Vericiguat in Heart Failure

Background on Heart Failure

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Background on Heart Failure

Learning objectives

By the end of this chapter, you should be able to:

- Illustrate the normal structure and function of the heart
- Define heart failure and understand its pathophysiology
- Recognise the global impact of the disease
- Identify the signs and symptoms presenting in a patient
- Describe the approach to making the diagnosis of heart failure

Sections

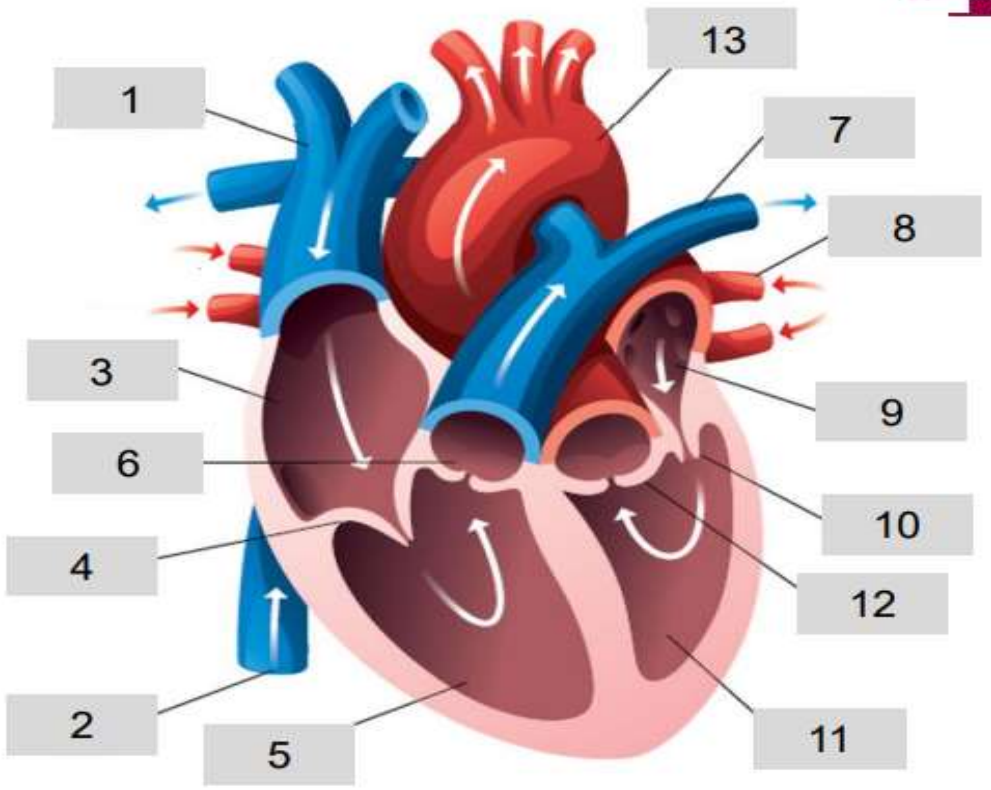
Structure and Function of the Heart
What is Heart Failure?
Diagnosis and Prognosis of HFrEF

Activity

Pump it!

Instructions:

- Here we see an image of the heart
- Let's see how many of the structures you know and can assign…



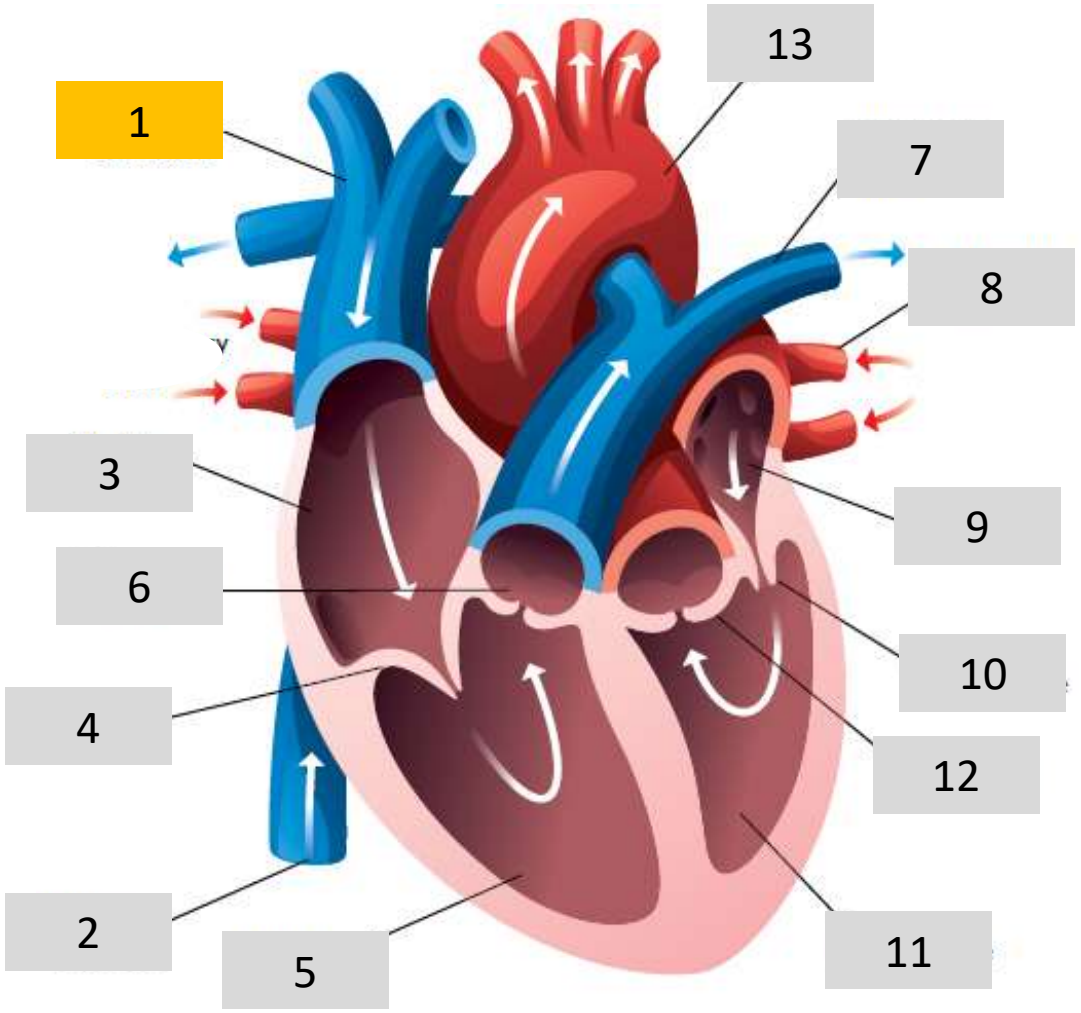
Verquvo vericiguat

BAYER | MSD

Pump it!

What is the correct label for [1]?

A. Superior vena cava
B. Inferior vena cava
C. Pulmonary artery
D. Pulmonary vein
E. Aorta



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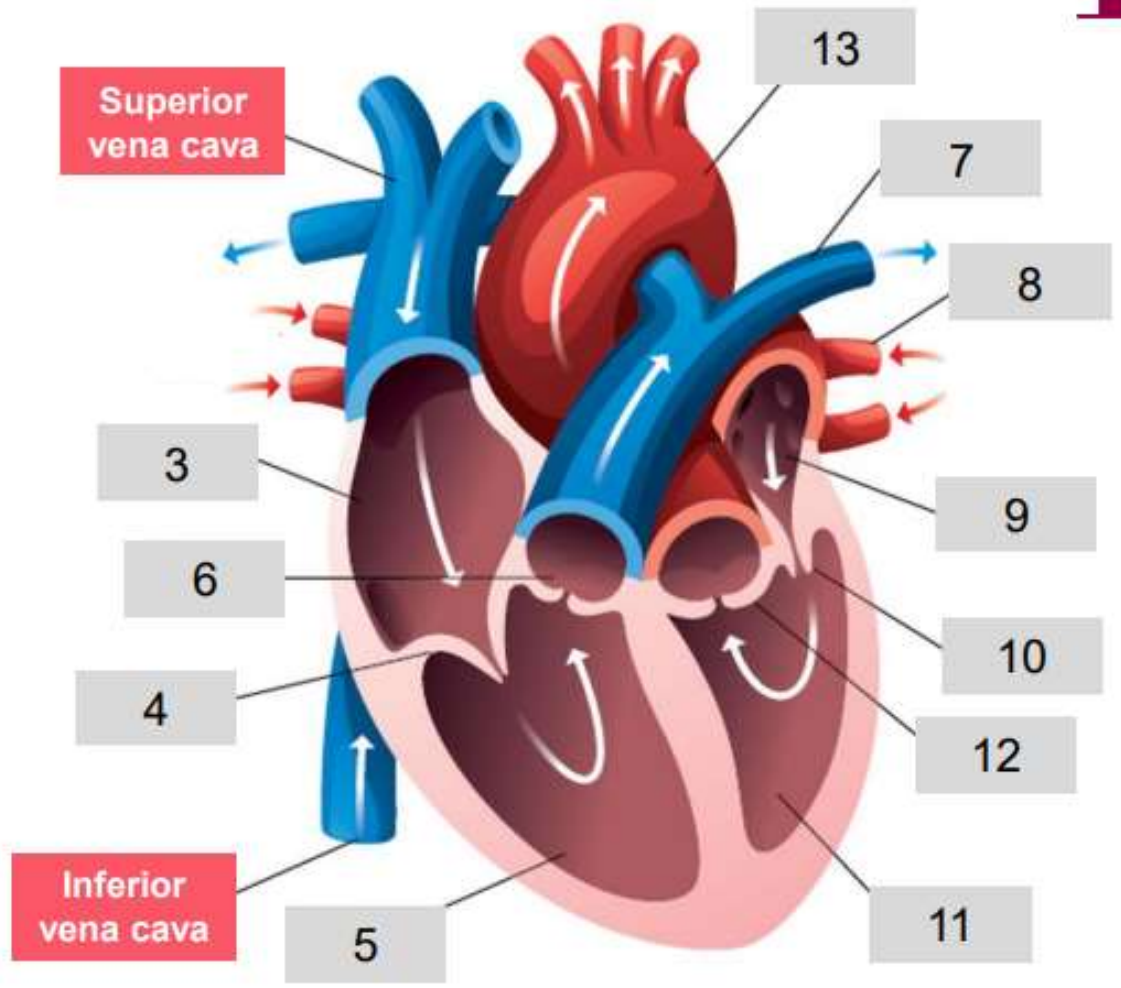
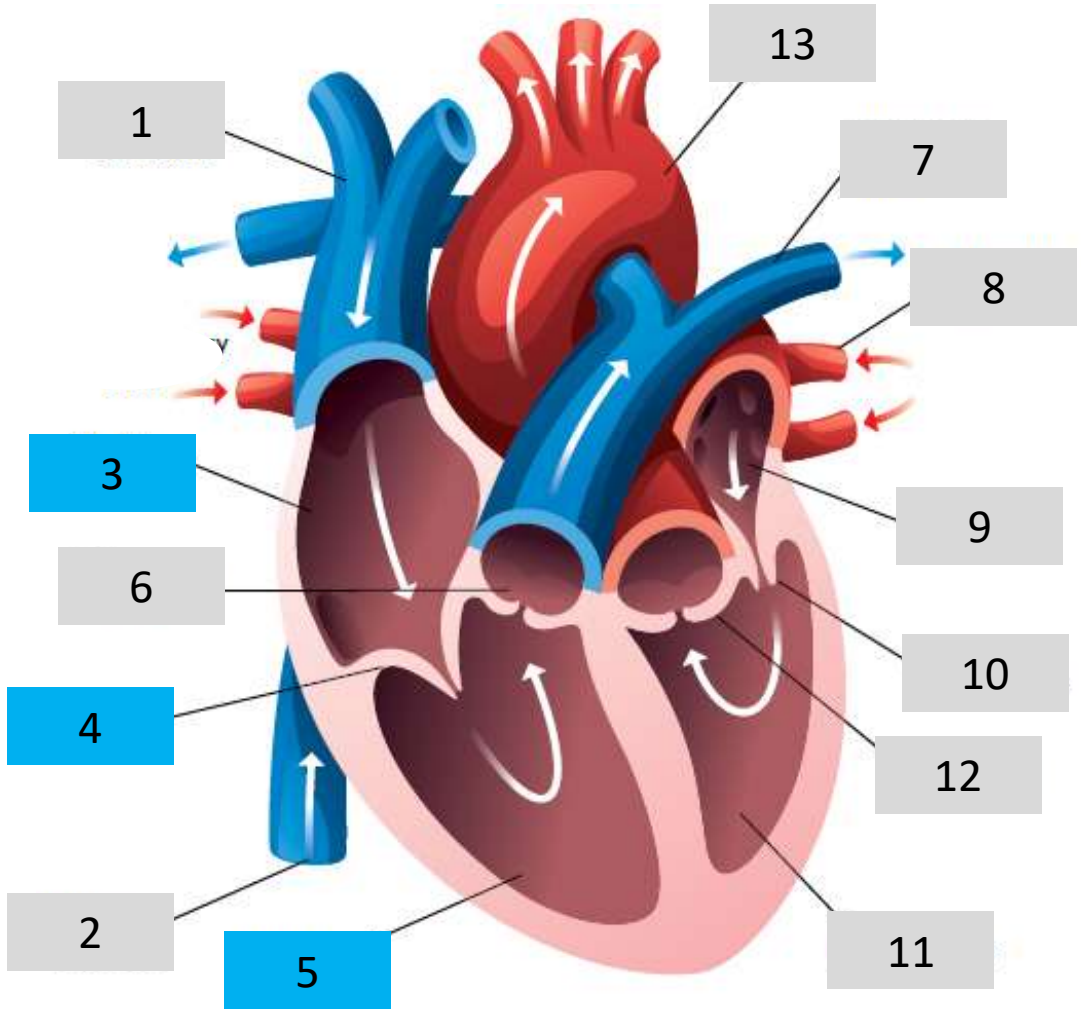


Pump it!

What are the correct labels for 3-4-5?

A. Right ventricle - Mitral valve - Right atrium
B. Left atrium - Tricuspid valve - Left ventricle
C. Right atrium - Tricuspid valve - Right ventricle
D. Left ventricle - Mitral valve - Left atrium
E. Right atrium - Pulmonary valve - Right ventricle



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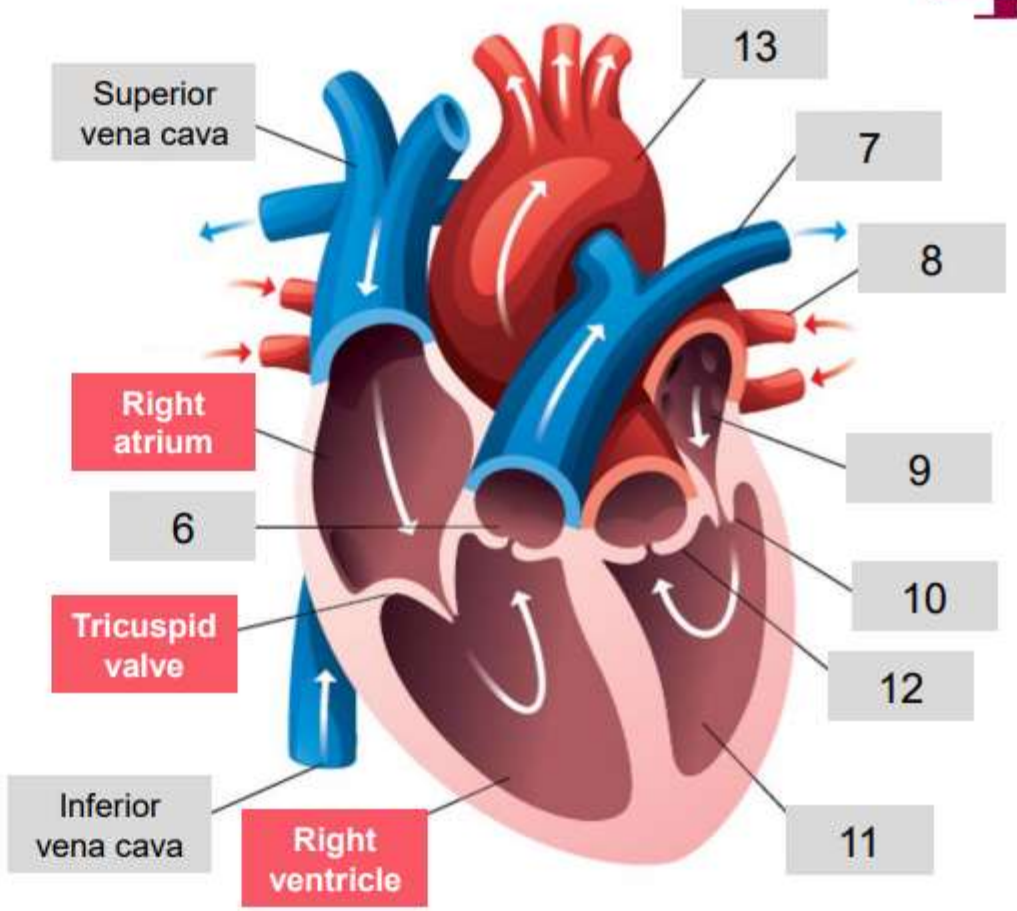
C. **Right atrium - Tricuspid valve - Right ventricle**

D. Left ventricle - Mitral valve - Left atrium

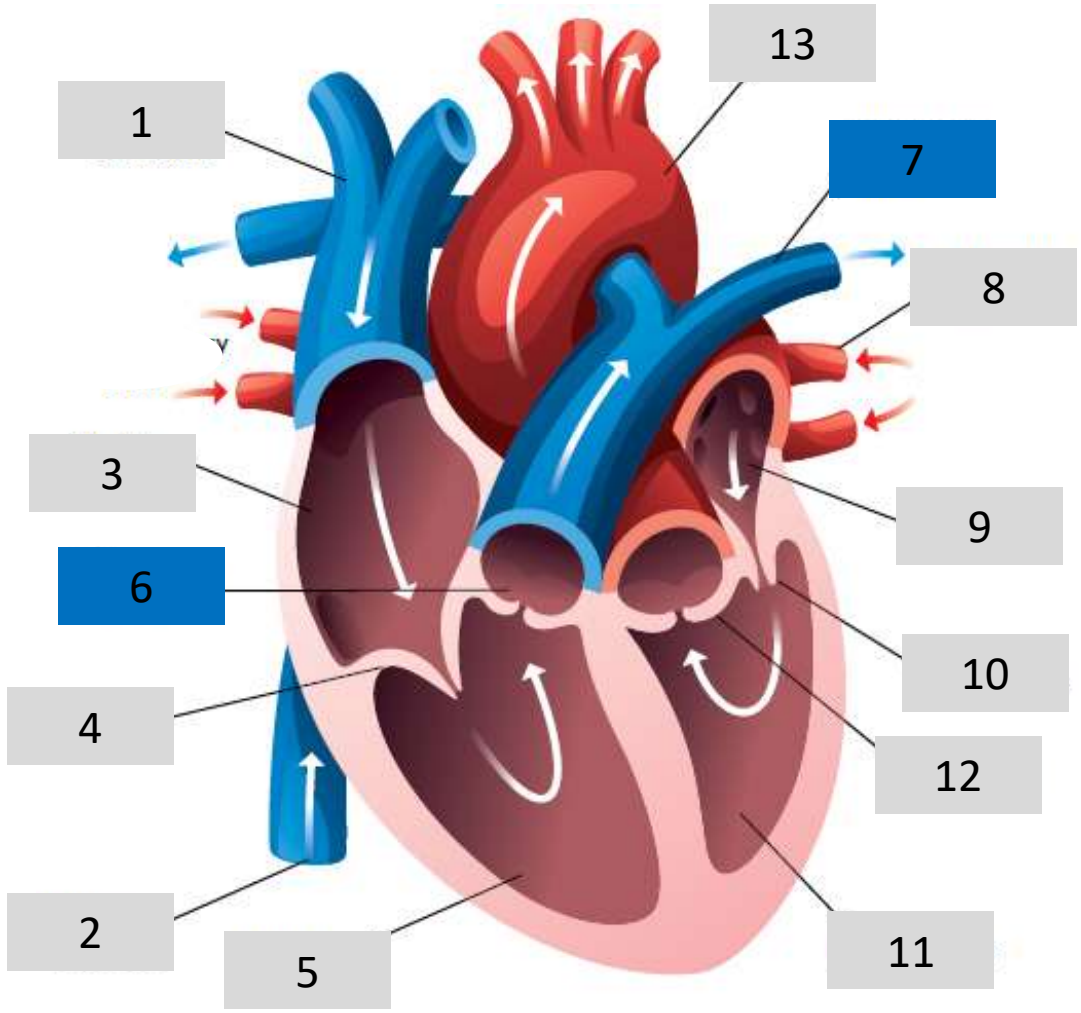
E. Right atrium - Pulmonary valve - Right ventricle



Pump it!

What are the correct labels for 6-7?

A. Aortic valve-Pulmonary vein
B. Mitral valve-Pulmonary artery
C. Mitral valve-Pulmonary vein
D. Pulmonary valve-Pulmonary artery
E. Pulmonary valve-Pulmonary vein



Pump it!

What are the correct labels for 6-7?

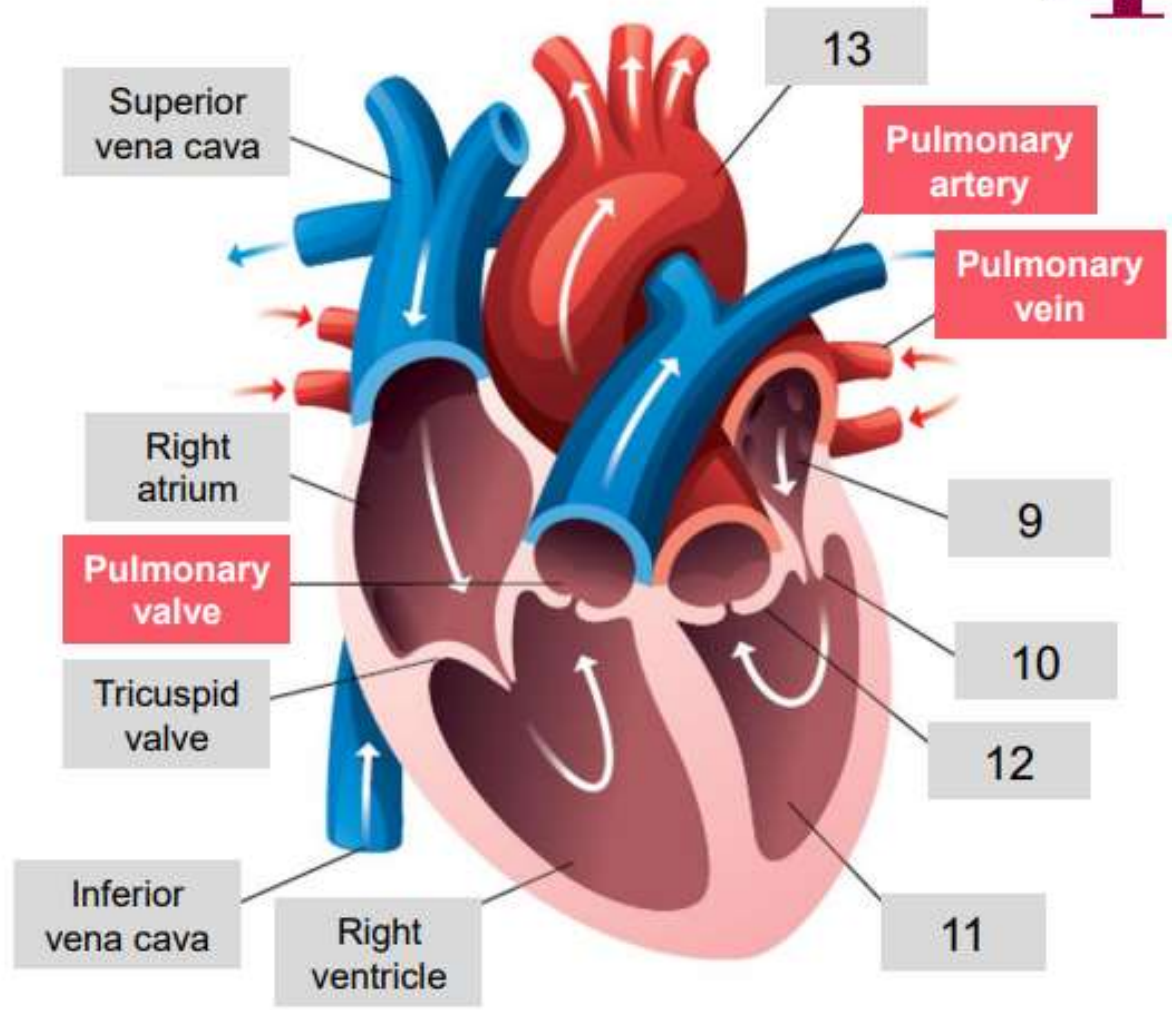
A. Aortic valve-Pulmonary vein

B. Mitral valve-Pulmonary artery

C. Mitral valve-Pulmonary vein

D. **Pulmonary valve-Pulmonary artery**

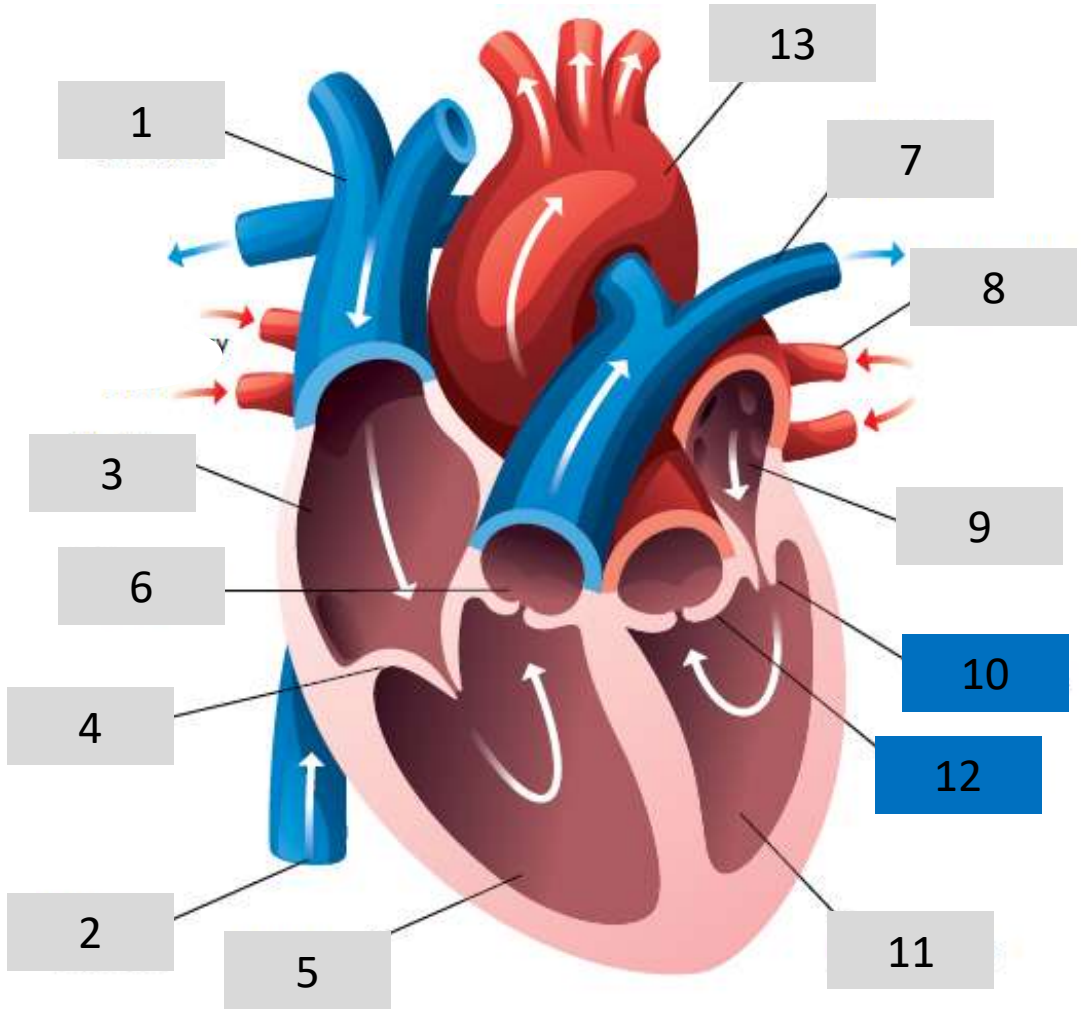
E. Pulmonary valve-Pulmonary vein



Pump it!

What are the correct names of the valves at 10 and 12, respectively?

A. Aortic valve, Mitral valve
B. Mitral valve, Aortic valve
C. Tricuspid valve, Mitral valve
D. Ventricular valve, Aortic valve
E. Mitral valve, Tricuspid valve



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D. Ventricular valve, Aortic valve

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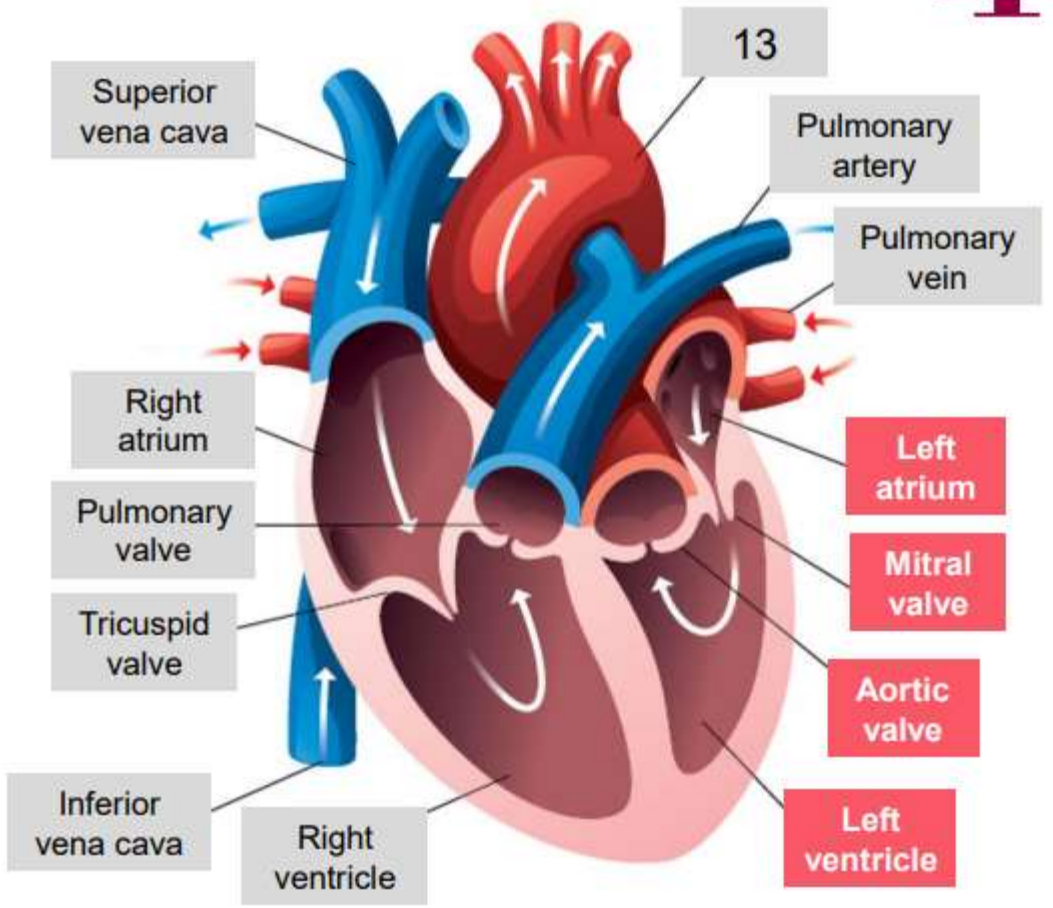
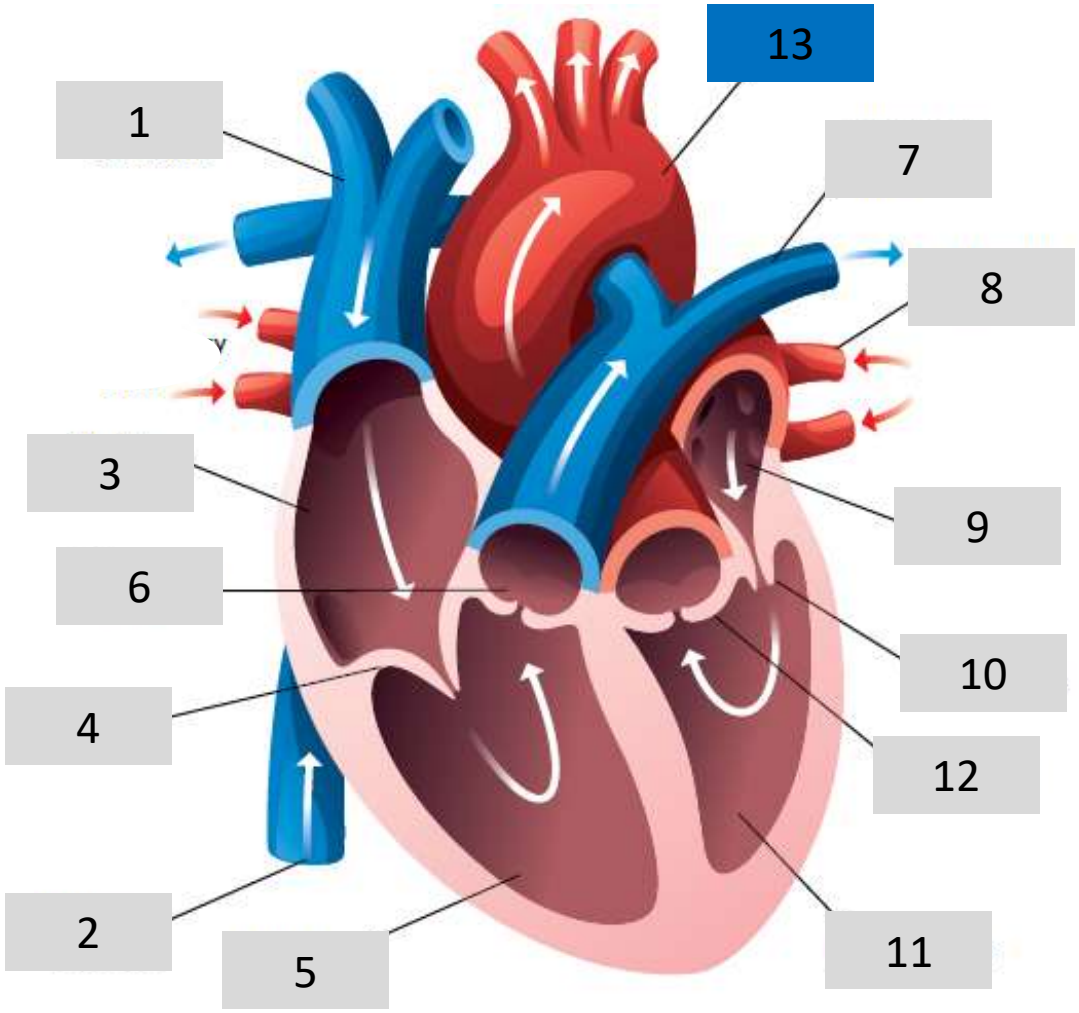


Pump it!

What is the name of [13]?

A. Aorta
B. Atrial septum
C. Epicardium
D. Apex
E. Endocardium



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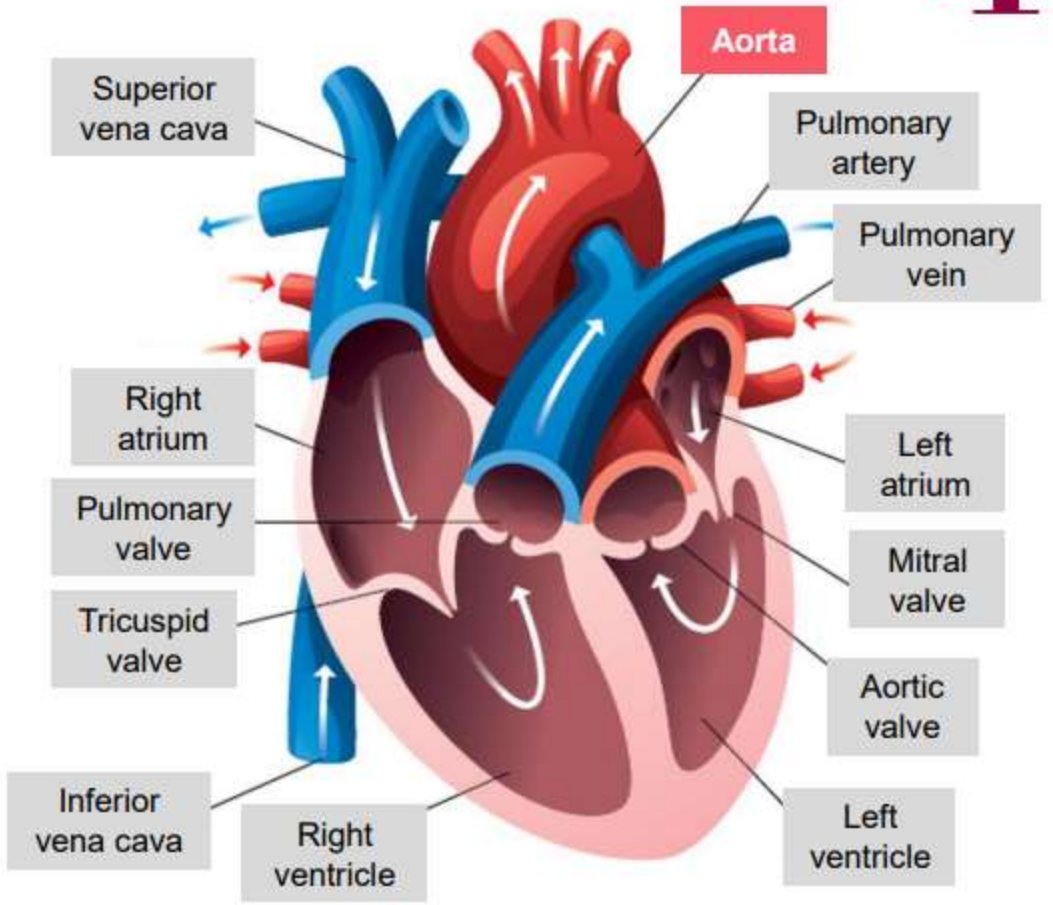


Structure of the Normal Heart

The heart consists of 4 chambers (2 on the left and 2 on the right)

Upper chambers: left and right atria

Lower chambers: left and right ventricles

The atrium on each side is connected with its corresponding ventricle through a one-way valve

The heart is a two-way pump

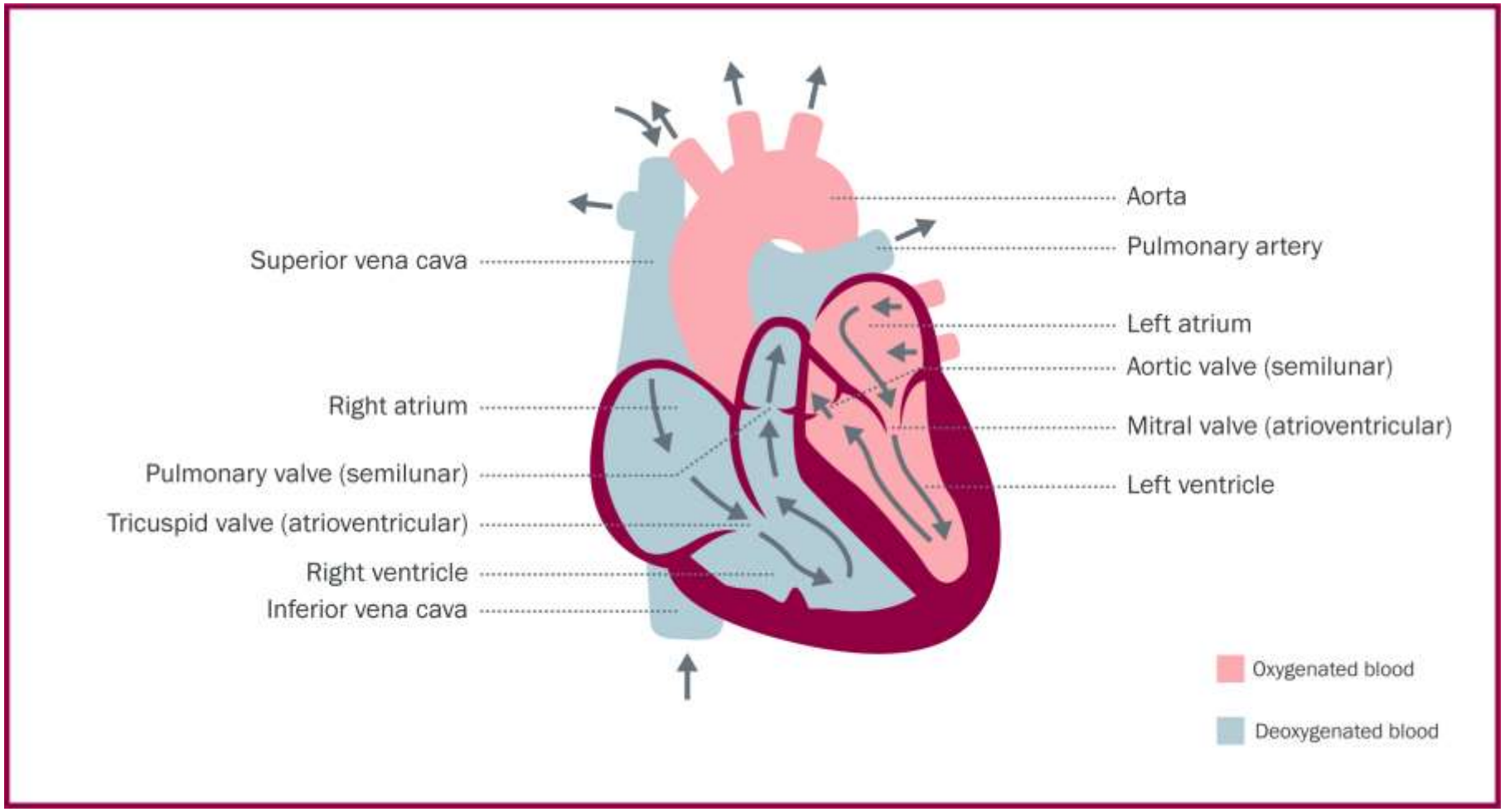
Right side: oxygen-poor blood from the body is pumped to the lungs through the pulmonary arteries

Left side: oxygen-rich blood from the lungs is pumped to the rest of the body through the aorta

The heart is primarily made of a thick muscle layer, the myocardium

The muscles of the left side are larger in order to pump blood out to the whole body in the systemic circuit

Structure of the heart and path of the circulating blood



Cardiac Cycle of the Left Ventricle

Although **similar mechanistic events take place in the right and left side of the heart**[1], the focus here is on the **left side**, particularly the left ventricle (LV)

The cardiac events that take place from the beginning of one heartbeat to the beginning of the next are called the **cardiac cycle**[1]

These events enable the forward movement of blood through various chambers of the heart

Each cardiac cycle consists of two phases:

- Systole, or ventricular contraction
- Diastole, divided into ventricular relaxation and filling

Ventricular contraction

Ventricular relaxation

Ventricular filling

Ventricular contraction

Contraction of the heart muscle, **ejecting** blood from within, is called **'systole'**[1]

The quantity of blood in the left or right ventricle at the end of contraction (maximal emptying) is the **end-systolic volume (ESV)**[2]

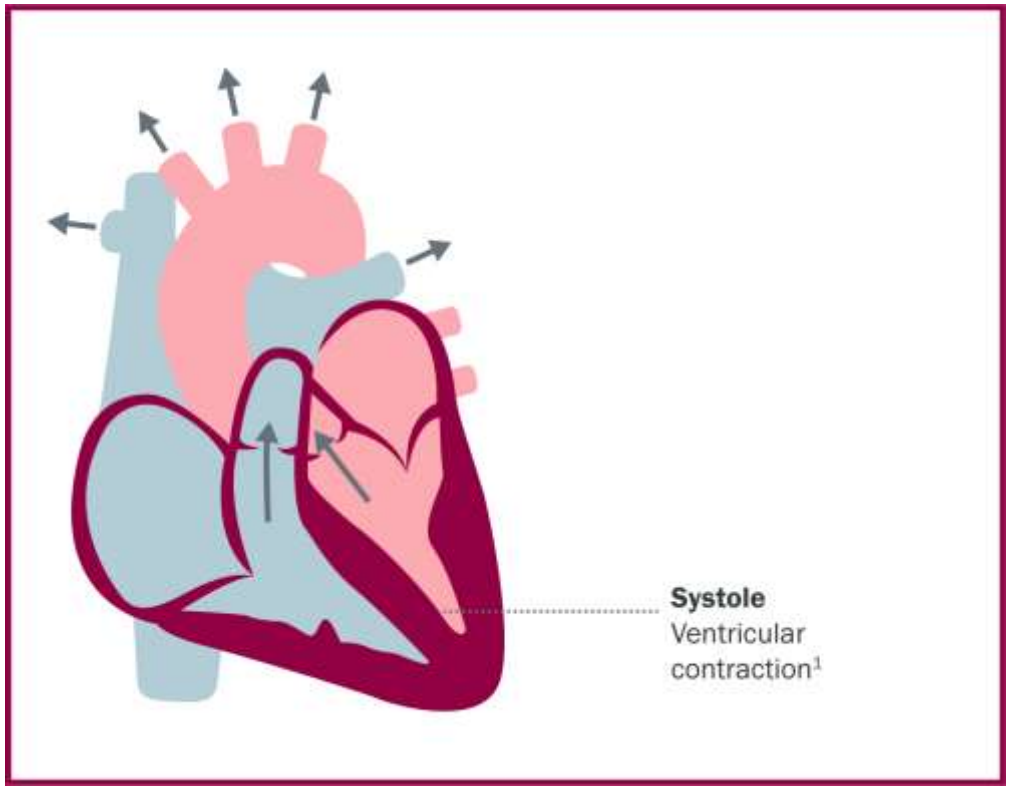
Isovolumic contraction:[2]

The LV begins to contract and once the pressure within exceeds that in the left atrium, the mitral valve closes

With both the mitral valve and aortic valve closed, the LV continues to contract, but the blood volume remains constant until LV pressure exceeds that in the aorta

Rapid ejection:[2]

When LV pressure exceeds that in the aorta, the aortic valve is forced open, causing rapid ejection of blood to the aorta



Ventricular relaxation

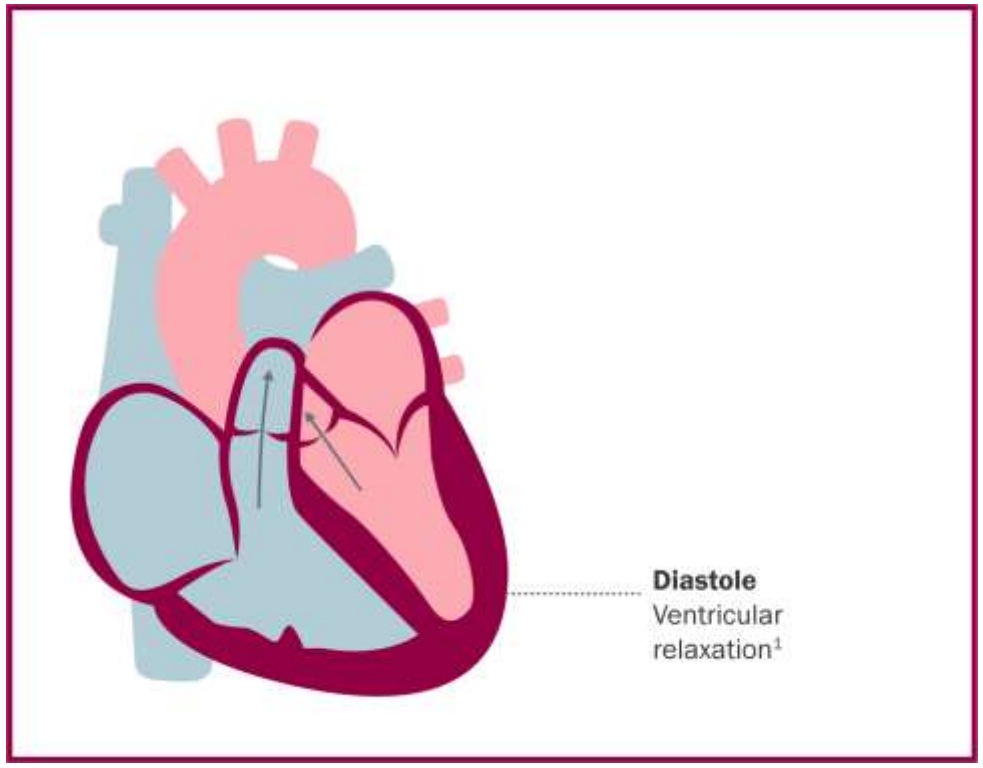
Reduced ejection:[2]

During LV relaxation, the rate of ejection of blood from the ventricle to the aorta decreases

The aortic valve closes as the pressure in the aorta exceeds the falling pressure in the LV

Isovolumic relaxation:[2]

The ventricle continues to relax; however, the volume within the chamber remains constant as both the mitral valve and the aortic valve are closed



Ventricular filling

The relaxation of the heart muscle, allowing the heart to **fill** with blood, is called **'diastole'**[1]

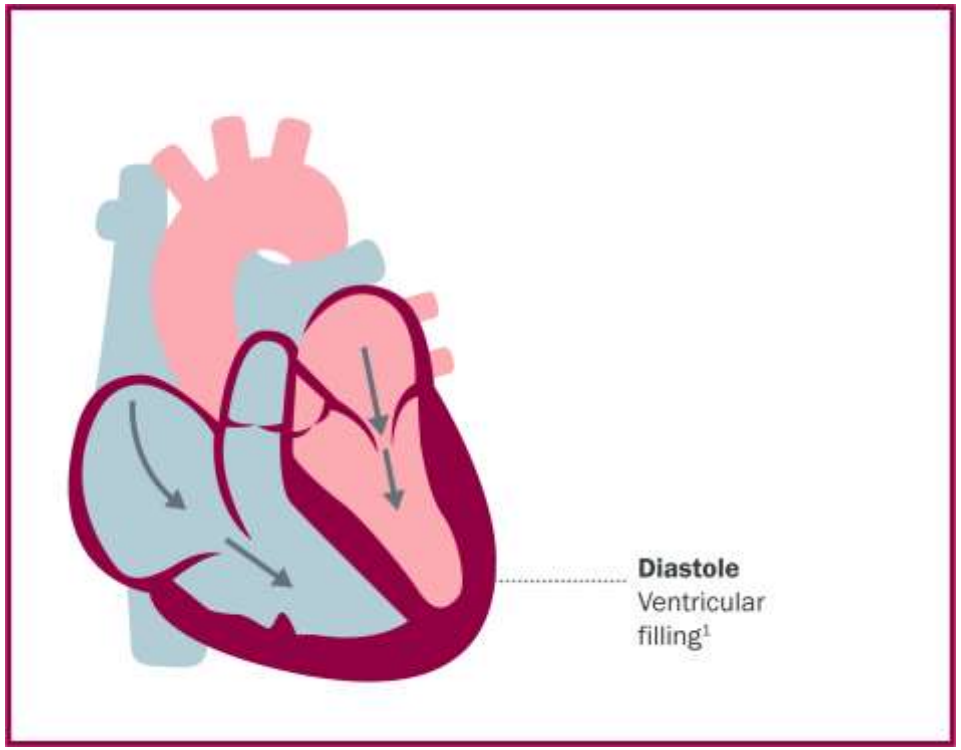
The quantity of blood in the left or right ventricle at the end of diastole (maximal filling) is the **end-diastolic volume (EDV)**[2]

Rapid filling:[2]

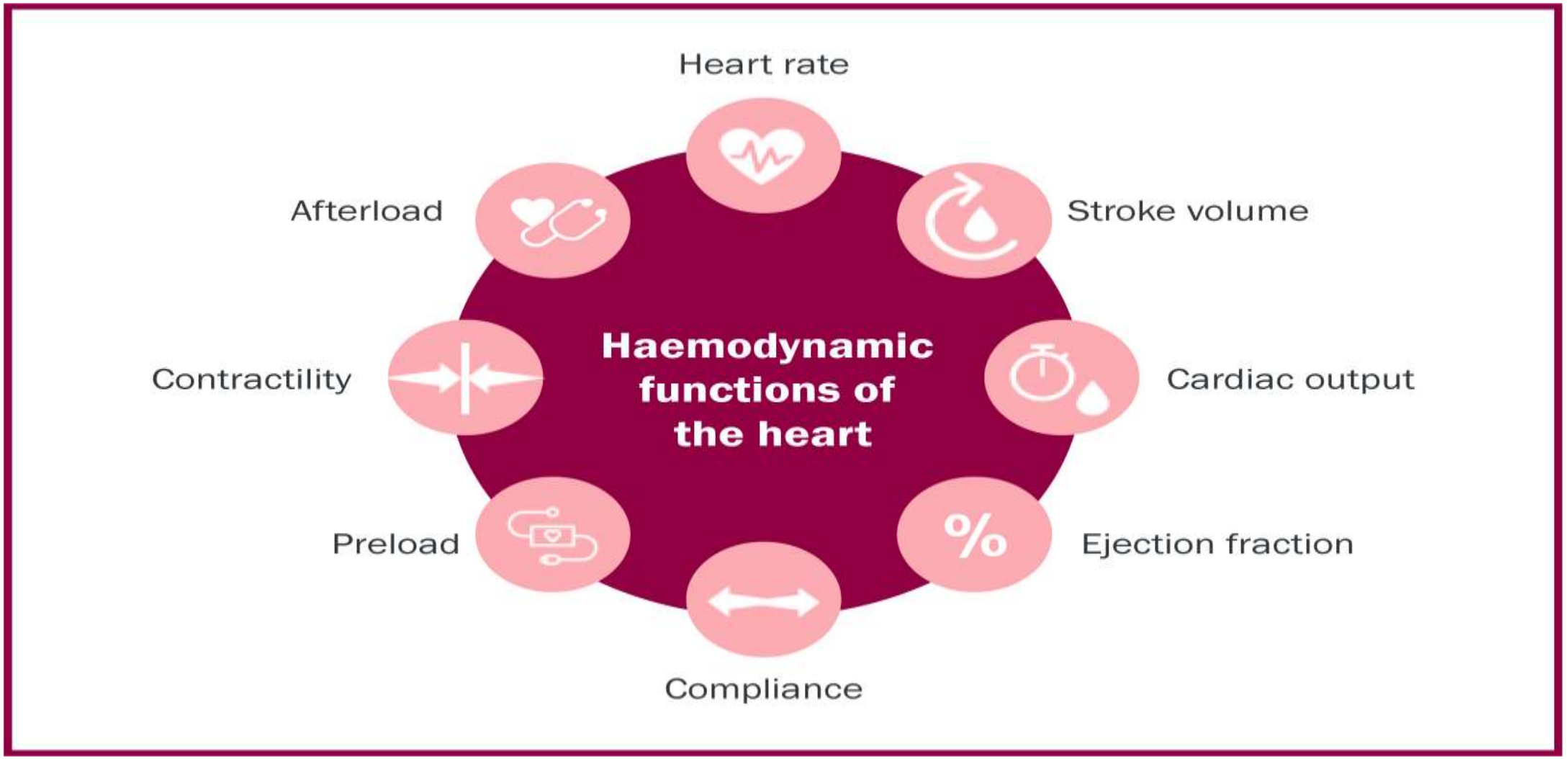
When LV pressure falls below that of the left atrium, the mitral valve opens to allow for LV filling (this accounts for most of the LV filling)

As the pressure in the atrium and the ventricle equalise, the ventricular filling virtually stops

This is followed by atrial contraction, which forces more atrial blood to enter the ventricle



Haemodynamic Functions of the Heart



Pop-ups: (each to pop up individually on the main page)

- **Heart rate (HR)** is the frequency of heartbeats (beats per minute; BPM)[1]
- A normal resting HR for an adult ranges from 60 to 100 BPM[2]
- A lower resting HR in a healthy person generally implies more efficient heart function and better cardiovascular (CV) fitness[2]

- **Cardiac output** is the amount of blood pumped from the heart per minute (heart rate [HR] x stroke volume [SV])[1]
- Under normal resting conditions, cardiac output is 4–8 L/min per ventricle[1]

- **Compliance** is the stretching ability of the ventricle (or other compartment) to accommodate increased content[4]
- The relationship is not linear, particularly at higher volumes, as the compliance decreases (stiffness increases) the more the wall is stretched[5]

- **Contractility** (cardiac inotropy) is the ability to increase the force of contraction, determined by the strength of the actomyosin filament interaction[6]
- Increasing or decreasing inotropy lead to equivalent changes in ejection fraction (EF)[7]
- Therefore, the EF is often used as a clinical index for evaluating the inotropic state of the heart[7]

- **Stroke volume (SV)** is the amount of blood pumped from each ventricle per cardiac cycle[1]
- The SV is the difference between the EDV and the ESV[1]
- A normal SV for adults can range from 55 to 100 mL[1]

- **Ejection fraction (EF)** is the ratio of blood ejected from the filled LV (stroke volume [SV]/EDV)[1]
- **The EF of the ventricle is normally 55–70%**[1]
- The EF is normally measured in the LV; hence it is often referred to as LVEF[3]

- **Preload** is the initial stretching of the cardiac myocytes prior to contraction[8]
- An increase in preload normally leads to an increase in stroke volume (SV) and cardiac output[1,8]
- Preload is affected by venous blood pressure and the rate of venous return, driven by respiratory activity and skeletal muscle pump activity; it increases with blood volume and sympathetic tone[8]

- **Afterload** is the stress or tension within the LV wall at the beginning of contraction, in order to effectively pump blood against proximal or distal resistances[1,9]
- It increases with aortic stenosis, systemic vascular resistance and systemic hypertension[9]
- In heart failure (HF), afterload is increased due to compensatory mechanisms causing arterial vasoconstriction[10]

Heart and the systemic circuit

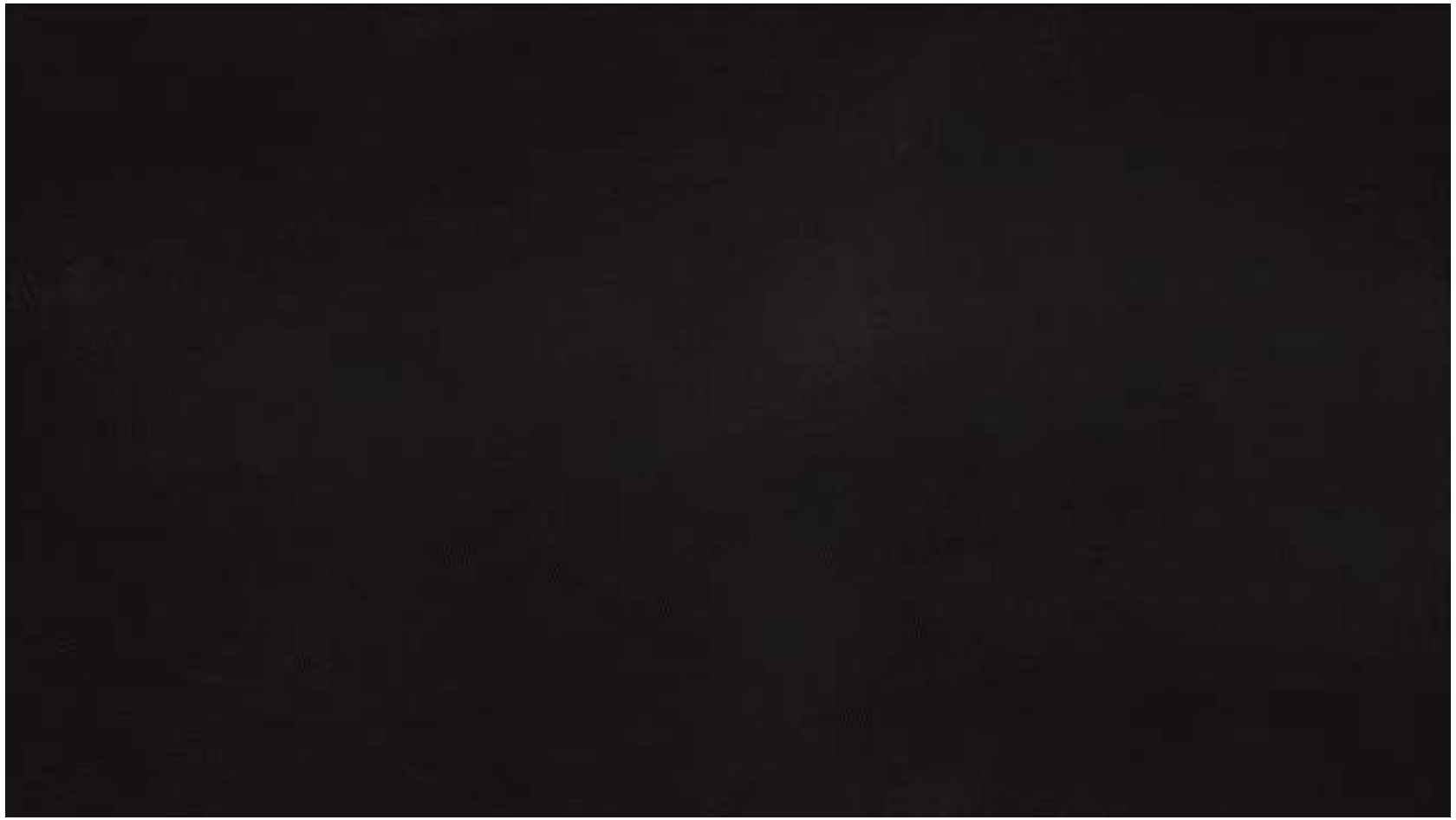
(953) Explainer: The Heart and the Systemic Circuit - YouTube

End of Section 1

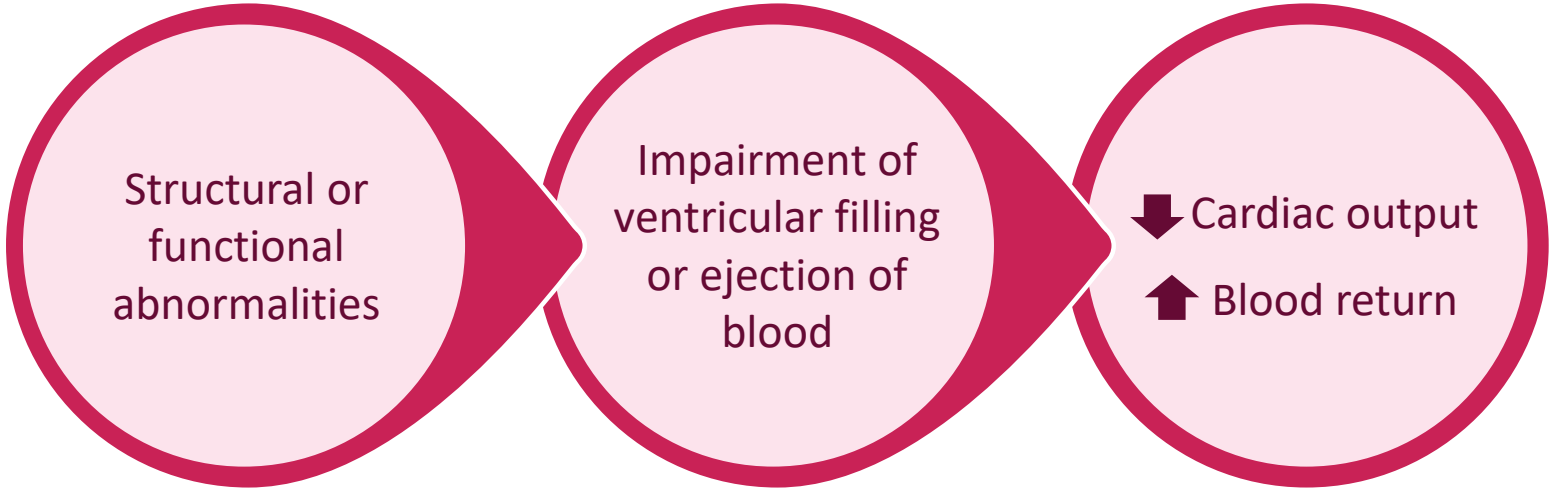
Heart Failure

Why is HF a growing concern?

What is Heart Failure?



Heart failure is a complex clinical syndrome[1]



Clinical guidelines issued by the **European Society of Cardiology (ESC)** in 2016 define HF as:[2]

*"…a clinical syndrome characterised by typical **symptoms** (e.g. **breathlessness**, **ankle swelling**, and **fatigue**) that may be accompanied by signs (e.g. **elevated jugular venous pressure**, **pulmonary crackles**, and **peripheral oedema**) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress."*

ESC, European Society of Cardiology; HF, heart failure.

1. Yancy CW, et al. *Circulation.* 2013;128:e240-327. 2. Ponikowski P, et al. *Eur Heart J.* 2016;37:2129-2200.

Definition of Heart Failure

HF is typically classified by **either systolic or diastolic dysfunction**, in which the **EF ranges from reduced to preserved**[1]

Differentiation based on EF is important due to different underlying aetiologies, demographics, comorbidities and response to therapies[1]

Concertina 1: HF classification according to ESC

Concertina 2: HF classification according to ACCF/AHA

Concertina 3: Comparison between the two guidelines

Concertina 4: Underlying pathology of HF classification

2021 ESC HF Guidelines: what is new ?

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

Identifying HFmrEF as a separate group will stimulate research into underlying characteristics, pathophysiology and treatment of this population

Table 3 **Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction**

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
European Heart Journal (2021) doi:10.1093/eurheartj/ehab368

HF classification according to ACCF/AHA[2]

The 2013 ACCF/AHA guidelines define HF as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood

Categorisation of HF according to LVEF:

HFrEF: LVEF ≤40%

HFpEF: LVEF ≥50%

HFpEF borderline: LVEF 41–49%

- Borderline or intermediate group. Characteristics, treatment patterns, and outcomes appear similar to those of HFpEF

HFpEF improved: LVEF >40%

- A subset of patients with HFpEF who have previously had HFrEF. May be clinically distinct from those with persistently preserved or reduced EF

Concertina:
Comparison between the two guidelines

Comparison of classification of HF by professional societies

EF classification	2016 ESC guidelines[1]	2013 ACCF/AHA guidelines[2]
HFrEF	<40%	≤40%
HFmrEF[1]/HFpEF borderline[2]	40–49%	41–49%
HFpEF improved	–	>40%
HFpEF	≥50%	≥50%

EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction.

The ESC guidelines also include additional criteria for both HFmrEF and HFpEF:[1]

Elevated natriuretic peptide (NP) levels

B-type NP (BNP) >35 pg/mL and/or N-terminal pro-BNP >125 pg/mL

At least one of the following:

Relevant structural heart disease (LV hypertrophy and/or left atrial enlargement)

Diastolic dysfunction

Concertina:
Underlying pathology of HF classification

The underlying pathology for each HF classification varies[1]

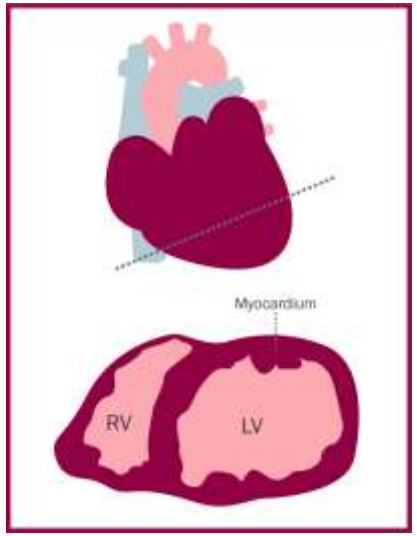
HFrEF

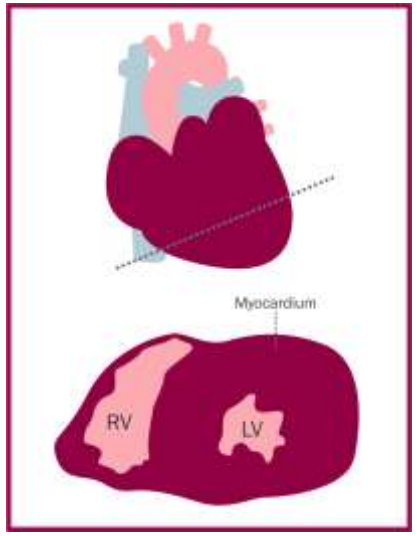
- is often characterised by a **large, dilated heart**[1,3]
- **Myocardial infarction** and **non-ischaemic cardiomyopathies** can damage, weaken and thin the myocardium, thereby leading to **dilatation of the ventricles**[1,3]
- HFrEF is usually also accompanied by **diastolic dysfunction**[1] since the myocardial necrosis (cell death) is accompanied by fibrosis (scarring), and the stiffened myocardium can neither contract nor fill normally[4]

HFpEF

is frequently characterised by LV hypertrophy (**thickening of the myocardium**) with a non-dilated ventricle[1,3]

The **passive elasticity of the ventricle is decreased**, thereby resulting in a **stiffened chamber** that requires a higher diastolic pressure to fill with any particular volume of blood[3]





LV, left ventricle;
RV, right ventricle.

Heart failure is the fastest growing cardiovascular disease[1,2]

Affects 60 million worldwide

General prevalence: 0.4%-2.2% in developed countries[3]

~15 million in Europe[4]

8-10 million people with HF in India,[4]

The incidence and prevalence of HF are age dependent, and the world's population is steadily ageing

In Europe, the lifetime risk of developing HF is approximately one in five for a 40 year old[5]

HF has an incidence of 10 cases per 1,000 after the age of 65, which then doubles every decade thereafter[6]

CAD, coronary artery disease; HF, heart failure; MI, myocardial infarction.

1. Benjamin EJ, et al. *Circulation.* 2018;137(12):e67-e492. 2. Mamas MA, et al. *Eur J Heart Fail.* 2017;19:1095-1104. 3. Shafie AA, et al. *Heart Fail Rev.* 2018;23:131-145. 4. Ambrosy AP, et al. *J Am Coll Cardiol.* 2014;63:1123-1133. 5. Mann DL, et al. Heart failure: pathophysiology and diagnosis. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine.* Volume 2. 19th ed. New York, NY: McGraw Hill Education; 2015:1500-1506. 6. Rosamond W, et al. *Circulation.* 2007;115:e69-e171.

Heart failure has significant impact on patients, HCP's and healthcare systems globally and in India

>60 million people worldwide have HF[1]

50% of HFrEF patients die within 5 years of diagnoses[2]

#1 **reason for hospitalization** in patients aged >65 years globally[3]

8-10 million people with HF in India,[4]

60% of HFrEF patients die within 5 years of diagnosis[5,6]

30% of HFrEF patients re-hospitalized for HF at 1-year [5]

HFrEF, HF with reduced ejection fraction

1. Vos D et al. GBD 2016. *Lancet.* 2017;390:1211–1259;2. 2. Benjamin EJ et al. Circulation. 2019;139:e56–e528; 3. Maggioni AP et al. Eur J Heart Fail. 2016;18:402–410; . 4. https://www.iccnhfr.org/the-current-situation, 5. .Harikrishnan S et al.International Journal of Cardiology oct 2020(online ahead of print) 6. Ganapathi S et al. ESC Heart Failure 2020; 467–473, .7. Harikrishnan S et al. Am Heart J.2017; vol189

The cost and burden of heart failure

Direct costs[1]

- Healthcare expenditure on hospital services
- Medications
- Physician costs
- Primary healthcare costs
- Follow-up

Indirect costs[1]

- Lost productivity resulting from morbidity and mortality
- Sickness benefit
- Welfare support

Severe physical limitations caused by shortness of breath, loss of energy, and fatigue impact work, social, and leisure activities. Psychosocial effects include[2]:

- Isolation
- Fear
- Anxiety
- Depression

The burden on family members or other caregivers can also be great.[2]

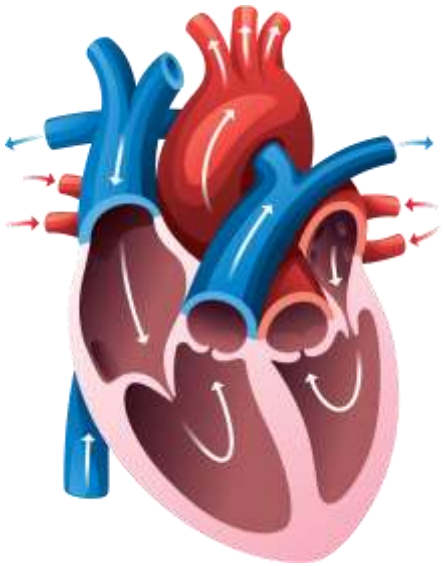
HF, heart failure.

1. Cook C, et al. *Int J Cardiol.* 2014:171:368-376. 2. Cowie MR, et al. *ESC Heart Failure.* 2014;1:110-145.

Heart Failure

What causes HF?

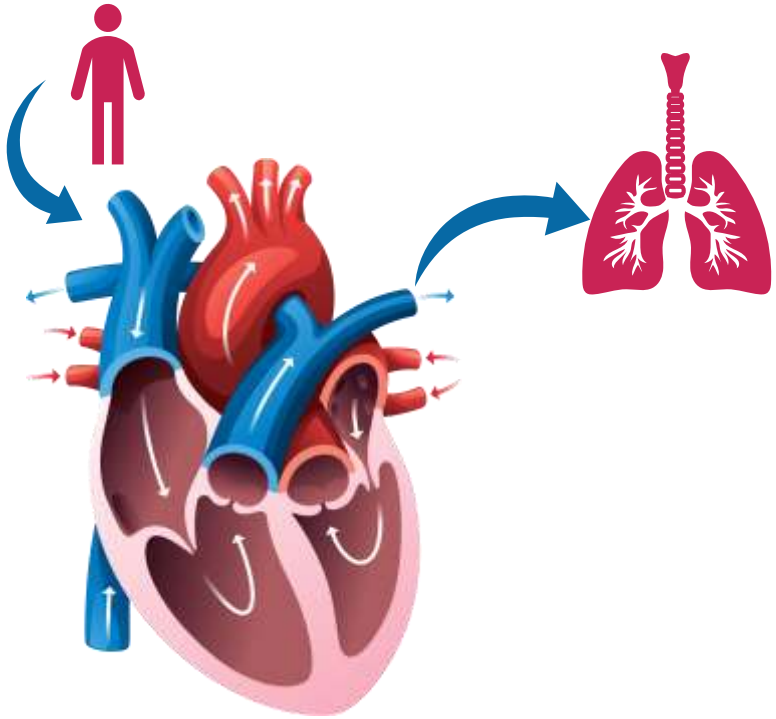
The heart is a two-way pump



1. Shah SJ. Heart failure. Merck Manual Consumer Version website. http://www.merckmanuals.com/home/heart-and-blood-vessel-disorders/heart-failure/heart-failure. Accessed January 2020.

The heart is a two-way pump

The right side of the heart pumps oxygen-poor blood from the body into the lungs[1]



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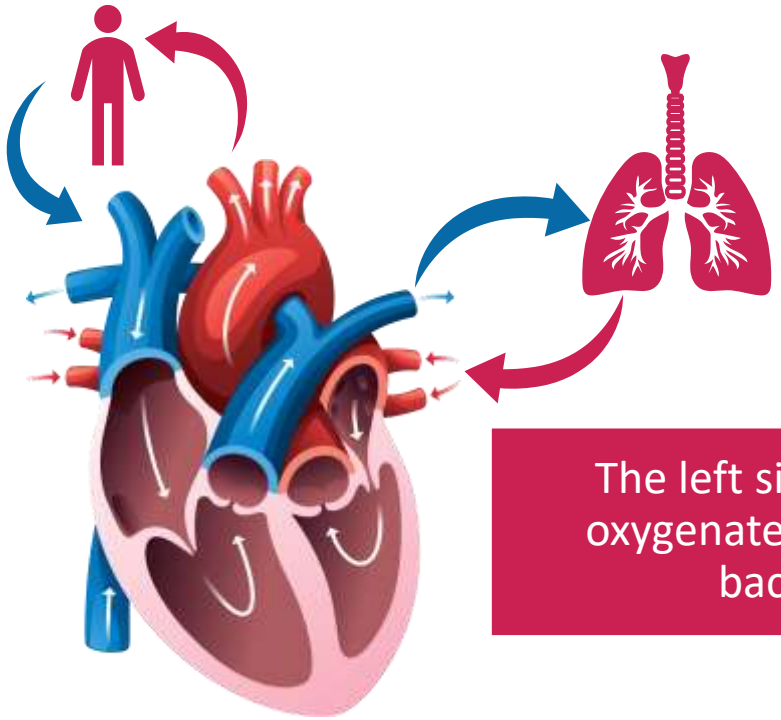
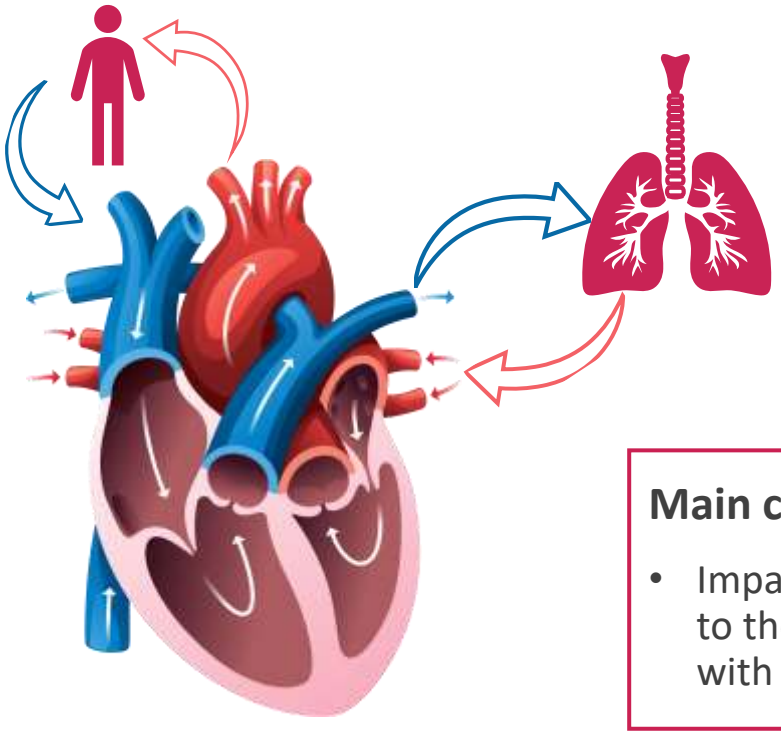


The left side of the heart pumps oxygenated blood from the lungs back into the body[1]

1. Shah SJ. Heart failure. Merck Manual Consumer Version website. http://www.merckmanuals.com/home/heart-and-blood-vessel-disorders/heart-failure/heart-failure. Accessed January 2020.

The pump can fail[1]



Main cause of failure:

- Impaired ejection (forcing out of blood) leads to the left ventricle failing to empty completely with each contraction[1]

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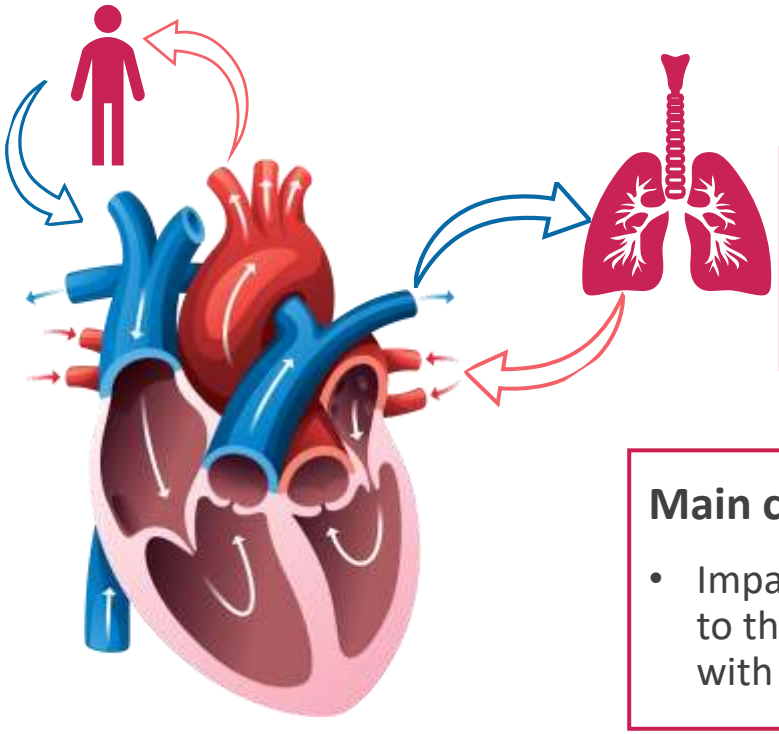
Failure leads to a build-up of pressure in heart and/or fluid overload[1]

2. Congestion on the right side leads to fluid accumulation (swelling) in parts of the body such as legs or the liver[1]



1. Rapid accumulation of fluid in the lungs can lead to swelling and shortness of breath[1]

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A variety of conditions are associated with different types of left heart failure

HF can be caused by:[1-5]

- A chronic condition, e.g. diabetes
- An acute event/index event, e.g. myocardial infarction
- Toxic damage, e.g. substance abuse

Different types of HF are associated with different precipitating conditions/events

HF, heart failure.

1. Mann DL, et al. Heart failure: pathophysiology and diagnosis. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *HPIM*. 2015;1500-1506. 2. Chumley H. Heart failure. In: Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *Color Atlas of Family Medicine*. 2nd ed. New York, NY: McGraw Hill Education; 2013:277-280. 3. Sato N. Congestion: historical and pathophysiological review and the concept of fundamental management for hospitalized heart failure. In: Sato N, ed. *Therapeutic Strategies for Heart Failure*. Tokyo, Japan: Springer; 2018:39-54. 4. Capote L, et al. *Pathophysiology and Pharmacotherapy of Cardiovascular Disease*. 2018;39-54. 5. Michaud K. Ischemic heart disease. In: Suvarna SK, ed. *Cardiac Pathology*. London, UK: Springer-Verlag; 2013:117-131.

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Impaired filling (also referred to as impaired ventricular relaxation or diastolic dysfunction) is usually related to:[4]

- Chronic hypertension
- Ischaemic heart disease

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Left ventricular ejection dysfunction can be precipitated by:[4,5]

- Coronary artery disease (CAD)
- Valvular heart disease
- Hypertension
- Toxin-induced cardiomyopathies
- Congenital heart disease
- Cancer chemotherapy (anthracyclines)

CAD, coronary artery disease; HF, heart failure.

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Left ventricular ejection dysfunction can be precipitated by:[4]

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CAD is believed to be the underlying cause of HF in approximately **two-thirds of patients**, from either acute or chronic injury to the heart[5]

CAD, coronary artery disease; HF, heart failure.

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How do precipitating conditions/events lead to heart failure?[1]

Precipitating condition/events can cause:

Damage to the heart muscle

E.g. coronary artery disease, toxic damage, infection

Increased cardiac workload

E.g. hypertension, valve and myocardium structural defects

Altered heart rhythm

E.g. atrial fibrillation (AF)

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Over time, reduced cardiac output leads to cardiac remodelling and progressive deterioration of the heart[1]

Damage to heart muscle[3]

→ ↓ Cardiac output
↓ Blood pressure
→ **Body compensatory mechanisms[3]**

RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

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- Cardiac output
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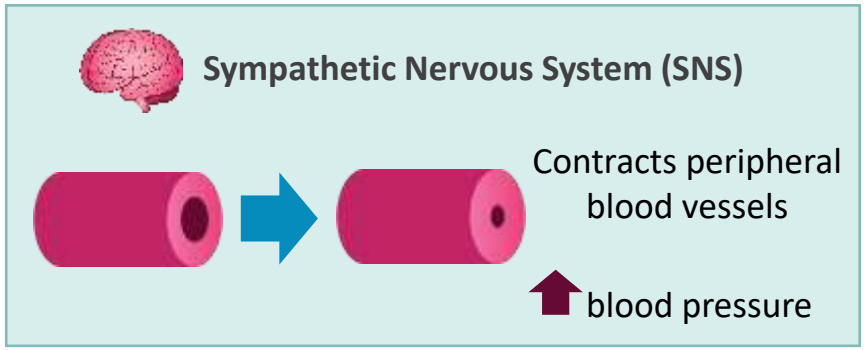
Body compensatory mechanisms[3]



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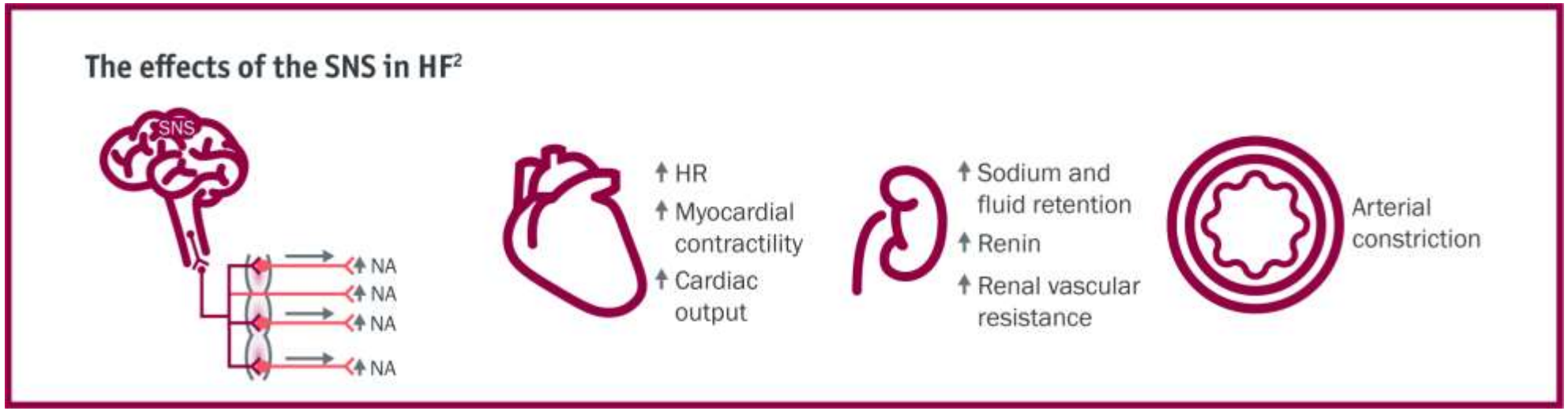
Sympathetic Nervous System Activation

The SNS exerts a wide variety of **CV effects**, particularly in HF, mainly via the release of:[1]

Noradrenaline (NA)[a] by cardiac nerve terminals

Adrenaline[a] by adrenal glands



[a](Nor)adrenaline is also referred to as (nor)epinephrine.
HF, heart failure; HR, heart rate; NA, noradrenaline, SNS, sympathetic nervous system.

Pop-up: Detrimental effects of long-term SNS activation[3]

Over time, reduced cardiac output leads to cardiac remodelling and progressive deterioration of the heart[1]

Damage to heart muscle[3]

↓ Cardiac output

↓ Blood pressure

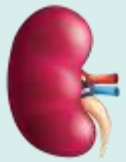
Body compensatory mechanisms[3]

Sympathetic Nervous System (SNS)

Contracts peripheral blood vessels

↑ Blood pressure

Renin-Angiotensin-Aldosterone System (RAAS)



Fluid retention

↑ Preload (amount of blood entering heart)

↑ Sodium reabsorption

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RAAS Activation

RAAS is activated later in the course of HF compared with the SNS[1]

Short-term effects of increased RAAS activation[2]

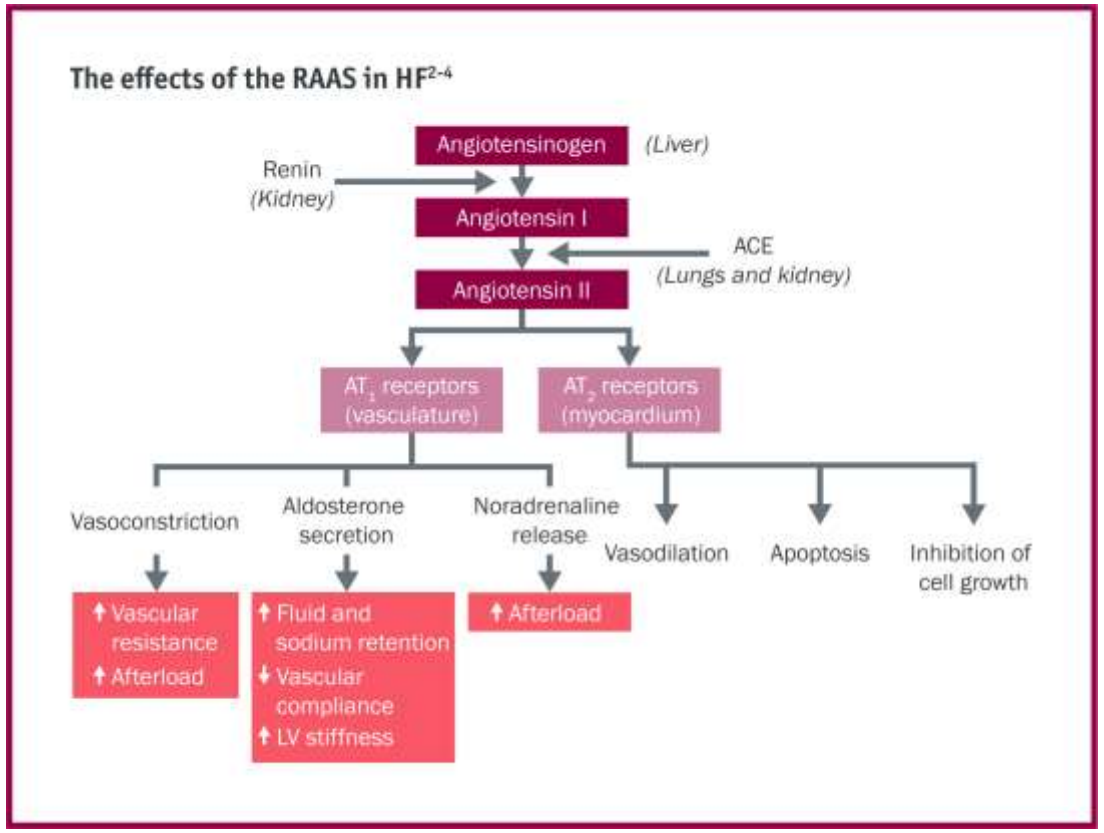
Maintenance of blood pressure through vasoconstriction as well as sodium and water retention, which increases preload and cardiac output

Long-term effects of increased RAAS activation[1,2]

HF progression due to increased afterload

Pulmonary and peripheral congestion due to fluid retention

Fibrosis of the heart, blood vessels and kidneys



ACE, angiotensin-converting enzyme; HF, heart failure; LV, left ventricle; RAAS, renin-angiotensin-aldosterone system.

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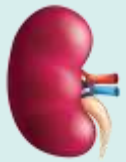

Fluid retention

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Short-term[1-4]

↑ Cardiac output, adequate volume for circulation

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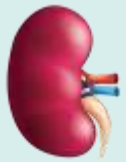

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Short-term[1-4]

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Over time[4]

Cardiac remodelling

E.g. hypertrophy (thickening of the cardiac muscle wall)

RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

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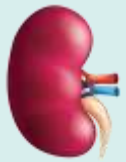

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Over time[4]

Cardiac remodelling

e.g. hypertrophy (thickening of the cardiac muscle wall)

Suppressing the process of cardiac remodeling and maintaining cardiac function form the main concepts of treatment for chronic HF[2]

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Chronic Neurohormonal Activation Triggered by Heart Failure

Neurohormonal mechanisms act to compensate for impaired LV contractility in HFrEF:[1,2]

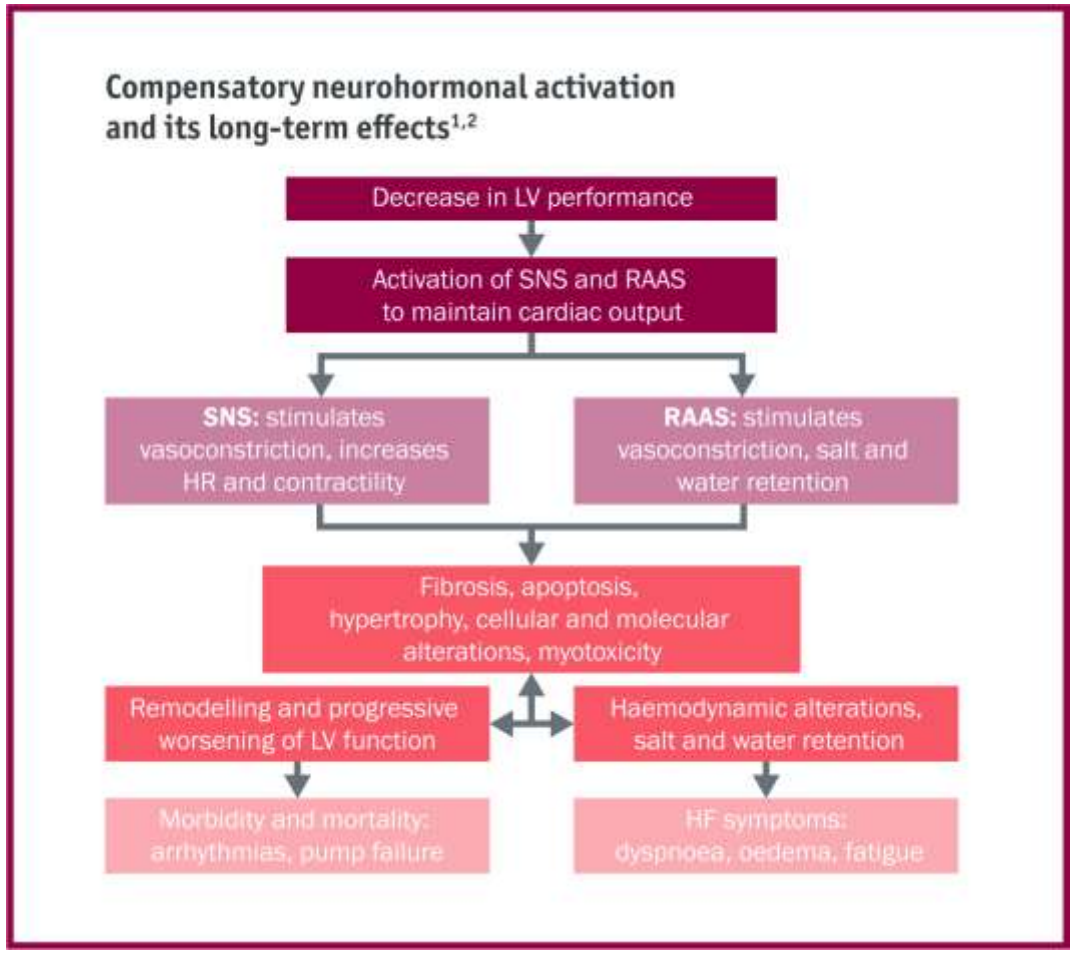
Increasing fluid retention and preload

Increasing vascular resistance and afterload

These mechanisms include:[1]

Activation of sympathetic nervous system (SNS)

Increased activity of renin-angiotensin-aldosterone system (RAAS)



HF, heart failure; LV, left ventricle; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

The Natriuretic Peptide System

The volume overload associated with excessive neurohormonal activation, which also triggers upregulation of the antidiuretic hormone vasopressin, results in myocardial stretch[1]

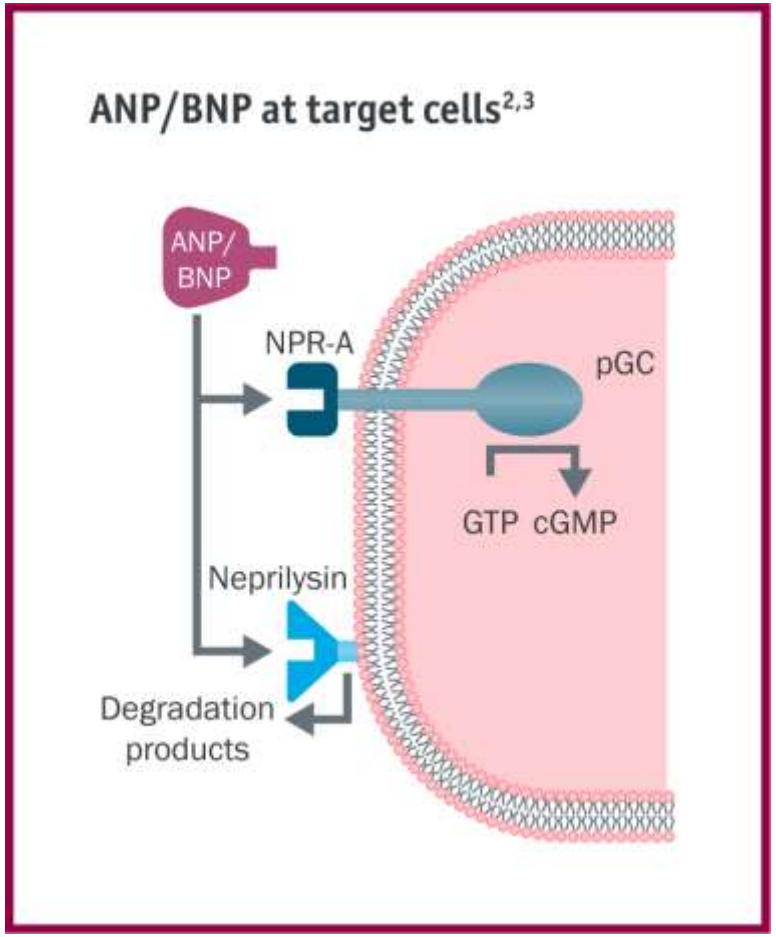
This stretching triggers the release of NPs – mainly atrial NP (ANP), BNP, and C-type NP (CNP) – that bind to high-affinity NP receptors, linked to a particulate guanylate cyclase (pGC), leading to an elevation of intracellular cyclic guanosine monophosphate (cGMP) to induce vasodilation, natriuresis, and diuresis[1-3]

ANP and BNP bind to the NP receptor (NPR)-A, present in large blood vessels, adrenal glands and kidney[2]

CNP is the natural ligand for the NPR-B, predominant in the brain, adrenal glands and kidney[2]

In the context of normal cardiac physiology, the RAAS and SNS are balanced by the NP system to maintain homeostasis[1]

However, as HF progresses, the NP system may not regulate the response of the neurohormonal compensatory mechanisms due to proposed mechanisms such as the NPs being degraded by neprilysin in the kidney and vasculature[1,2]



ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NPR, nucleoprotein receptor; pGC, particulate guanylate cyclase.

NO-sGC-cGMP Signalling

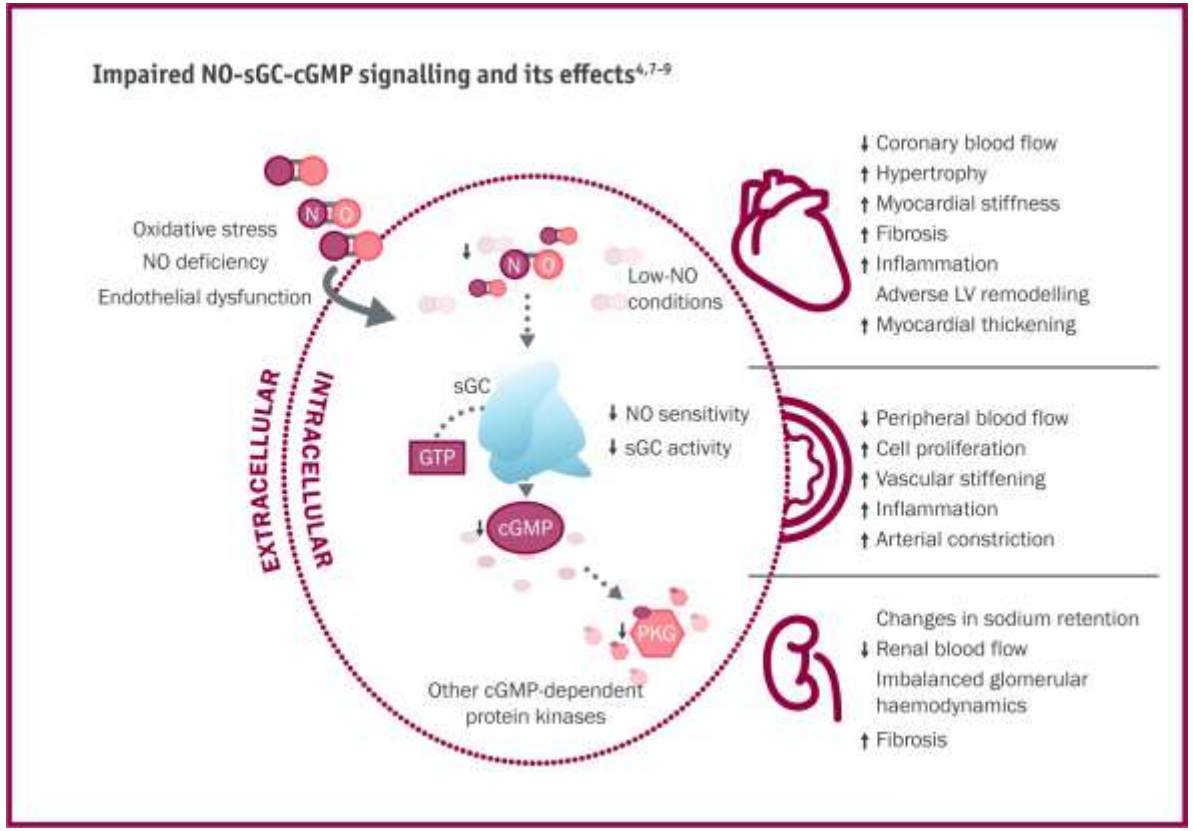
Another pathway responsible for the production of cGMP, independent of the SNS and RAAS, is driven by the enzyme soluble guanylate cyclase, or soluble guanylyl cyclase (sGC)[1–3]

Normal sGC activity plays a major role in the protection against myocardial injury, ventricular remodelling and cardiorenal syndrome[4]

In normal cardiac function and performance, nitric oxide (NO) binds to sGC, the only intracellular receptor for NO, which catalyses the conversion of GTP to cGMP[1,5]

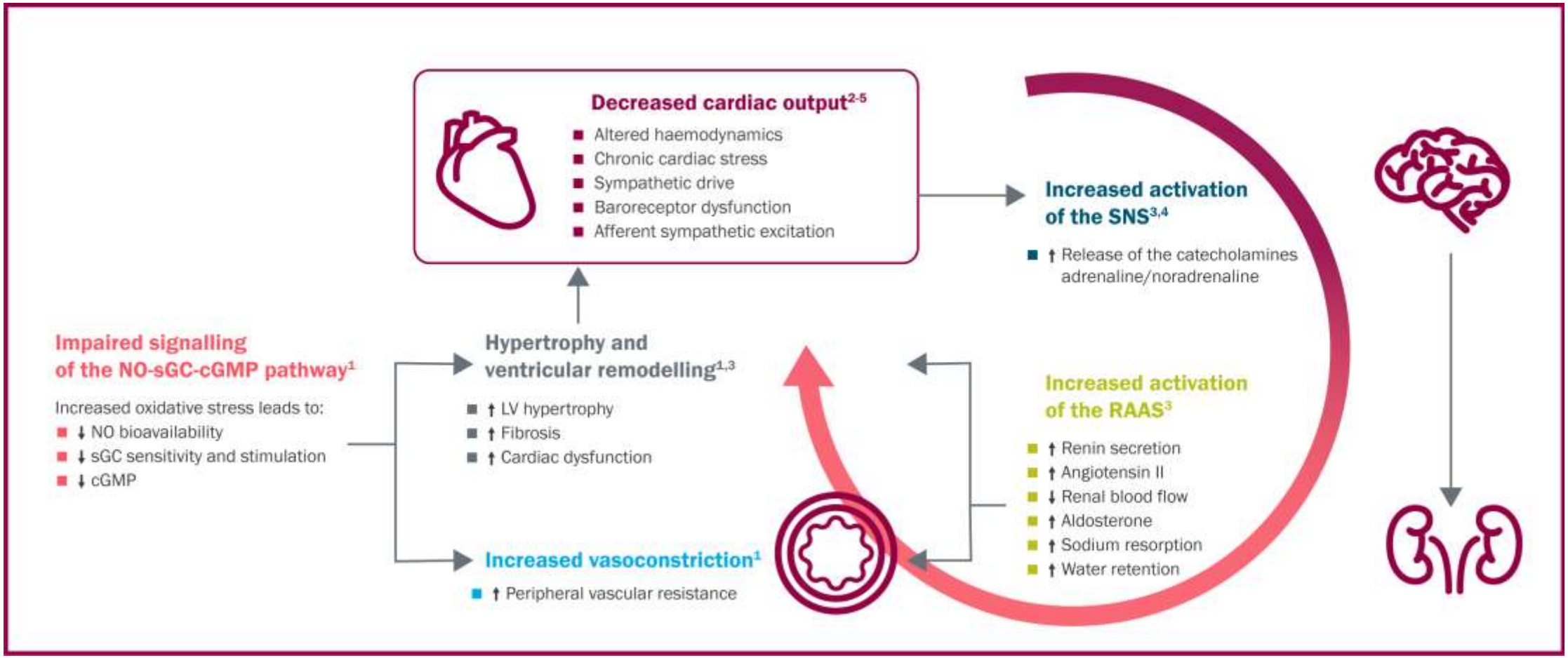
Under conditions of oxidative stress, there is a decrease in the NO-sensitive form of sGC, decrease in NO bioavailability, and/or increase in NO inactivation[4,6]

This leads to insufficient stimulation of the sGC, decreased production of cGMP, and subsequent CV dysfunction and HF[4]



cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; LV, left ventricle; NO, nitric oxide; PKG, protein kinase G; sGC, soluble guanylate cyclase.

Overview of Contributors to Heart Failure Pathology



cGMP, cyclic guanosine monophosphate; HF, heart failure; LV, left ventricle; NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system; sGC, soluble guanylate cyclase; SNS, sympathetic nervous system.

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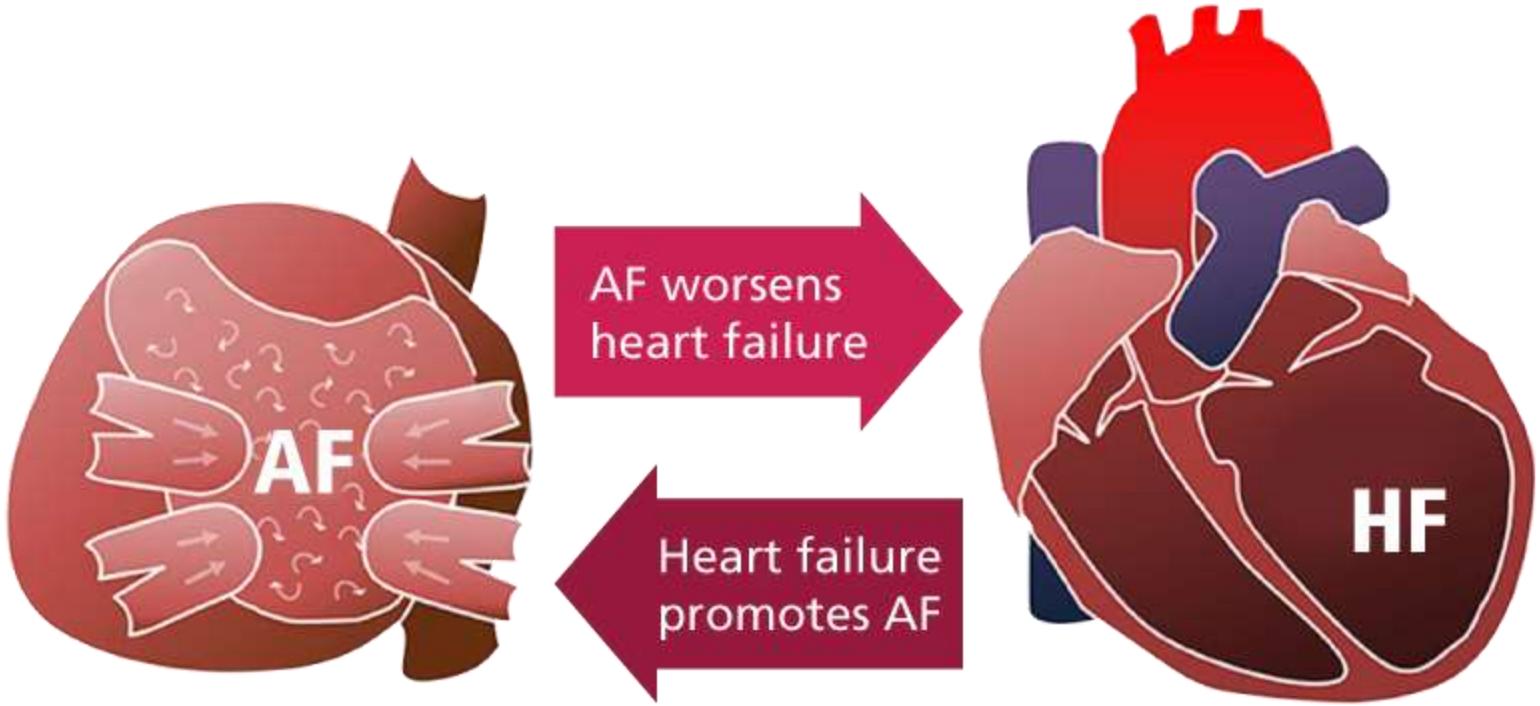
1. Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-2200

Heart failure and atrial fibrillation have a close, bidirectional relationship[1]



AF, atrial fibrillation; HF, heart failure.

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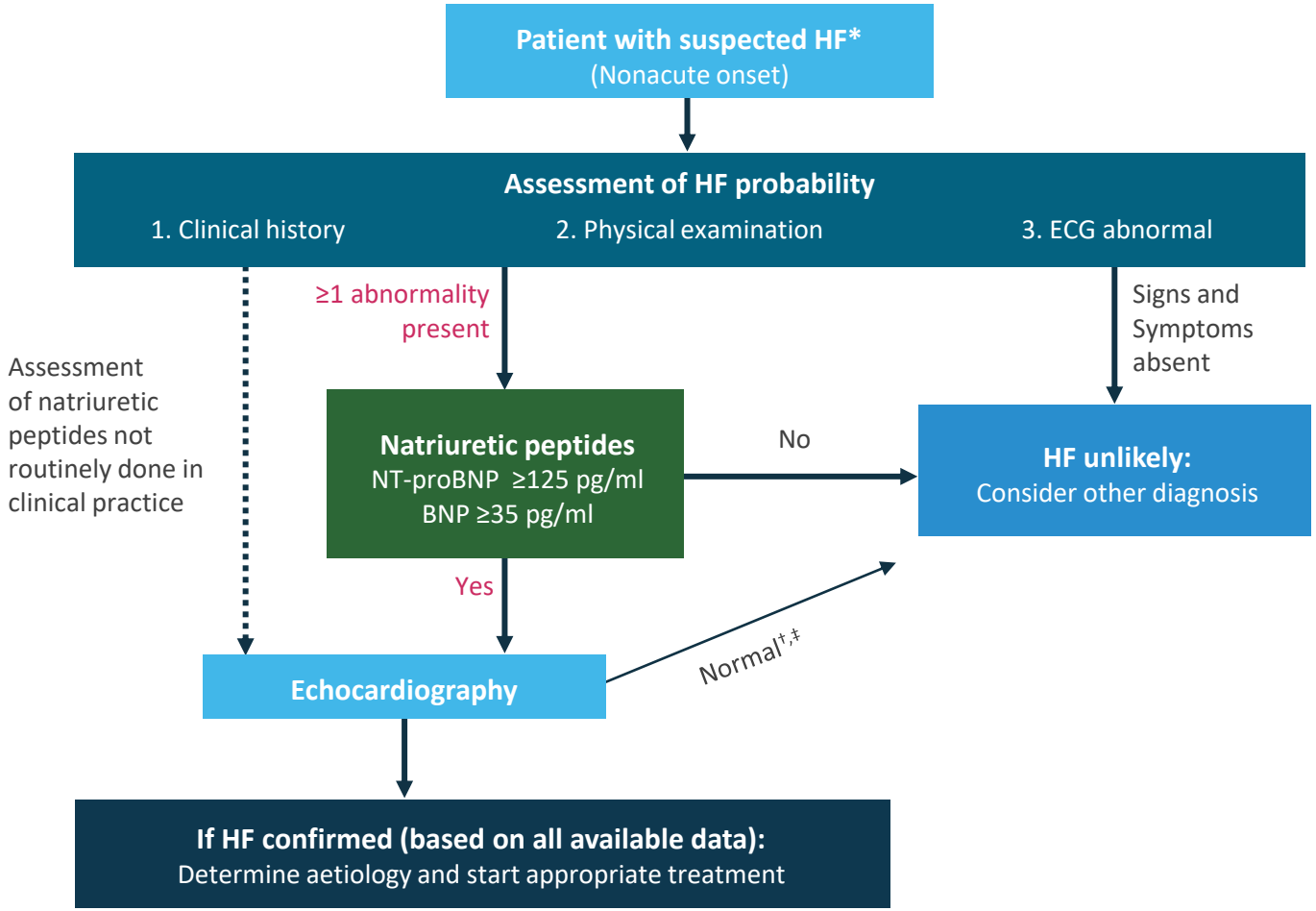
Heart Failure

How is it diagnosed?

Suspected heart failure: Clinical diagnosis

ESC diagnostic algorithm for chronic HF[1]



BNP, B-type natriuretic peptide; ECG, electrocardiogram; ESC, European Society of Cardiology; HF, heart failure; NT-proBNP, N-terminal pro-B type natriuretic peptide.

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Suspected heart failure: Clinical diagnosis

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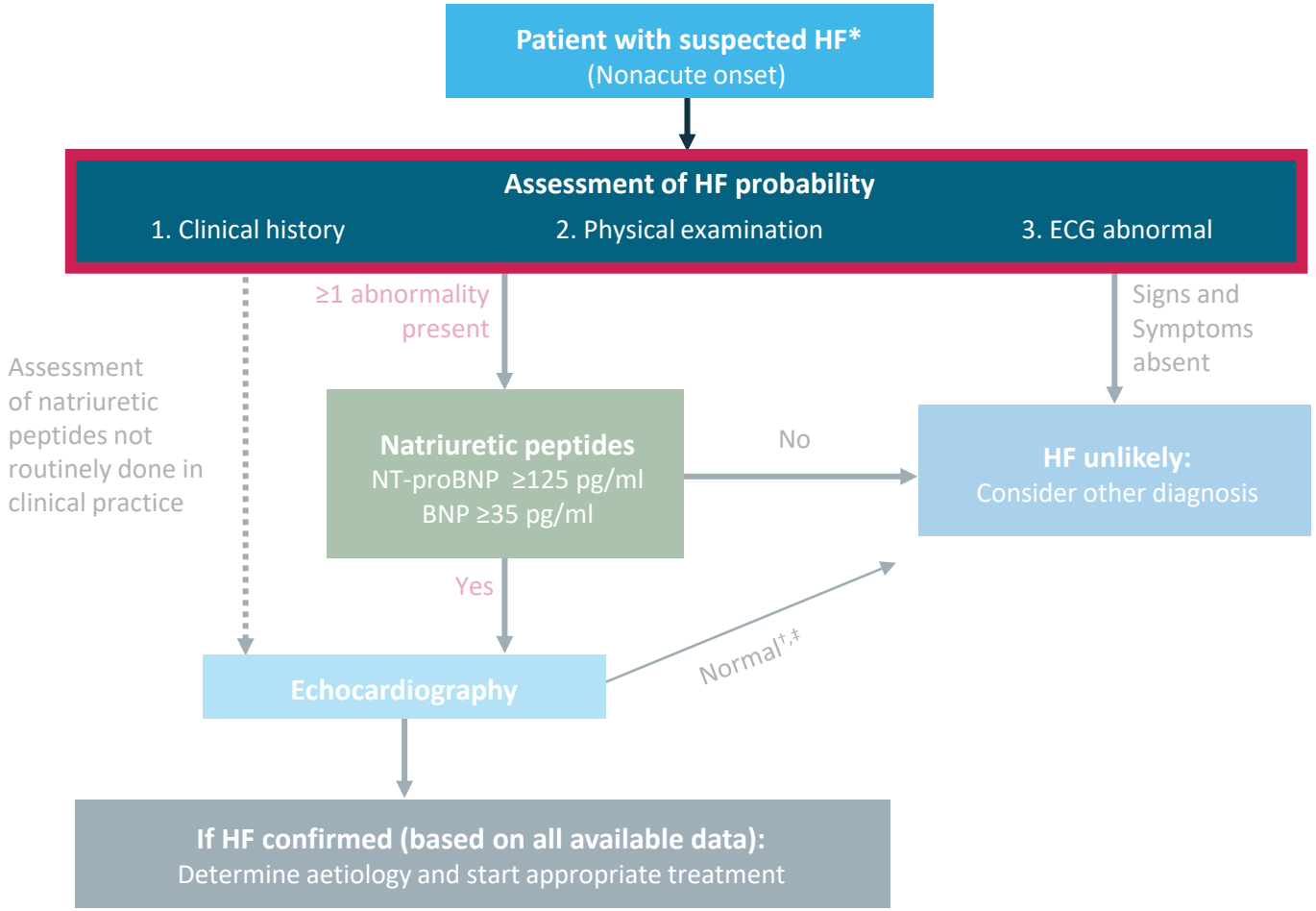

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Suspected heart failure: Clinical diagnosis

Clinical history

- Obtain detailed history for a patient with suspected HF[1]

Physical examination

- Symptoms often nonspecific[2]
- The Framingham criteria are well-recognised diagnostic criteria for HF: patients must present with **two major**, or **one major and two minor**, criteria concurrently[3]

Framingham criteria

Minor[3]

- Ankle oedema
- Night cough
- Dyspnoea on exertion
- Hepatomegaly
- Pleural effusion
- Decreased vital capacity
- Tachycardia (heart rate ≥120/min)

Major[1,3]

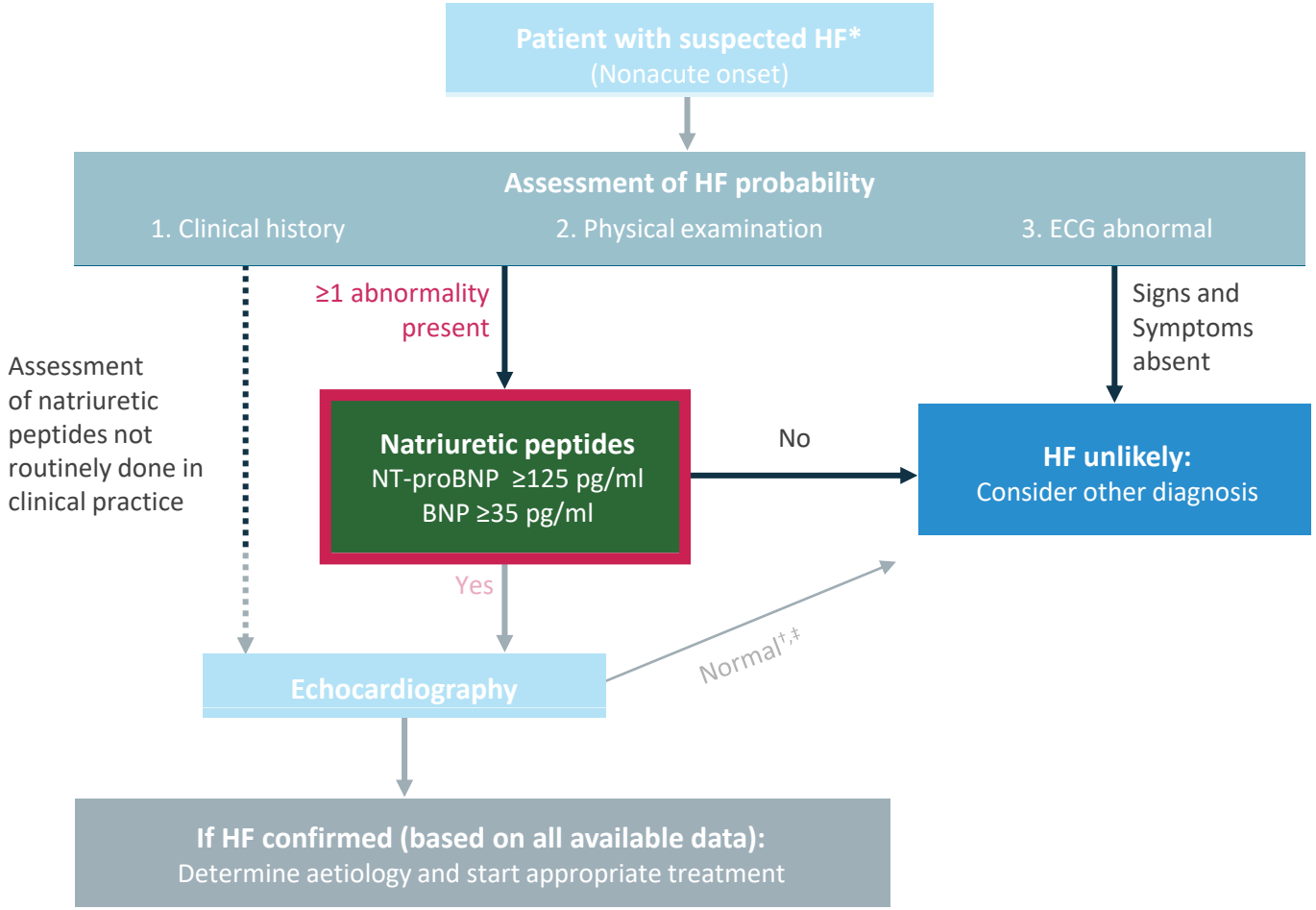
- Paroxysmal nocturnal dyspnoea/orthopnoea
- Hepatojugular reflux
- Crackles
- Cardiomegaly
- Acute pulmonary oedema
- Gallop rhythm
- Increased venous pressure (>16 cm of water)
- Circulation time ≥25 sec

HF, heart failure; MI, myocardial infarction.

1. Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-2200. 2. Shah SJ. Heart failure. Merck Manual Consumer Version website. http://www.merckmanuals.com/home/heart-and-blood-vessel-disorders/heart-failure/heart-failure. Accessed January 2020.
3. McKee PA, et al. *N Engl J Med*. 1971;285:1441-1446.

Suspected heart failure: Clinical diagnosis

ESC diagnostic algorithm for chronic HF[1]



BNP, B-type natriuretic peptide; ECG, electrocardiogram; ESC, European Society of Cardiology; HF, heart failure; NT-proBNP, N-terminal pro-B type natriuretic peptide.

1. Ponikowski P, et al. *Eur Heart J.* 2016;37:2129-2200. 2. Pandit K, et al. *Indian J Endocr Metab.* 2011;15(4);S345-S353. 3.Yancy CW, et al. *J Am Coll Cardiol.* 2018;71(2):201-230.

Laboratory Testing to Further Assess Heart Failure Diagnosis

- Laboratory assessment in patients presenting with symptoms of HF generally includes **blood count, serum electrolyte, blood glucose, renal function, liver function, thyroid function and lipid profile testing**[1]
- In addition to these assessments, **BNPs and N-terminal pro BNP (NT-proBNP) are important biomarkers** with established roles in the diagnosis of HF[1]
- **Elevated levels of BNP and NT-proBNP** are associated with a wide variety of CV and non-CV causes[1]
- These biomarkers may assist in the diagnosis of HF, particularly when symptoms such **as dyspnoea are present**, and HF is suspected as the cause[1]
- **BNP are cleared from the circulation with a plasma half-life of ~20 minutes and NT-proBNP have a longer half-life of 60–90 minutes. Studies suggest that NT-proBNP may be a more discerning biomarker than BNP in certain cases**[2,3]

What are NPs?

Diagnostic and prognostic value

Factors affecting NT-proBNP levels[2,7,9]

Emerging biomarkers in HF diagnosis

Pop-up 1:
What are NPs?

NPs are hormones – mainly secreted by the heart – that have important properties in stimulating the release of sodium (natriuresis), potassium (kaliuresis), and water from the kidneys.[2,4]

The main ones associated with HF are:[2]

A-type NP (ANP)

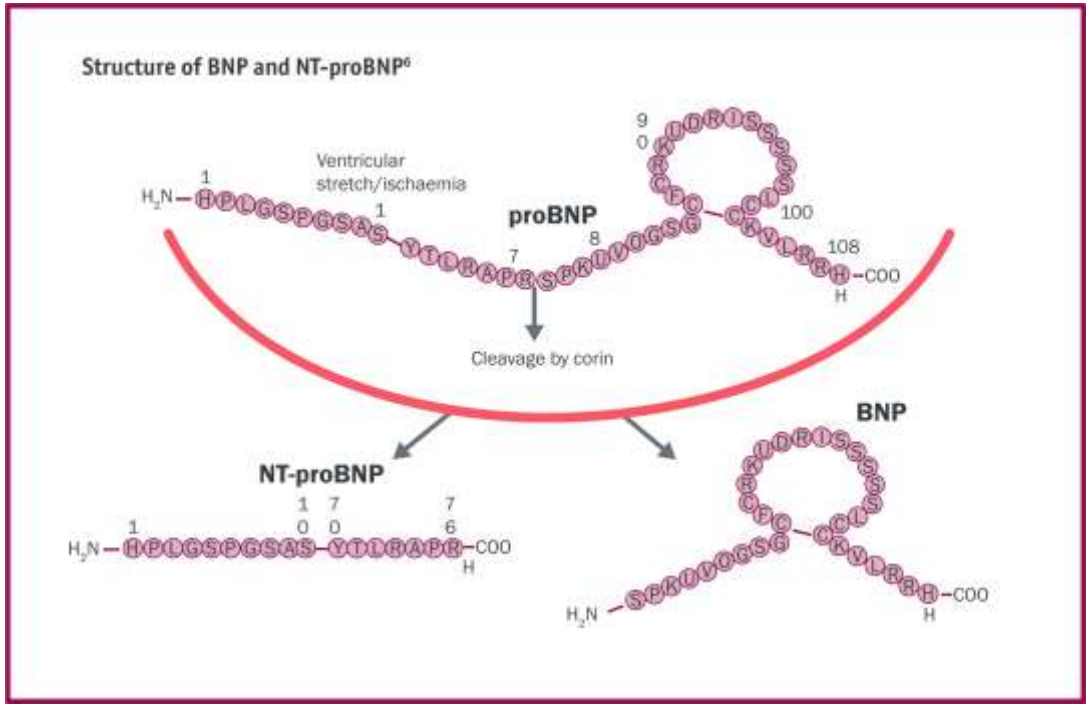
BNP

NT-proBNP (the N-terminal 76-amino-acid segment of BNP) is an inactive pro-hormone, cleaved from the parent protein to release BNP

In HF, myocardial stretching triggers the release of BNP, which has:[1,2,4]

Diuretic, natriuretic, and antihypertensive effects, which are exerted by inhibiting the RAAS

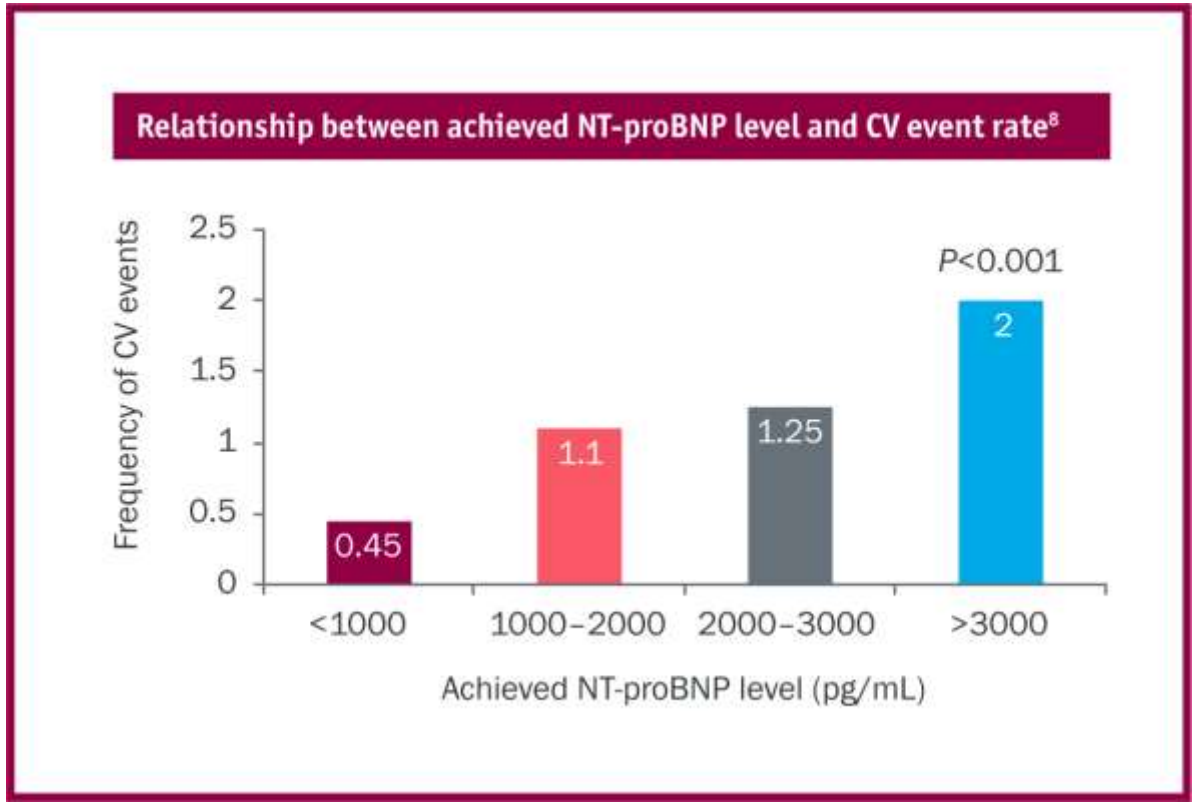
Potential to provide a protective effect against the detrimental fibrosis and remodelling that occurs in progressive HF[5]



The parent protein of BNP, proBNP, is cleaved by the enzyme corin in order to produce the inactive NT-proBNP and active BNP.[4] Adapted from Gandhi and Pinney.[6]
BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; BNP, B-type natriuretic peptide.

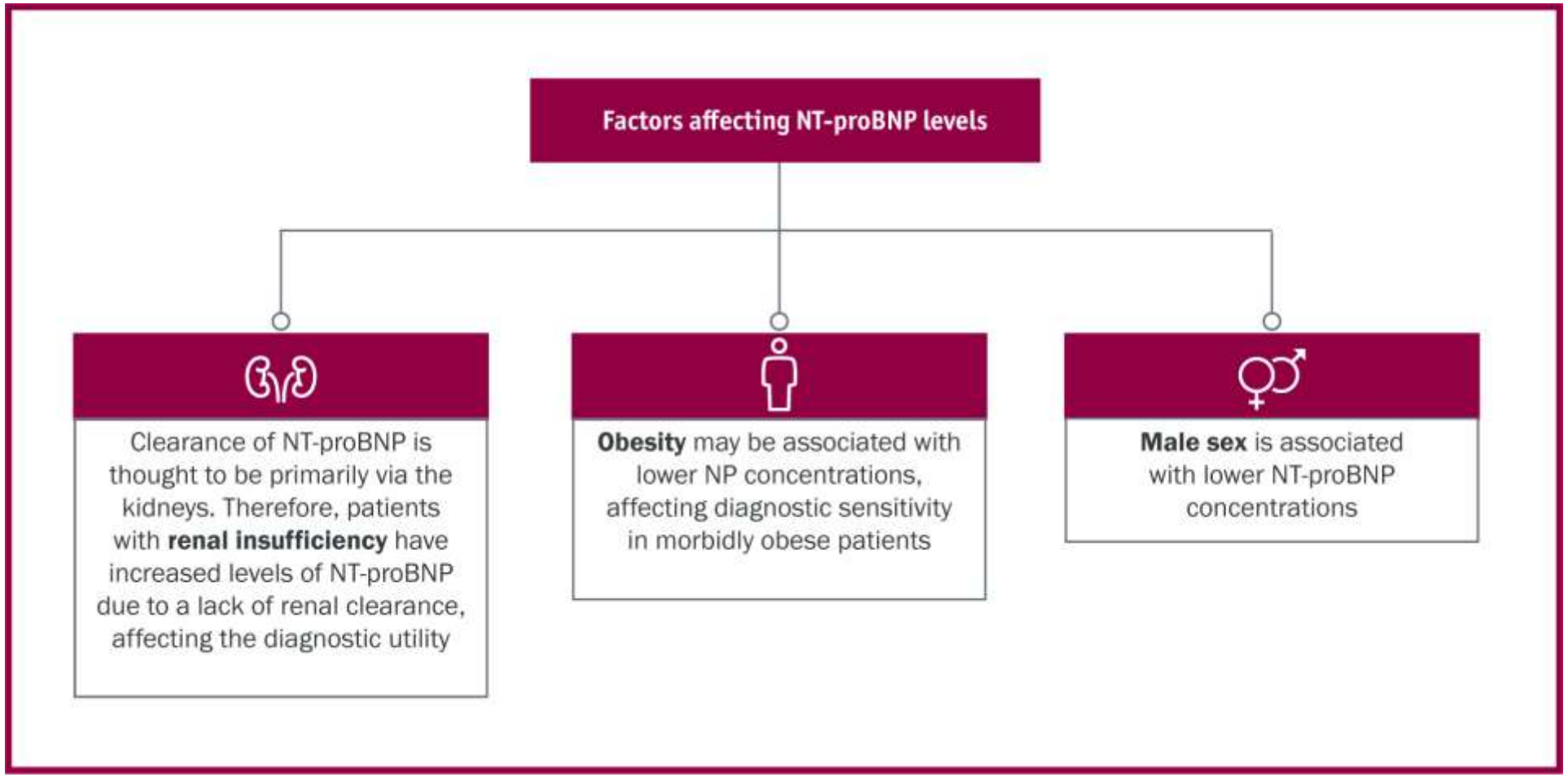
Pop-up 2:
Diagnostic and prognostic value of NPs

- Measuring NPs as an initial diagnostic test may be helpful when echocardiography is not immediately available[7]
- Elevated NPs help establish an initial working diagnosis by identifying patients who require further cardiac investigation; i.e. patients with normal plasma NP concentrations do not require echocardiography because they are unlikely to have **HF**[7]
- **The upper limit of serum concentrations in the non-acute setting is 35 pg/mL for BNP and 125 pg/mL for NT-proBNP**[7]
- **The higher the NT-proBNP plasma level, the higher the risk of CV events**[8]



CV, cardiovascular; NT-proBNP, N-terminal pro B-type natriuretic peptide.

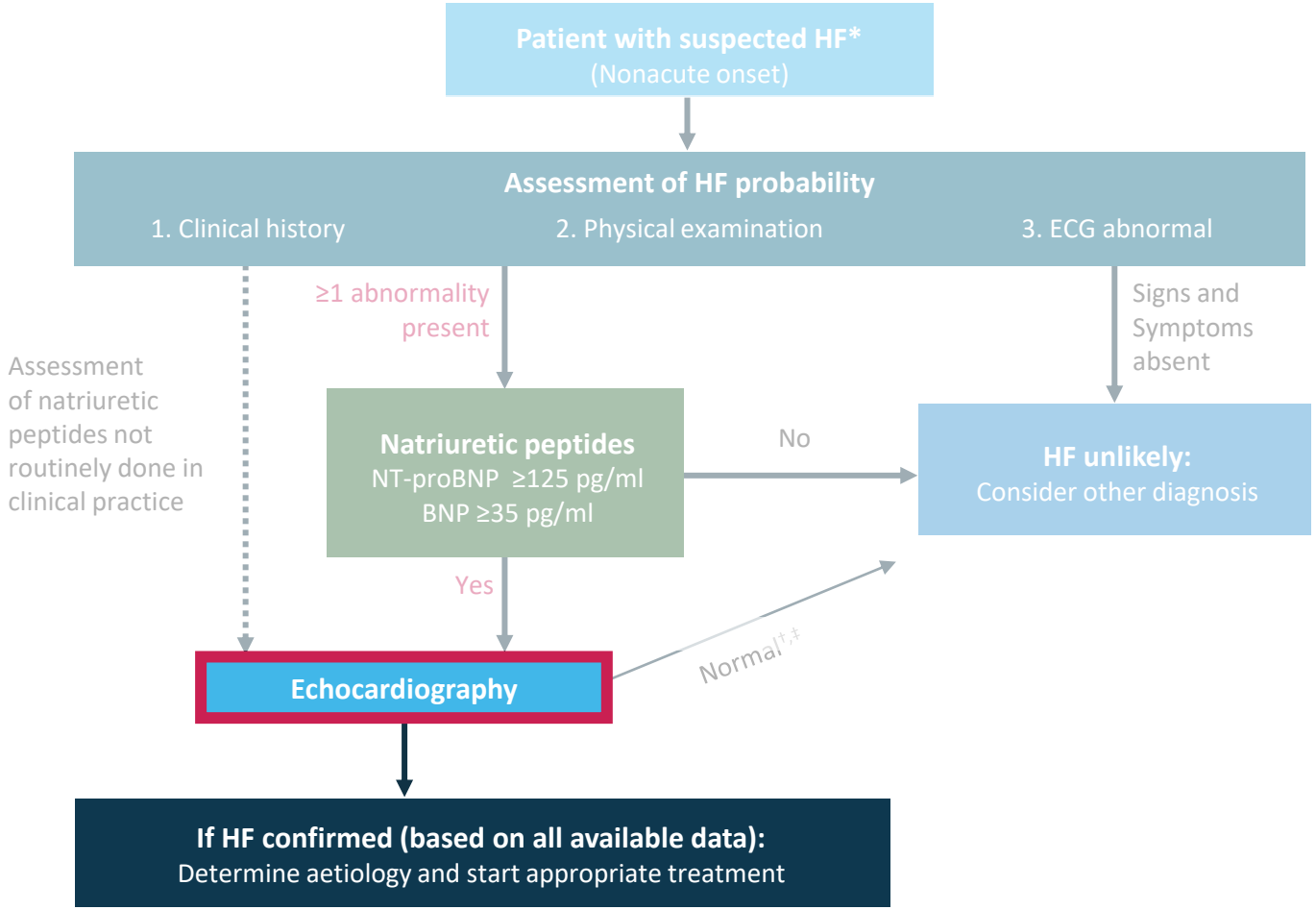
Pop-up 3:
Factors affecting NT-proBNP levels[2,7,9]



NP, natriuretic peptide; NT-proBNP, N-terminal pro B-type NP.

Suspected heart failure: Clinical diagnosis

ESC diagnostic algorithm for chronic HF[1]



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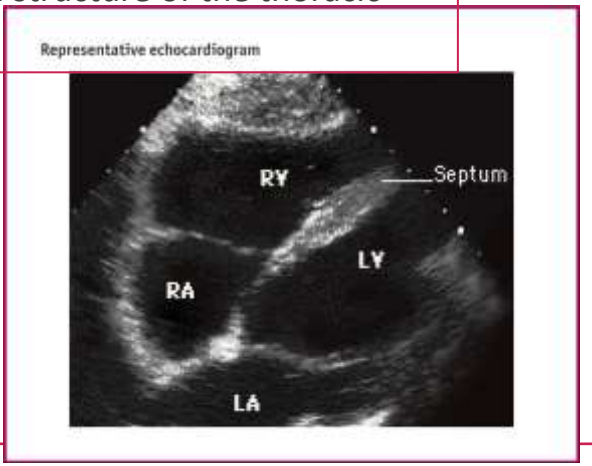
Echo is used to determine LVEF, which helps to diagnose and categorise heart failure[2]

- Left ventricle is the heart's main pumping chamber, pumping oxygenated blood to the body, so ejection fraction is usually measured in that chamber[1]

$$\text{LVEF}^{2} = \frac{\text{Volume pumped out on contraction (systole)}}{\text{Total volume by end of relaxation (diastole)}} \times 100$$

- Ultrasound imaging technique, including 2D/3D echocardiography, colour-flow Doppler, pulsed and continuous wave Doppler, and tissue Doppler imaging.[3]
  - It is the **method of choice among the available imaging modalities for patients with suspected HF** due to its reliability, accuracy, availability (including portability), safety and cost[1,3]
- Provides immediate information on ventricular systolic and diastolic function, cardiac chamber volumes, valve function, wall thickness and pulmonary hypertension[1,2]
  - Can observe pumping function of the ventricles, including LVEF and the structure and function of the valves
  - Can assess pericardial effusions
  - Can observe the blood flow and structure of the thoracic aorta and pulmonary artery



HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

1. Mankad, R. Ejection fraction: What does it measure? Mayo Clinic website. https://www.mayoclinic.org/ejection-fraction/expert-answers/faq-20058286?p=1. Updated July 2019. Accessed March 2020. 2. Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-2200. 3. Yancy CW, et al. *J Am Coll Cardiol*. 2018;71(2):201-230. 4. Mann DL, et al. Heart failure: pathophysiology and diagnosis. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. Volume 2. 19th ed. New York, NY: McGraw Hill Education; 2015:1500-1506.

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ESC diagnostic criteria[2-4]

	LVEF <40%	LVEF 40%-49%	LVEF ≥50%
Clinical evidence	Symptoms and signs*		

	No other criteria necessary	• Elevated natriuretic peptide levels†
		• At least one additional criterion:
		  • Left ventricular hypertrophy
		  • Left atrial enlargement
		  • Diastolic dysfunction	

HF diagnosis	HF with **reduced ejection fraction** (HFrEF)	HF with **mildly reduced-ejection fraction** (HFmrEF)	HF with **preserved ejection fraction** (HFpEF)

*Signs may not be present in the early stages of heart failure (especially in HFpEF) and in patients treated with diuretics. †B-type natriuretic peptide >35 pg/ml and/or NT-pro-BNP >125 pg/ml.
HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

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The New York Heart Association (NYHA) developed a classification of heart failure according to limitation of physical activity[1]

Class	Limitation of physical activity	Symptoms
I	None	Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea
II	Slight	Person is comfortable at rest. Ordinary physical activity causes fatigue, palpitation or dyspnoea
III	Marked	Person is comfortable at rest. Less than ordinary activity causes fatigue, palpitation or dyspnoea
IV	Severe	Person is unable to carry on any physical activity without discomfort. Person has symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases

HF, heart failure; NYHA, New York Heart Association.

1. Shah SJ. Heart failure. Merck Manual Consumer Version website. http://www.merckmanuals.com/home/heart-and-blood-vessel-disorders/heart-failure/heart-failure. Accessed January 2020.

Heart Failure

What is Symptomatic chronic HF following a worsening HF event?

What is a Worsening Heart Failure event?

Despite a period of stabilization, patients with HFrEF may experience a worsening HF event

Worsening chronic HF is characterized by:[1-3]

- Development of progressively **escalating signs and symptoms of HF** requiring intensification of therapy
- Experience of a prior worsening HF event:
  - Need for IV diuretics, regardless of setting
  - HF hospitalisation
  - Need for an urgent HF visit

In a real-world study linking registry and claims data of >11,000 patients with HFrEF, 1 in 6 patients developed worsening HF* within 18 months of initial diagnosis[1]

*Defined in PINNACLE-HF as the development of progressively escalating symptoms and signs of HF requiring intravenous diuretic treatment in the outpatient, emergency department, or hospitalised setting.
HF, heart failure; HFrEF, heart failure with reduced ejection fraction.
1. Butler J, et al. *J Am Coll Cardiol*. 2019;73(8):935-944. 2. Greene SJ, et al. *JAMA Cardiol*. 2018;3(3):252-259. 3. EMA CPMP/EWP/235/95, Rev.2. Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure. 20 July 2017. Accessed July 23, 2019.

Changes in the classification of HF from the 'Universal definition and classification of HF' consensus statement[1,2]

New onset/ de novo HF	Worsening HF	Improving HF	Persistent HF	HF in remission
• Newly diagnosed HF • No former history of HF	• Worsening symptom/signs/ functional capacity, and/or requiring escalation of therapies such as IV or other advanced therapies • and/or hospitalization	• Improving symptoms/signs and/or functional capacity	• Persistent HF with ongoing symptoms/signs and/or limited functional capacity	• Resolution of symptoms and signs of HF, with resolution of previous structural/ functional heart disease after a phase of symptomatic HF

"Worsening HF" in VICTORIA[3]

- Recent HF decompensation
  - HF hospitalization within 6 months
  - Outpatient IV diuretic use within 3 months

HF, heart failure; IV, intravenous.

References: 1. Bozkurt B *et al. J Cardi Fail* 2021;27:387–413; **2.** Bozkurt B *et al.* ESC. 27–30 August 2021; presentation; **3.** Armstrong PW *et al. N Engl J Med* 2020;382:1883–1893.

Challenges in the Definition of a ‘Worsening HF Event’

There are numerous criteria that define a ‘worsening HF event’[1]

- In order to qualify as an episode of worsening HF, objective evidence of the following should be provided:
  - Signs and symptoms of deteriorating clinical conditions
  - Signs of cardiac overload and changes in biomarkers
- The need for acute treatments for chronic HF should be included, such as:
  - Increase in diuretic dose
  - IV diuretics
  - IV vasodilators/inotropes

“*There is no widely accepted nomenclature for HF syndromes requiring hospitalisation*”[2]

Patients are described as having:

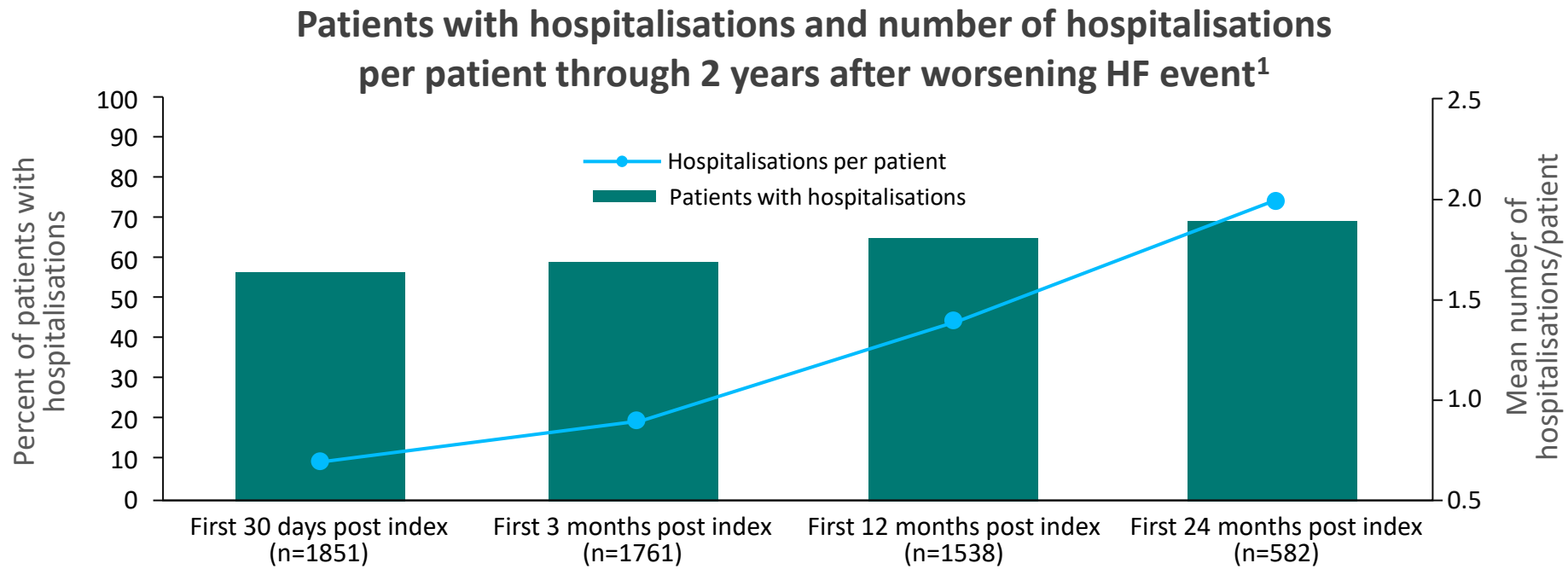
- Acute HF
- Acute HF syndromes
- **Acute(ly) decompensated HF**
  - **This last phrase has its limitations (e.g., does not make the important distinction between those with a de novo presentation of HF from those with worsening of previously chronic stable HF)**

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; IV, intravenous.

1. EMA. CPMP/EWP/235/95, Rev.2. Published July 20, 2017. Accessed July 23, 2019; 2. Yancy CW et al. *Circulation*. 2013;128:e240–e327.

Heart Failure

More than half of patients with symptomatic chronic HF following a worsening HF event may require rehospitalisation within a month of the event



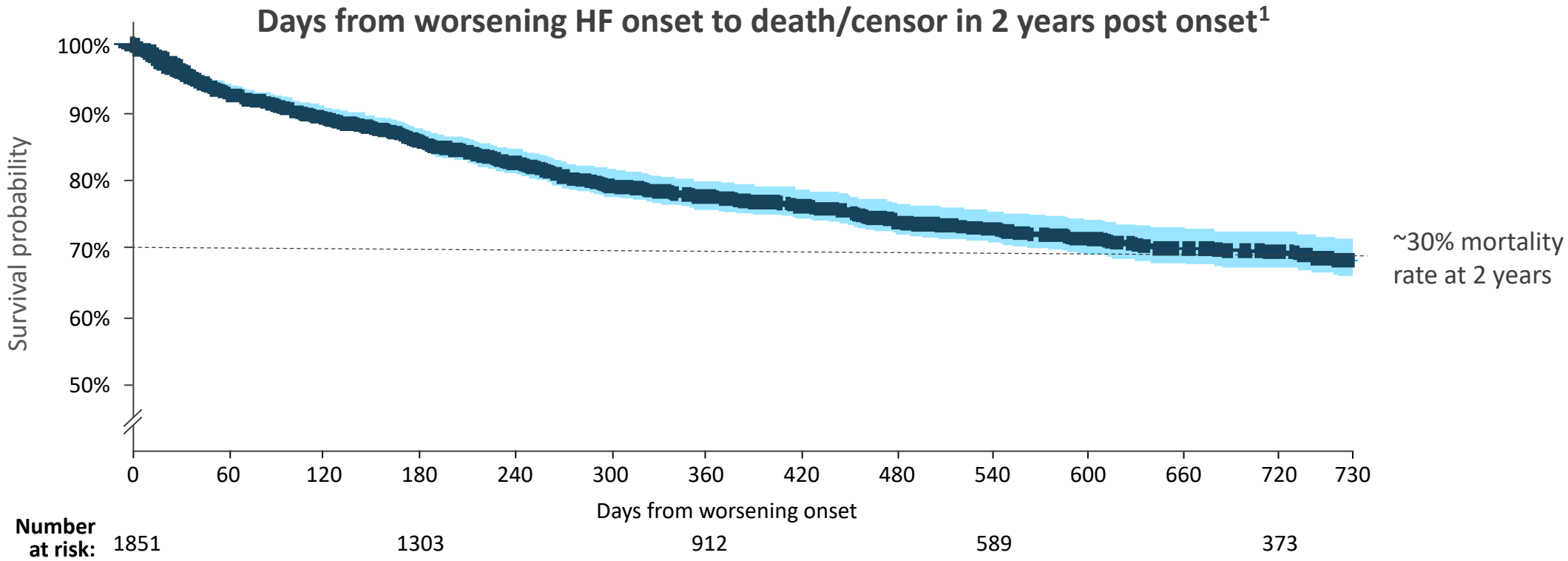
56% of patients were readmitted to hospital within 30 days of the worsening HF event, and the number of HF-related hospitalisations increased with time[1]

Note that worsening is defined in PINNACLE-HF as the development of progressively escalating symptoms and signs of HF requiring intravenous diuretic treatment in the outpatient, emergency department, or hospitalized setting.

HF, heart failure.

1. Butler J, et al. *J Am Coll Cardiol*. 2019;73(8):935-944.

Despite available therapies, these patients remain at a high risk of death after a worsening heart failure event



There was a rapid decline in survival in the 2 years following a worsening HF event[1]

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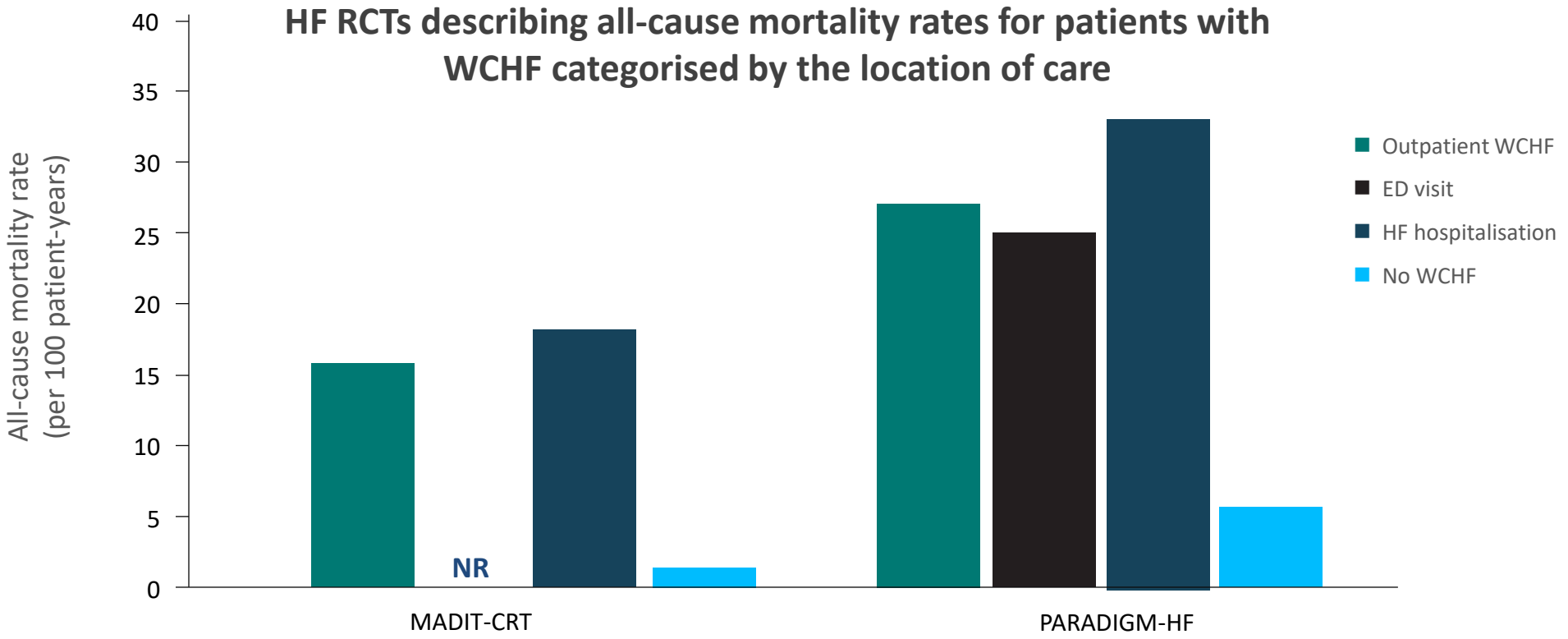
HF, heart failure.

1. Butler J, et al. *J Am Coll Cardiol*. 2019;73(8):935-944.

Regardless of the location of care, patients with symptomatic chronic HF following a worsening HF event still have a high risk of mortality[1]



ED, emergency department; HF, heart failure; RCT, randomized controlled trial; NR, not reported; WCHF, worsening chronic heart failure.

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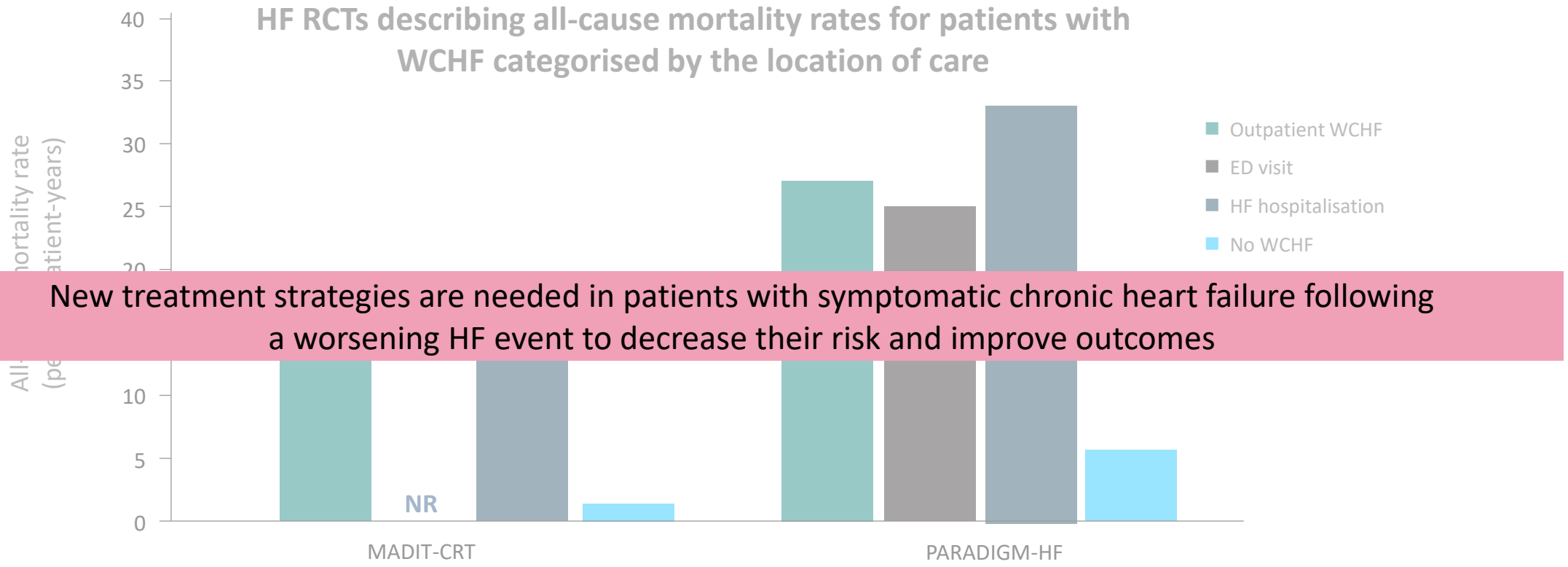

New treatment strategies are needed in patients with symptomatic chronic heart failure following a worsening HF event to decrease their risk and improve outcomes

ED, emergency department; HF, heart failure; RCT, randomized controlled trial; NR, not reported; WCHF, worsening chronic heart failure.

1. Greene SJ, et al. *JAMA Cardiol*. 2018;3(3):252-259.

Summary

- HF is the fastest growing cardiovascular disease
- It impacts patients' health-related quality of life (e.g. due to physical disability or effect on work or interpersonal relationships)
- HF is triggered by a condition/event that damages heart muscle or its ability to contract normally, leading to cardiac remodelling
- Causes of HF include diseases that damage heart muscle (e.g. CAD) or alter heart rhythm (e.g. AF), as well as abnormal loading conditions
- HF is categorised according to LVEF:
  - HF with preserved ejection fraction (HFpEF; ≥50%)
  - HF with mid-range ejection fraction (HFmrEF; 40%-49%)
  - HF with reduced ejection fraction (HFrEF; <40%)
- Worsening chronic HF is the progressive escalation of symptoms and signs requiring intensification of treatment
- In patients with symptomatic chronic heart failure following a worsening HF event:
  - 2-year mortality rate was ~30%
- Despite contemporary treatment options, patients with symptomatic chronic HF, especially those who have experienced a worsening HF event, remain at increased risk

New treatment strategies are needed in patients with symptomatic chronic HF to decrease their risk and improve outcomes

AF, atrial fibrillation; CAD, coronary artery disease; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Any questions?

Activity: Understanding patients with HF

Understanding patients with HF

Follow the journey of three patients and find their diagnoses.

Objectives:

- To recall risk factors that may contribute toward HF
- To recap the key stages of diagnosing HF and HFrEF
- To understand the criteria for worsening chronic HF

Time:

- 30 minutes (including discussion)

Understanding patients with HF

Instructions:

1. Read the first card (Medical history and physical examination) and answer the questions on the for each patient
   - Any history suggestive of HF?
   - Which signs and symptoms suggest HF?
2. Once complete, ask for the second card showing the results of different tests
   - What is the diagnosis for each patient? Why?
3. Once you have a diagnosis, ask for the final card
   - Are there any causes for concern?

Barry is a 63 year old shop owner. He has gone to see his

Understanding patients with HF:

Patient card #1: Medical history and physical examination

- Barry is a 63-year-old shop owner. He has gone to see his GP complaining of a racing heart beat and swollen ankles and feet. He is concerned as he thought he had gotten his diabetes under control (after many years of poor control). He was also diagnosed with high blood pressure last year. The GP did a physical exam and found that Barry appeared quite breathless, even after sitting in the waiting room for 10 minutes, and when listening to his heart there was a third heart sound (gallop rhythm).
- Tricia is a 40-year-old teacher. She made an appointment with her GP because she has been getting short of breath with simple activities; she feels that her chest is 'heavy' and is finding her ankles are always swollen. Last year she had a pulmonary embolism and is concerned that she might have another one. On examination, the GP confirmed that she experienced breathlessness on exertion; the GP also found out that Tricia is always tired but was blaming the latter on her job.
- Heather is a 52-year-old sales manager. She went to see her GP as she had been experiencing shortness of breath and repeated nausea. She also mentioned that her legs felt quite 'puffy'. Going through her medical history, her GP noticed that she was an ex-smoker and had a mild heart attack two years ago. With further examination and questioning, the GP found out that Heather was tachycardic, out of breath, and that her sleep was being disturbed by coughing.

Understanding patients with HF:

Patient card #2: Test results

	Barry	Tricia	Heather
Framingham criteria	• Major: dyspnoea and gallop rhythm • Minor: ankle oedema	• Major: (none) • Minor: dyspnoea on exertion, ankle oedema	• Major: dyspnoea • Minor: ankle oedema, night cough, tachycardic
ECG	Abnormal	Normal	Abnormal
BNP levels	126 pg/ml	21 pg/ml	208 pg/ml
LVEF	34%	(echo not performed)	39%

Artworked material for Understanding patients with HF:

Patient card #2: Test results

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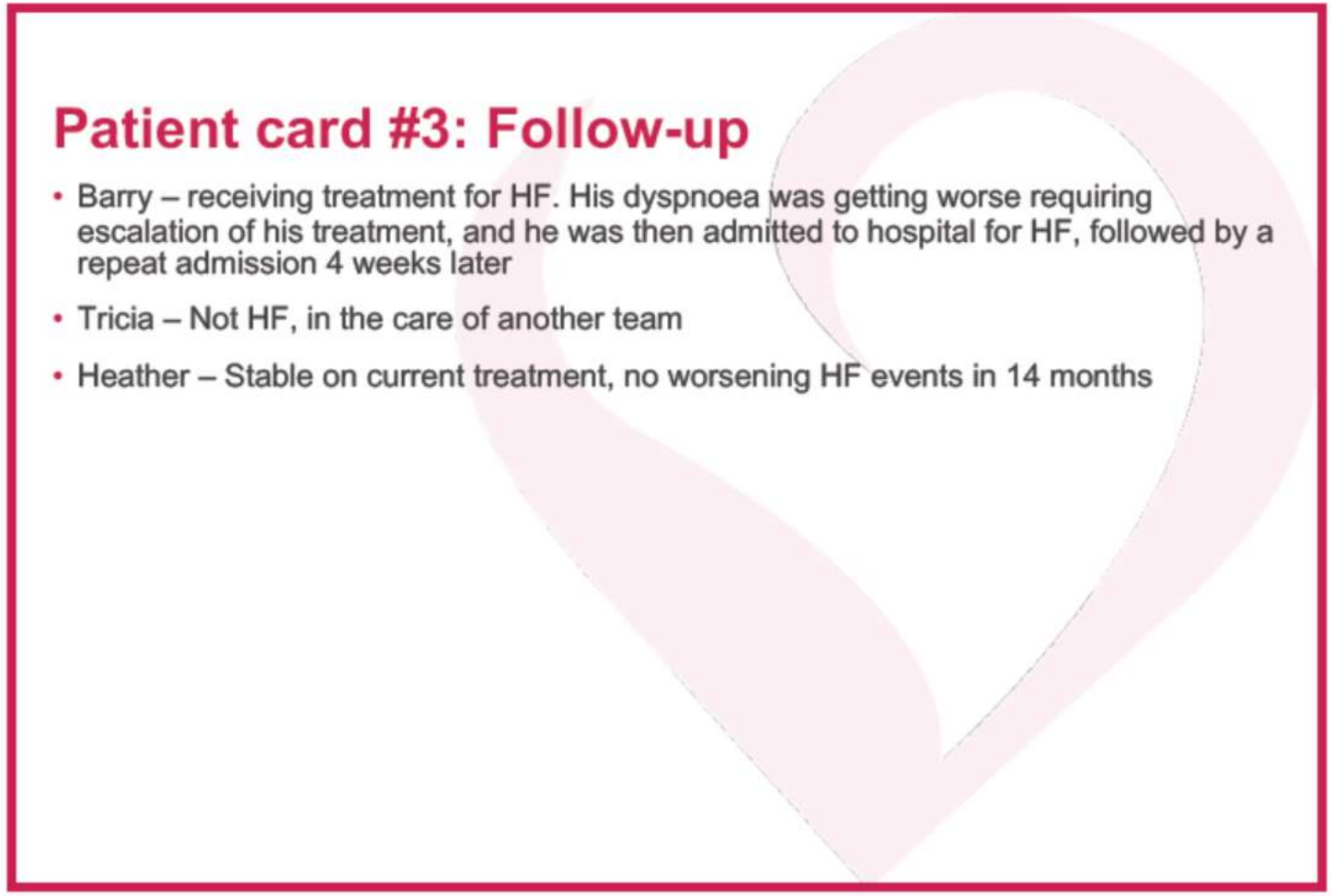

Card #1: Medical history and physical examination

History suggestive of HF

- Barry is a 63-year-old shop owner. He has gone to see his GP complaining of a racing heart beat and swollen ankles and feet. He is concerned as he thought he had gotten his **diabetes** under control (after many years of poor control). He was also diagnosed with **high blood pressure** last year. The GP did a physical exam and found that Barry appeared quite breathless, even after sitting in the waiting room for 10 minutes, and when listening to his heart there was a third heart sound (gallop rhythm).
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Answers

Card #1: Medical history and physical examination

Signs and symptoms of HF

- Barry is a 63-year-old shop owner. He has gone to see his GP complaining of a **racing heart beat** and **swollen ankles and feet**. He is concerned as he thought he had gotten his diabetes under control (after many years of poor control). He was also diagnosed with high blood pressure last year. The GP did a physical exam and found that Barry appeared quite **breathless**, even after sitting in the waiting room for 10 minutes, and when listening to his heart there was a **third heart sound (gallop rhythm**).
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Answers

Card #1: Medical history and physical examination

Signs and symptoms of HF – Framingham criteria Major/minor

- Barry is a 63-year-old shop owner. He has gone to see his GP complaining of a racing heart beat and **swollen ankles** and feet. He is concerned as he thought he had gotten his diabetes under control (after many years of poor control). He was also diagnosed with high blood pressure last year. The GP did a physical exam and found that Barry appeared quite **breathless**, even after sitting in the waiting room for 10 minutes, and when listening to his heart there was a **third heart sound (gallop rhythm**).

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Answers

Card #2: Test results

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ECG	Abnormal	Normal	Abnormal
BNP levels	126 pg/ml	21 pg/ml	208 pg/ml
LVEF	34%	(echo not performed)	39%
Diagnosis	**HFrEF LVEF <40%. No other criteria necessary**	**Not HF. Normal ECG and BNP not above 35. Consider other causes**	**HFrEF LVEF <40%. No other criteria necessary**

Answers

Card #3: Follow-up

- Barry – receiving treatment for HF. **His dyspnoea was getting worse requiring escalation of his treatment, and he was then admitted to hospital for HF, followed by a repeat admission 4 weeks later**.
- **Repeated worsening HF events means that Barry has worsening chronic HF and needs a new treatment strategy to decrease his risk and improve his outcomes**

Understanding patients with HF

Summary/discussion:

- How did you find the activity?
- What were the challenges in diagnosing HF?
- Any other comments or questions?