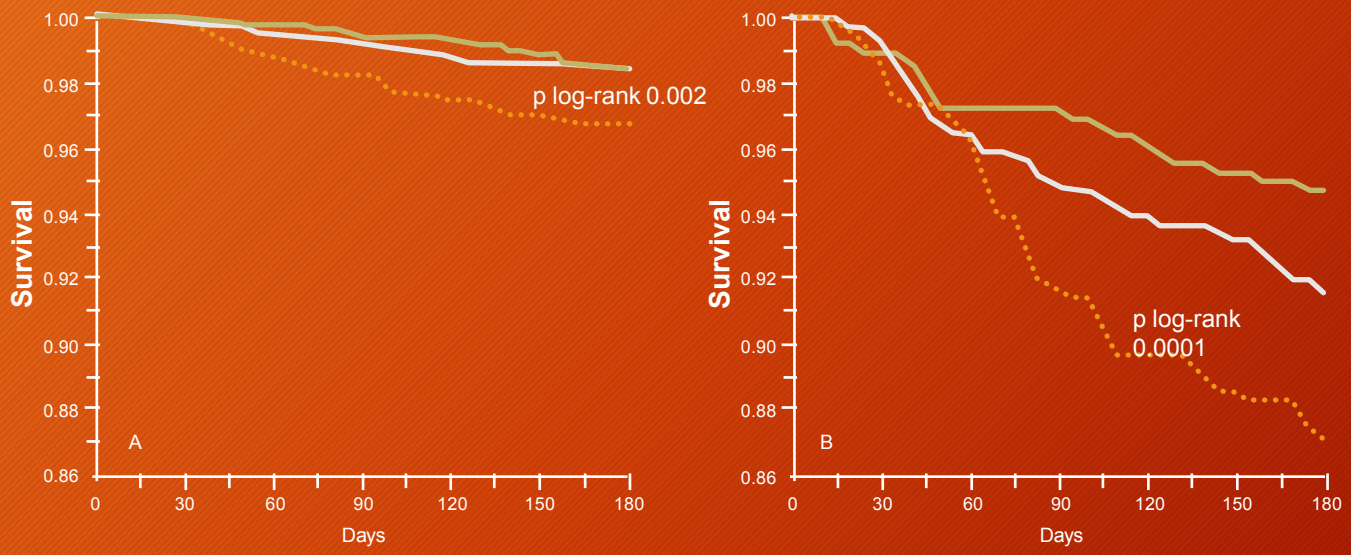
Influence of EF on Survival in Patients with Heart Failure



Vasan RS et al. J Am Coll Cardiol. 1999;33:1948-55

Survival is worse as EF is worse

Risk of Sudden Death c/w EF



Patients without LV Dysfunction

(LVEF >35%)

No PVBs

1-10 PVBs/h

> 10 PVBs/h

Patients with LV Dysfunction

(LVEF ≤ 35%)

Maggioni AP. **GISSI-2 Trial** Circulation. 1993;87:312-322.

HF is a major and growing public health problem

H[5]

~2%

of the population in Europe have HF[1]

~15 million

As many as **1 in 5** people aged 70–80 years have HF[1]

HF is the leading cause of hospitalization in people aged ≥65 years[5,6]

Why HF is on the rise?

① Increasing prevalence of risk factors[5,6]
obesity, smoking
diabetes

② An aging population[5]
nowadays we see more older people

③ Improved post-MI survival[5]
with the thrombolytics, caths & stents

HF=heart failure; MI=myocardial infarction; ‡Calculated using the incidence rate of HF in 1997 for Hong Kong and applying it to the Chinese population

1. Dickstein et al. Eur Heart J 2008;29:2388–442; 2. Go et al. Circulation 2013;127:e6–e245; 3. Allender et al. Coronary Heart Disease Statistics 2008; 4. Hung et al. Hong Kong Med J 2000;6:159–62; 5. Hunt et al. J Am Coll Cardiol 2009;53:e1–90; 6. Kearney et al. Lancet 2005; 365:217–23; ; 5. Forman et al. Am Heart J 2009;157:1010–17; 6. Healthcare Cost and Utilization Project 2009 (http://www.hcup-us.ahrq.gov/reports/factsandfigures/2009/TOC_2009.jsp Accessed January 2013

HF imposes a significant economic burden on the healthcare system

70% OF THE COST OF HF IS **DUE TO HOSPITALIZATIONS**[1]
دخولا تهم متكررة

~**10%** OF THE COST OF HF IS **DUE TO PHARMACOLOGICAL TREATMENT**[2]

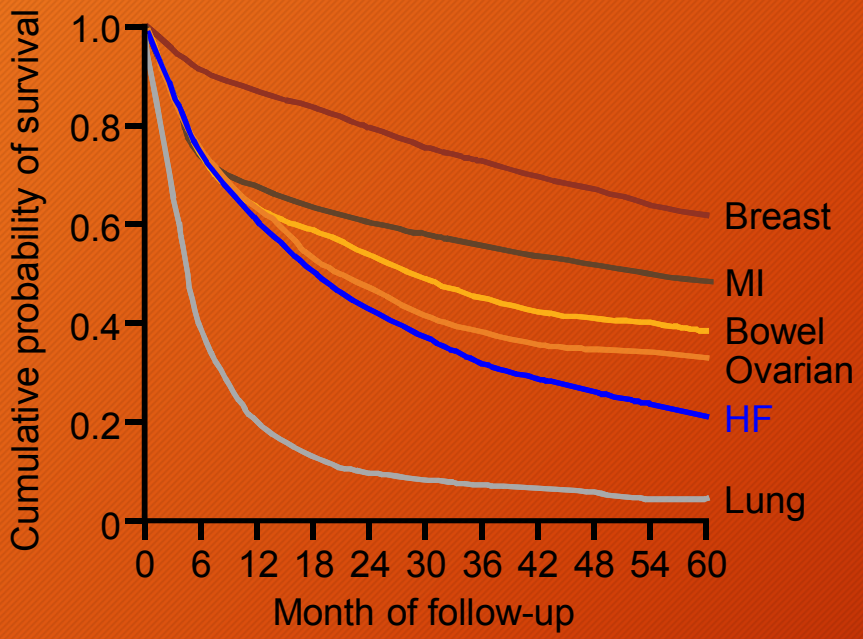
THE TOTAL COST OF HF IN THE USA ALONE IS **EXPECTED TO INCREASE** **~120% by 2030**[‡3]

HF=heart failure; ‡USA estimate includes direct costs (total annual medical spending) and indirect costs (lost productivity due to morbidity and mortality)

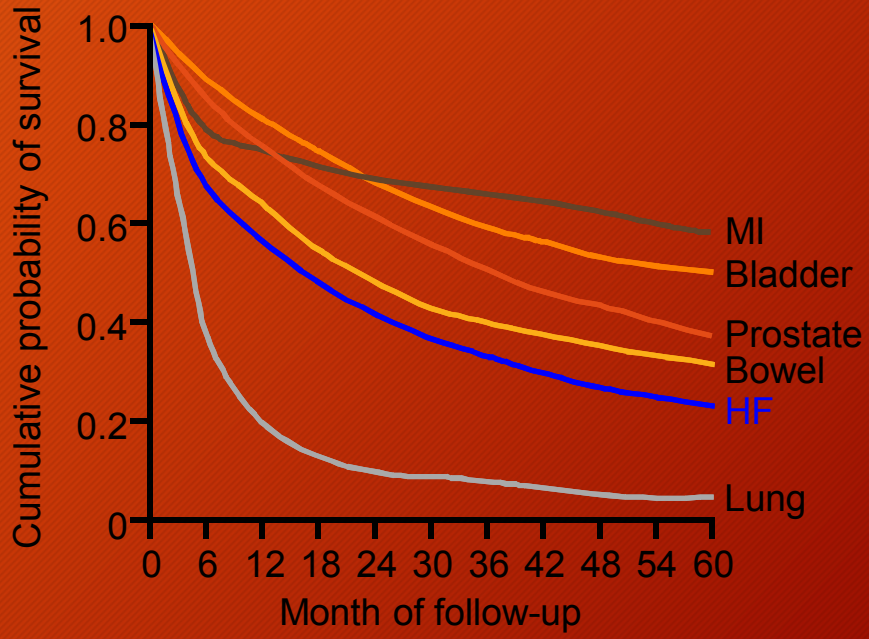
1. Dickstein et al. Eur Heart J 2008;29:2388-442; 2. Hunt et al. J Am Coll Cardiol 2009;53:e1-90; 3.Go et al. Circulation 2013;127:e6-e245

Mortality following admission for acute heart failure exceeds that of most cancers

Female survival rates (%):
HF, MI and other malignancies



Male survival rates (%):
HF, MI and other malignancies

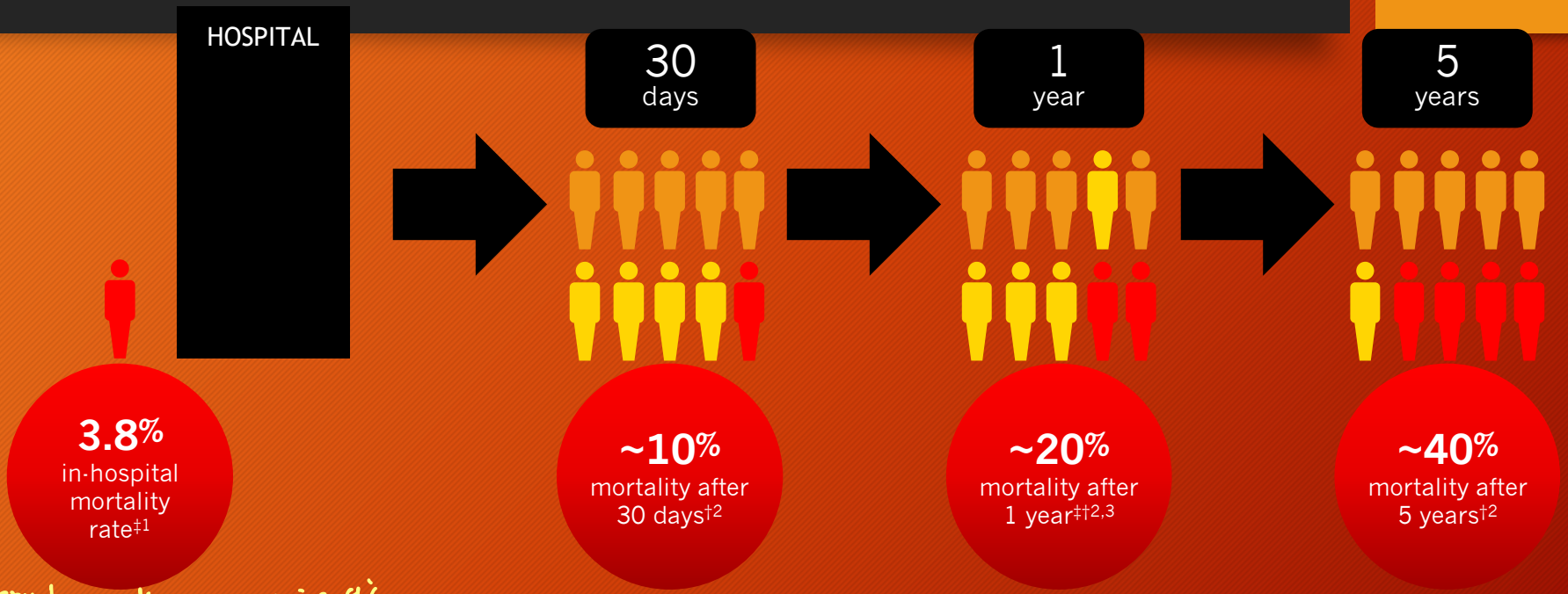


Lung → worse prognosis in both → then comes HF

All patients with a first admission to any Scottish hospital in 1991 for HF, MI or the four most common types of cancer specific to men and women were identified, and 5-year survival rates compared

Stewart et al. Eur J Heart Fail 2001;3:315–22

Still HF is associated with significant mortality



Every hospitalization carries 4% mortality, why?

① [illegible] → needs intubation → Respiratory failure leads to mortality

② patient is taking diuretics → electrolyte imbalance → hypokalemia, hypomagnesemia

③ patient with cardiogenic shock → hypotensive

④ due to poles catheter infection, cannula infection

HF=heart failure

‡Data from 1,892 European patients with acute heart failure in the European Society of Cardiology Heart Failure (ESC-HF) Pilot study

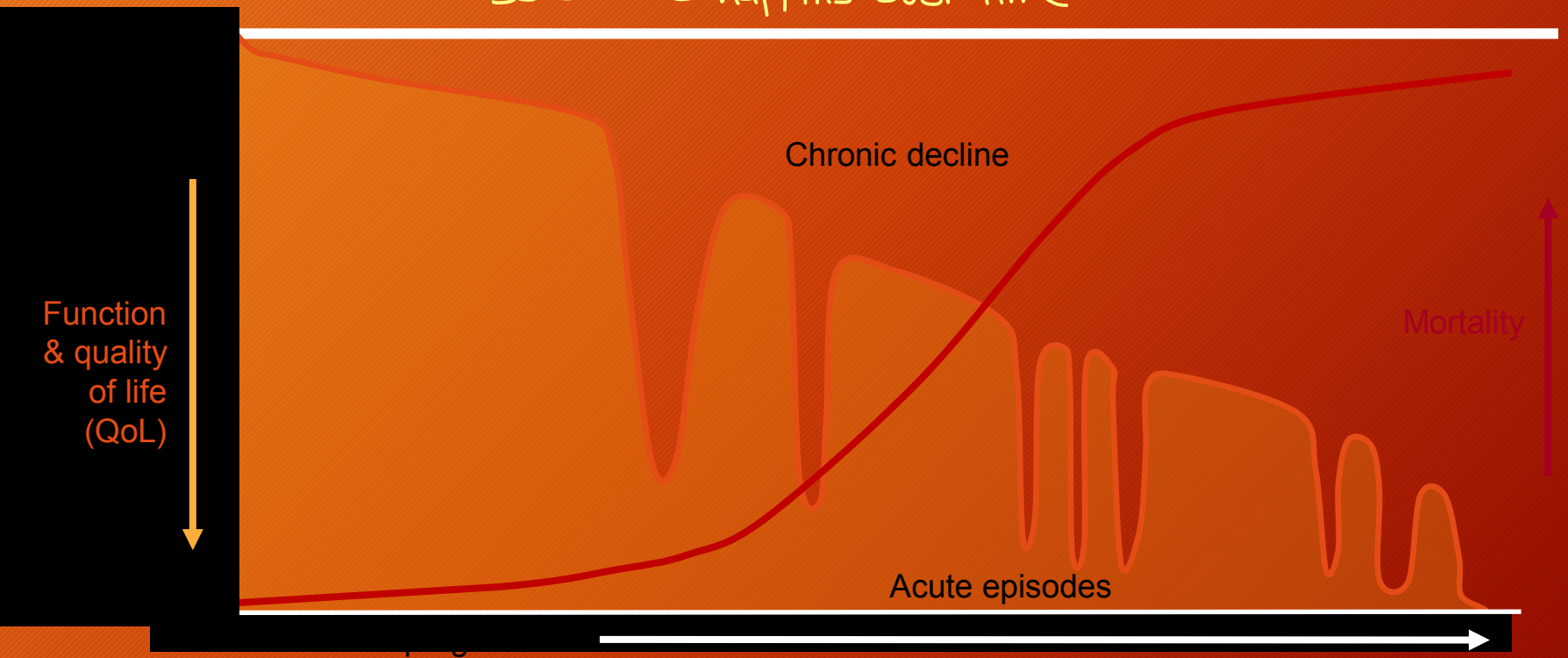
†Analysis of HF data from 1,282 incident cases of heart failure in the Atherosclerosis Risk in Communities (ARIC) population-based study of n=15,792 individuals from four communities in the USA (1987–2002)

1. Maggioni et al. Eur J Heart Fail 2010;12:1076–84; 2. Loehr et al. Am J Cardiol 2008;101:1016–22; 3. Maggioni et al. Eur J Heart Fail 2013;15:808–17

Heart failure is a progressive condition with high morbidity and mortality

- Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality
- With each acute event, myocardial injury may contribute to progressive LV dysfunction

so decline happins over time



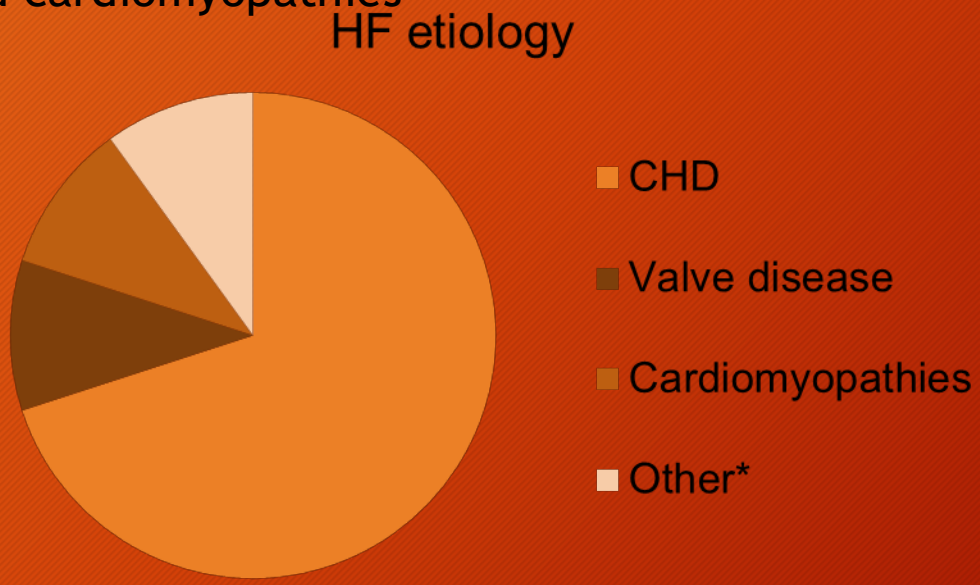
decompensated HF? hyperload

pulmonary congestion

Gheorghiade et al. Am J Cardiol 2005;96:11G–17G;
Gheorghiade & Pang. J Am Coll Cardiol 2009;53:557–73

Heart failure has a number of common causes

- Most patients with HF experience symptoms due to impaired LV myocardial function[1]
- The most common causes of HF are coronary heart disease (CHD), valve disease and cardiomyopathies[2]



*Including hypertension, diabetes, exposure to cardiotoxic agents, peripartum cardiomyopathy, etc.

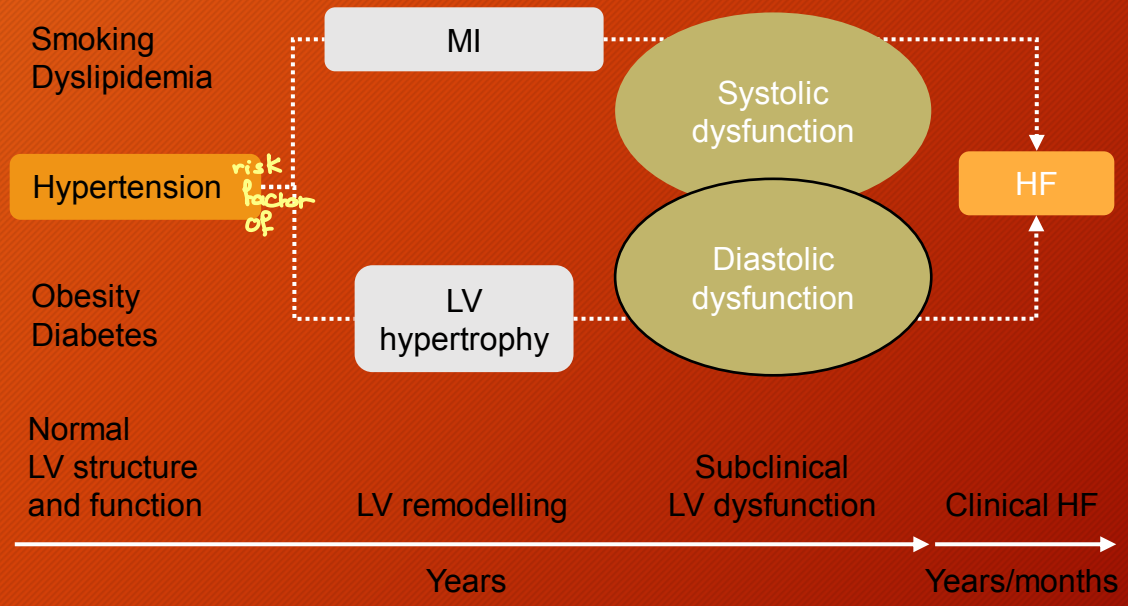
- CHD is the underlying cause of 60–70% of acute HF cases[3]

1. Hunt et al. J Am Coll Cardiol 2009;53:e1–90
2. Dickstein et al. Eur Heart J 2008;29:2388–442
3. Nieminen et al. Eur Heart J 2005;26:384–416

LV = left ventricular

High Prevalence of multiple co-morbidities

- Many patients with chronic HF have a range of co-morbidities that contribute to the cause of the disease and play a key role in its progression and in the response to therapy
  - hypertension*
  - ischemic heart disease*
  - diabetes mellitus
  - cardiac arrhythmias
  - ventricular arrhythmias
  - atrial fibrillation
  - respiratory disorders
  - cognitive dysfunction
  - hyperlipidemia
  - chronic anemia
  - renal failure
  - arthritis



- This can result in patients burdened with multiple pills per day, each with different dosage schedules, with an increased potential for drug–drug interactions

*Major contributors to development of HF

Krum, Gilbert. Lancet 2003;362:147–58

Guideline Development

ACCF-AHA 2013

ESC 2012

HFSA 2010

NICE AHF 2014/ CHF 2010

Level of Evidence	
A	Multiple populations evaluated* Data from **multiple randomized clinical trials** or meta-analyses ACG
B	Limited populations evaluated* Data from **single randomized clinical trial** or nonrandomized studies
C	Very limited populations evaluated* **Consensus of opinion** of the experts, case studies, or standard-of-care

Class of Recommendation	
I	**Benefit >>> Risk** Procedure/Treatment ***SHOULD*** be performed/administered
IIa	**Benefit >> Risk** (Additional studies with focused objectives needed) ***IT IS REASONABLE*** to perform procedure/administer treatment probable
IIb	**Benefit ≥ Risk** (Additional studies with broad objectives needed; additional registry data would be helpful) Procedure/Treatment ***MAY BE CONSIDERED*** possible
III	**No Benefit**: Procedure/test is not helpful and treatment has no proven benefit **Harm**: Procedure/test is expensive, without benefit or harmful, and treatment is potentially harmful to patients

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

Heart Failure Definition

Heart Failure

the guidelines define **heart failure (HF)** as a clinical syndrome in which patients have **typical symptoms and signs** resulting **from** an **abnormality of cardiac structure or function** which **impairs the ability of the ventricle to fill with or eject blood**.

- **symptoms** (e.g. breathlessness, orthopnea, paroxysmal nocturnal dyspnoea, ankle swelling, fatigue, and reduced exercise tolerance)
- **signs** (e.g. elevated jugular venous pressure, hepatojugular reflux, third heart sound [gallop rhythm], cardiac murmur, and displaced apex beat)

Acute HF is recognized as **a separate entity** by most of the guidelines**, except AHA 2013** and HFSA 2010.

- AHF is defined as the rapid onset of (de novo), or change in, symptoms and signs of HF (decompensated HF)

AHF, acute heart failure; HF, heart failure

Classification of Heart Failure

Based on the LVEF

Based on the Functional Status

Based on Clinical Progression

Based on Hemodynamic Status

The guidelines differ with respect to the LVEF cut-off limits for classification of HF as HFrEF and HFpEF

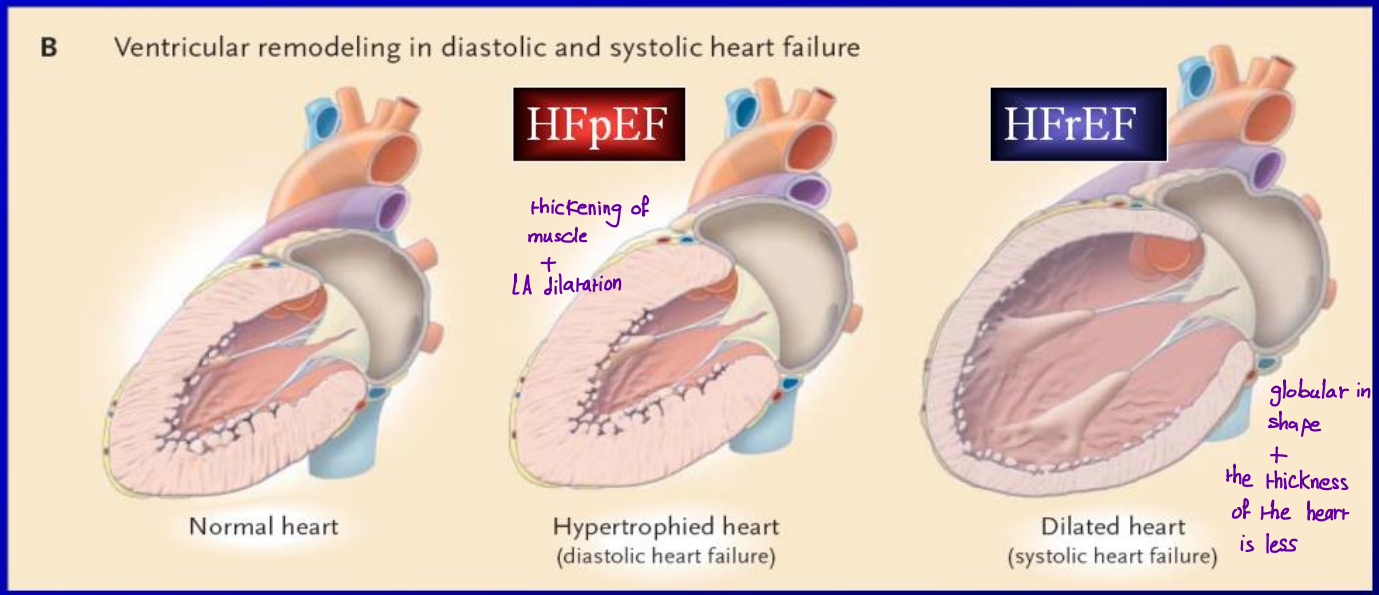
Types	ACCF-AHA 2013	ESC 2012	HFSA 2010	NICE 2010
HFrEF	≤40%	≤35%	<50%	No thresholds of LVEF defined
HFpEF	≥50% MRHF → mildly reduced HF • 41%-49% (HFpEF, borderline) • >40% (HFpEF, improved) ٤٠٪ ارتفع لـ ٣٥٪ كانت	>50% • 35–50% 'grey area'; most probably have primarily mild systolic dysfunction	≥50%	

10 point rise from what it was to what we are ⇓ HF with improved EF

HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction

HF with preserved EF (HFpEF;HFnEF;DHF) vs HF with reduced EF (HFrEF;SHF): distinct HF phenotypes

olvg



HFpEF:
* Preserved systolic LV function
* No LV dilatation
* Concentric LV remodeling/hypertrophy
* Diastolic LV dysfunction

HFrEF:
* Systolic LV dysfunction
* LV dilatation
* Eccentric LV remodeling
* Diastolic LV dysfunction

Jessup, NEJM 2003;348:2007

Classification of Heart Failure

- Based on the LVEF
- **Based on the Functional Status**
- Based on Clinical Progression
- Based on Hemodynamic Status

The guidelines classify patients with HF based on the severity of their symptoms and physical activity (New York Heart Association [NYHA] functional classification)

Class	Severity of symptoms and limitation of physical activity
I	**No limitation** of physical activity low EF but functioning normally Ordinary physical activity does not cause symptoms of HF (breathlessness, fatigue, or palpitations)
II	**Slight limitation** of physical activity Comfortable at rest, but **ordinary physical activity results in symptoms of HF**
III	**Marked limitation** of physical activity leads to dyspnea Comfortable at rest, but **less than ordinary physical activity causes symptoms of HF***
IV	**Unable** to carry on any physical activity without discomfort/symptoms of HF, or symptoms of HF at rest may be present If any physical activity is undertaken, discomfort is increased

HF, heart failure; NYHA, New York Heart Association

Classification of Heart Failure

Based on the LVEF

Based on the Functional Status

Based on Clinical Progression

Based on Hemodynamic Status

- ACCF-AHA 2013 guidelines classify patients with HF based on the development and progression of HF
- **These stages provide complementary information to the NYHA classification regarding the severity of HF**

Stages of HF	Development and progression of HF	Corresponding NYHA Class
A	At **high risk** for HF but **without structural heart disease or symptoms** of HF	**None**
B	**Structural** heart disease but **without signs or symptoms** of HF	**I**
C	**Structural** heart disease **with prior or current symptoms** of HF	**I**
		II
		III
D	**Refractory HF** requiring specialized interventions	**IV**

HF, heart failure; NYHA, New York Heart Association

Classification of Heart Failure

- Based on the LVEF
- Based on the Functional Status
- Based on Clinical Progression
- **Based on Hemodynamic Status**

perfusion or congestion

ACCF-AHA 2013 guidelines classify hospitalized patients with HF based on their hemodynamic status, including the degree of congestion ("dry" versus "wet"), as well as the adequacy of peripheral perfusion ("warm" versus "cold")

		Congestion at rest? (e.g. orthopnea, elevated jugular venous pressure, pulmonary rales, S3 gallop, edema)	
		No	**Yes**
Low perfusion at rest? (e.g. narrow pulse pressure, cool extremities, hypotension)	**No**	best scenario Warm and Dry appropriate ↵ CO ↳ no congestion compensated	Warm and Wet
	Yes	Cold and Dry	Most difficult & challenging patients to treat Cold and Wet Low perfusion ↵ Fatigue ↳ congested e.g. ↳ 70/50 cardiogenic shock, congested Pt.

HF, heart failure

Symptoms


LEFT SIDED FAILURE
• Paroxysmal Nocturnal Dyspnea
• Elevated Pulmonary Capillary Wedge Pressure
• Pulmonary Congestion
- Cough
- Crackles
- Wheezes
- Blood-Tinged Sputum
- Tachypnea
• Restlessness
• Confusion
• Orthopnea
• Tachycardia
• Exertional Dyspnea
• Fatigue
• Cyanosis
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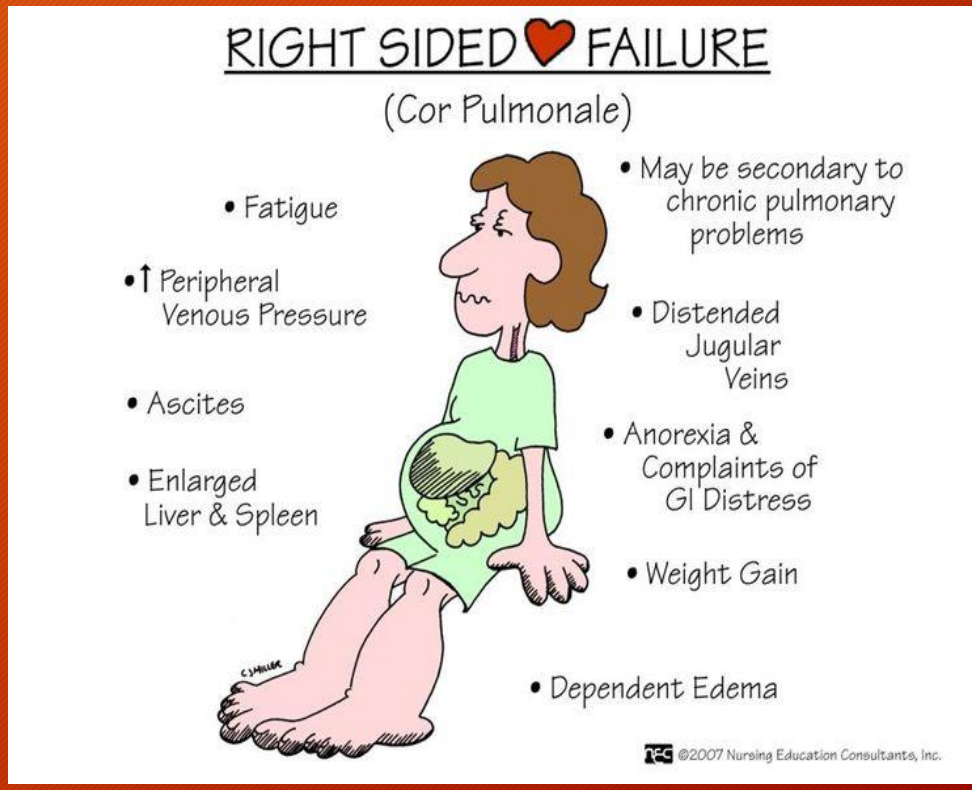
RIGHT SIDED FAILURE
(Cor Pulmonale)
• Fatigue
• ↑ Peripheral Venous Pressure
• Ascites
• Enlarged Liver & Spleen
• May be secondary to chronic pulmonary problems
• Distended Jugular Veins
• Anorexia & Complaints of GI Distress
• Weight Gain
• Dependent Edema
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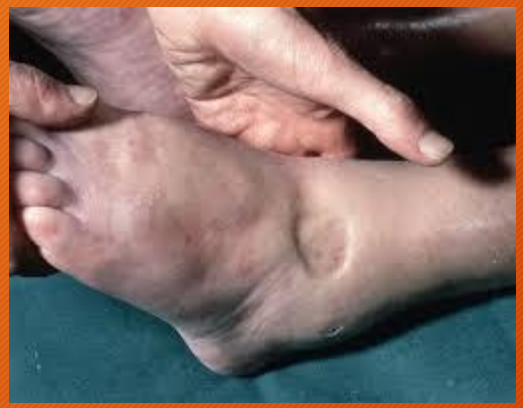
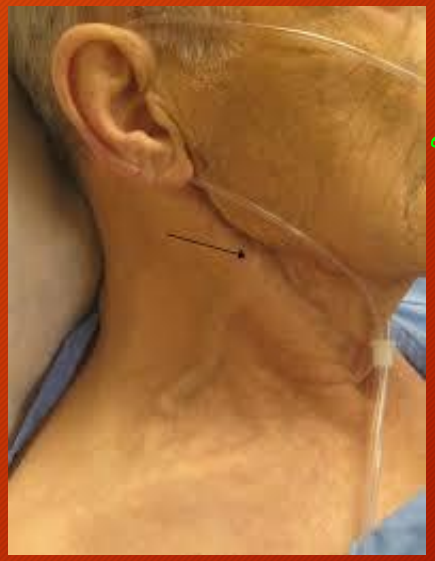
Signs

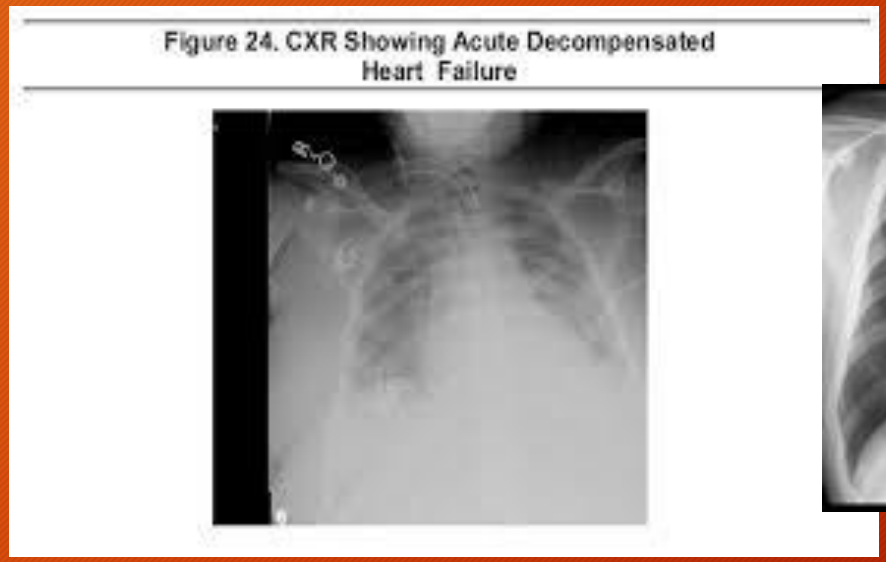
Pitting edema

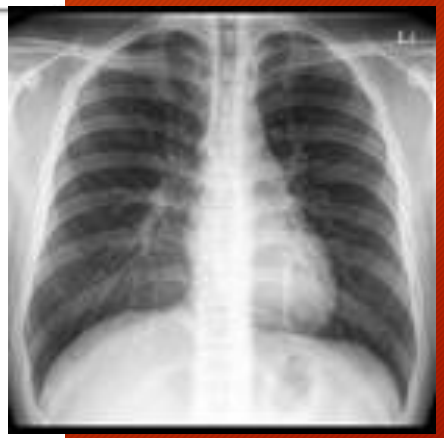


increas in weight



elevated JVP



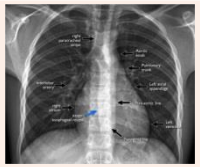


CXR showing congested lungs

Fissure line

edema

Investigations to consider in all patients

Method	ESC*	Purpose
ECG	IC	Shows the heart rhythm and electrical conduction. Important for decisions about treatment (e.g. rate control and anticoagulation for AF, pacing for bradycardia, or CRT if the patient has LBBB). It may show evidence of LV hypertrophy or Q waves (indicating loss of viable myocardium), giving a possible clue to the etiology of HF.
Chest X-ray 	IIaC	Most useful in identifying an alternative, pulmonary explanation for a patient's symptoms and signs. It may show pulmonary venous congestion or edema in a patient with HF.
Echocardiogram 	IC	Provides immediate information on chamber volumes, ventricular systolic and diastolic function, wall thickness, and valve function.

The echocardiogram and electrocardiogram are the most useful tests in patients with suspected HF

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

Investigations to consider in selected patients

Laboratory tests

Method	ESC*	Purpose
Biochemical and hematological investigations 	IC	1. Determine whether RAAS blockade can be initiated safely (renal function and potassium). 2. Exclude anemia (can mimic or aggravate HF).
Natriuretic Peptide (NP) Brain Renal Function	IIaC	1. Where the availability of echocardiography is limited, an alternative approach to diagnosis is to measure the blood concentration of NP. **2. NP levels also increase with age, renal insufficiency, but may be reduced in obese patients.** **3. A normal NP level in an untreated patient virtually excludes significant cardiac disease, making an echocardiogram unnecessary.**

*ESC recommendation, class and level of evidence

NP: natriuretic peptide; RAAS: renin-angiotensin-aldosterone system

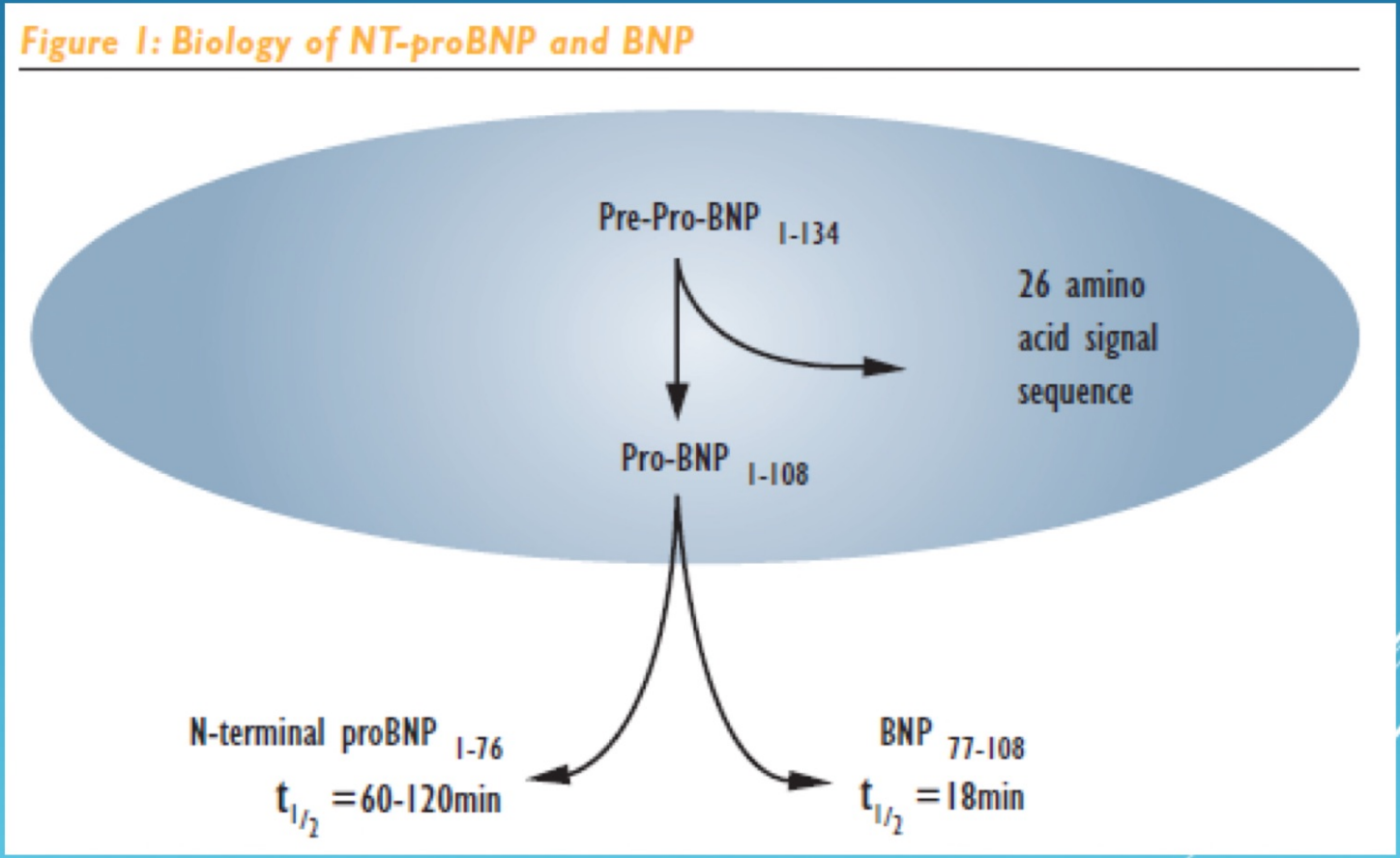
McMurray et al. Eur Heart J 2012;33:1787–847

CARDIAC NATRIURETIC PEPTIDES

- What is BNP?
  - A 32 amino acid polypeptide
  - Belong to a class of structurally similar natriuretic peptides (classes A,B,C and D)
  - Secreted by cardiac myocytes (mainly left) in response to excessive distension of the Heart ventricles
  - Similar to ANP (Atrial Natriuretic Peptide) but has longer t1/2 (~20mins, double that of ANP)
    Named after extracts found in Pig-brain
- What is NT-proBNP?
  - NT-proBNP is a biologically inactive 76 amino acid N-terminal fragment
  - Co-secreted with BNP
  - Even longer t1/2 than BNP (~1-2hrs vs ~20mins)
- Biological effects of Cardiac Natriuretic peptides
  - Increase Natriuresis

SYNTHESIS IN MYOCYTES

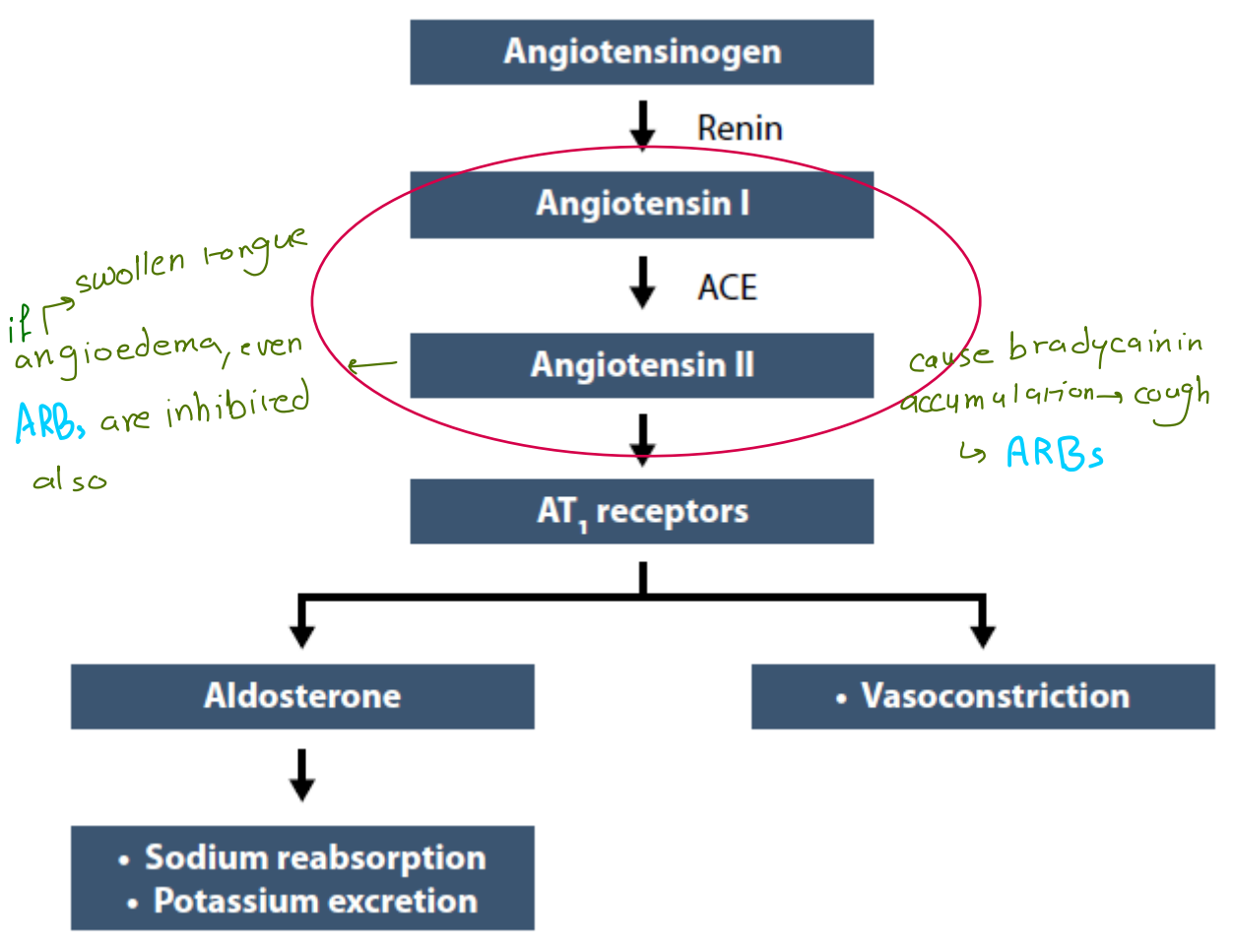
- Synthesis



What are the oral pharmacological options?

What are the oral pharmacological options?

ACEIs: how they work - RAAS



ACEI: types, brands, indications

Types of ACEI	Brands®	Indications
Captopril	Capoten	Chronic HF
Enalapril	Renitec*	Symptomatic HF
Fosinopril sodium	None	Congestive HF
Lisinopril	Zestril*	Symptomatic HF
Perindopril	Coversyl*	Symptomatic HF
Quinapril	Acuitel*	Congestive HF
Ramipril	Tritace*	Symptomatic HF

*A non-proprietary drug is available for all these brands.

- 4 ACEi's are indicated for (reduced EF) heart failure (**captopril, enalapril, lisinopril, quinapril)**
- 2 ACEi (**ramipril and trandolapril**) are indicated for heart failure post-MI

هو موجودة بالجديد

ACEIs: risks

Hypotension

Worsening renal function

↓GFR

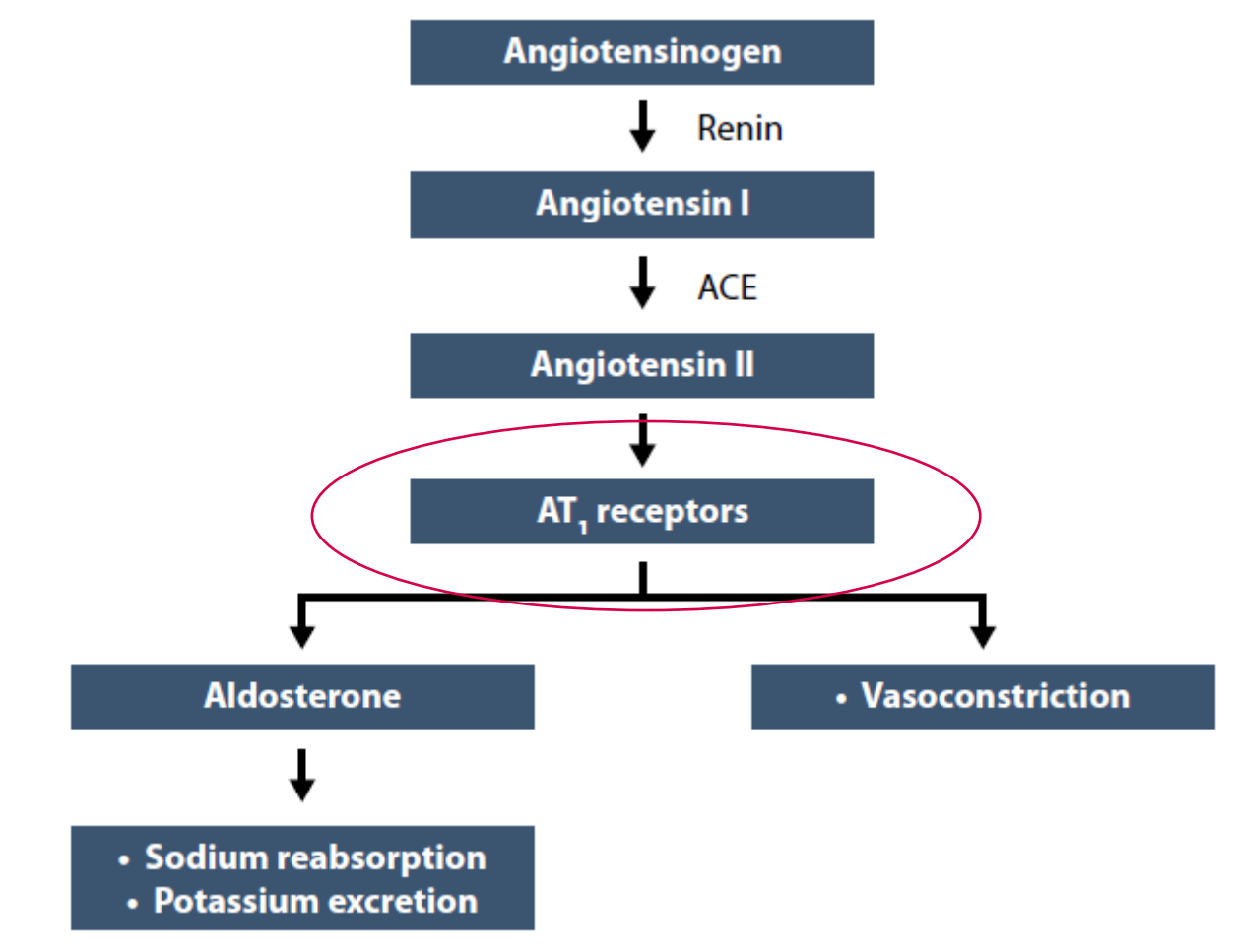
Raised potassium levels

↑ K^+

Persistent cough

Angiotensin II receptor blockers (ARBs)

ARBs: how they work - RAAS



ARBs: dosage

Types of ARB	Dosage
Candersartan	4 mg once daily, increased at ≥2 week intervals to 32 mg once daily
Losartan	12.5 mg once daily, increased weekly. Max dose 150 mg/day
Valsartan	40 mg twice daily, increased at ≥2 week intervals. Max dose 160 mg twice daily

هو موجودة بالجديد

*A non-proprietary drug is available for all these brands.

ARBs: risks

Dizziness

Hypotension

Hyperkalaemia

$\uparrow K^+$

مو موجودة بالجهيه

Adrenergic beta antagonist/blockers (BBs)

membrane stabilizer for myocytes / ↓demand → ↑ perfusion ↑ CO

Beta blockers: the facts

-ve ionotrope, cronotrope

Types of ARB	Brands®	Indications
Bisoprolol	Cardicor*	Stable chronic HF with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides
Carvedilol	None	Symptomatic chronic HF, as adjunct to diuretic, digoxin or ACEI
Nebivolol	Nibilet, Hypoloc*	Stable mild-moderate chronic HF in patients aged ≥70 years, as adjunct therapy

has NO
no risk on sexual

given when pt is in u-volumeia

*A non-proprietary drug is available for all these brands.

هو موجودة بالجبديه

Beta blockers: risks (1)

Side effects (excluding rare and very rare)	Bisoprolol	Carvedilol	Nebivolol
Bronchospasm	✓	✓	✓
Gastrointestinal disturbance	✓	✓	✓
Bradycardia	✓	✓	✓
Headache	✓	✓	✓
Fatigue	✓	✓	✓
Dizziness	✓	✓	✓
Paraesthesia	✓	✓	✓
Heart failure	✓		✓
Hypotension	✓	✓	✓
Conduction disorders	✓		✓
Peripheral vasoconstriction, e.g. claudication and Raynaud's	✓		✓
Dyspnoea	✓	ð	✓
Sleep disturbances	✓		✓
Vertigo	✓		✓
Psychosis	✓		✓
Sexual dysfunction	✓		✓

ð Postural hypotension. Δ Exacerbation of previous condition. ∏ Also eye irritation. ∫ Also painful extremities.

Mineralocorticoid receptor antagonists (MRAs)

Mineralocorticoid antagonists (MRAs): the facts

AKI, hypercalemia

care: advanced renal failure not used

Mechanism of action	Indication	Types & brands
Inhibit the binding of aldosterone to the mineralocorticoid receptor	Adjunct therapy for patients who continue to demonstrate symptoms of HF despite treatment with both ACEI and BB	1. Spironolactone (Aldactone®)* 2. Eplerenone (Inspra®)**
Dosage	**Risks**	**Key trials**
Both start at relatively low dose, then titrated up according to efficacy and tolerability	Both agents associated with gastrointestinal disturbances, dizziness, electrolyte disturbances, gynaecomastia and renal impairment	RALES (Spironolactone) EMPHASIS-HF (Eplerenone)

*A non-proprietary drug is available
** A non-proprietary drug is not available

Diuretics


What are the oral pharmacological options?
Angiotensin -converting enzyme inhibitors (ACEIs)
Angiotensin receptor antagonist/ blockers (ARBs)
Adrenergic beta antagonist/ blockers (BBs)
Mineralocort -icoid receptor antagonists (MRAs)
Diuretics
Ivabradine
Digoxin
Hydralazine and isosorbide dinitrate

Diuretics: the facts

Mechanism of action	Indication	Types & brands
Thiazide diuretics - inhibit the reabsorption of sodium in the kidney's distal convoluted tubule Loop diuretics - inhibit absorption from the kidney's loop of Henle	Patients with HF who are deemed to have fluid overload	1. Bendroflumenthiazide (thiazide) (Aprinox®, Neo-Naclex®)* 2. Chlortalidone (thiazide-related) (Hygroton®)** 3. Furosemide (loop) (Rusyde®, Frusol®)* 4. Bendroflumenthiazide (loop)(Torem®)*
Dosage	**Risks**	**Key trials**
Bendroflumenthiazide: 5-10 mg daily Chlortalidone: 25-30 mg daily Furosemide: 40 mg mg daily Bendroflumenthiazide: 5 mg daily	Both types of diuretics associated with mild gastrointestinal side effects, postural hypotension, metabolic and electrolyte disturbances, blood disorders	Paucity of trial evidence for the efficacy of diuretics in HF. They are recommended for their beneficial effects on dyspnoea and oedema

*A non-proprietary drug is available

** A non-proprietary drug is not available

Lasix class 1C → life saving

Ivabradine


What are the oral pharmacological options?
Angiotensin -converting enzyme inhibitors (ACEIs)
Angiotensin receptor antagonist/ blockers (ARBs)
Adrenergic beta antagonist/ blockers (BBs)
Mineralocort -icoid receptor antagonists (MRAs)
Diuretics
Ivabradine
Digoxin
Hydralazine and isosorbide dinitrate

- Acts as a specific bradycardic agent, lowers heart rate by specific action on the sino-atrial node controlled by If current without affecting other cardiac ionic currents. It has no negative inotropic effect and has beneficial effects on left-ventricular systolic dysfunction. The only negative effects are vision disturbances which are mild and transient.

for pt. have contraindin to β-blocker

cause sinus arrythemia

- Ivabradine is the first selective sinus node If channel inhibitor that results in a decrease in the slope of the diastolic depolarization in the SA node cells
- It is rapidly and almost completely absorbed after oral administration with a peak plasma level reached in approximately 1 hour under fasting condition.
- The absolute bioavailability of the 10mg dose is around 40%
- No side effects like sexual disturbances, respiratory side effects, bradycardia or rebound phenomena

- Indication
- Angina pectoris (2005) CHF (2012 in EU, 2015 in US); for use in heart failure patients inadequately controlled with optimal dose of beta-blocker (or intolerant) and whose heart rate is >75 bpm in EU and ≥70 bpm in US

Digoxin


What are the oral pharmacological options?
Digoxin
Hydralazine and isosorbide dinitrate
Angiotensin -converting enzyme inhibitors (ACEIs)
Angiotensin receptor antagonist/ blockers (ARBs)
Adrenergic beta antagonist/ blockers (BBs)
Mineralocort -icoid receptor antagonists (MRAs)
Diuretics
Ivabradine

Digoxin

high toxicity
narrow safe index
↓ stay in hospital
placebo ما حد

Cardiac glycoside

Addresses heart failure symptoms by increasing myocardial contraction and reducing conductivity in atrioventricular node

Generally considered for patients with persistent symptoms

Despite other treatments - ACEI and BB + other agents e.g. spironolactone, ARB, or hydralazine/nitrate

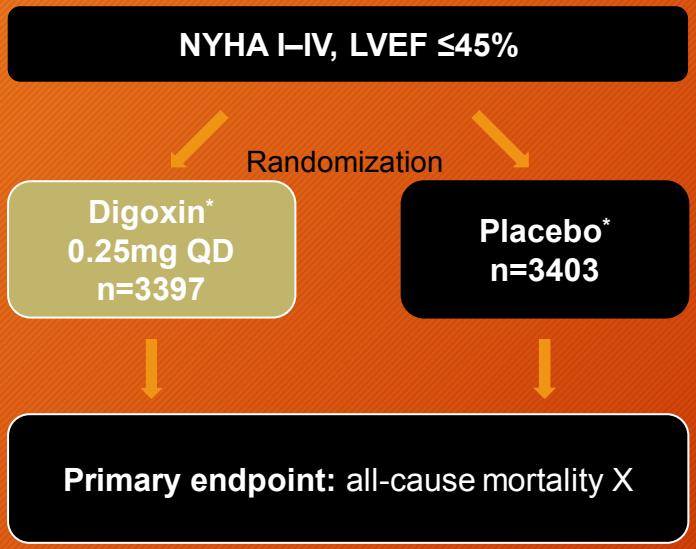
Digoxin: the facts

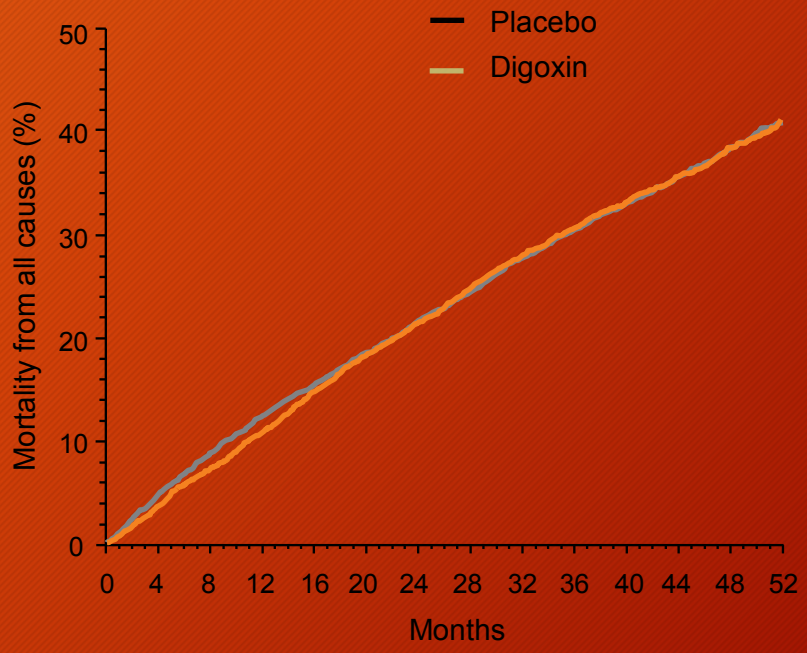
Mechanism of action	Indication	Brand
Improves the symptoms of HF by increasing myocardial contraction and reducing conductivity in the atrioventricular node	Chronic HF dominated by systolic dysfunction. Its therapeutic benefit is greatest in those patients with ventricular dilatation	Lanoxin®*
Dosage	**Side effects**	**Key trial**
62.5 mg -125 mg once daily	variable Nausea, vomiting, diarrhoea, arrhythmias, conduction disturbances, dizziness, visual disturbances, rash, eosinophilia and, less commonly, depression bidirectional V tachy	DIG

*A non-proprietary drug is available

Digitalis (1997)

Digoxin in patients with chronic heart failure





Conclusions: Digoxin* did not reduce all-cause mortality but reduced hospitalization and worsening HF

*On top of diuretics and ACEIs

LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; QD: once daily

The Digitalis Investigation Group. N Engl J Med 1997;336:525–533

مو موجودة بالجديد

Hydralazine and isosorbide dinitrate

Hydralazine and isosorbide dinitrate: the facts

safe on kidney

Mechanism of action	Indication	Brand
Both have vasodilatory (and hence hypotensive) effects, while nitrate therapy also reduces venous return, thereby lessening the work of the left ventricle	Moderate-severe congestive HF (reduces afterload), where optimal doses of diuretics and cardiac glycosides prove insufficient. In patients with high left ventricular filling pressure, it is recommended to combine hydralazine with a nitrate	Apresoline®*
Dosage	**Side effects**	**Key trial**
25 mg 3-4 times daily, increased every 2 days if necessary. Usual maintenance dose 50-75 mg 4 times daily	Both agents may cause tachycardia, flushing, hypotension, gastrointestinal effects, headache, dizziness	A-HeFT

*A non-proprietary drug is available

A-HeFT trial (2004)

Hydralazine-Isosorbide Dinitrate in black patients with advanced HF

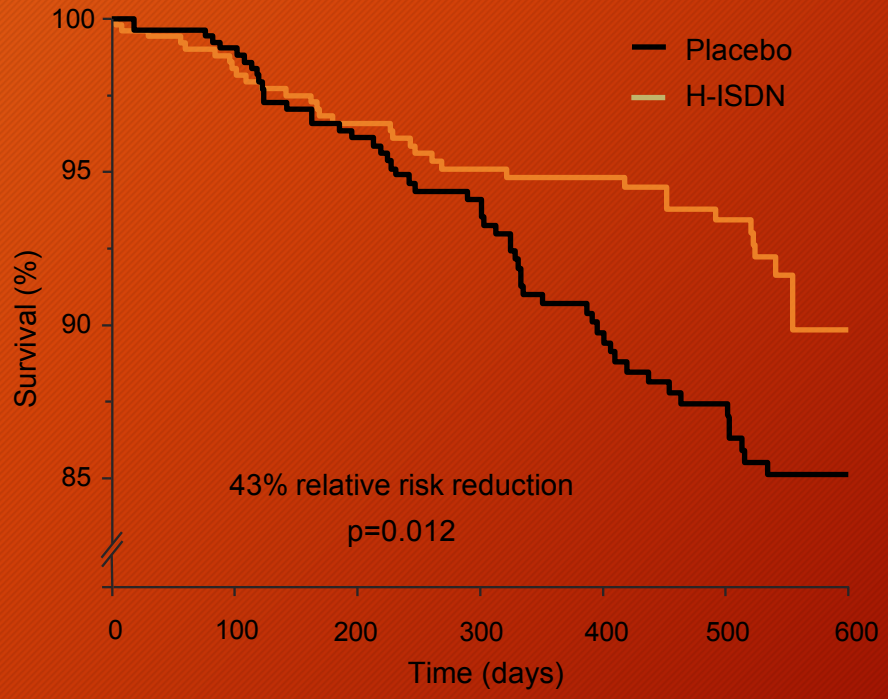
NYHA III–IV, LVEF ≤35%

Randomization

H-ISDN* 225/120 mg QD n=518

Placebo* n=532

Primary endpoint: composite of death, first hospitalization for HF



Conclusions: H-ISDN plus standard therapy significantly increased survival vs placebo among black patients with advanced HF

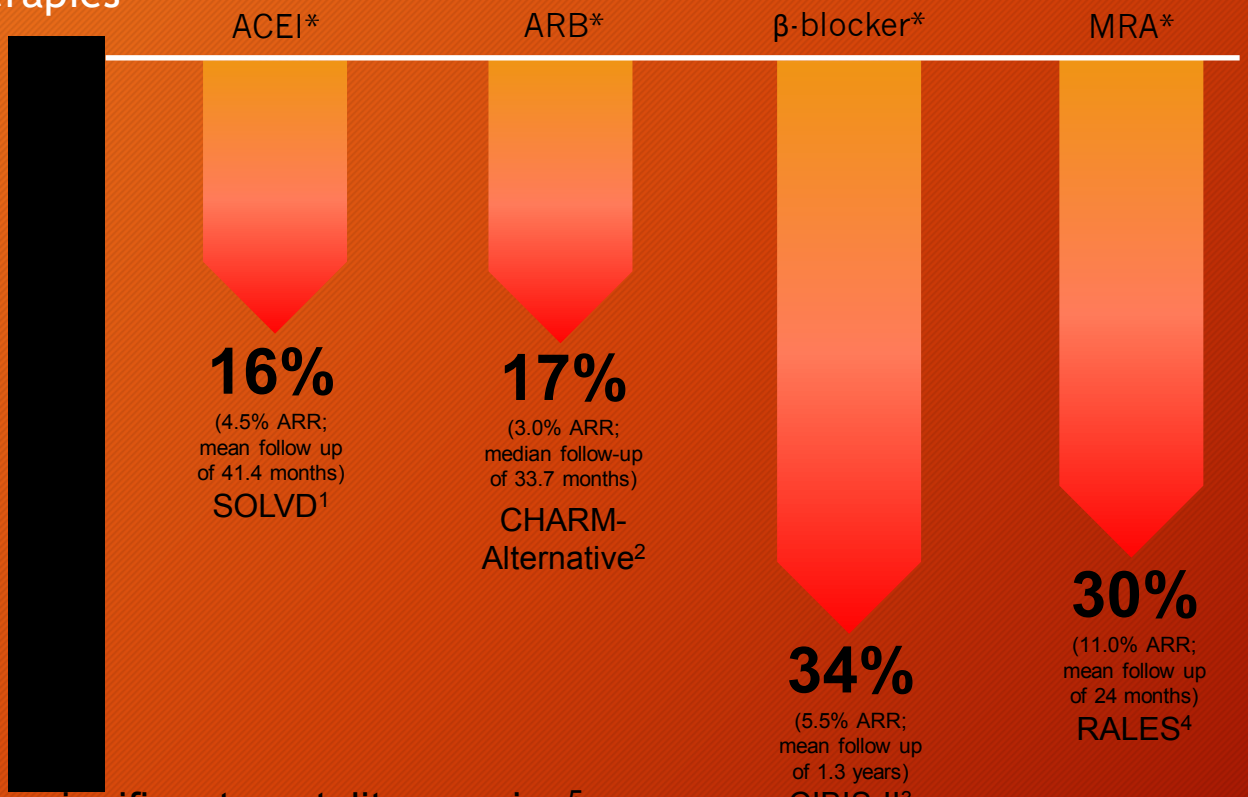
*On top of standard therapy for HF

H-ISDN: Hydralazine-Isosorbide Dinitrate; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; QD: once daily

Taylor et al. N Engl J Med 2004;351:2049–2057

Successful intervention by adressing neurohormonal activiation

- Chronic HFrEF survival rates have improved over time with the introduction of new therapies

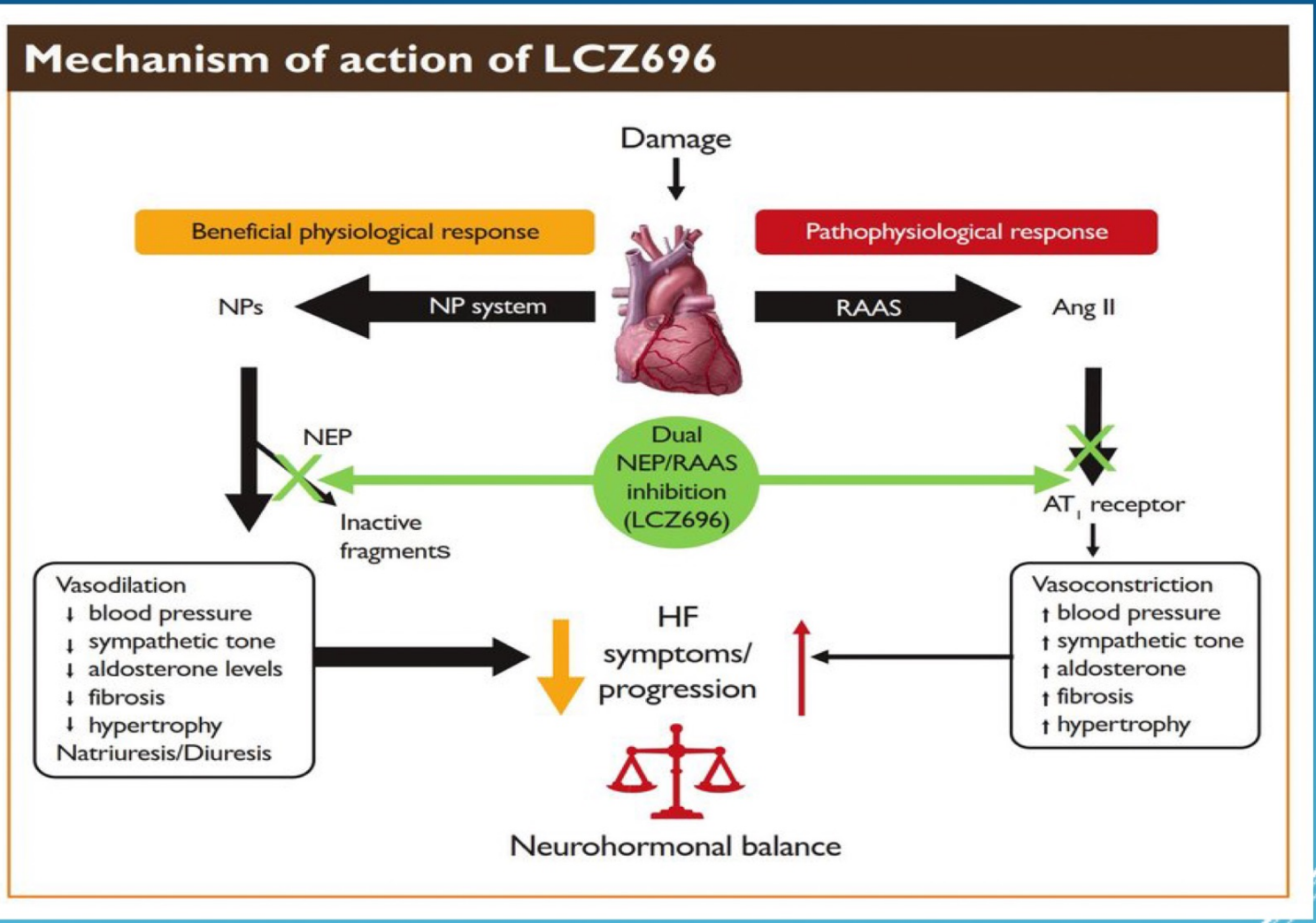


- However, significant mortality remains[5]

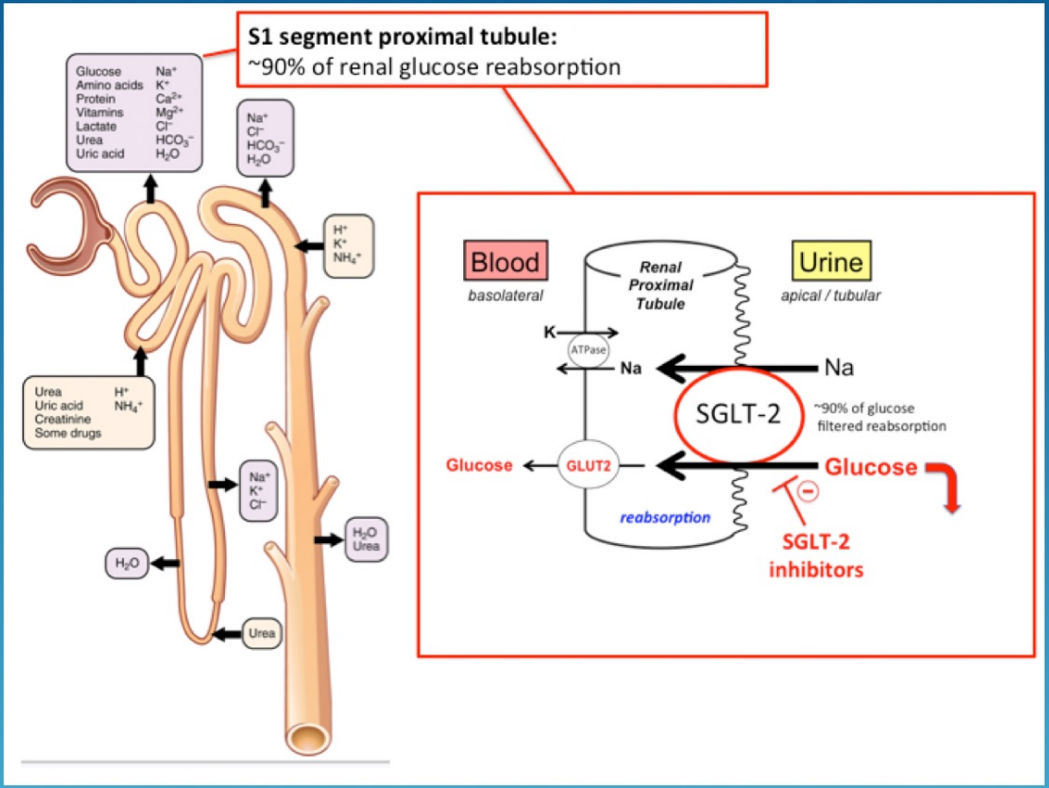
*On top of standard therapy at the time of study (except in CHARM-Alternative where background ACEI therapy was excluded). Patient populations varied between trials and as such relative risk reductions cannot be directly compared. SOLVD (Studies of Left Ventricular Dysfunction), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) and RALES (Randomized Aldactone Evaluation Study) enrolled chronic HF patients with LVEF≤35%. CHARM-Alternative (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) enrolled chronic HF patients with LVEF≤40%.

ARR=absolute risk reduction; MRA=mineralocorticoid receptor antagonist; RRR=relative risk reduction

1. SOLVD Investigators. N Engl J Med 1991;325:293–302; 2. Granger et al. Lancet 2003;362:772–6
3. CIBIS-II Investigators. Lancet 1999;353:9–13; 4. Pitt et al. N Engl J Med 1999;341:709-17; 5. Roger et al. JAMA 2004;292:344–50



ARNI (SACUBITRIL/VALSARTAN)



SGLT2 INHIBITORS

CHF – level of recommendations

Drug Classes

Level of Recommendations (1/2)

ACCF-AHA 2013

ESC 2012

HFSA 2010

NICE 2010

Pharmacological therapies	ACCF-AHA 2013	HFSA 2010	ESC 2012	NICE CHF-2010
ACEI	IA	A	IA	A
Beta blockers	IA	A	IA	A
Loop diuretics	IC	A	-	C
ARBs				
• In patients who are intolerant to ACEI	IA*	A	IA	A
• In patients with persisting symptoms despite treatment with ACEI and BB, who are intolerant MRA	IIb A	-	IA	-
• Patients with persisting symptoms despite treatment with ACEI and a beta-blocker	-	A	-	✓†
• Individual ARBs may be considered as initial therapy rather than ACEI for HF patients post-MI	-	A	-	-
MRAs				
• Patients with persisting symptoms and EF ≤35%, despite treatment with an ACEI and beta-blocker	-	A‡	IA	A#
• Patients with NYHA class II-IV, LVEF≤35%, in addition to the standard therapy	IA	A**	-	-

symptomatic pt. or not

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blockers; EF, ejection fraction; HFrEF, heart failure and reduced ejection fraction; HF, heart failure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association

CHF – level of recommendations

Drug Classes

Level of Recommendations (2/2)

ACCF-AHA 2013

ESC 2012

HFSA 2010

NICE 2010

Pharmacological therapies	ACCF-AHA 2013	HFSA 2010	ESC 2012	NICE CHF-2010
Digoxin				
• In patients with persisting symptoms despite treatment with ACEI/ARB, BB and MRA	IIa B	B/C*	IIb B	A
• In patients with sinus rhythm, EF≤45% who are unable to tolerate a beta-blocker (should be given with ACEI+MRA)	-	-	IIb B	-
H-ISDN				
• In symptomatic African-American patients, NYHA class III-IV, despite optimized standard therapy	IA	A/B†	-	✓‡
• In patients unable to tolerate an ACEI/ARB due to hyperkalemia or renal dysfunction	IIa B	C	IIb B	A
• Patients with persisting symptoms despite optimized standard therapy (ACEI/ARB, beta-blocker and MRA)	-	C	IIb B	-
Ivabradine				
• In patients with sinus rhythm with an EF ≤35%, HR ≥70 bpm, and persisting symptoms despite treatment with beta-blocker, ACEI and an MRA	-	-	IIa B	✓‡#
• Patients with sinus rhythm with an EF ≤35% and a HR ≥70 bpm who are unable to tolerate beta-blocker	-	-	IIb C	✓‡#

*NYHA class II-III: **level of recommendation B**, NYHA class IV: **level of recommendation C**; †NYHA class II: **level of recommendation B**.

http://publications.nice.org.uk/ivabradine-for-treating-chronic-heart-failure-ta267/guidance

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blockers; EF, ejection fraction; HF, heart failure; HR, heart rate; MRA, mineralocorticoid receptor antagonist; MI, myocardial infarction; NYHA, New York Heart Association;

2021 ESC HF GUIDELINES RECOMMENDATIONS FOR THE MANAGEMENT OF PATIENTS WITH HFREF

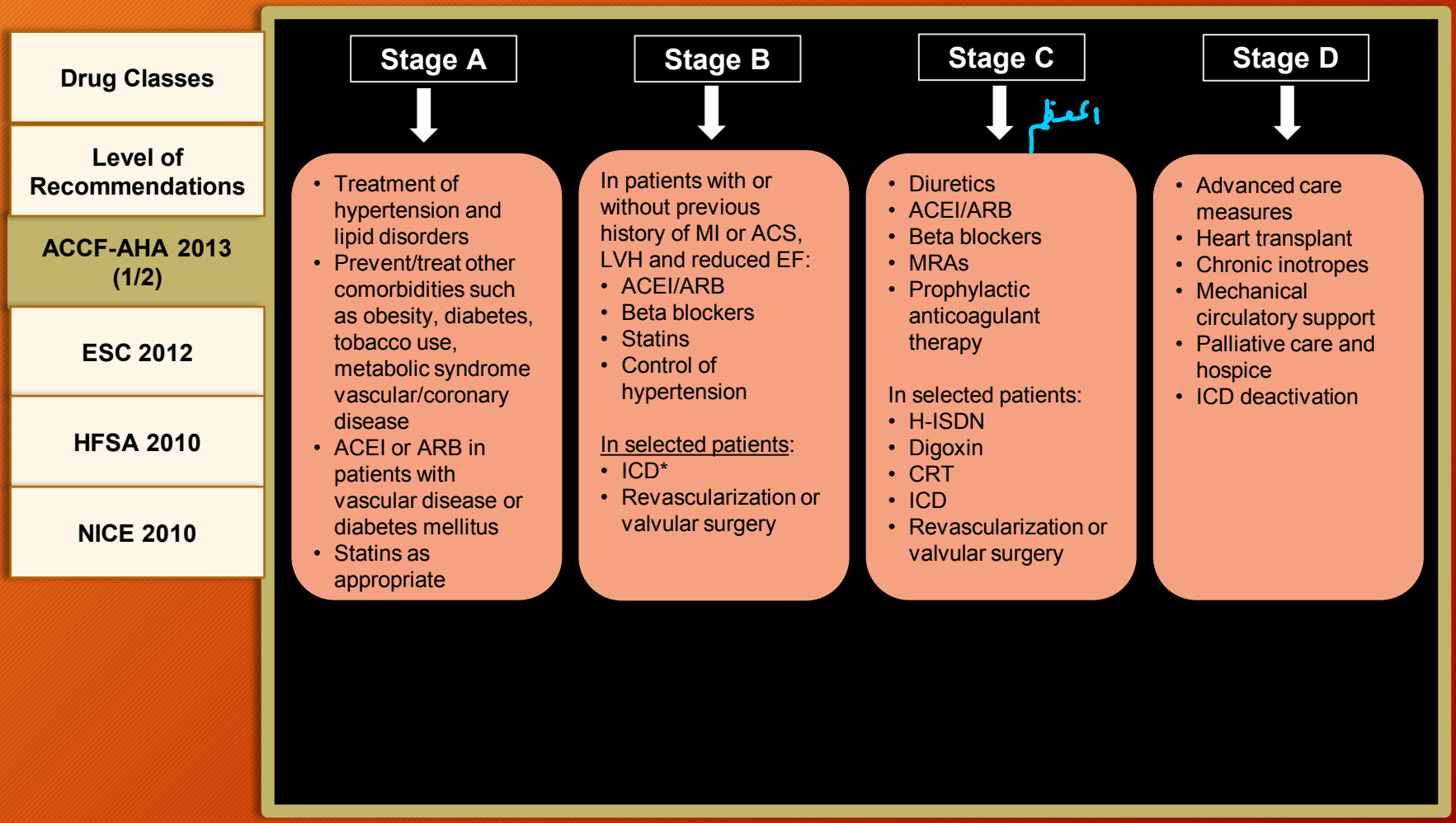
Management of patients with HFrEF1

- The 2021 ESC HF Guidelines now recomme

Pharmacological treatments indicated in patients with HFrEF (LVEF ≤40%; NYHA class II–IV)

Recommendations	Class of recommendation	Level of evidence
An ACEi is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
A BB is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
Dapagliflozin / empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
Sacubitril/valsartan is recommended as a replacement for an ACEi in patients with HFrEF to reduce the risk of HF hospitalization and death	I	B

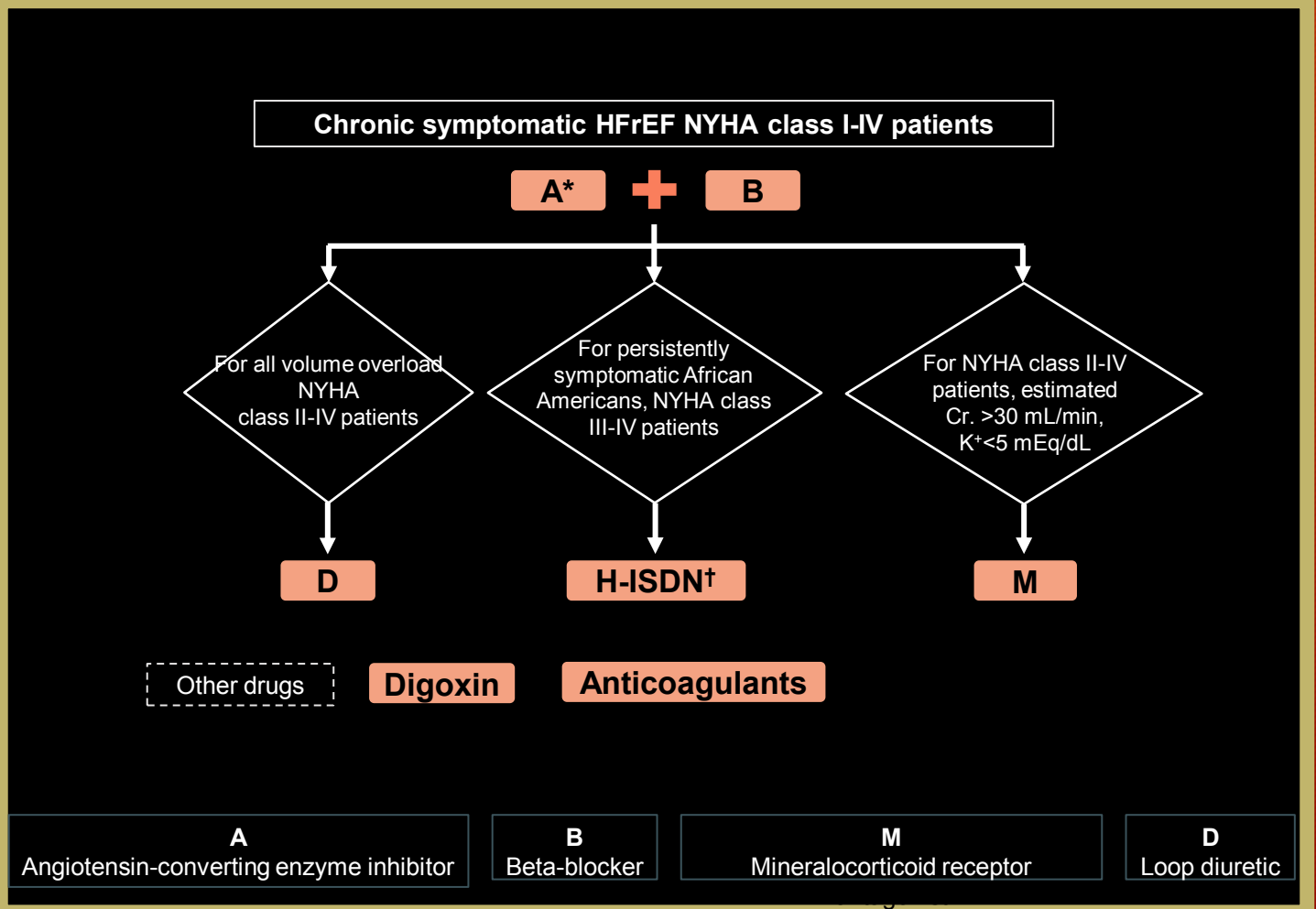
Pharmacological Therapy - CHF



ACEI, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; EF, ejection fraction; H-ISDN, hydralazine and isosorbide dinitrate; ICD, implanatable cardioverter-defbrillator; LVH, left ventricular hypertrophy; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist

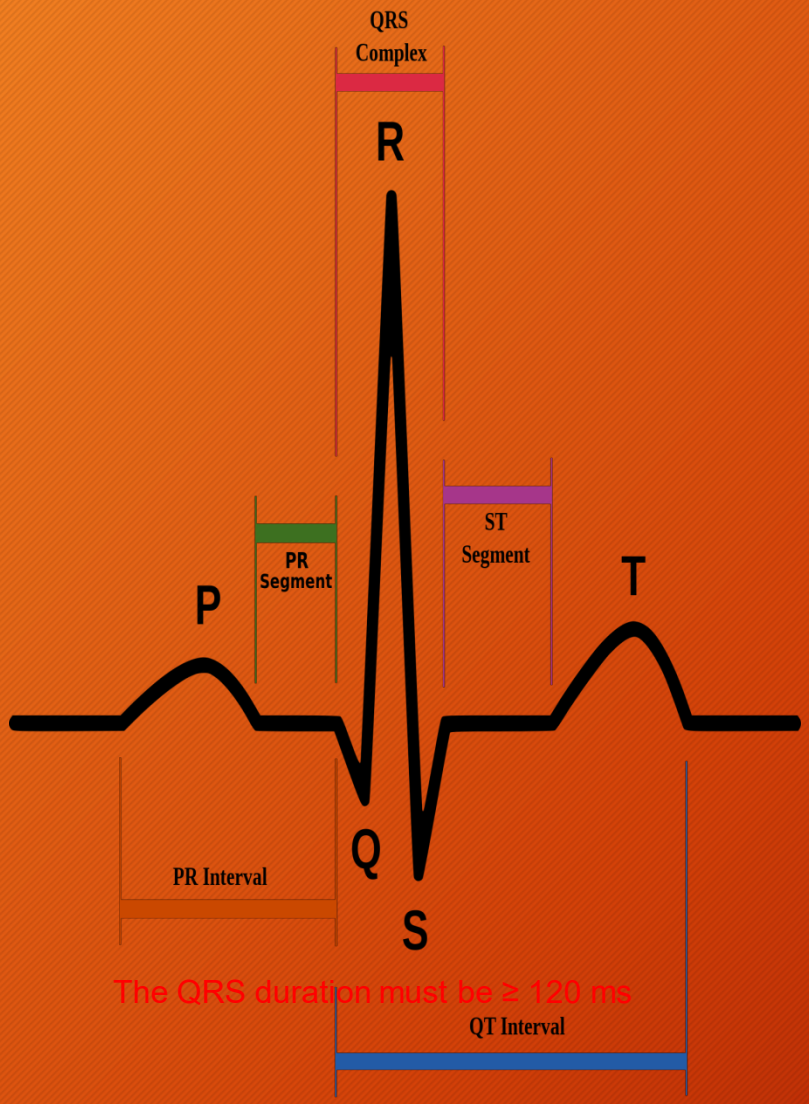
Pharmacological Therapy - CHF

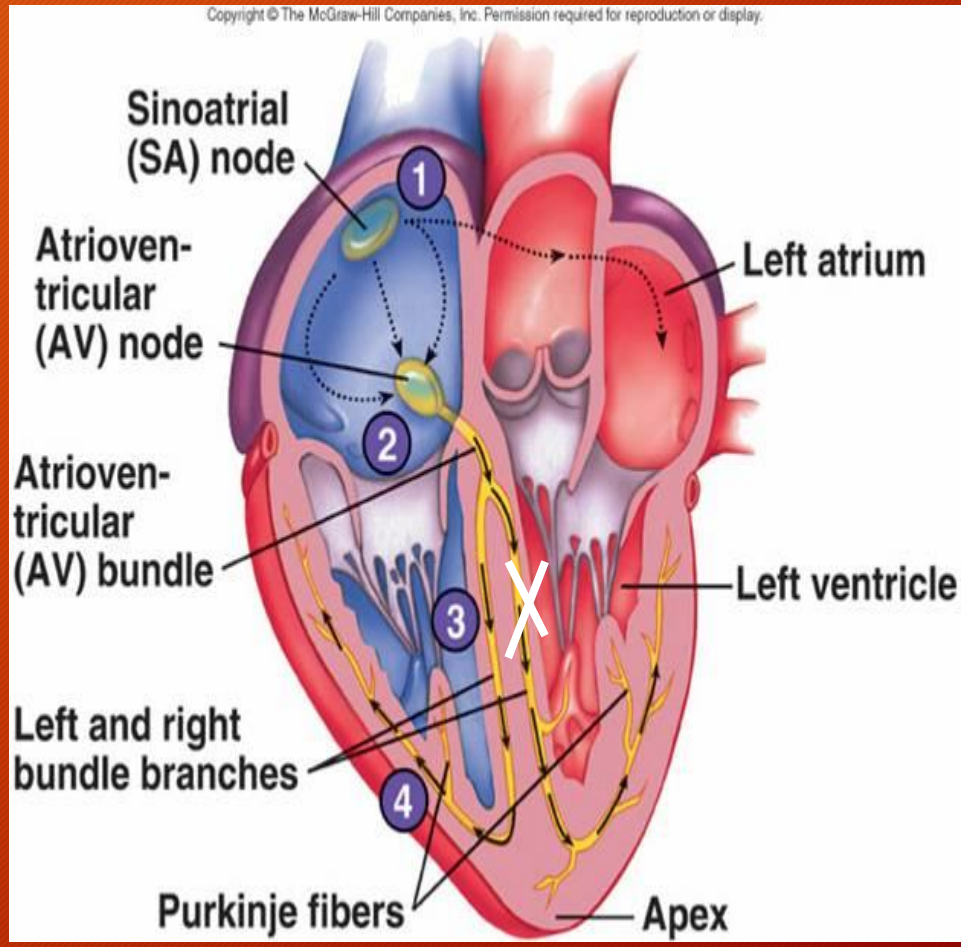
- Drug Classes
- Level of Recommendations
- **ACCF-AHA 2013 (2/2)**
- ESC 2012
- HFSA 2010
- NICE 2010



ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; Cr., creatinine; HFrEF, heart failure and reduced ejection fraction; NYHA, New York Heart Association

LBBB → septum is activated before the wall → wide QRS → dys-sincrony





ICD

Device implantable inside the body, able to perform both cardioversion, defibrillation and pacing of the heart

Indications

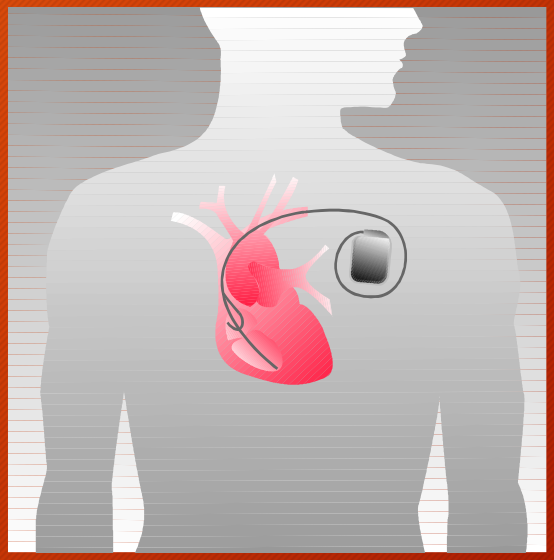
- Ventricular tachycardia and ventricular fibrillation. → secondary prevention
- Prevention of sudden cardiac death (SCD). , patients with EF < 35% → primary prevention
- Atrial flutter, atrial fibrillation.
- Long QT Syndrome
- Bradycardia
- Sick Sinus Syndrome

مع موجودية بالجديد

CRT: Cardiac Resynchronization Therapy

simultaneous توصيل كهربا

1. Improved hemodynamics
   - Increased CO
   - Reduced LV filling pressures
   - Reduced sympathetic activity
   - Increased systolic function w/o MVO2
2. Reverse LV remodeling/architecture
   - Decreased LVES/ED volumes (end-systolic / end-diastolic)
   - Increased LVEF



CRT

The implantation of a biventricular pacemaker (BVP) capable of stimulating both ventricles simultaneously. It is particularly beneficial for patients with dilated cardiomyopathy, a condition where the electrical signal spreads unevenly to the right and left sides of the heart due to LBBB, causing the heart to enlarge and pump less efficiently

CRT is delivered with devices that are either pacemakers (CRT-P) alone, or are combined with ICD therapy (CRT-D)

Indications

- Improved exercise tolerance
- Reduce symptoms
- Reduced remodeling
- Reduced mortality
- Reduce need for hospitalization rhythm

Thank you