

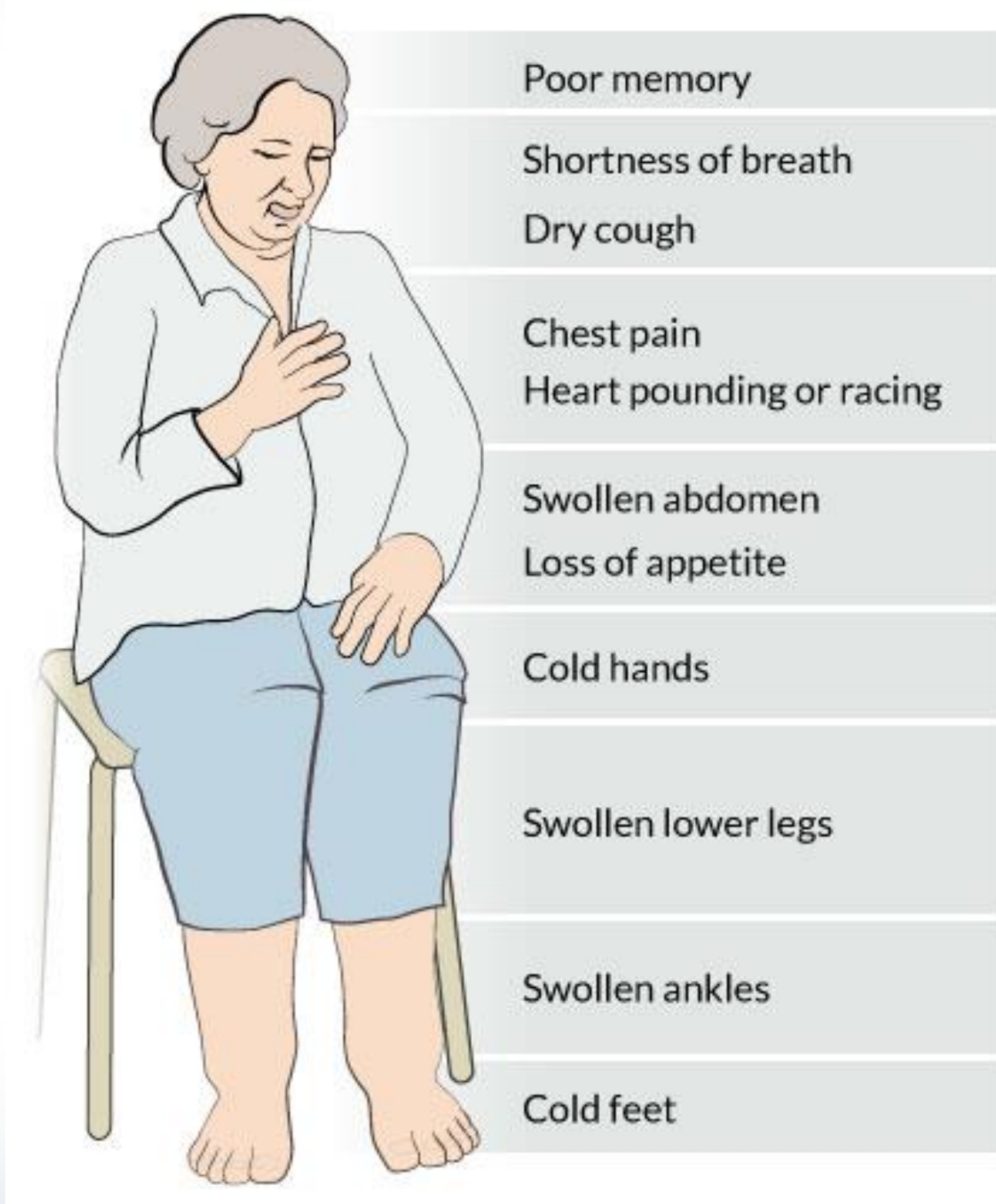
# Harley Street Heart Failure Symposium: Introduction

**Dr. Reginald Liew**

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# What is a typical heart failure patient?



Singaporeans suffer heart failure about 10 years earlier than Americans and Europeans: Study **THE STRAITS TIMES**

© PUBLISHED JUN 16, 2016, 2:09 PM SGT | UPDATED JUN 16, 2016, 6:03 PM



## Regional and ethnic differences among patients with heart failure in Asia: the Asian sudden cardiac death in heart failure registry

**THE STRAITS TIMES**

🕒 PUBLISHED JUN 16, 2016, 2:09 PM SGT | UPDATED JUN 16, 2016, 6:03 PM

SINGAPORE- Singaporeans suffer from heart failure at the average age of 61, about 10 years earlier than Americans and Europeans, a study on Asian patients has found.

Singaporeans also have a higher prevalence of coronary artery disease, hypertension, and diabetes, the three most common diseases that lead to heart failure, compared to Asians as a whole, Americans and Europeans.

In Singapore, 58 per cent of patients in the study had diabetes, compared to 40 per cent in Asia, and the United States and 33 per cent in Europe.

The study, involving more than 5,000 patients from the region, also found that Malays from countries such as Singapore, Malaysia and Indonesia are at the highest risk of heart failure. It found that 62 per cent of Malays had hypertension, compared to 58 per cent of Chinese and 43 per cent of Indians.

# Symptoms and signs of heart failure

Symptoms	Signs
Typical	More specific
Breathlessness Orthopnoea Paroxysmal nocturnal dyspnoea Reduced exercise tolerance Fatigue, tiredness, increased time to recover after exercise Ankle swelling	Elevated jugular venous pressure Hepatojugular reflux Third heart sound (gallop rhythm) Laterally displaced apical impulse

Less typical	Less specific
Nocturnal cough Wheezing Bloating feeling Loss of appetite Confusion (especially in the elderly) Depression Palpitations Dizziness Syncope Bendopnea <sup>53</sup>	Weight gain (>2 kg/week) Weight loss (in advanced HF) Tissue wasting (cachexia) Cardiac murmur Peripheral oedema (ankle, sacral, scrotal) Pulmonary crepitations Reduced air entry and dullness to percussion at lung bases (pleural effusion) Tachycardia Irregular pulse Tachypnoea Cheyne Stokes respiration Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure



# Definition of heart failure with reduced (HFrEF), mid (HFmrEF) and preserved (HFpEF) ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs <sup>a</sup>	Symptoms ± Signs <sup>a</sup>	Symptoms ± Signs <sup>a</sup>
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides <sup>b</sup> ; 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 <sup>b</sup> ; 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).

BNP = B-type natriuretic peptide; 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; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

<sup>a</sup>Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

<sup>b</sup>BNP > 35 pg/ml and/or NT-proBNP > 125 pg/mL.

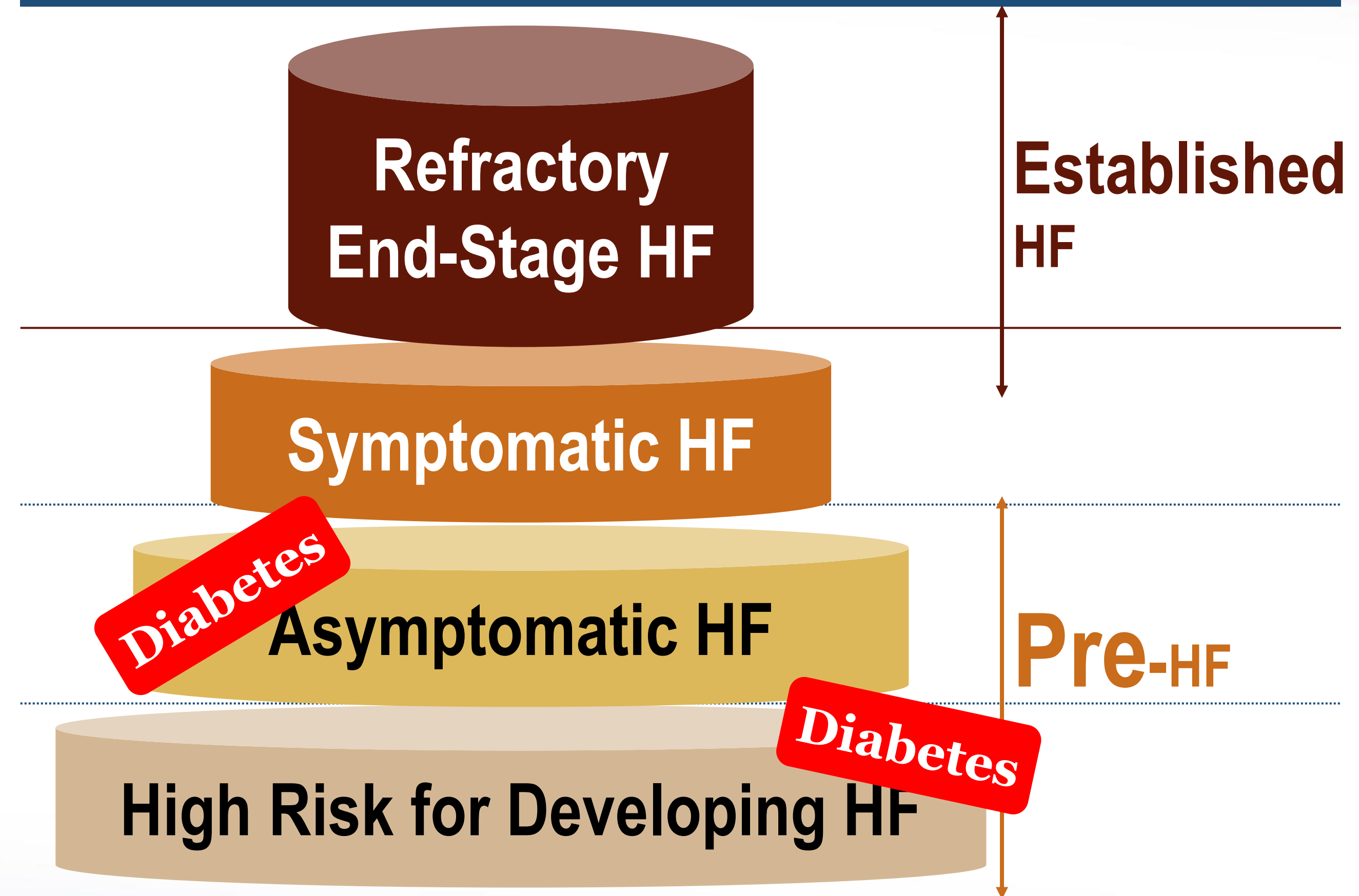


# Stages of heart failure

## ACCF/AHA stages of HF

- D** **Refractory** HF requiring specialized interventions
- C** **Structural heart disease with** prior or current of HF
- B** **Structural heart disease but without** signs or symptoms of HF
- A** **At high risk for HF but without structural** heart disease or symptoms of HF

## NYHA Classification





# Presentations

- |         |   |
|---------|---|
| 01.40pm | Introduction<br><i>by Dr Reginald Liew</i>  |
| 01.45pm | Essentials of Diagnosis and Monitoring of Heart Failure in Primary Care<br><i>by Dr Rohit Khurana</i> |
| 02.10pm | Diabetes & Heart Failure: A Dangerous Intersection<br><i>by Dr Michael MacDonald</i>                  |
| 02.35pm | Overview of heart failure therapies and case studies<br><i>by Dr Reginald Liew</i>                    |
| 03.00pm | Questions & Answers   |



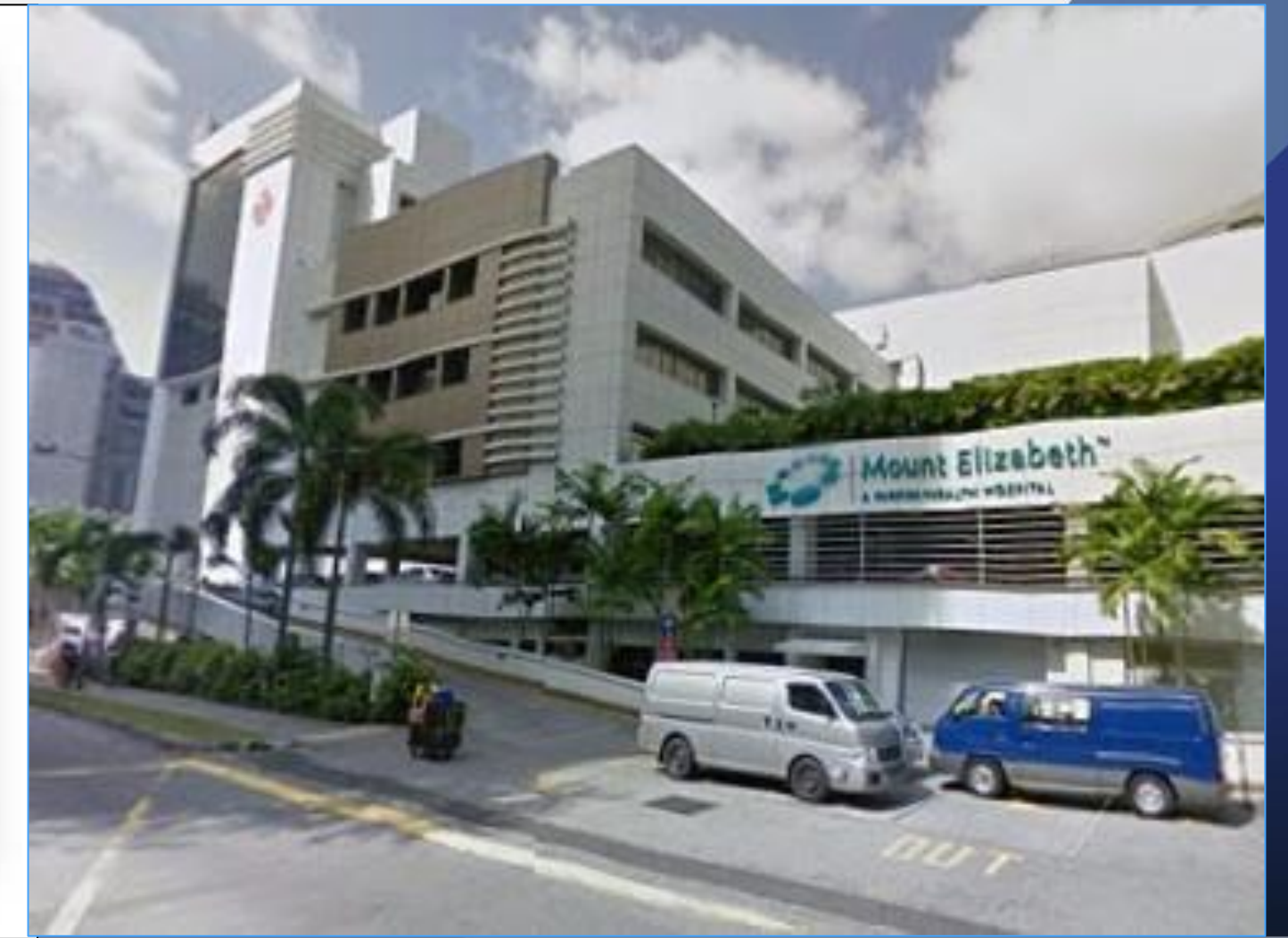
# ***Essentials of Diagnosis and Monitoring of Heart Failure in Primary Care***

**Dr. Rohit Khurana**

***MA (Oxon), MBBCh (Oxon), PhD (Lond)***

***FRCP (UK), FESC, FACC***

**Senior Consultant Cardiologist**



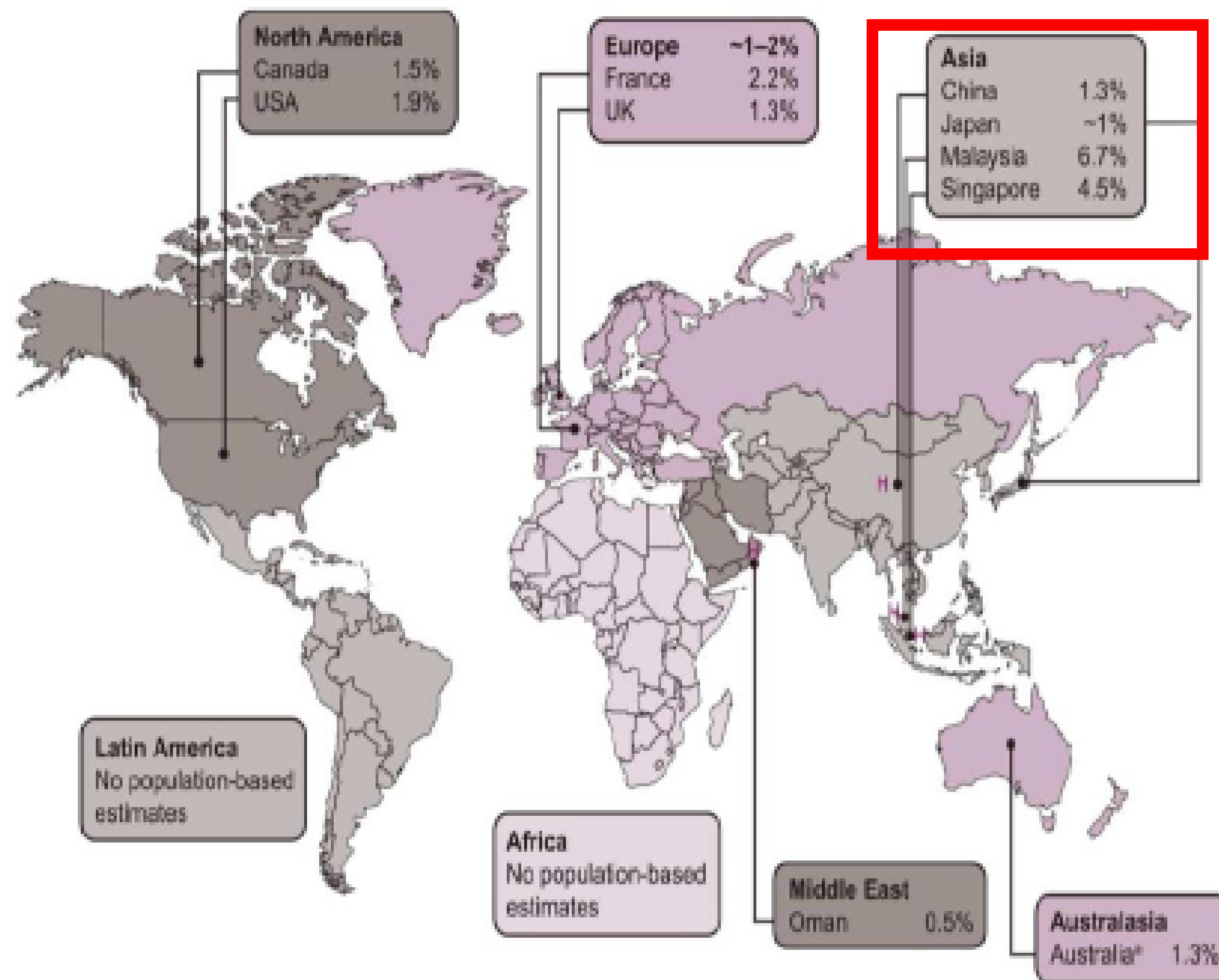


## **2016 ECS/HFA definition of heart failure:**

**A clinical syndrome** characterized by typical **symptoms** that may be accompanied by **signs** 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.

Ponikowski et al. Eur Heart J. 2016;37:2129-2200

# Heart Failure in SE Asia: Facts and Numbers



Proportion of the population living with heart failure in individual countries across the globe

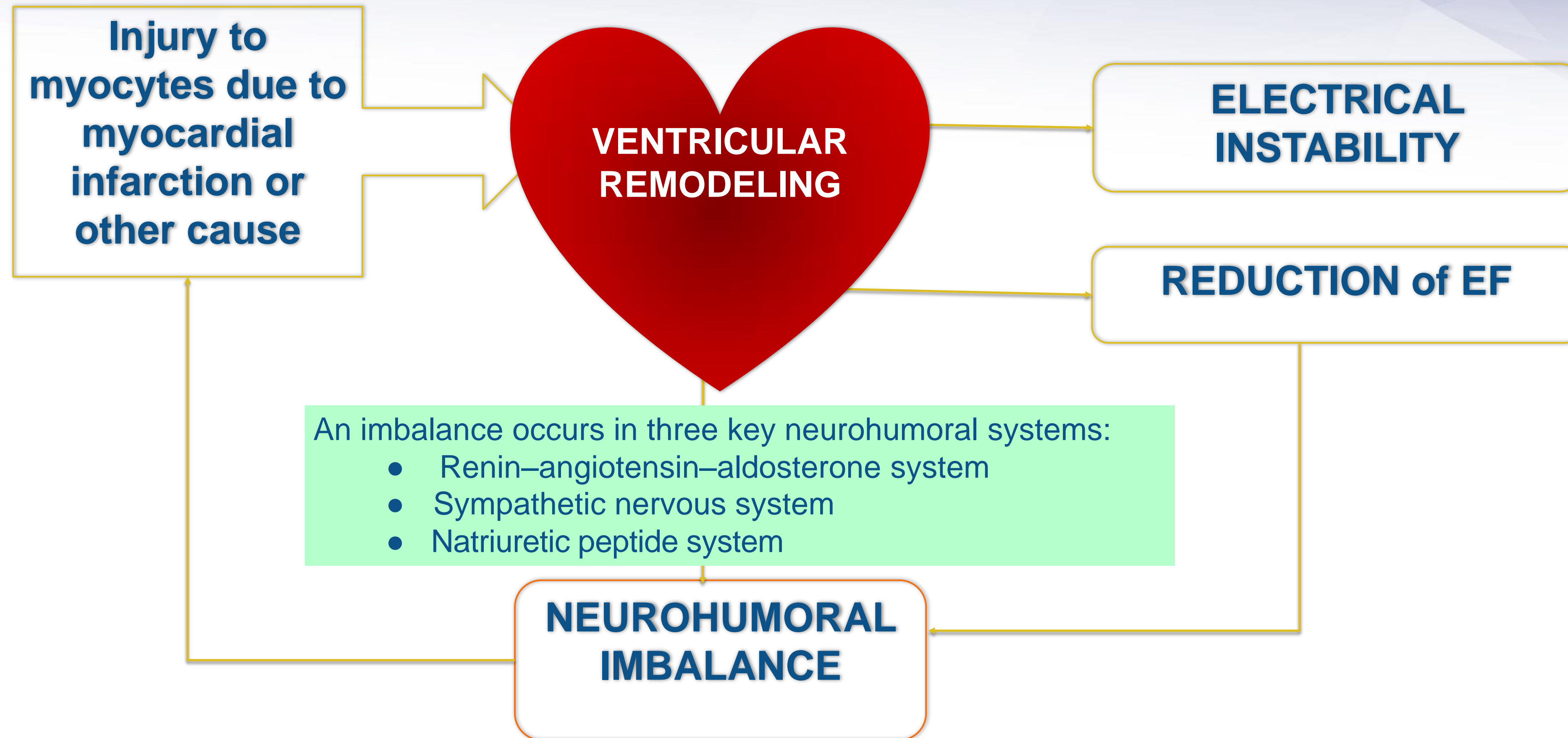
Adapted from: Carolyn S.P. Lam, *ESC Heart Failure* 2015; 2: 46–49

- **Prevalence of HF in Southeast Asian countries is higher compared with countries in the rest of the world (4.5–6.7% vs. 0.5–2% respectively)**
- **Southeast Asian patients present with acute HF at a younger age (54 years) compared with USA patients (75 years) but**
  - have more severe clinical features, higher rates of mechanical ventilation,
  - longer lengths of stay (6 vs. 4.2 days) and
  - higher in-hospital mortality (4.8 vs. 3.0%)
- **Under-usage of disease-modifying HF therapies was reported in the ADHERE Asia-Pacific cohort,**
  - with ACEi or ARBs prescribed upon discharge in 63%,
  - $\beta$ -blockers in 41% and MRAs in 31% of patients.
- **Important inter-ethnic differences exist, wherein Malay patients appear to fare worse than Indian or Chinese patients, for reasons that are poorly understood**





# Pathophysiology of HF



The systemic responses in the renin–angiotensin–aldosterone and sympathetic nervous systems cause further myocardial injury, and have detrimental effects on the blood vessels, and various organs, thereby creating a pathophysiological 'vicious cycle'. The natriuretic peptide system has a protective function, which can counterbalance these detrimental effects.

# DIAGNOSING HEART FAILURE

Early detection and intervention is essential



# Principles of diagnosis of HF

All diagnostic steps are equally important

- **Consider:** *Medical history, signs, symptoms*
- **Confirm:** *Natriuretic peptides, Echocardiography*
- **Classify phenotype:** *HFrEF vs. HFpEF*
- **Assess etiology:** *Angiography (CT/Invasive), cMRI, Biopsy (?)*
- **Risk stratification**
- **Work-up for targeted therapies**

# How Patients Present

- Clinical Symptoms



Dyspnoea (100% sensitivity)  
Swelling/Dependent oedema  
Fatigue, Weight gain

- Risk Factors:

- *Traditional CV Risk factors [ Hypertension, Obesity, Smoking, Physical inactivity, Diabetes], Renal impairment*



# Heart Failure

## Symptoms

### Typical

Breathlessness

Orthopnea

Paroxysmal nocturnal dyspnea

Reduced exercise tolerance

Fatigue, tiredness, increased time to recover after exercise

Ankle swelling

### Less typical

Nocturnal cough

Wheezing

Weight gain (>2 kg/week)

Bloated feeling

Confusion (especially in the elderly)

Palpitations

Syncope

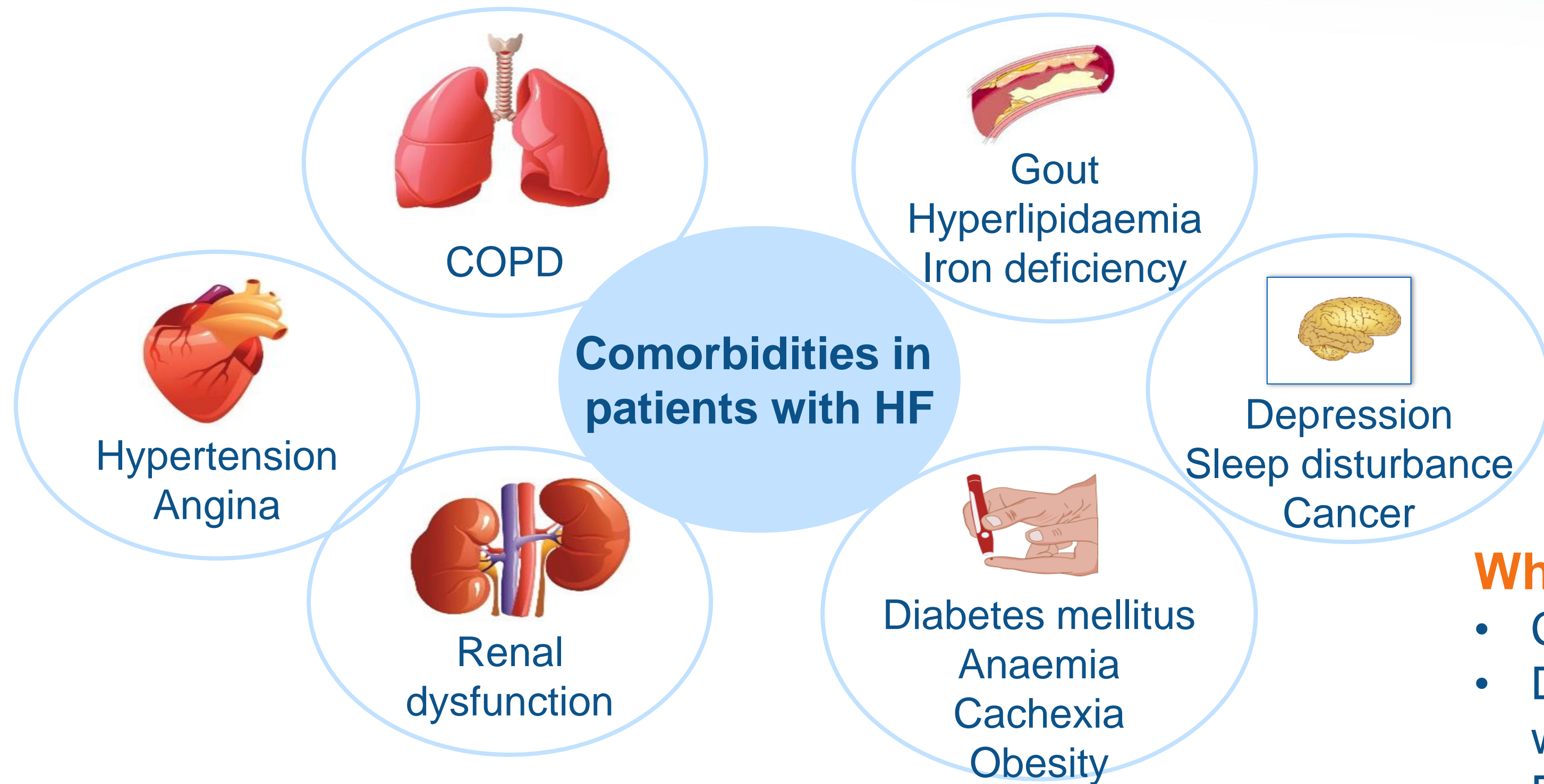
## Suspect HF when...

- Hx of CAD, diabetes, hypertension
- Atrial fibrillation
- Chest infection/URTI that is persistent
- COPD that is deteriorating fast
- Unexplained fatigue or fluid retention in the elderly



# Comorbidities in HF

Comorbidities impact prognosis in patients with HF<sup>1,2</sup>



## Why comorbidities are relevant in HF<sup>1</sup>:

- Comorbidities may affect the use of treatments for HF
- Drugs used to treat comorbidities may cause worsening of HF
- Drugs used to treat HF and comorbidities may interact and reduce patient adherence
- Most comorbidities are associated with worse clinical status and are predictors of poor prognosis in HF

# Evidence of volume overload is a common physical finding of heart failure

- **Neck exam**
  - Elevated jugular venous pressure
- **Auscultation of the lungs**
  - Rales or crackles
- **Auscultation of the heart**
  - Third or fourth heart sound (S3 or S4) sometimes called a gallop rhythm
  - Murmur
- **Edema in dependent areas**
  - Sacrum
  - Feet/ankles/lower legs

Elevated jugular venous pressure



Pitting edema of the ankle





# Initial Diagnostic Tests

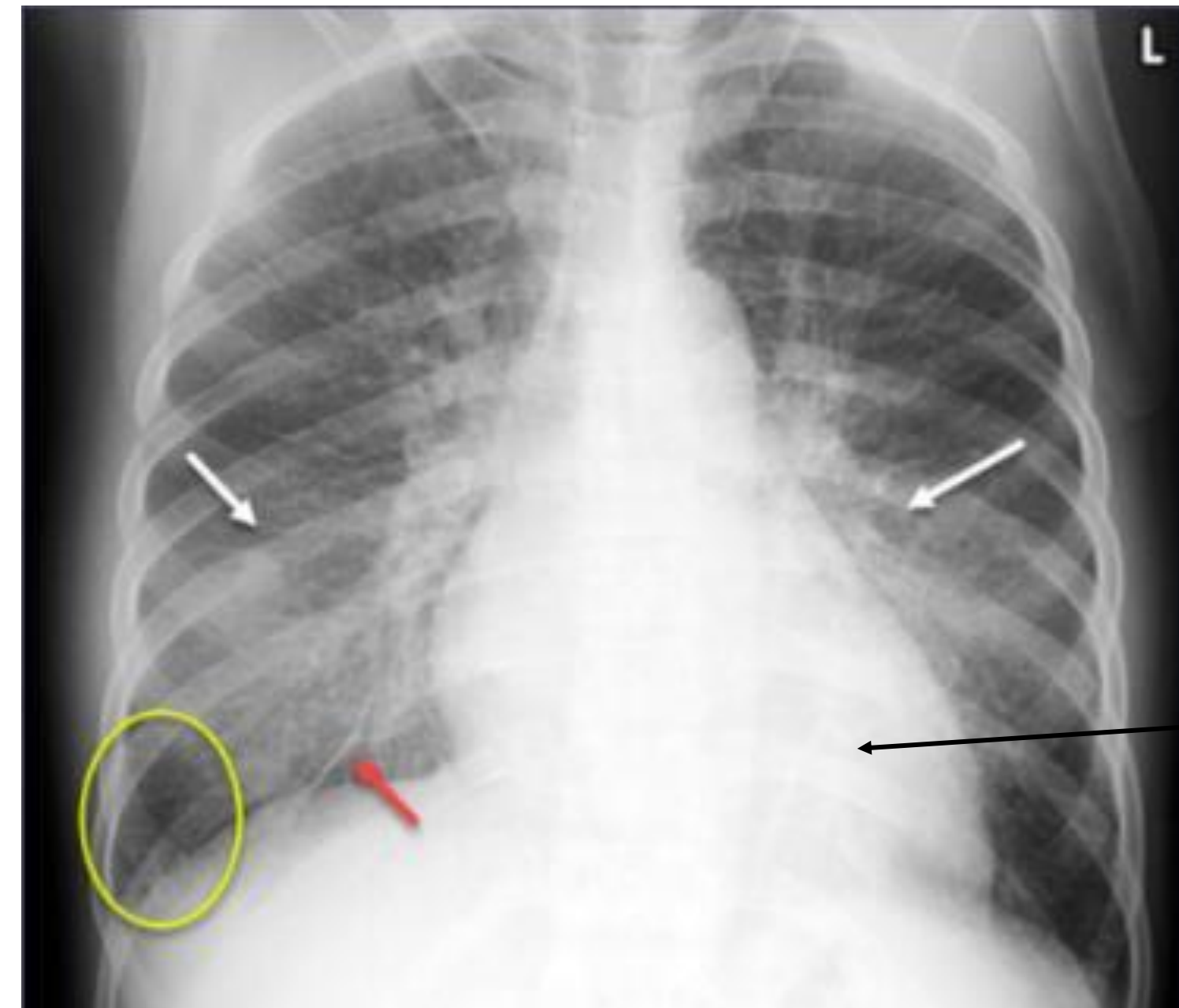
**ECG** can identify potential causes of HF:

- Arrhythmias (irregular heart rhythms)
- Past myocardial infarctions (MIs)
- Left ventricular hypertrophy

**Chest X-ray** can identify:

- Size and shape of the cardiac silhouette
- Evidence of fluid accumulation in the lungs

**Chest X-ray showing evidence of heart failure**



**Enlarged cardiac silhouette (black arrow), perihilar congestion (white arrows), fluid in the inferior accessory fissure (red arrow), and Kerley B lines (yellow oval).**



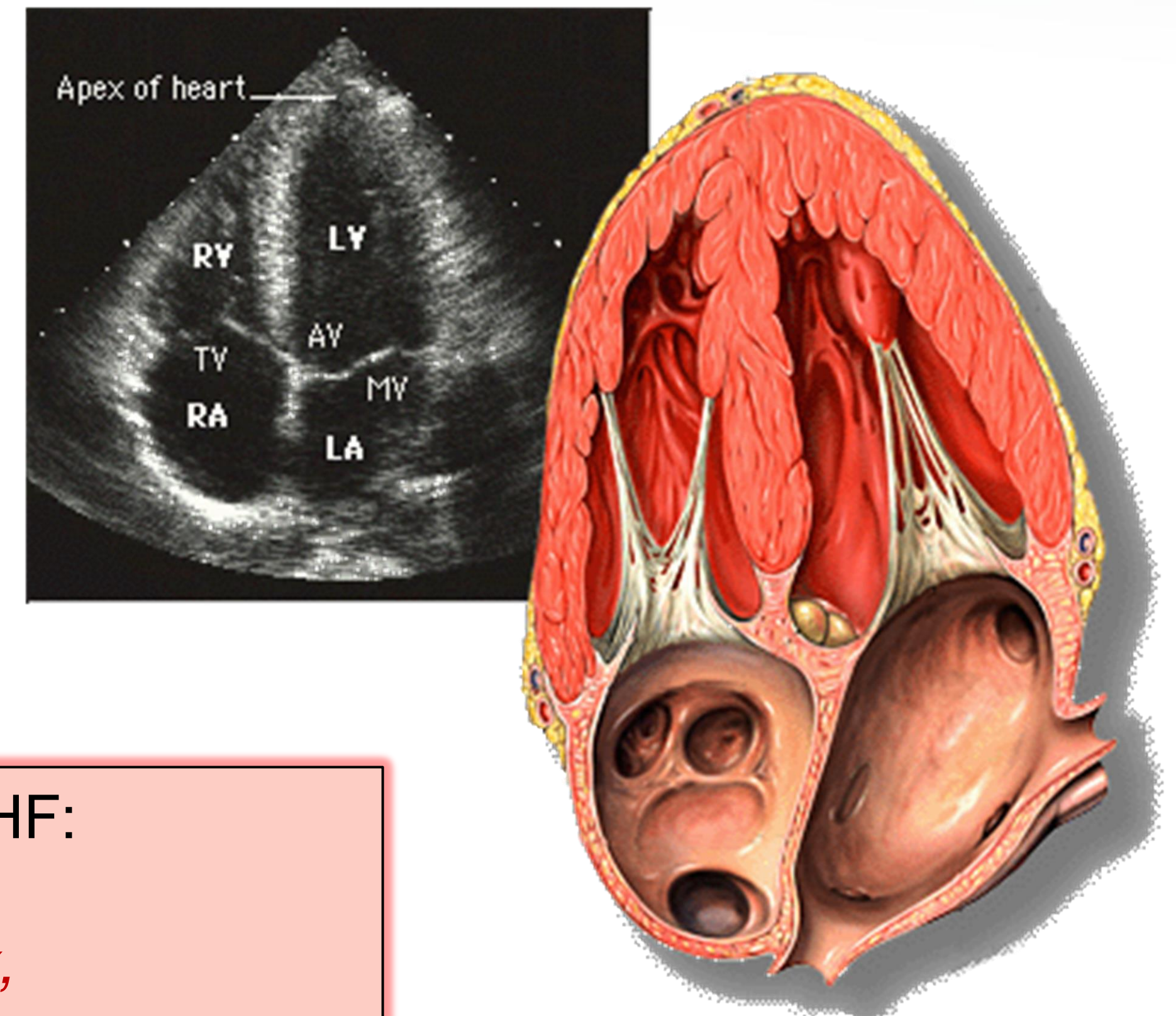
# Guidelines recommend echocardiography as the single most useful diagnostic test

**Transthoracic echocardiography (TTE)** is the preferred method for documentation of cardiac dysfunction<sup>1</sup>

- **Echocardiograms reveal<sup>1,2</sup>**

- Chamber size
- Right and left ventricular function
- Regional wall motion abnormalities (evidence of MI)
- Evidence of impaired LV filling (ie, stiffness of the walls), a feature of diastolic dysfunction
- Valvular heart disease
- Diseases of the pericardium
- Ejection fraction

**2D echocardiogram**



ECHO criteria for HF:

↑ *E/e'*

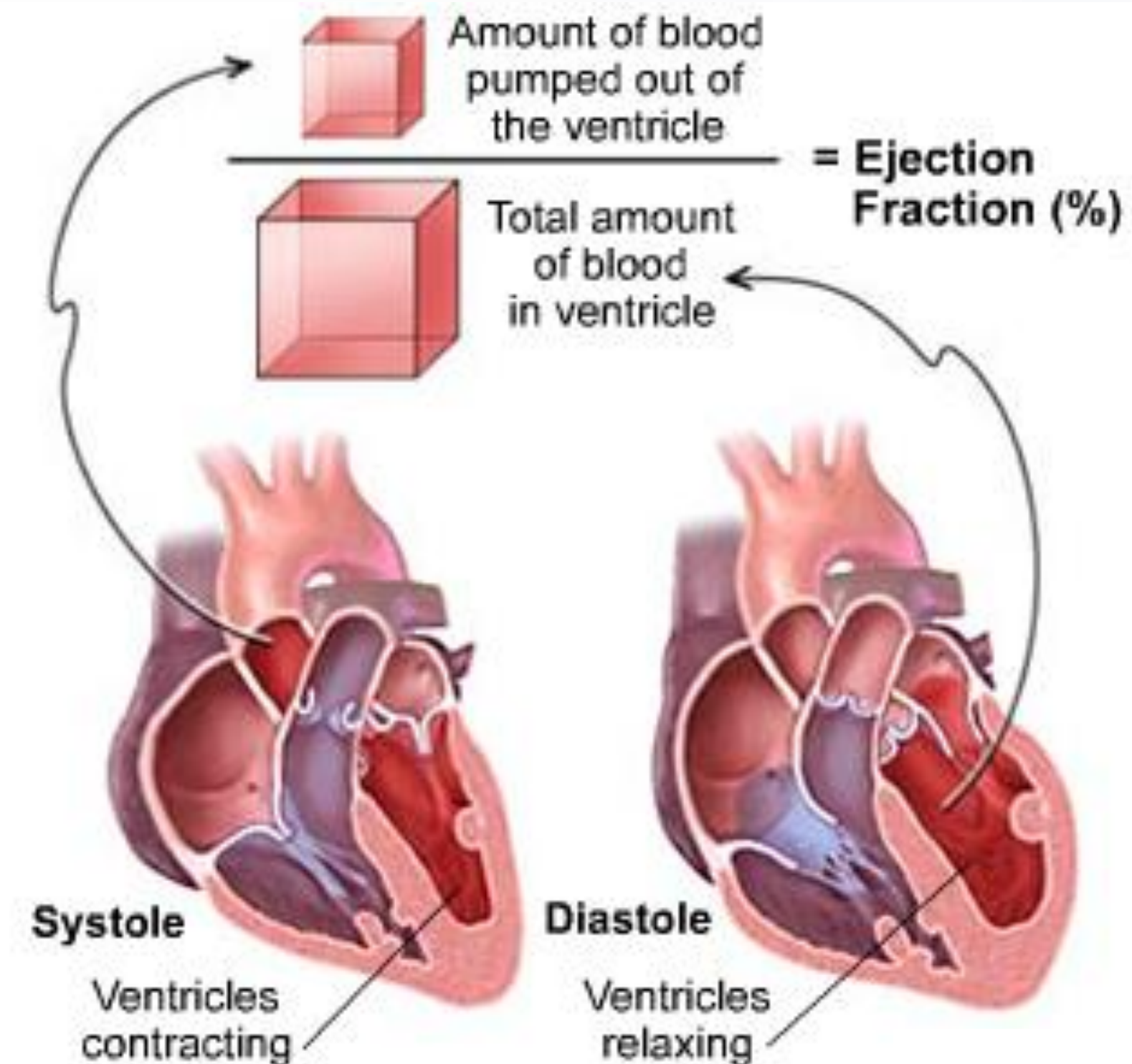
↑ *LA volume index,*

↑ *Pulmonary artery pressure*



# Ejection fraction (EF) is a key criterion in heart failure management

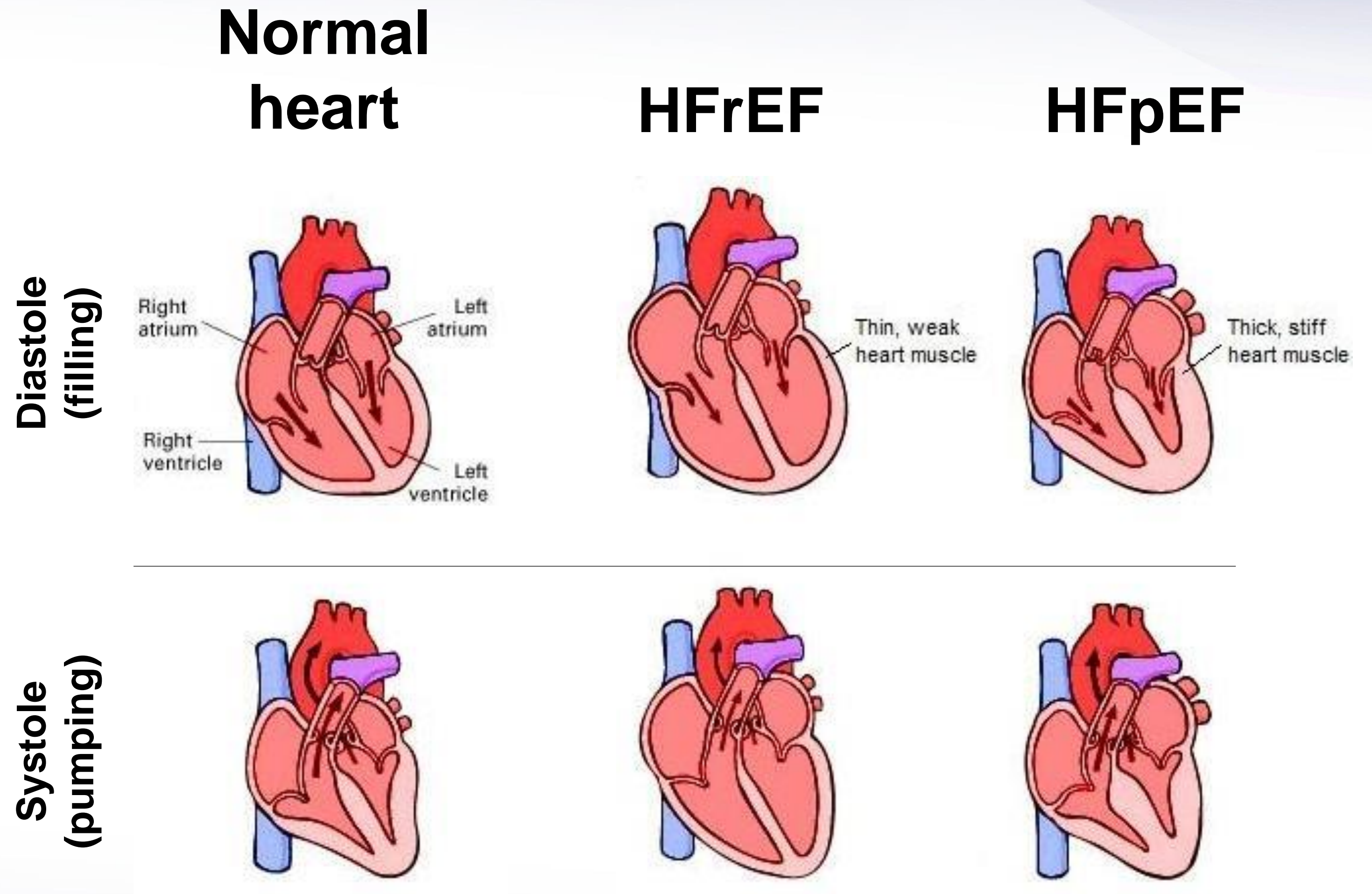
- The ejection fraction, commonly referred to as **EF**, is the percentage of blood that is pumped out of the heart during each beat
- A **normal EF** is  $\geq 50\%$
- Heart failure with an  $EF \leq 40\%$  is known as **heart failure with reduced ejection fraction (HFrEF)**
- Heart failure in the setting of a normal EF is known as **heart failure with preserved ejection fraction (HFpEF)**





# While HFrEF and HFpEF are both “heart failure”, the pathophysiology is different

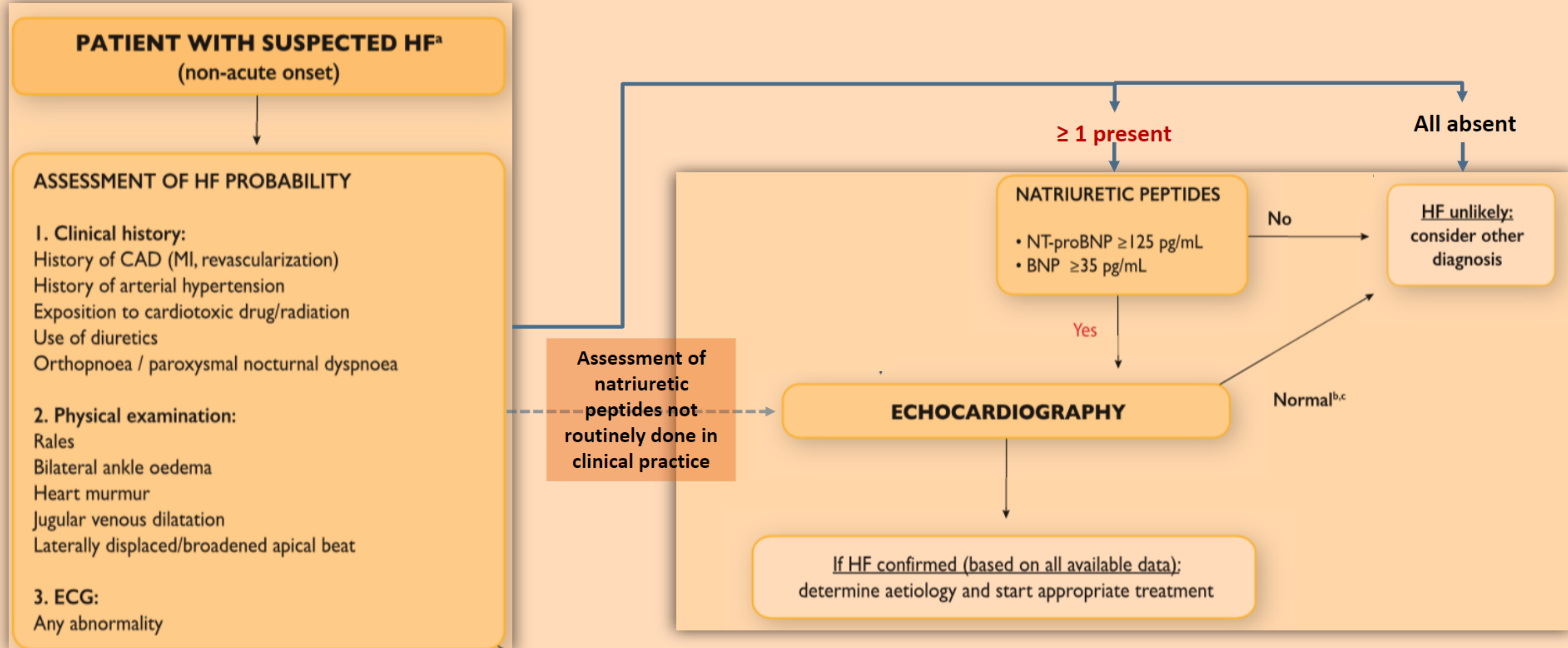
- In **HFrEF**, the LV is unable to eject an adequate amount of blood during systole
- In **HFpEF**, less blood is able to fill the LV in diastole, due to myocardial stiffness. Thus the LV has less blood to eject during systole



HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle.



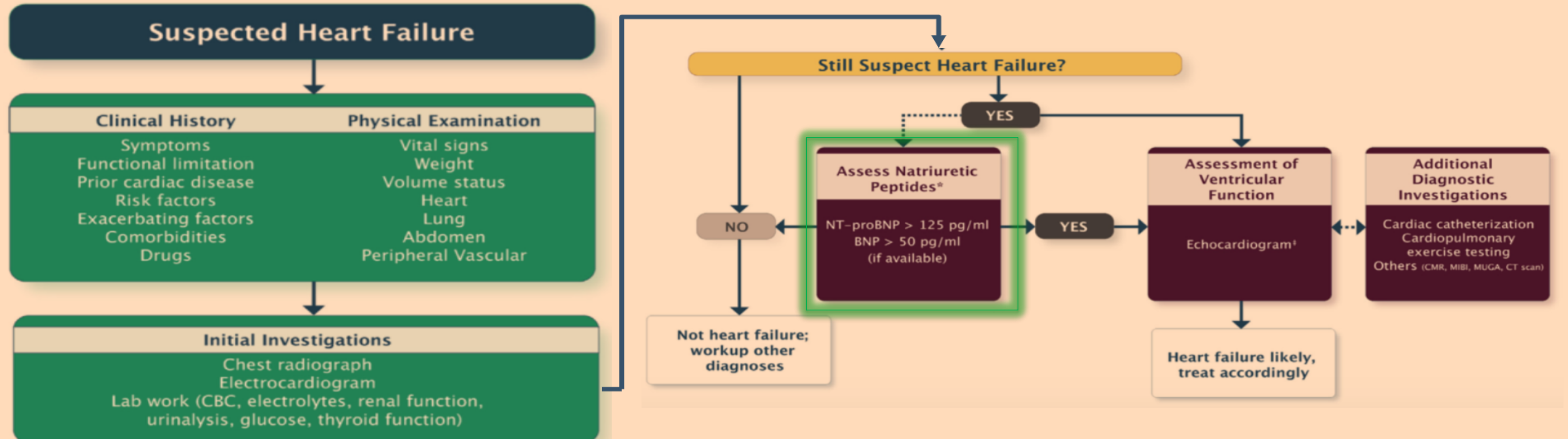
# Algorithm for the diagnosis of heart failure



Ponikowski et al. 2016 ECS/HFA Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37:2129-2200.



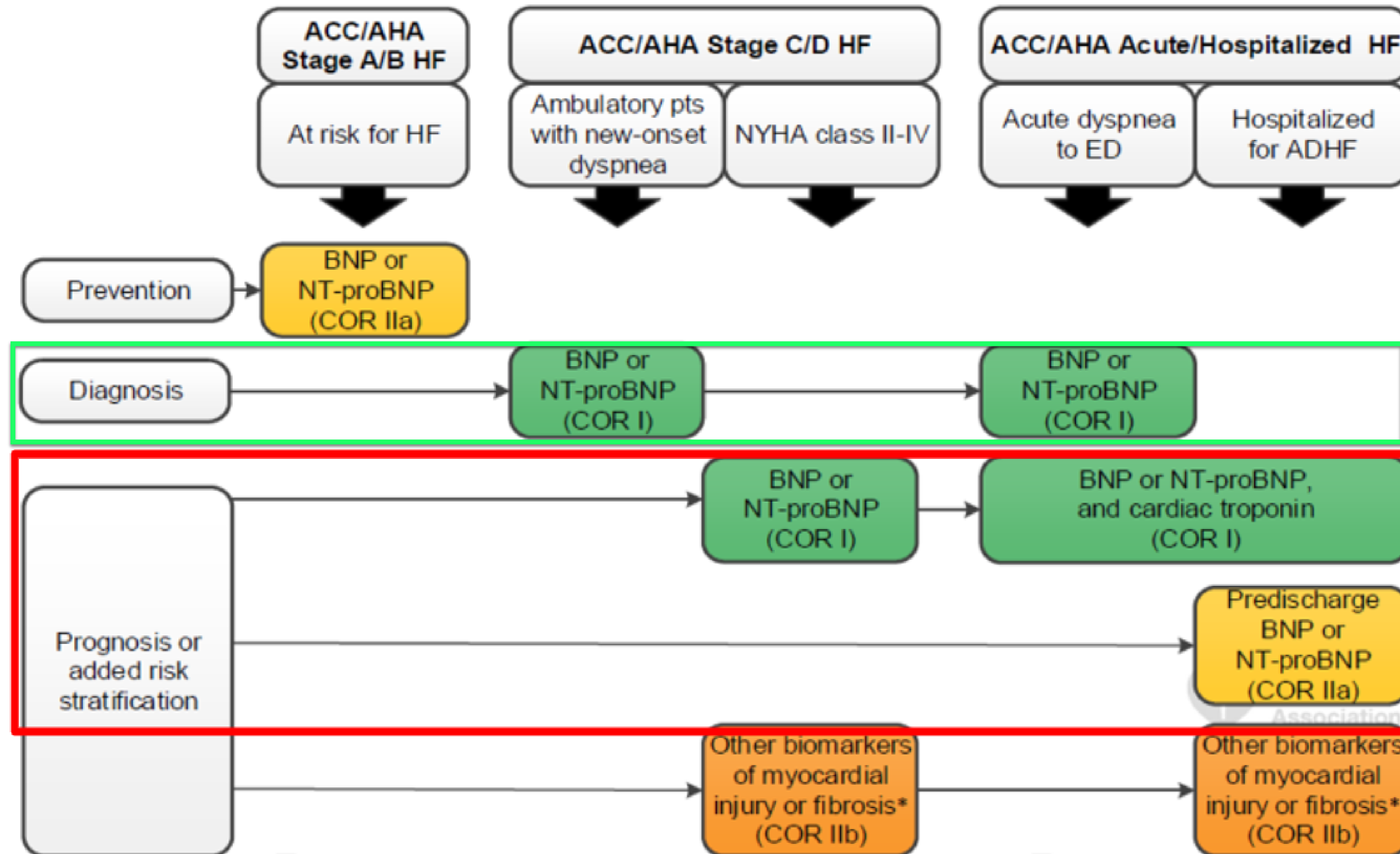
# 2017 Canadian CS Guidelines for the management of heart failure



Ezekowitz J et al. Canadian Journal of Cardiology 33 (2017) 1342e1433

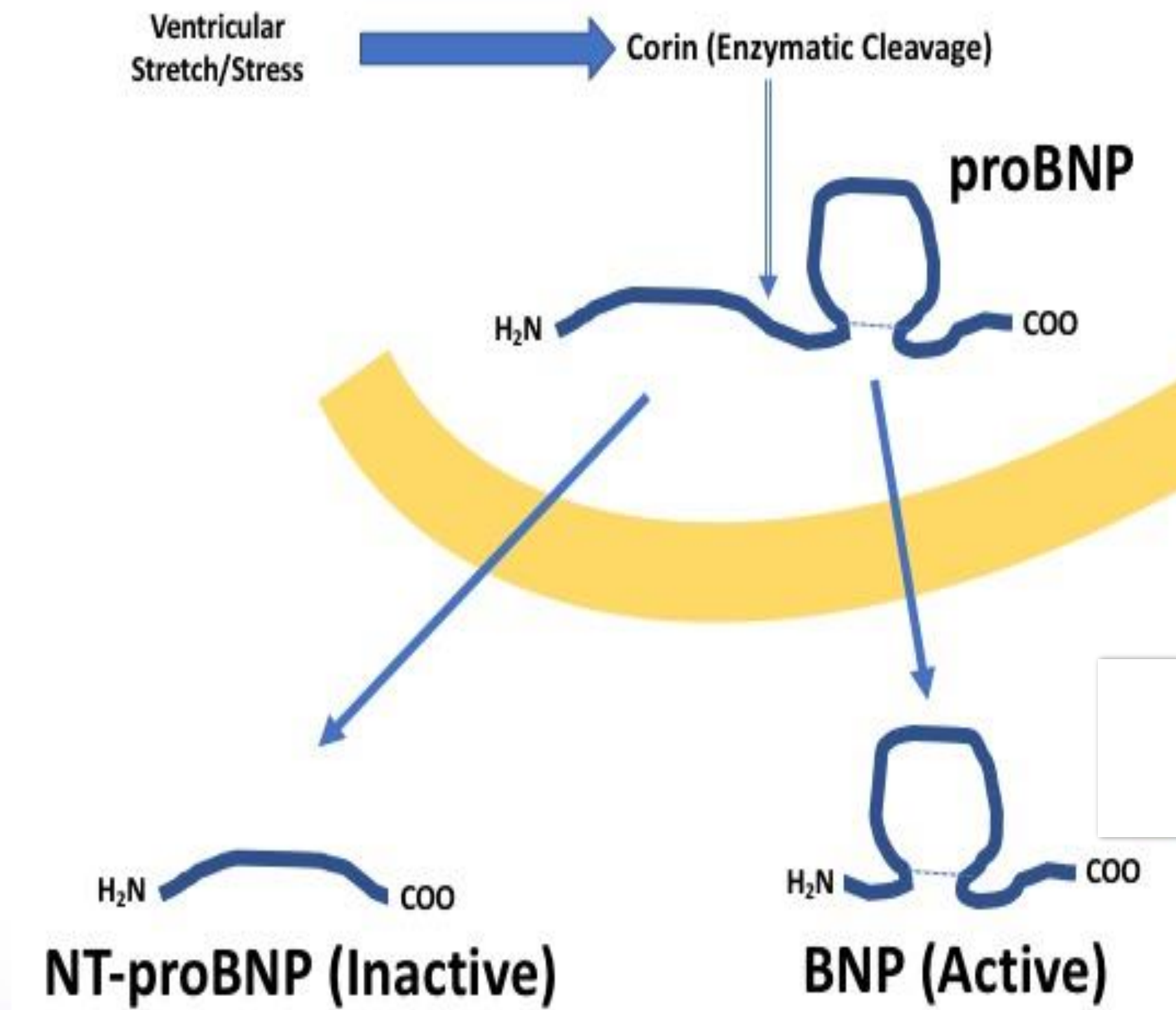


# 2017 ACC/AHA HF Guideline



Yancy, et. al. 2017 ACC/AHA Heart Failure Focused Update

# BNP, NT-proBNP



- Equally good sensitivity/specificity in diagnosing CHF
- BNP = < 125 unlikely CHF and > 300 likely CHF
- Increases with age, renal disease/arrhythmia, sepsis, CAD
- Decreased in obesity
- Acute HF: predictor of mortality and cardiovascular events when >200
- Limited evidence in serial monitoring in outpatient setting
  - *Support clinical decision making*
  - *Establish prognosis and disease severity*



# Particular relevance of BNP

- Diagnosis
- Staging
- Risk stratification
- Monitor/titrate therapy
- Admission/discharge decisions:
  - > rule out symptomatic LV dysfunction

A normal natriuretic peptide level in an untreated patient virtually excludes significant cardiac disease

Consider different cut-off values in various clinical situations

# Classification of heart failure:

## Heart failure phenotypes

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs <sup>a</sup>	Symptoms ± Signs <sup>a</sup>	Symptoms ± Signs <sup>a</sup>
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	—	1. Elevated levels of natriuretic peptides <sup>b</sup> ; 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 <sup>b</sup> ; 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).

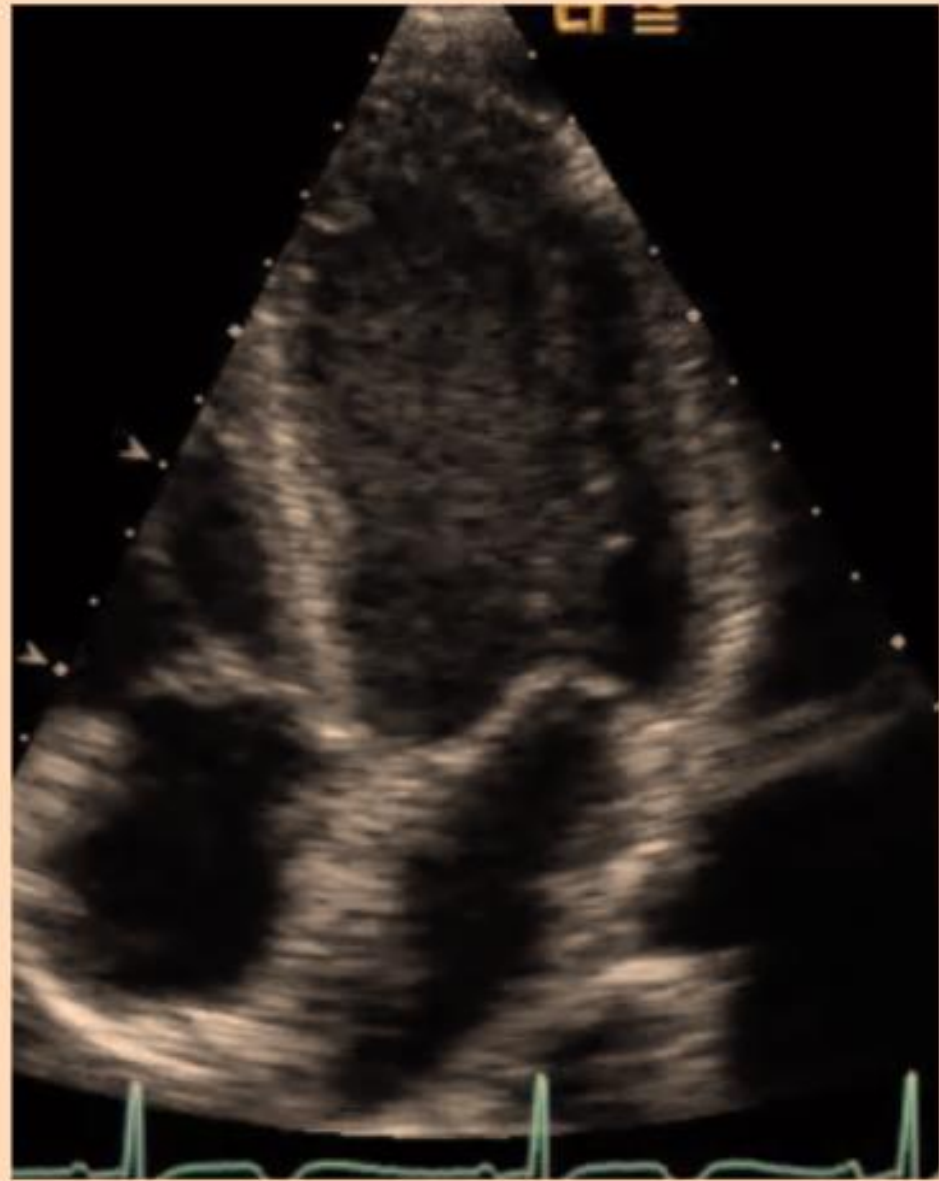
<sup>a</sup>Signs may be absent in the early stages  
<sup>b</sup>BNP ≥ 35 pg/mL and/or NT-proBNP ≥125 pg/mL.

Ponikowski et al. Eur Heart J. 2016;37:2129-2200.

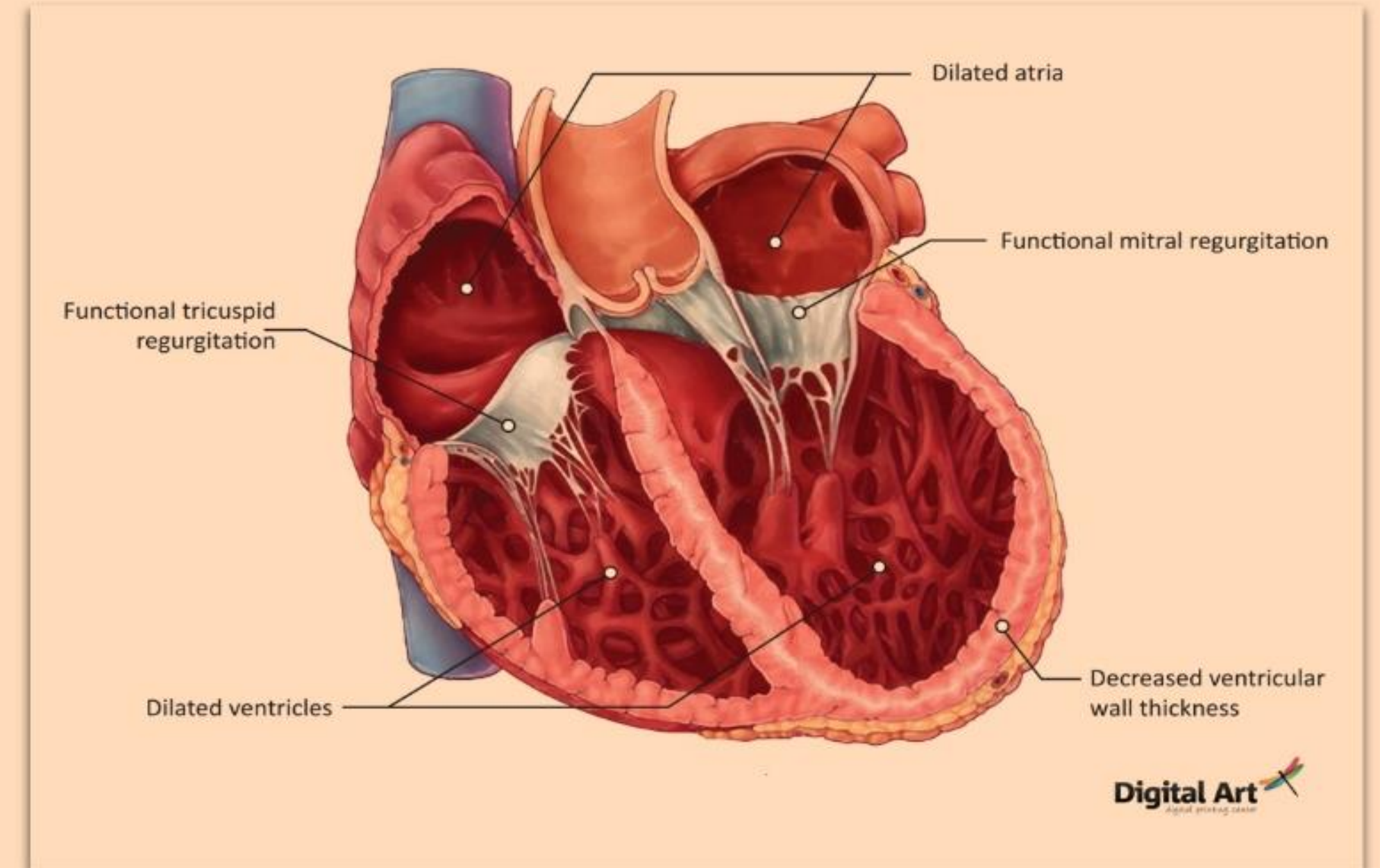
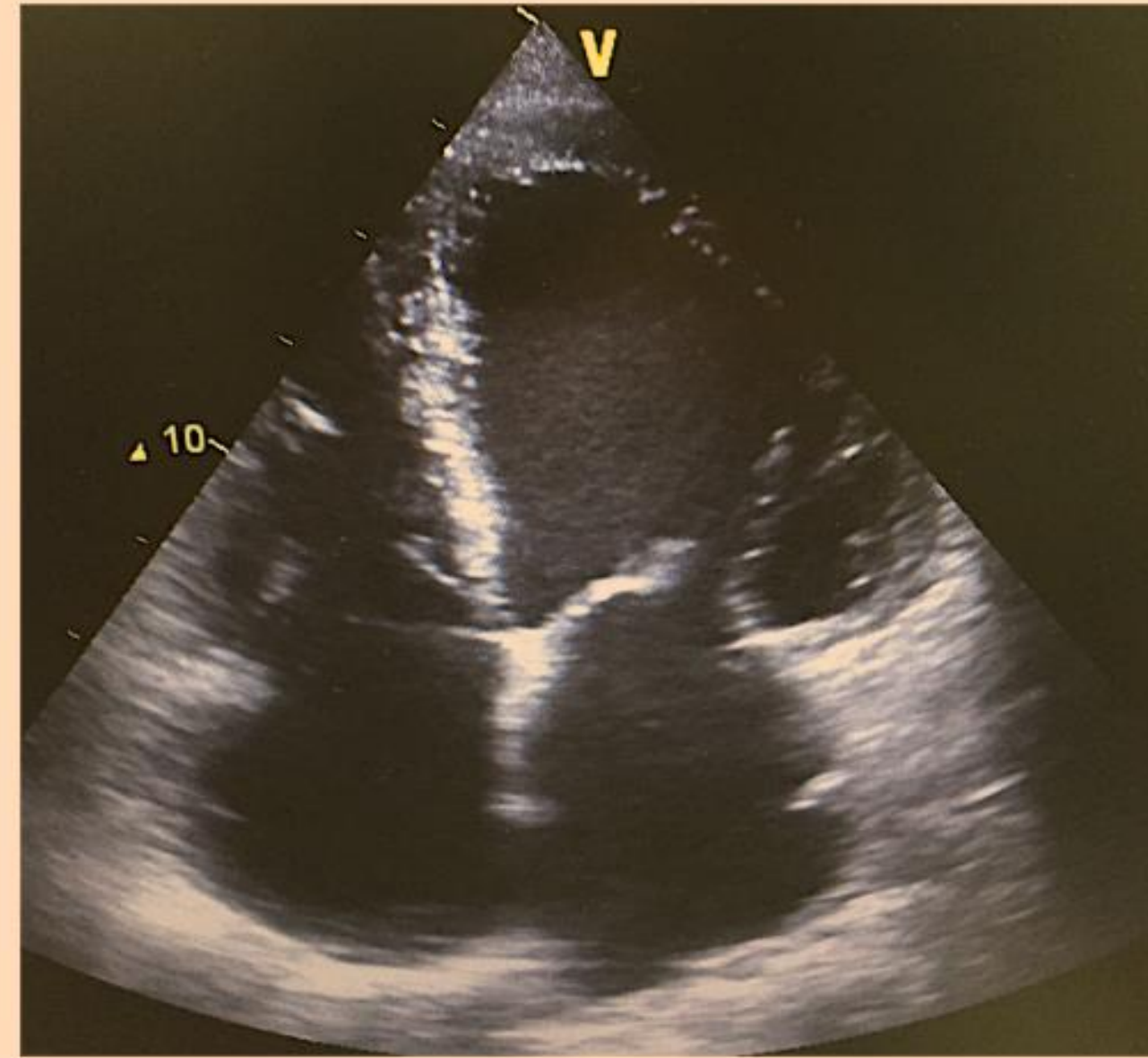


# Heart failure with reduced ejection fraction

Signs / symptoms and LVEF <40%



Normal heart



## Typical features of HFrEF:

Reduced contractile function.  
Dilated LV, dilated atria.  
Functional MR.

**HFrEF is usually not a diagnostic challenge.**

Ponikowski et al. Eur Heart J. 2016;37:2129-2200.  
Seferović, PM et al. Eur J Heart Fail; 2019; 21: 553-576



# Heart failure with preserved ejection fraction

Signs / symptoms +

“Preserved” LVEF / diastolic dysfunction and/or elevated NTs

## Ejection fraction:

- LVEF  $\geq 50\%$

## Structural abnormalities:

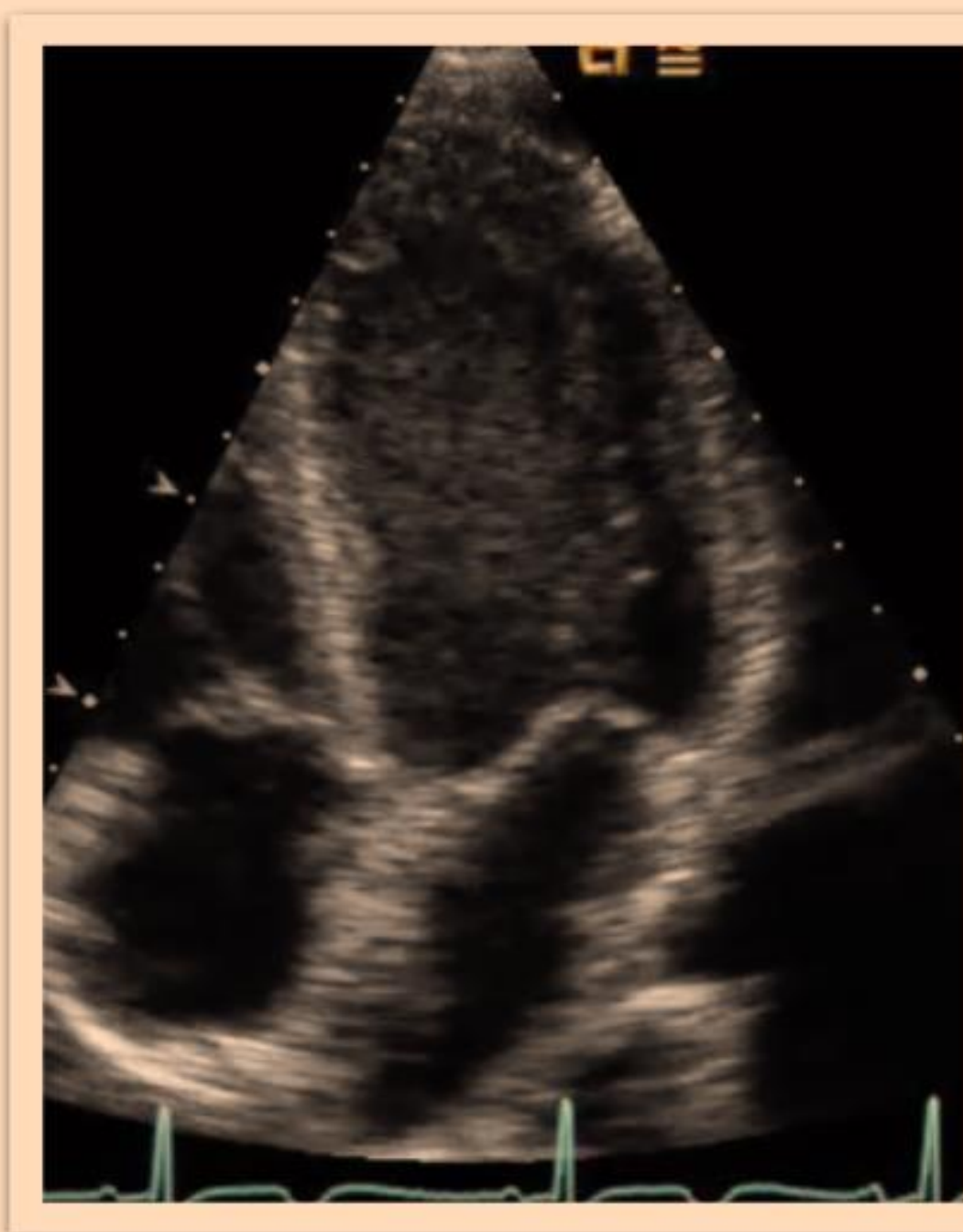
- LAVI  $>34$  mL/m<sup>2</sup> or
- LVMI  $\geq 115$  mg/m<sup>2</sup> (male)  
 $\geq 95$  mg/m<sup>2</sup> (female)

## Functional abnormalities:

- E/e'  $\geq 13$
- e' (mean septal and lateral)  $<9$  cm/s

## Natriuretic peptides:

- NT-pro BNP  $> 125$  pg/mL
- BNP  $>35$  pg/mL



Normal heart



## HFpEF

Normal contractile function  
Normal LV dimensions.  
LV hypertrophy, dilated atria

**The diagnosis of HFpEF is often challenging!**



# Diagnosing HF

**The diagnosis of HFpEF is more difficult than the diagnosis of HFrEF**

**The diagnosis of HFrEF requires three conditions to be satisfied**

- 1. Symptoms typical of HF**
- 2. Signs typical of HF**
- 3. Reduced LVEF**

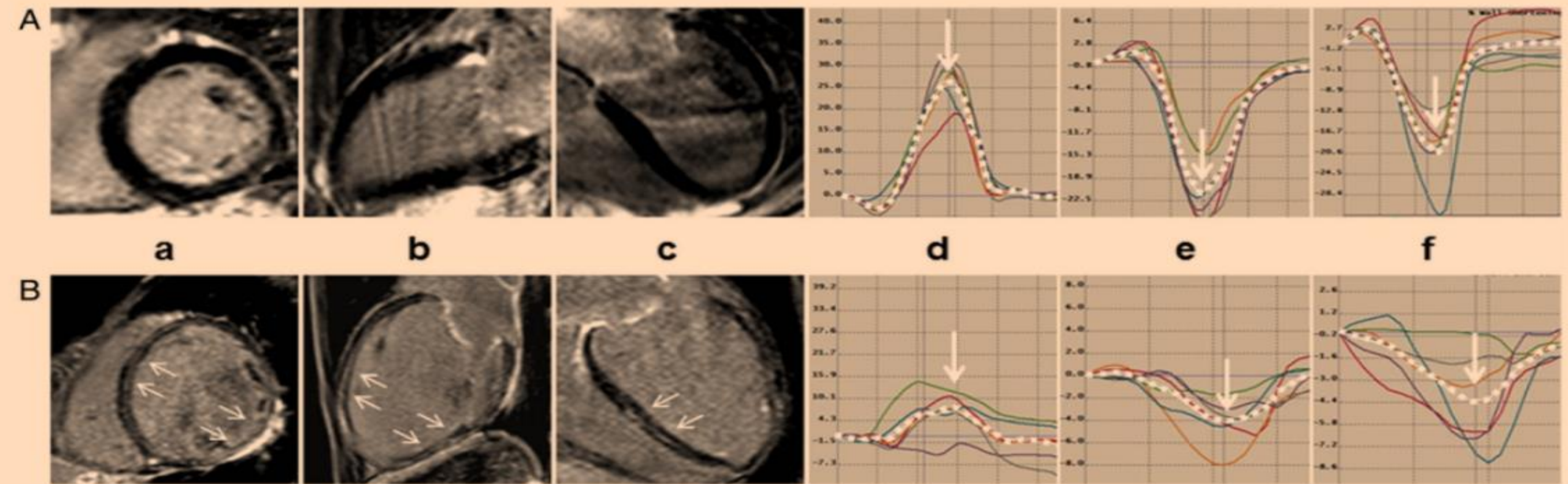
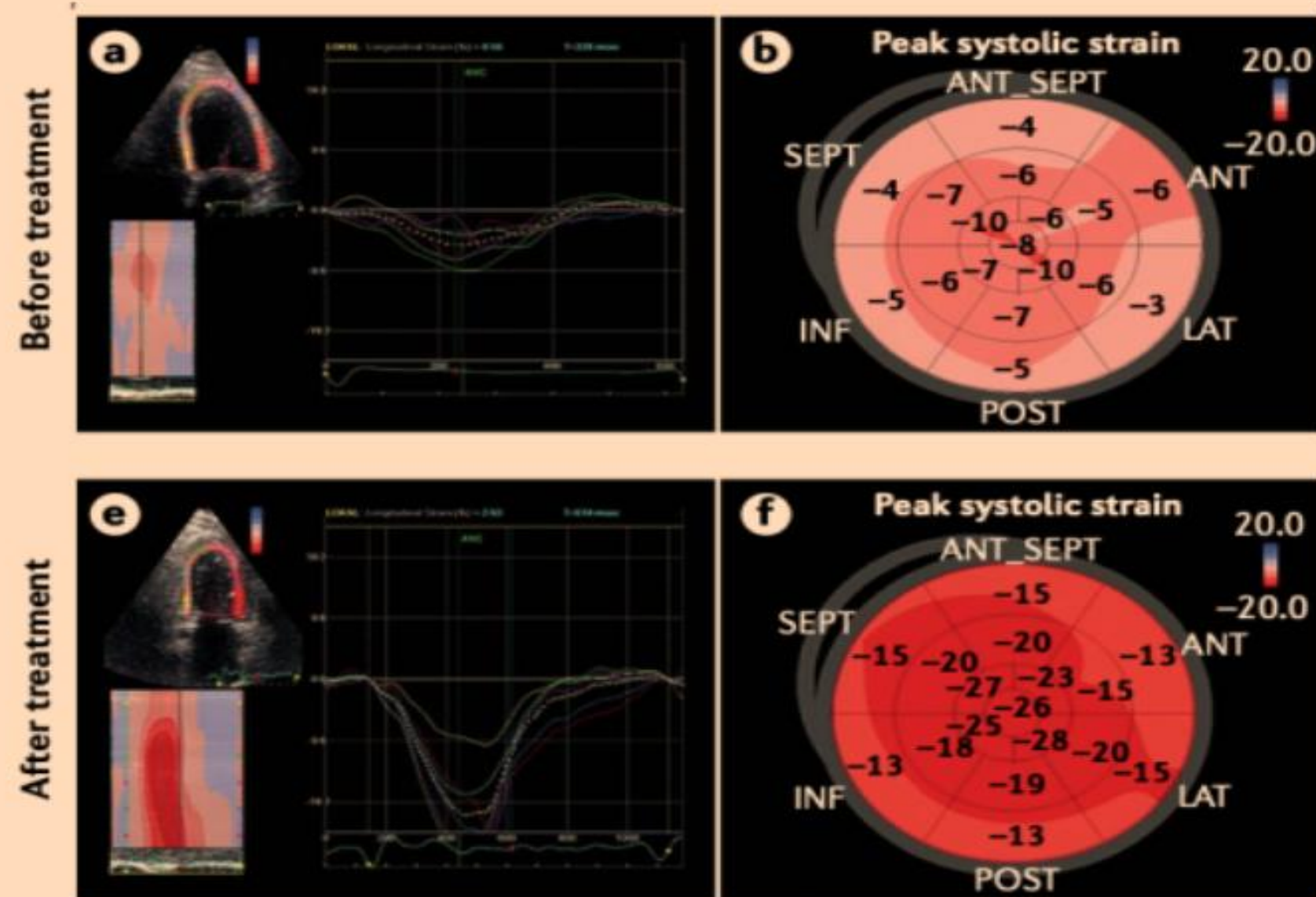
**The diagnosis of HFpEF requires four conditions to be satisfied**

- 1. Symptoms typical of HF**
- 2. Signs typical of HF**
- 3. Normal or only mildly reduced LVEF and LV not dilated**
- 4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction**



# Refinement of diagnostic assessment in heart failure

## Echocardiography: Global longitudinal strain



Speckle-tracking echocardiographic images:  
 A) at baseline (before treatment).  
 F) Follow-up of LV functional recovery with treatment.

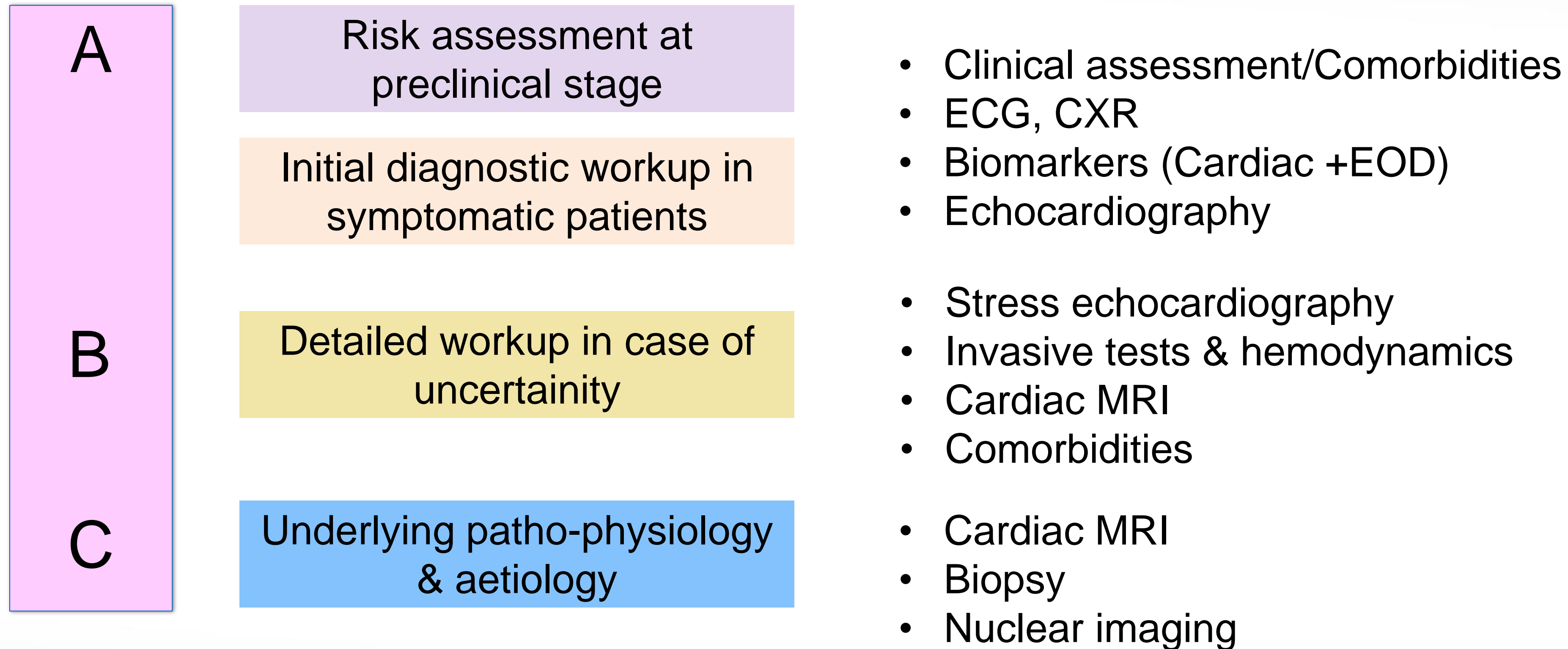
Combining global longitudinal strain and LGE could be useful in the assessment of SCD risk and probability for LV functional recovery

Schultheiss HP et al. Nat Rev Dis Primers. 2019;5:32

Chimura M et al. Heart. 2017;103:679-686



# The diagnosis of HF is a staged process



# Aetiology of HF

## VALVULAR HEART DISEASE

- Mitral
- Aortic
- Tricuspid
- Pulmonary

## PERICARDIAL DISEASE

- Constrictive pericarditis
- Pericardial effusion

## HIGH OUTPUT STATES

- Anaemia
- Sepsis
- Thyrotoxicosis
- Paget's disease
- Arteriovenous fistula

## VOLUME OVERLOAD

- Renal failure
- Iatrogenic (e.g. post-operative fluid infusion)

## MYOCARDIAL DISEASE

- Coronary artery disease
- Hypertension
- Cardiomyopathy

## ENDOCARDIAL DISEASE

- With/without hypereosinophilia
- Endocardial fibroelastosis

## HEART FAILURE

## ARRHYTHMIA

- Tachyarrhythmia
- Atrial
- Ventricular
- Bradyarrhythmia
- Sinus node dysfunction

## CONDUCTION DISORDERS

- Atrioventricular block

## CONGENITAL HEART DISEASE

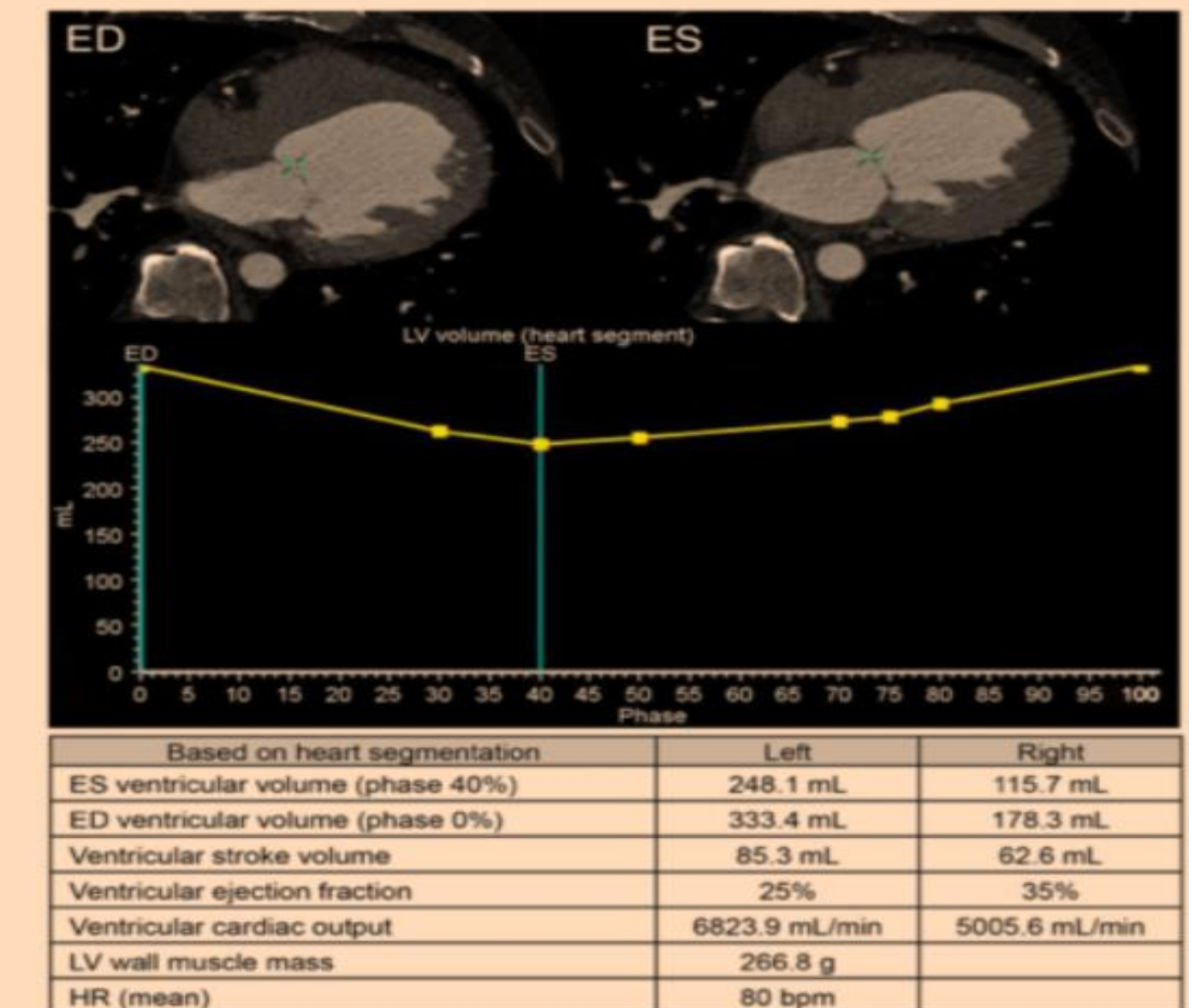
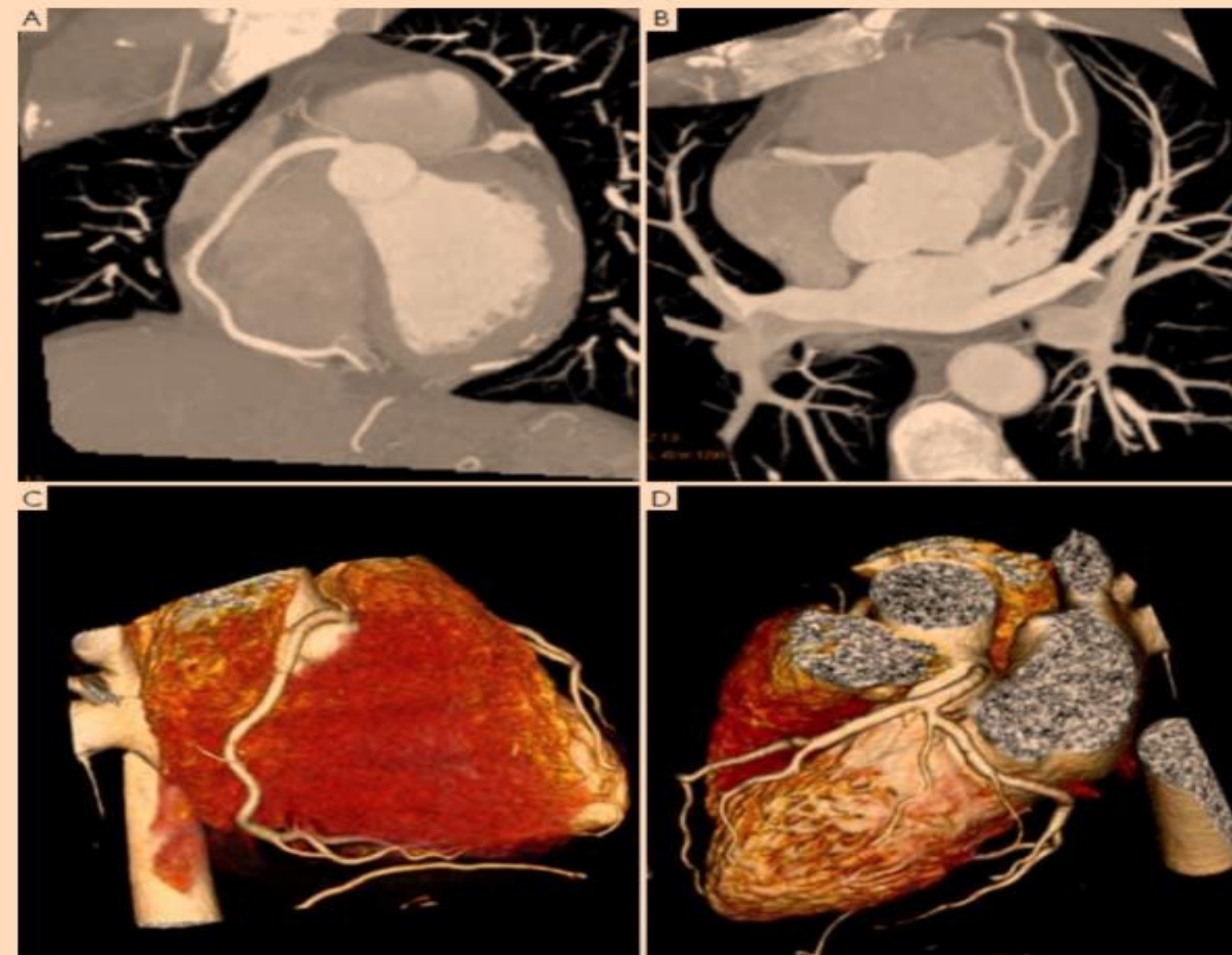


## Refinement of diagnostic assessment in heart failure

# Cardiac CT angiography

## Etiological clarification

- Ischaemic vs. non-ischaemic CM
- LV non-compaction
- Hypertrophic CM
- Arrhythmogenic right ventricular CM
- LV functional recovery



Levine A et. Al. J Nucl Med 2015; 56:46S–51S





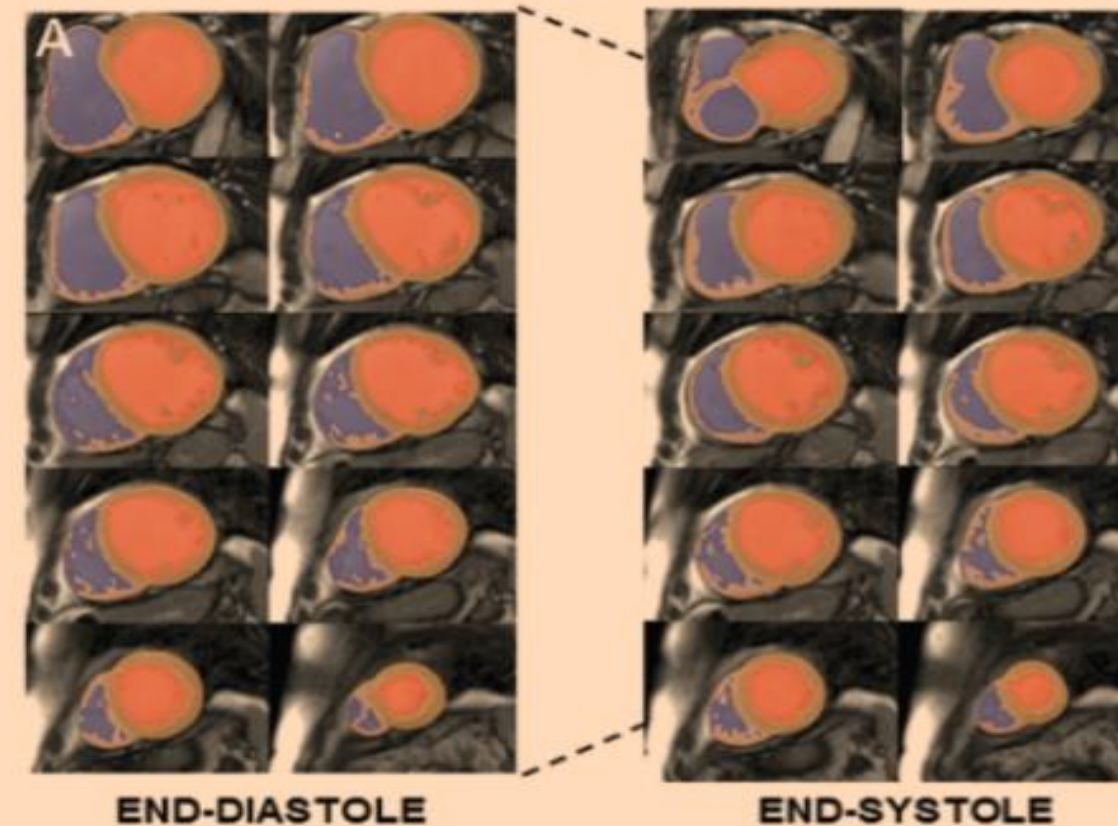
## Refinement of diagnostic assessment in heart failure

# Cardiac magnetic resonance

- Assessment of LV and RV volumes and ejection fraction.
- Assessment of LA volume.
- T2-weighted assessment of oedema (myocarditis).
- LGE-CMR and T1-weighted detection of replacement fibrosis.
- Tissue characteristics (sarcoidosis, amyloidosis).
- T2\*-weighted detection of myocardial iron overload.

Fancone M. ISRN Radiol. 2014; 2014: 365404.  
Peterzan MA et al. Card Fail Rev; 2016;2:115–22  
Japp AG et al. J Am Coll Cardiol 2016;67:2996–3010

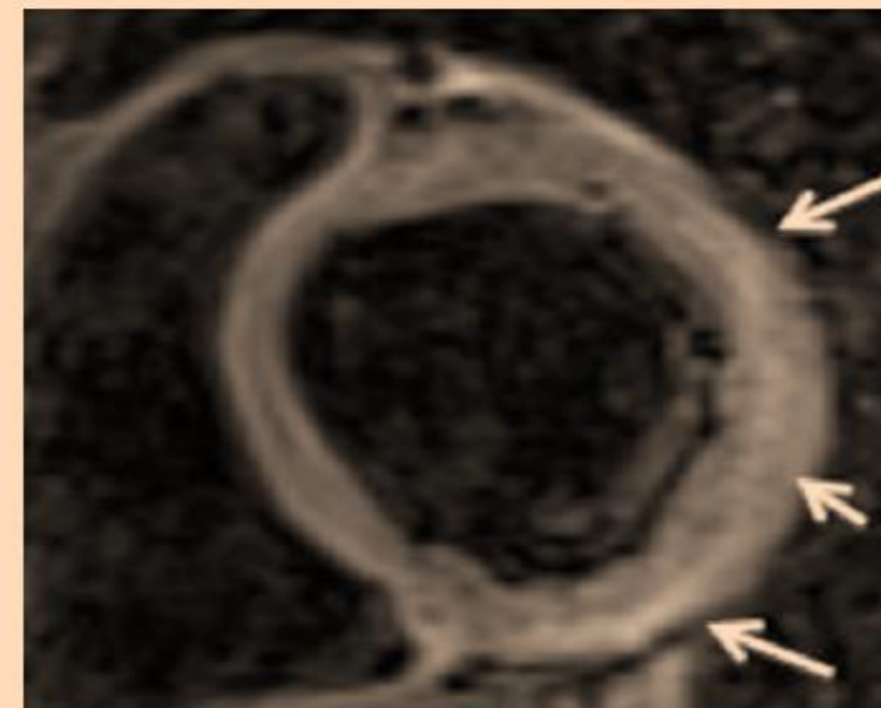
Volumes and function



Fibrosis



Oedema



Iron overload





# Severity of heart failure: classification

ACC/AHA stages of HF (based on morphology and symptoms)		NYHA functional classification (based on symptoms or physical limitation)	
<b>Stage A</b>	At high risk for HF, but without structural or functional abnormality No signs or symptoms	<b>Class I</b>	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea
<b>Stage B</b>	Developed structural heart disease strongly associated with development of HF, but without signs or symptoms	<b>Class II</b>	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in HF symptoms
<b>Stage C</b>	Symptomatic HF associated with underlying structural heart disease	<b>Class III</b>	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in HF symptoms
<b>Stage D</b>	Advanced structural heart disease and marked symptoms of HF at rest, despite maximal medical therapy	<b>Class IV</b>	Symptoms of HF present at rest. If any physical activity is undertaken, discomfort is increased



# Diagnosis of Heart failure (HF): Summary

- Global burden of HF is increasing in number and complexity, due to an aging patient population, often with multiple comorbidities. Reducing readmissions can limit the burden for healthcare systems.
- Many causes of HF that result in ventricular remodeling, reduction of the left ventricular ejection fraction, and neurohumoral imbalance. HF is a silently progressive condition.
- Many of the symptoms of HF are non-specific. HF severity can be classified based on structure and damage to heart (ACC/AHA) or based on symptoms or physical activity (NYHA).
- Adequate diagnosis of HF requires confirming the clinical suspicion with objective diagnostic measures, and identifying the underlying phenotype and aetiology
- HFrEF and HFpEF may present similarly within the clinical syndrome of HF. The diagnosis of HFpEF is more difficult than the diagnosis of HFrEF because it is largely one of exclusion
- Measuring natriuretic peptide levels can help diagnosis. A normal natriuretic peptide level virtually excludes significant cardiac disease



***Thank you***





# Diabetes and Heart Failure: A Dangerous Intersection

**Dr Michael Ross MacDonald**

*MB ChB, BSc (Hons), MD (Res)*

*MRCP (UK), FESC (Europe)*

**Senior Consultant Cardiologist**



# Conflicts of Interest

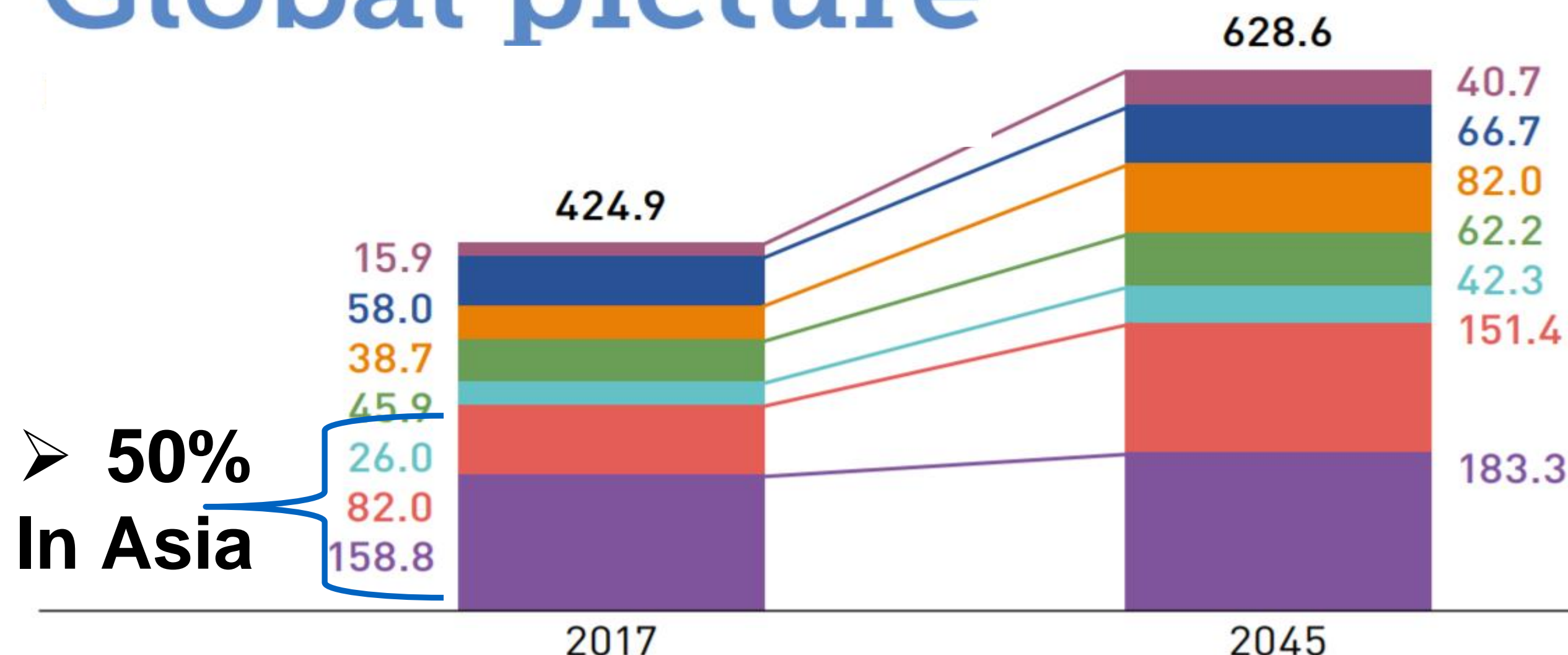
- None



# The Diabetes Epidemic

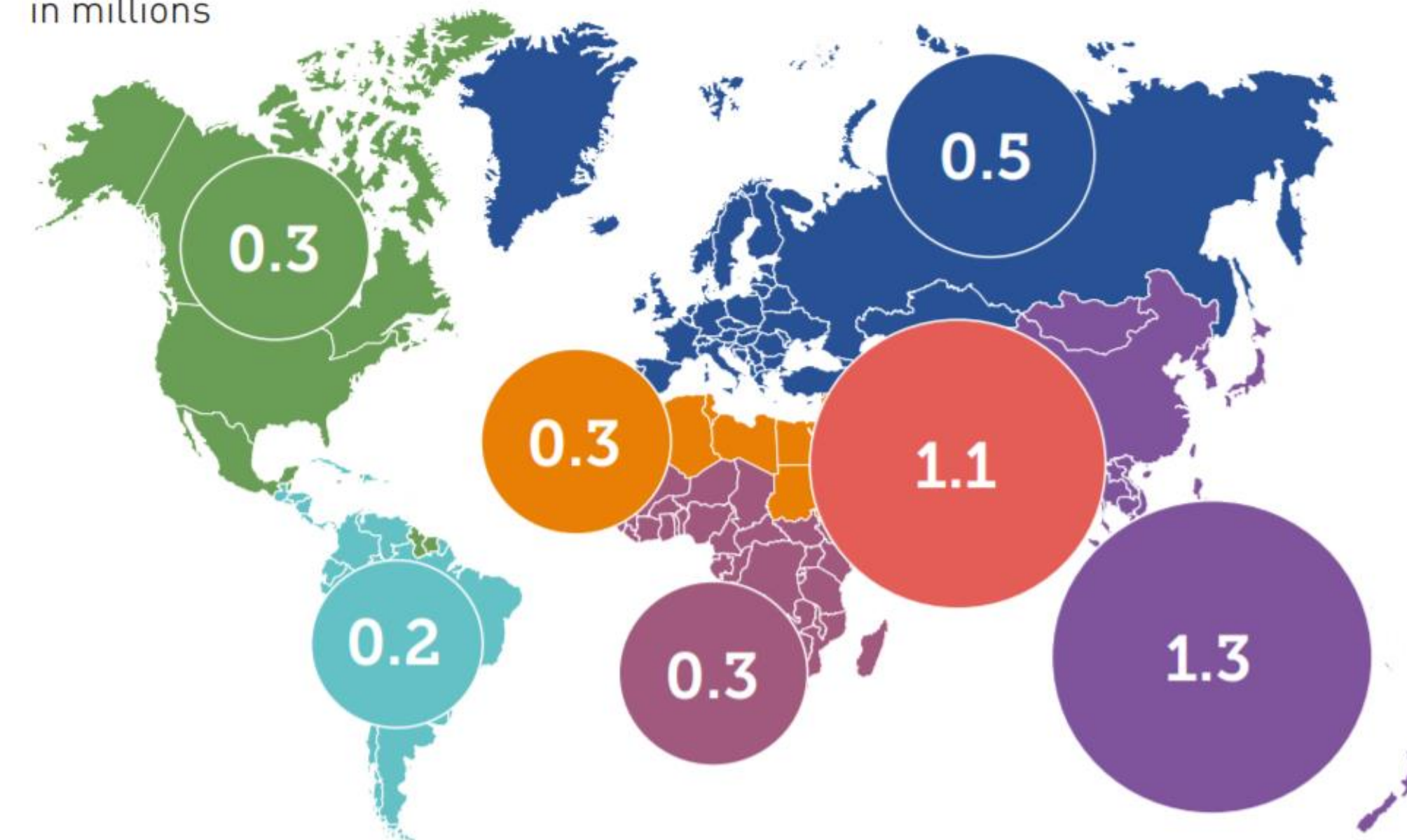


## Global picture



## Deaths Due To Diabetes 2017

in millions

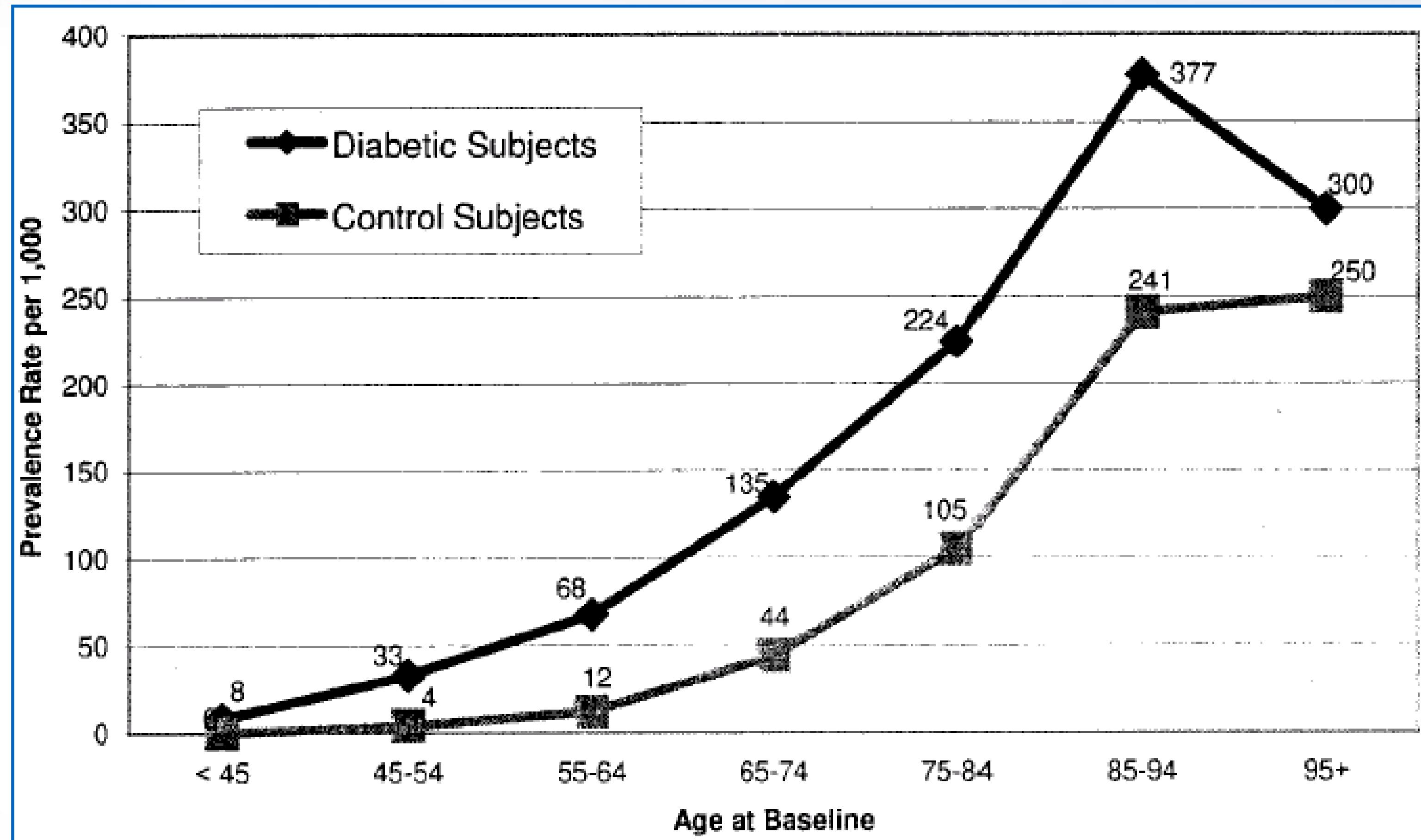


- AFR
- EUR
- MENA
- NAC
- SACA
- SEA
- WP

\*Numbers expressed in millions



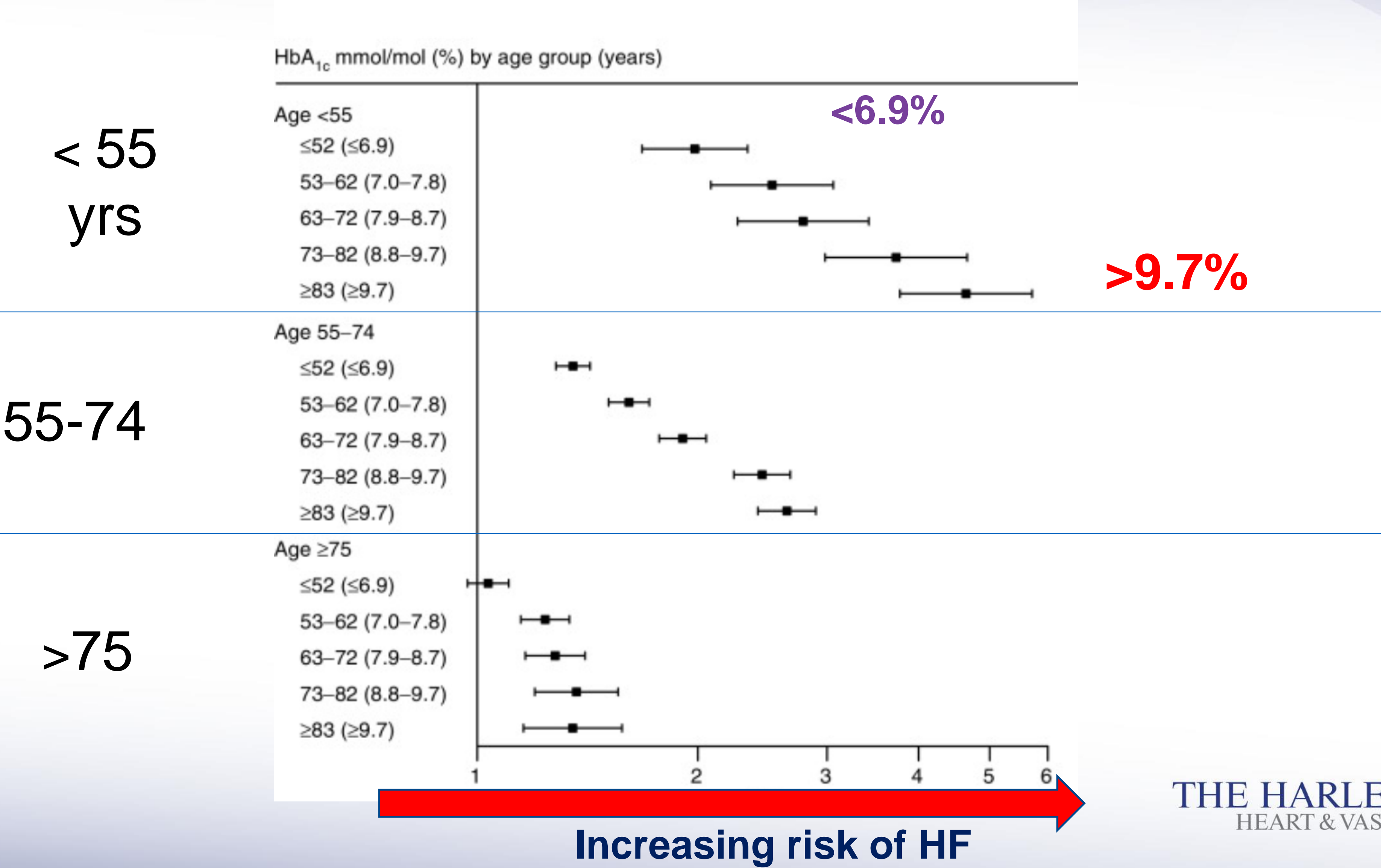
# Patients with diabetes are 2 to 5 X more likely to develop HF



**The overall prevalence of HF in diabetes is between 10-30%**

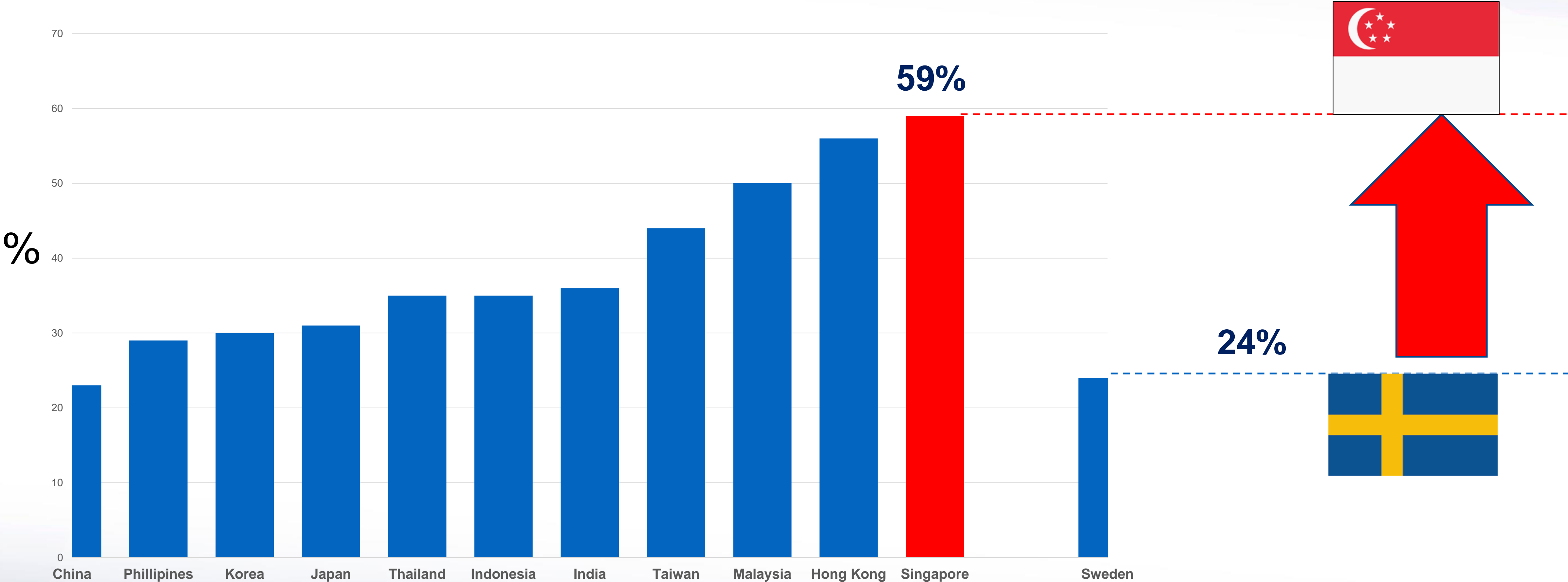


# The Risk of HF Rises with HBA1c in Young Patients



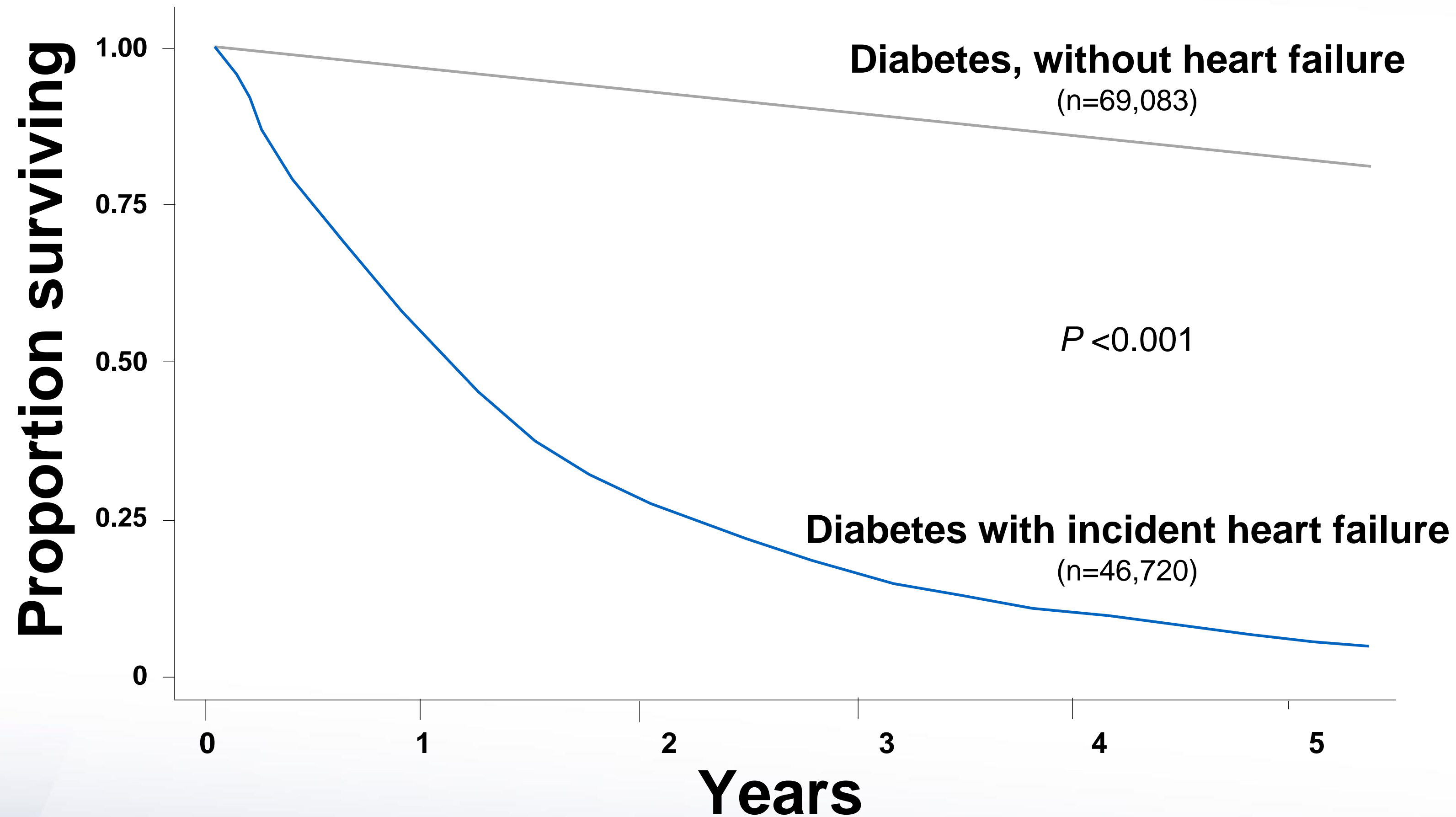


# The Prevalence of Diabetes in Asian HF patients





# The Presence of HF in Patients with Diabetes is Associated with an Increase in Death

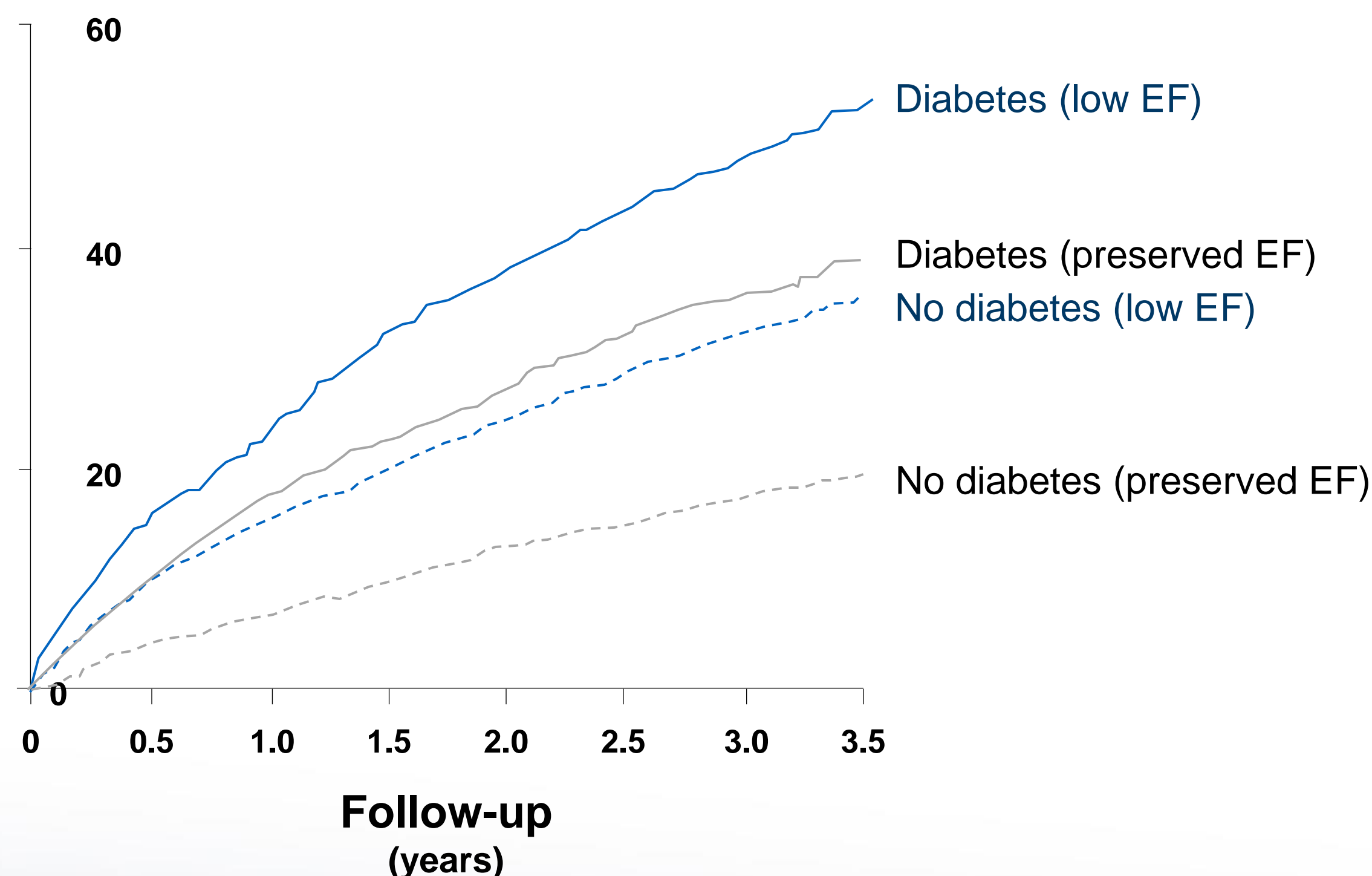


- Medicare data
- n = 115,803
- >65 years

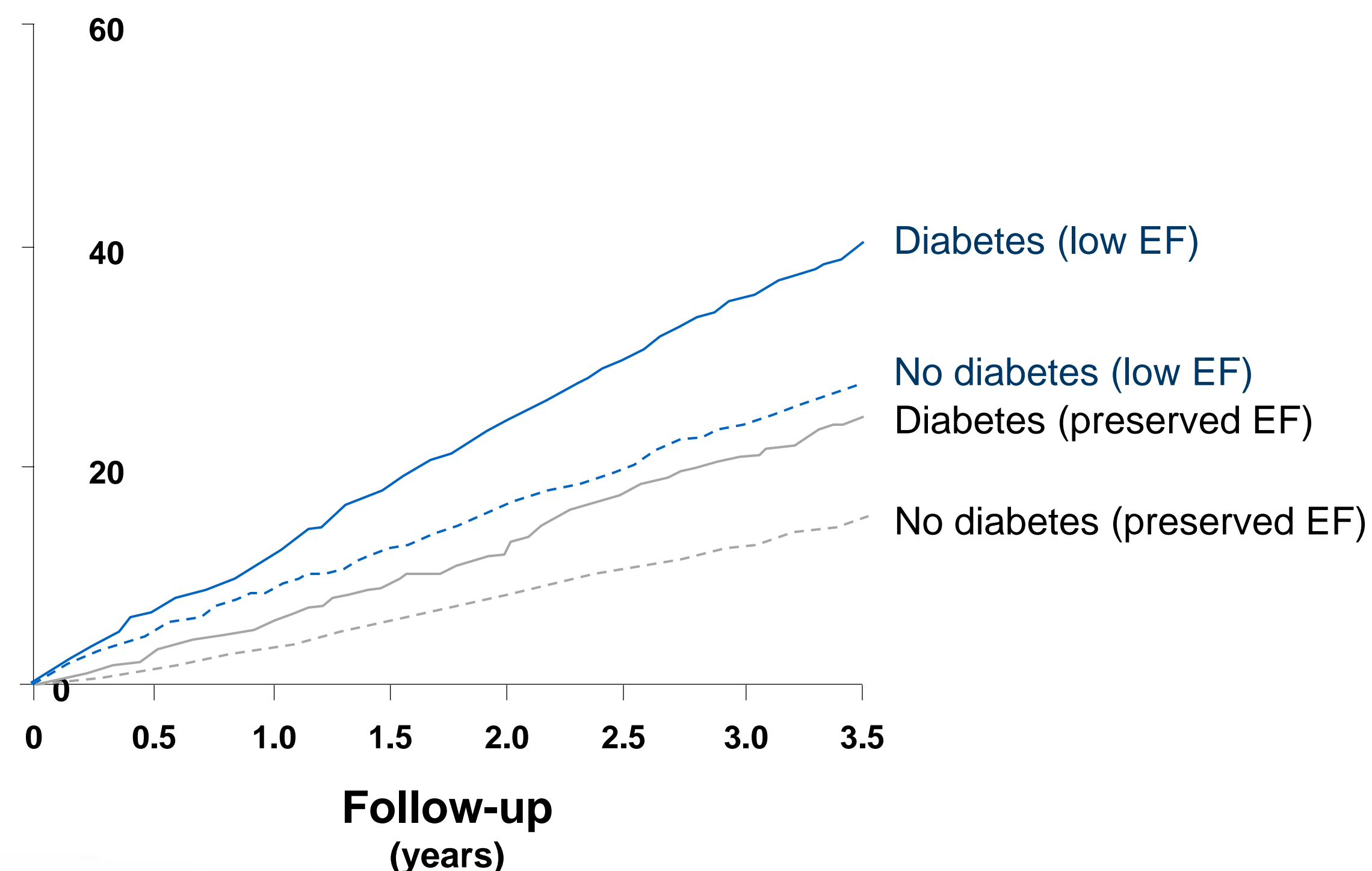


# The Presence of Diabetes Increases the Risk of Death and HF Hospitalisation in HFrEF and HFpEF

**CV death or hospitalisation due to HF**  
(Cumulative incidence, %)



**All-cause mortality**  
(Cumulative incidence, %)





# Patients with both diabetes and HF

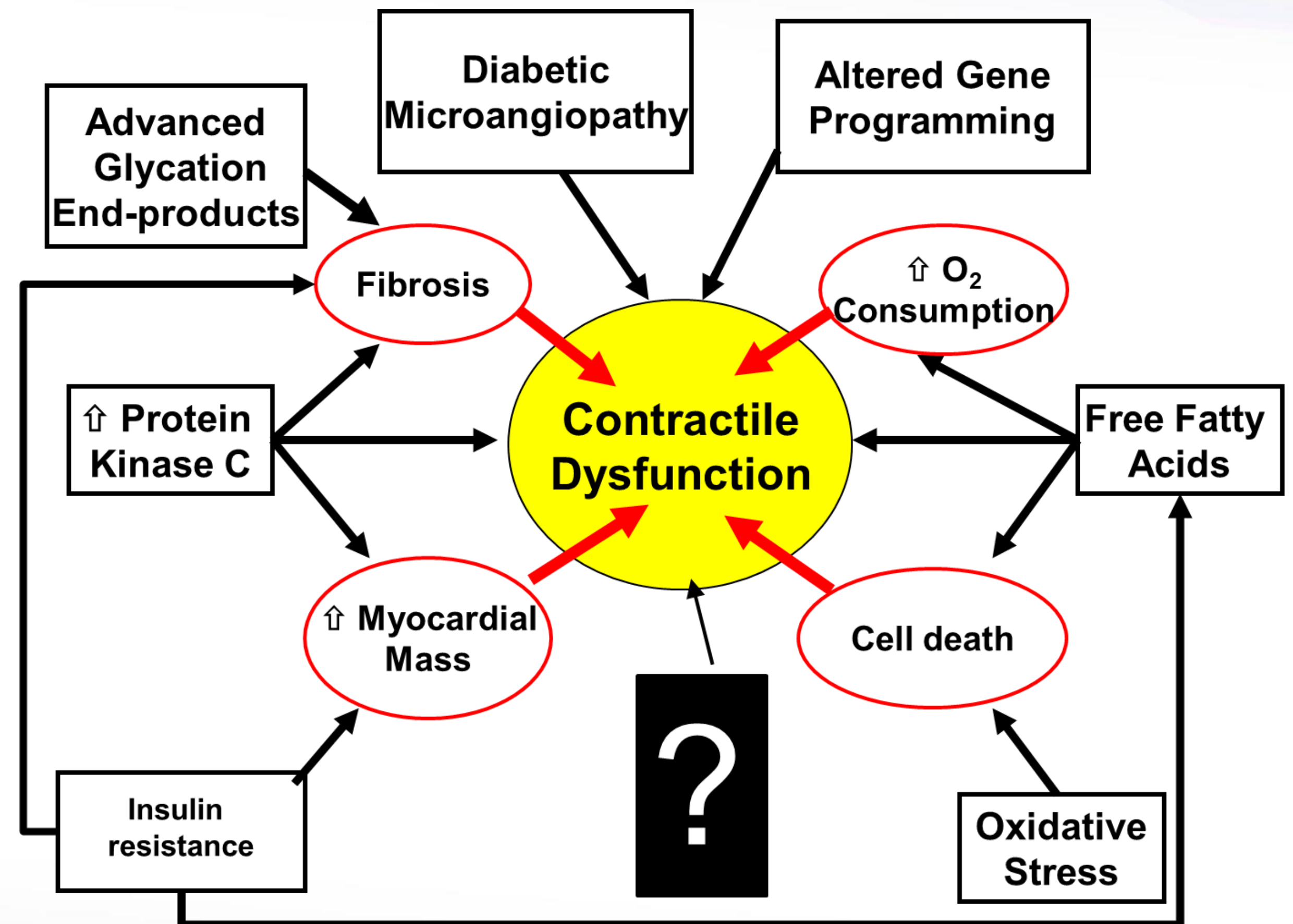
Die earlier

Have more symptoms

End up in hospital more often

# Why does Diabetes Cause Heart Failure?

- **Hypertension**  
*Better control reduces risk of developing HF*
- **Coronary artery disease**  
*Often accelerated, severe, diffuse and silent*
- **Diabetes may have a direct effect on the myocardium**



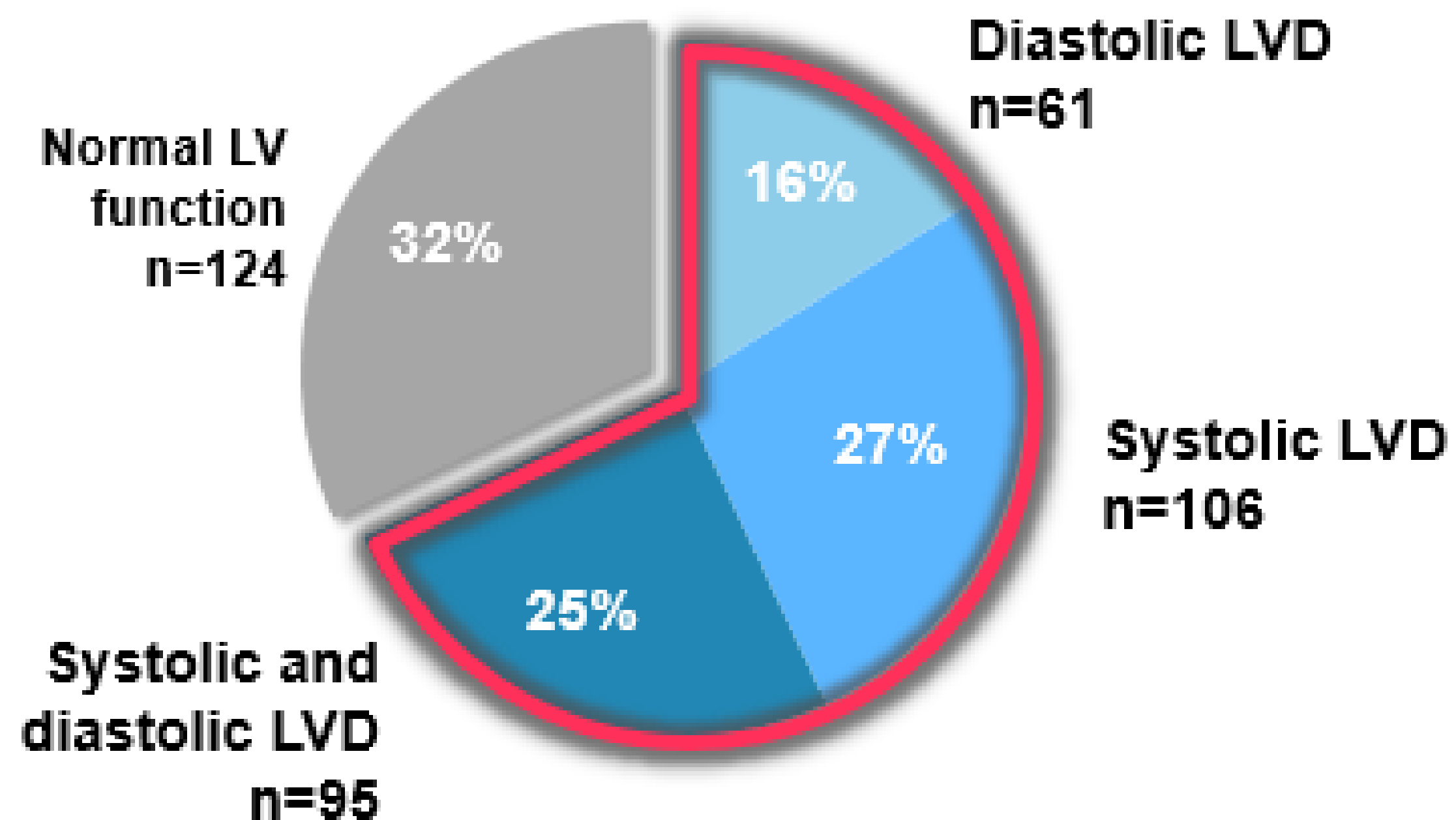


# Screening

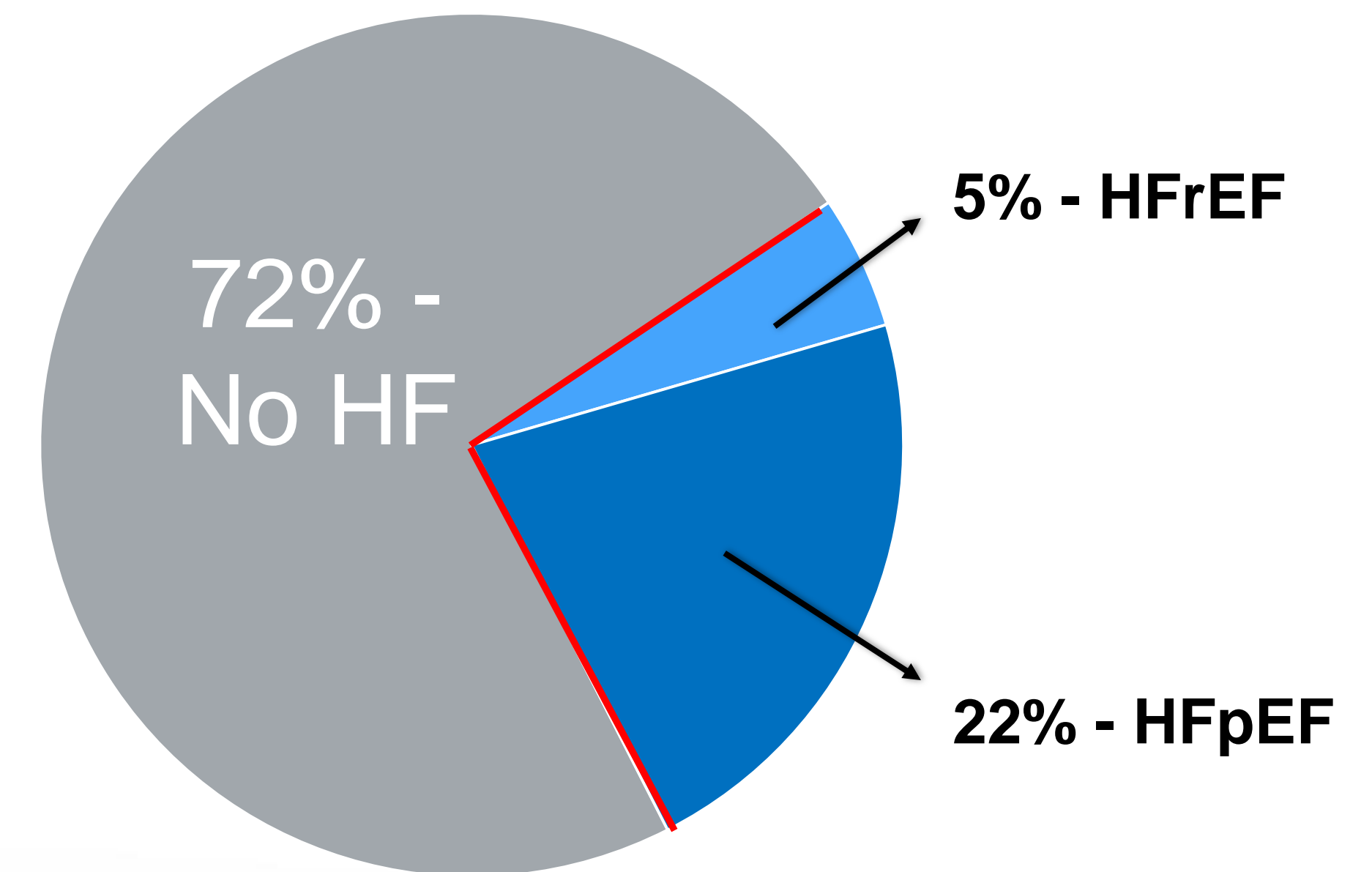
# It is Common for Diabetics to Have Unrecognized HF and Cardiac Dysfunction

## 386 DM without CVD

68% of patients with T2D had evidence of LV dysfunction 5 years after T2D diagnosis<sup>1</sup>



## 605 DM without known HF HbA1c 6.7%





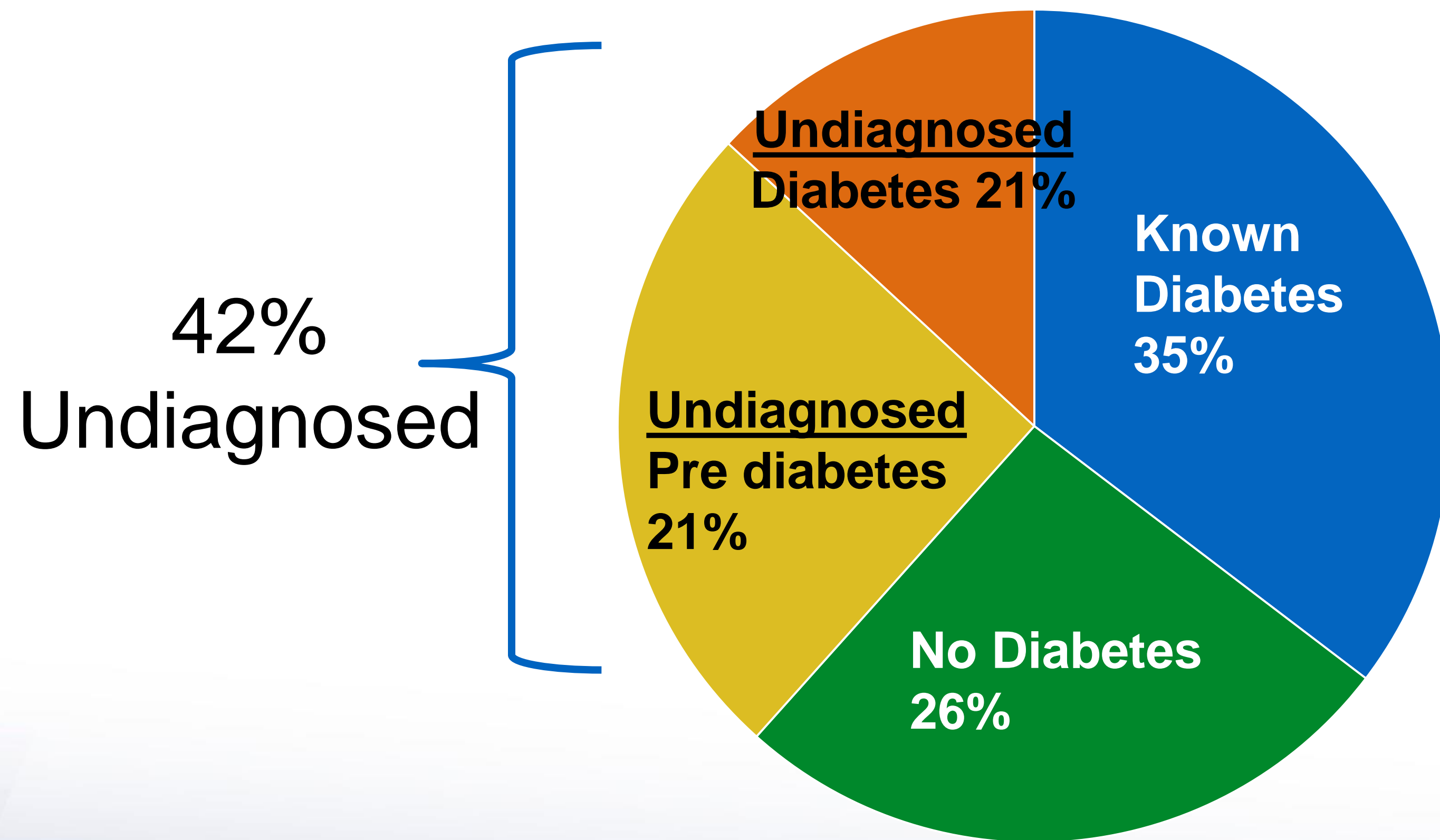
# Should We Screen Patients with Diabetes for HF?

The HF Association of the ESC recommends

**Consider screening with Echocardiography/NTproBNP in higher risk groups**

- Older patients
- history of IHD/TIA or stroke
- Dyspnea
- Increased BMI
- Laterally displaced apex beat

# Glucose Abnormalities are Commonly Undiagnosed in Patients with HF



We need to regularly screen HF patients for Diabetes





# Treatment

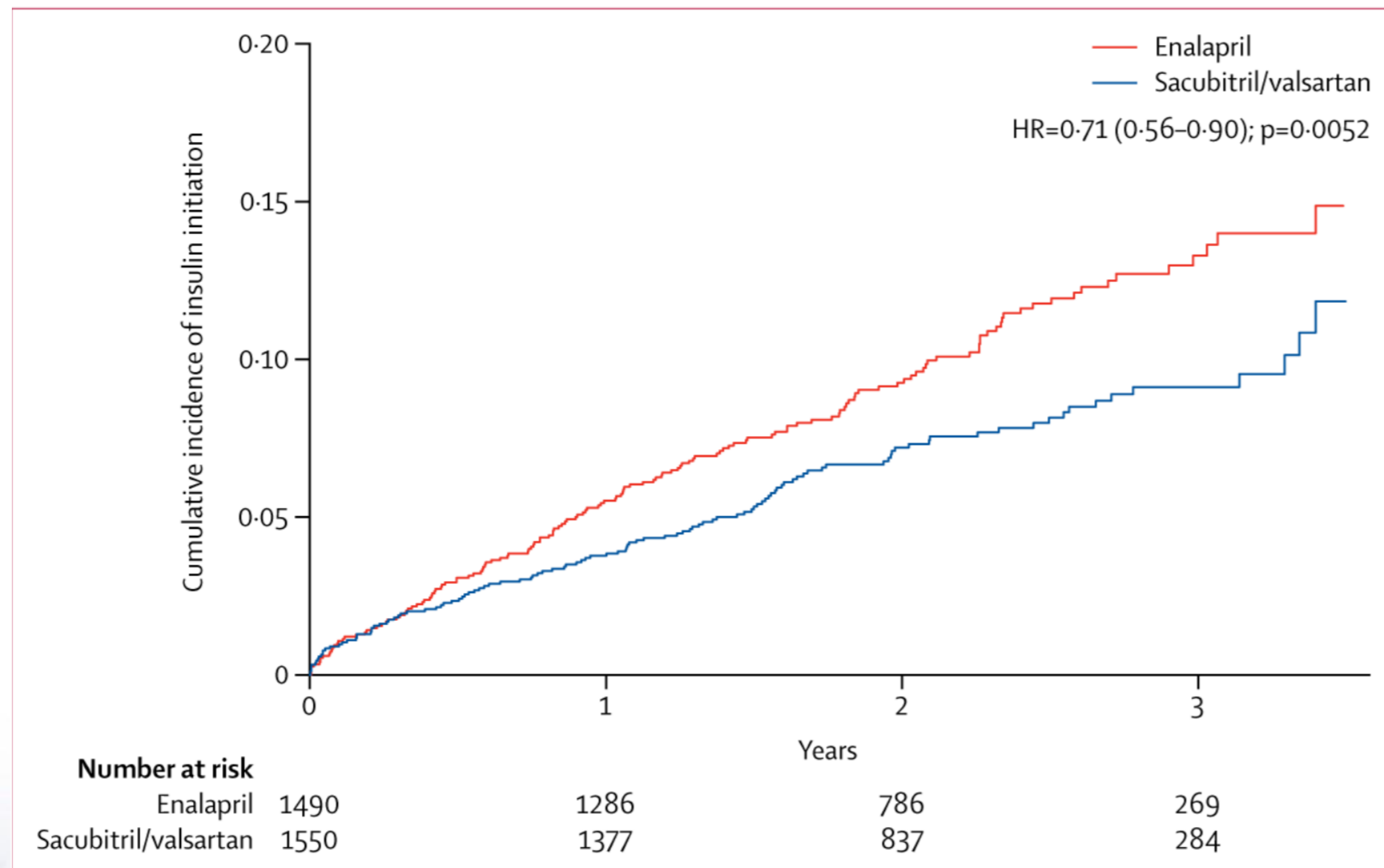
# Treatment of HF in Diabetes Patients

**All standard HF  
drugs/devices work equally  
well in diabetics and non-  
diabetics**

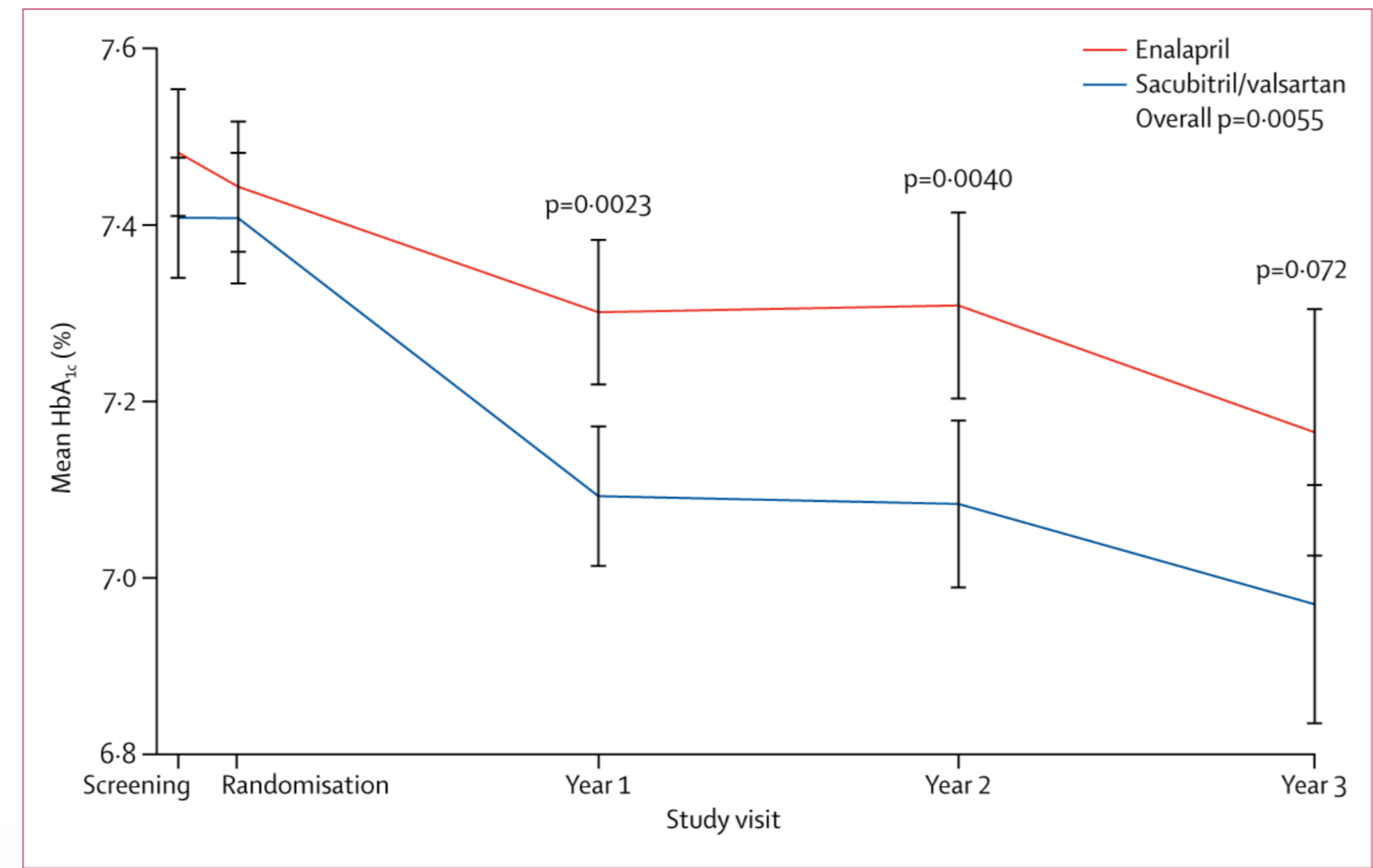


# Entresto may have benefits on glycemia

Less conversion to insulin



Greater reduction in HbA1c



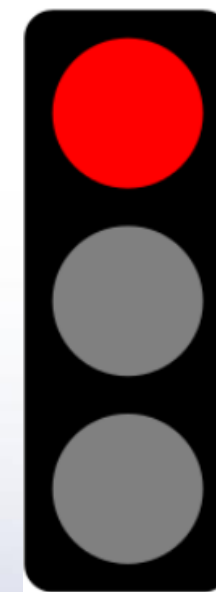
# Antidiabetic Drugs in HF



**Potential beneficial effect on the risk  
of HF**



**Neutral effect on HF risk**



**Unfavorable effects in HF risk**

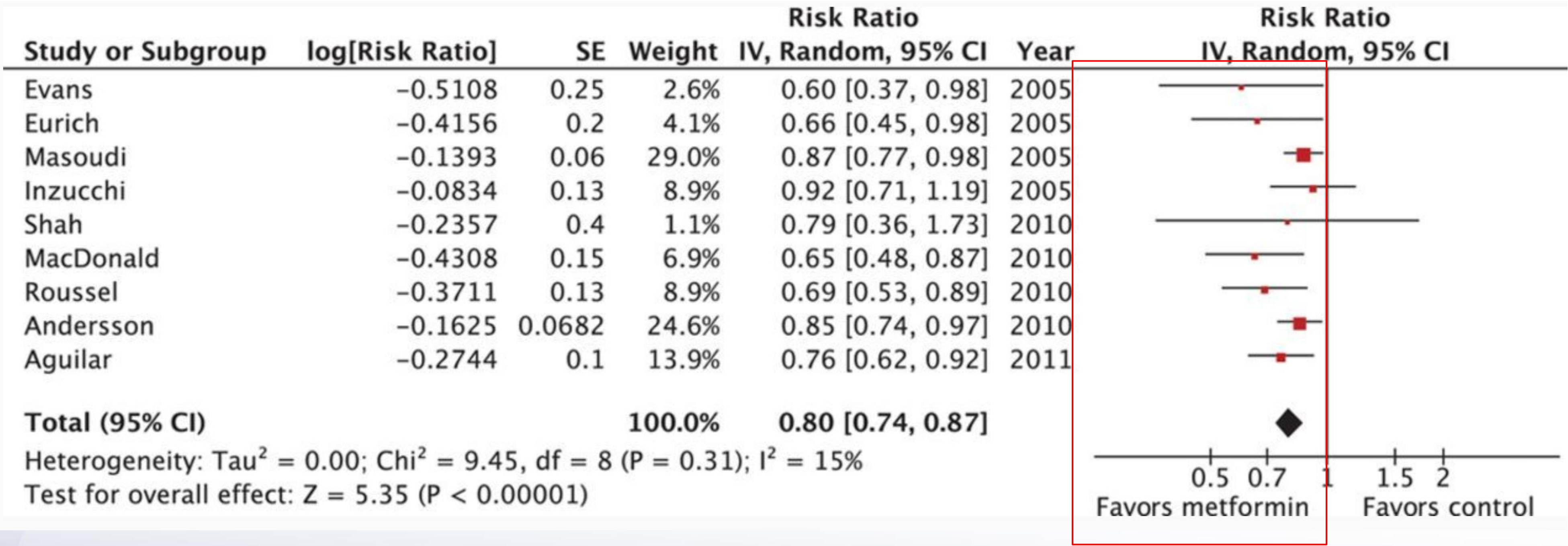


# Antidiabetic Drugs in HF: Metformin

34000 Patient Meta-analysis: Observational Studies

Reduction in Mortality

Metformin appears to have a favourable effect on outcomes in patients with HFrEF



# Antidiabetic Drugs in HF: **Sulfonylureas**

## **Early data**

UKPDS, ADOPT – No increased HF signal

## **Recent Observational Data in non-HF populations**

### **VAD database in USA**

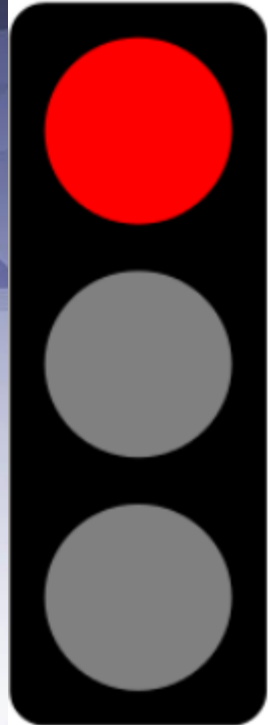
Sulfonylureas associated with increased HF-related and CV mortality compared with metformin

### **Canadian observational Study**

Signal for increased mortality and CV risk particularly in South Asian and Chinese Patients



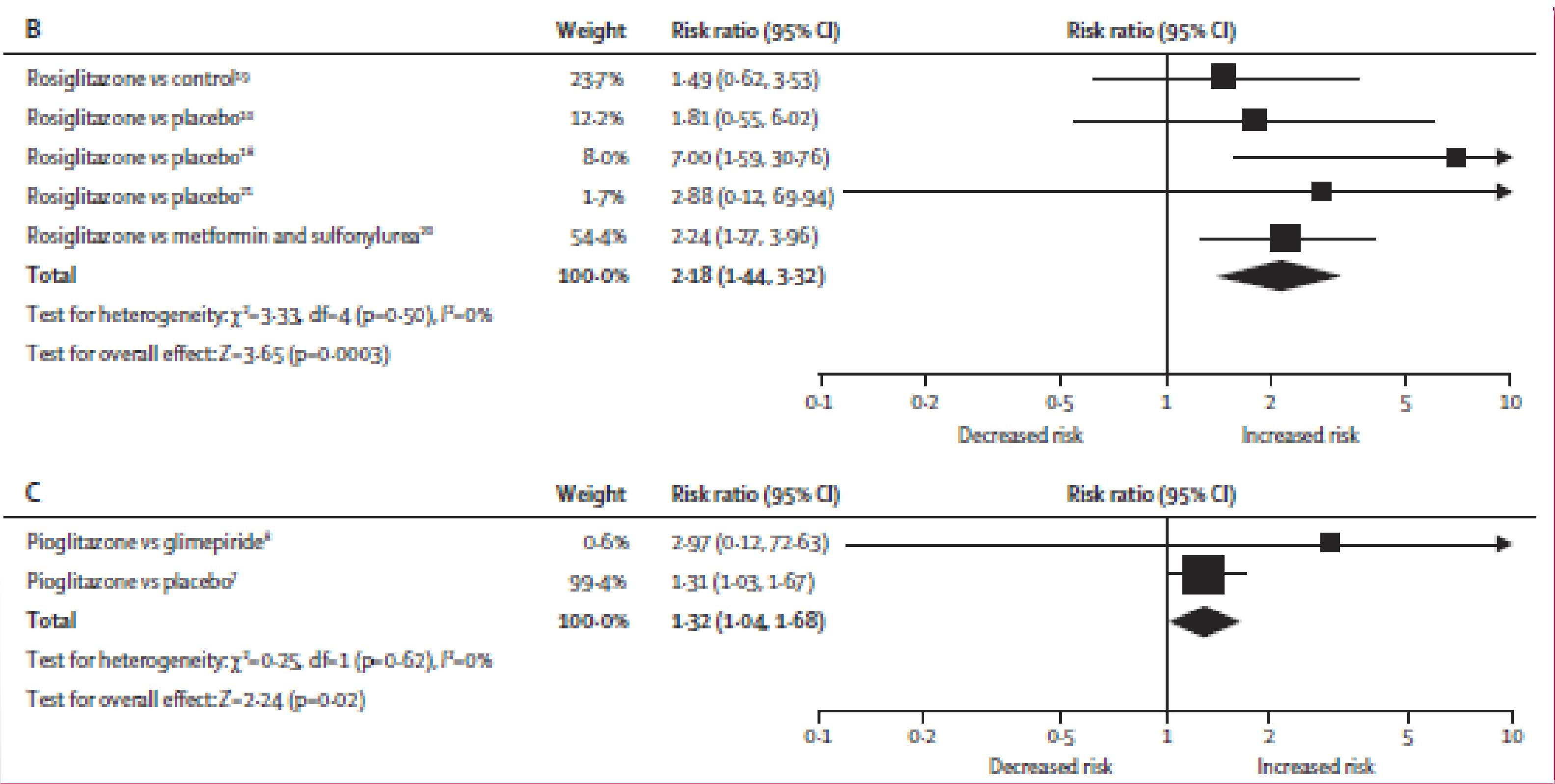
# Antidiabetic Drugs in HF: Thiazolidinediones



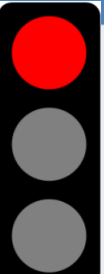

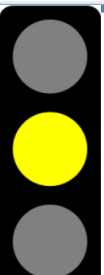



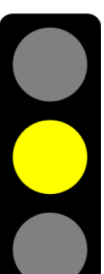
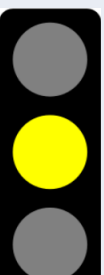

TZDs increase the risk of HF hospitalization

In RECORD – patients that developed HF had a higher risk of death

**CONTRAINDICATED IN HEART FAILURE**



# Antidiabetic Drugs in HF: DPP4 Inhibitors

Medication		RCT	Patients, n	Patients with HF	Median follow-up (years)	HR (95% CI)
Saxagliptin			8,280	13%	2.1	<b>1.27 (1.07–1.51)</b>
Alogliptin			2,701	28%	1.5	1.07 (0.79–1.46)
Sitagliptin			7,257	18%	3.0	1.00 (0.83–1.20)
Vildagliptin		VIVID	254	All patients NYHA class I-III HF and EF <40%	1.0	No effect on LVEF; an increase in LV volumes
Linagliptin			6,979	27%	2.2	0.90 (0.74 – 1.08)

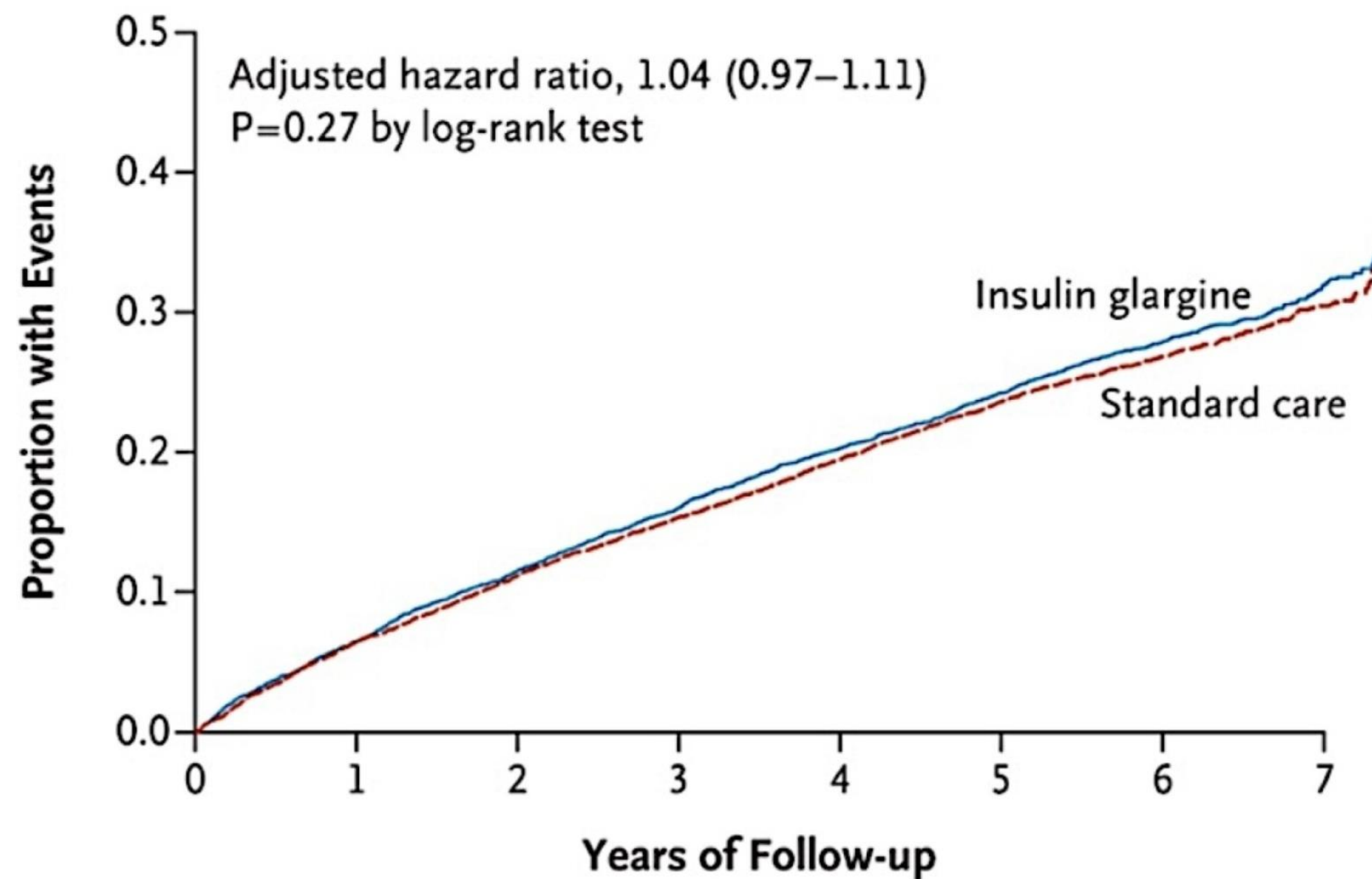
Green JB et al. N Engl J Med. 2015;373:232-42;  
 Scirica BM et al. N Engl J Med. 2013;369:1317-26;  
 White WB et al. N Engl J Med. 2013;369:1327-35;  
 McMurray JJR et al. JACC Heart Fail. 2018;6:8-17  
 Rosenstock J et al. JAMA. 2019;321:69-79.



# Antidiabetic Drugs in HF: Insulin

ORIGIN Trial: RCT of Insulin on CV outcomes  
12537 Patients without HF but at increased CV risk

Coprimary Outcome plus Revascularization or Hospitalization for Congestive Heart Failure



Insulin Glargine had a neutral effect on risk of HF hospitalization

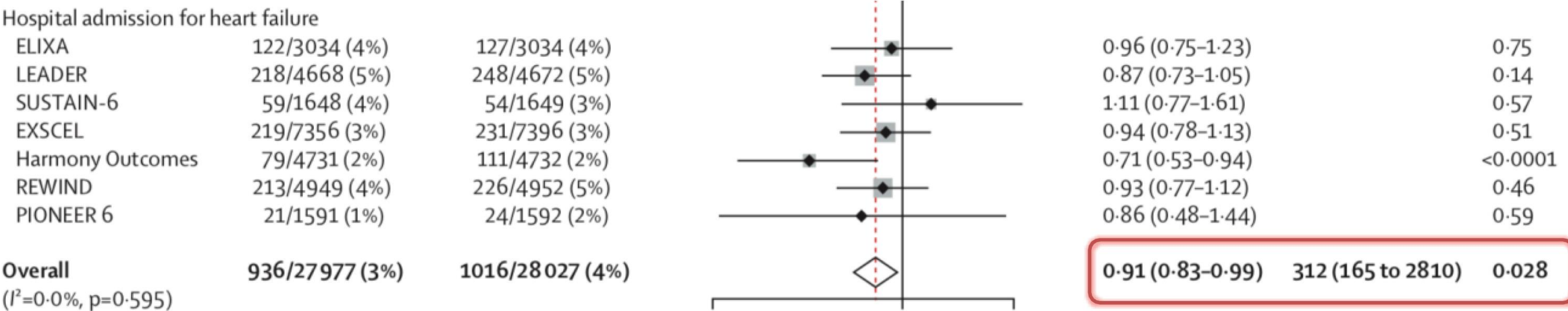


# Antidiabetic drugs in HF: GLP-1 agonists



Meta – Analysis 56000 patients  
GLP – 1 significantly reduced CV Death, Stroke and MI by 12%

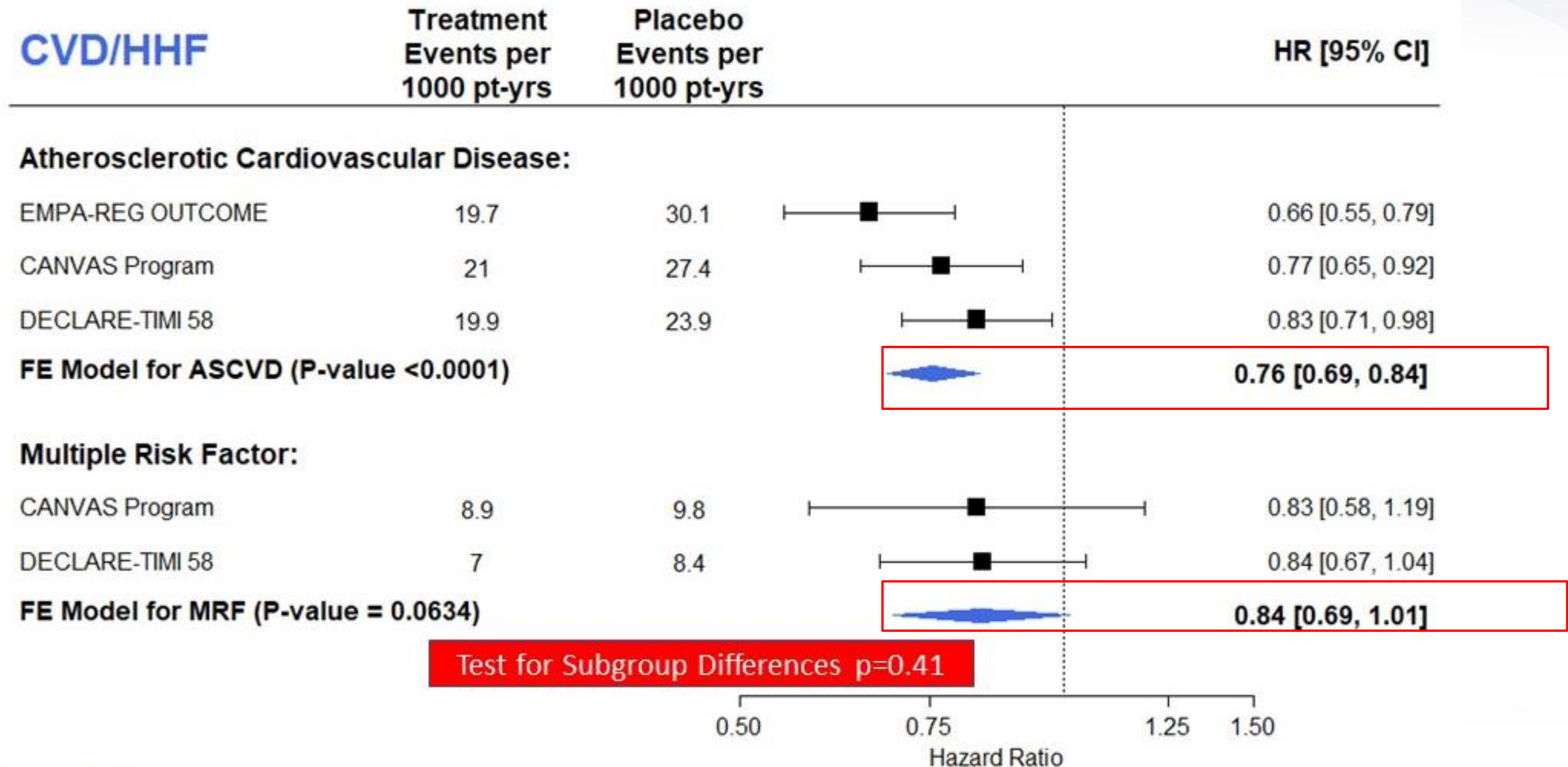
9% reduction in HF hospitalisation versus placebo





# Antidiabetic drugs in HF: **SGLT2**




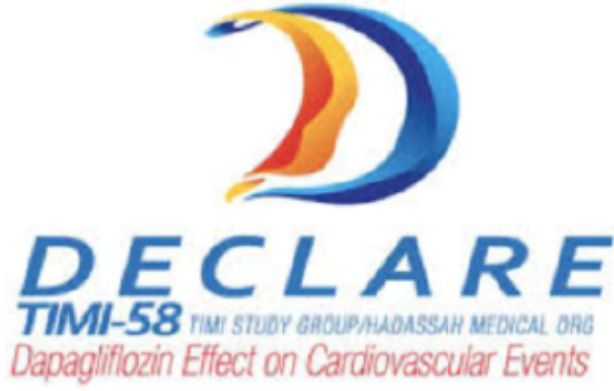
## Meta – Analysis of CVOTs: CVD and HHF





# Antidiabetic drugs in HF: **SGLT2**

## Risk reduction for HF Hospitalisation

Medication	RCT	Patients, n	Characteristics	History of HF	Follow-up (years)	HF hospitalisation (HR, 95% CI)
Empagliflozin		7,020	CVD (100%)	10.2%	3.1	<b>0.65 (0.50-0.85)</b>
Canagliflozin		10,142	CVD (66%); CV risk factors (34%)	14.4%	3.2	<b>0.67 (0.52–0.87)</b>
Canagliflozin		4,401	Albuminuric CKD CVD (50%)	14.9%	2.6	<b>0.61 (0.47–0.80)</b>
Dapagliflozin		17,160	CVD (41%) CV risk factors (59%)	10.0%	4.2	<b>0.73 (0.61-0.88)</b>

Zinman B, et al N Engl J Med. 2015;373:2117-28.

Neal B, et al. N Engl J Med. 2017;377:644-57.

Perkovic V et al. N Engl J Med. 2019;380:2295-2306

Wiviott, S. D., et al. N Engl J Med 2019; 380: 347-357.



# Just Presented At ESC – Published 20 Sept 2019

## DAPA – HF Trial – 4744 Patients

- Dapagliglozin 10mg V Placebo
- In patients with heart failure and reduced ejection fraction (HFrEF) both *with and without* T2D
- LVEF  $\leq 40\%$
- Symptomatic
- Raised NT-pro BNP

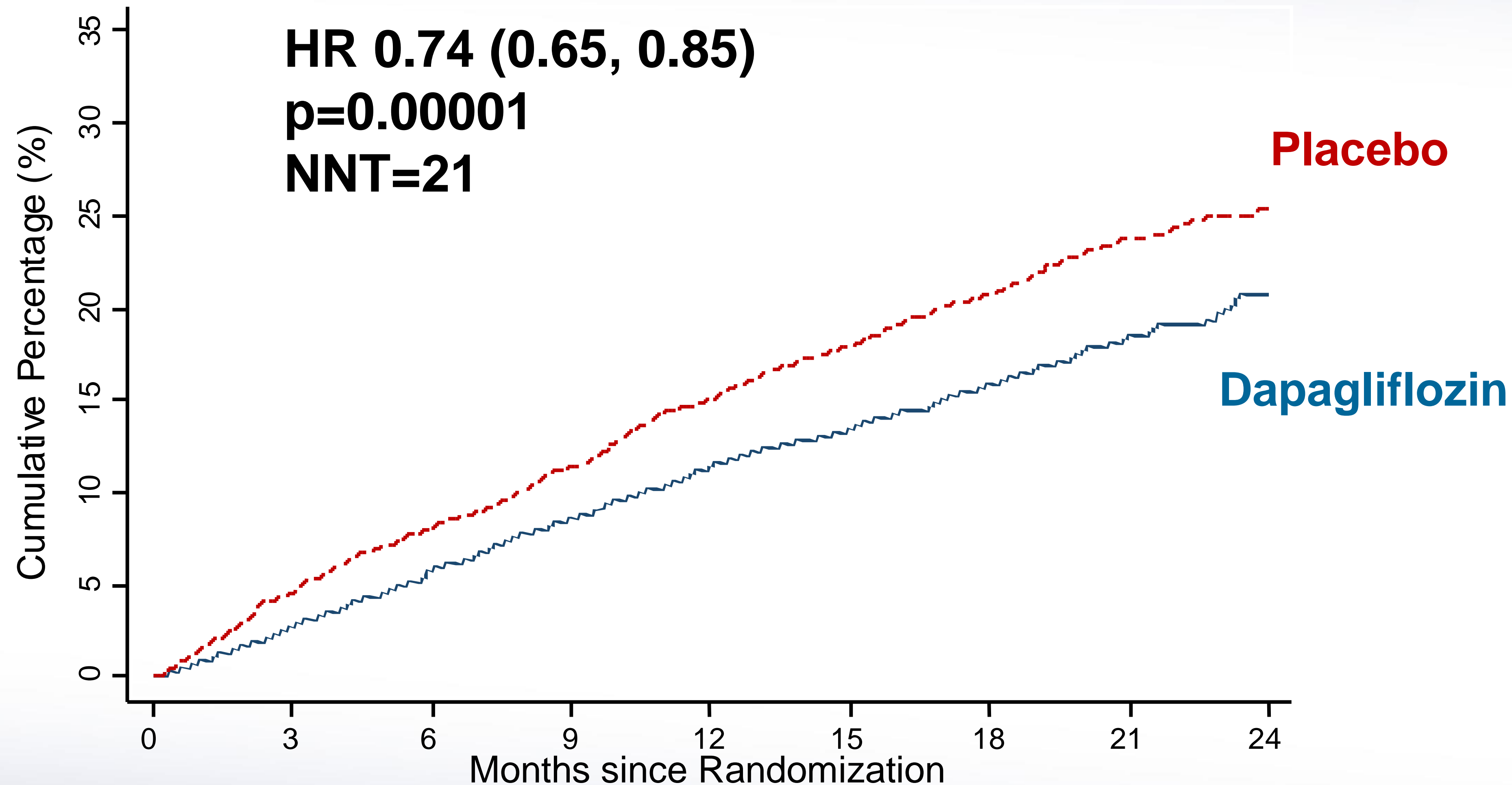
**Key exclusions:** *Egfr*  $< 30 \text{ ml/min/1.73 m}^2$

**Primary endpoint:** Worsening HF or CV Death

This is new data and dapagliflozin can not currently be endorsed as a standard treatment for heart failure.

# Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

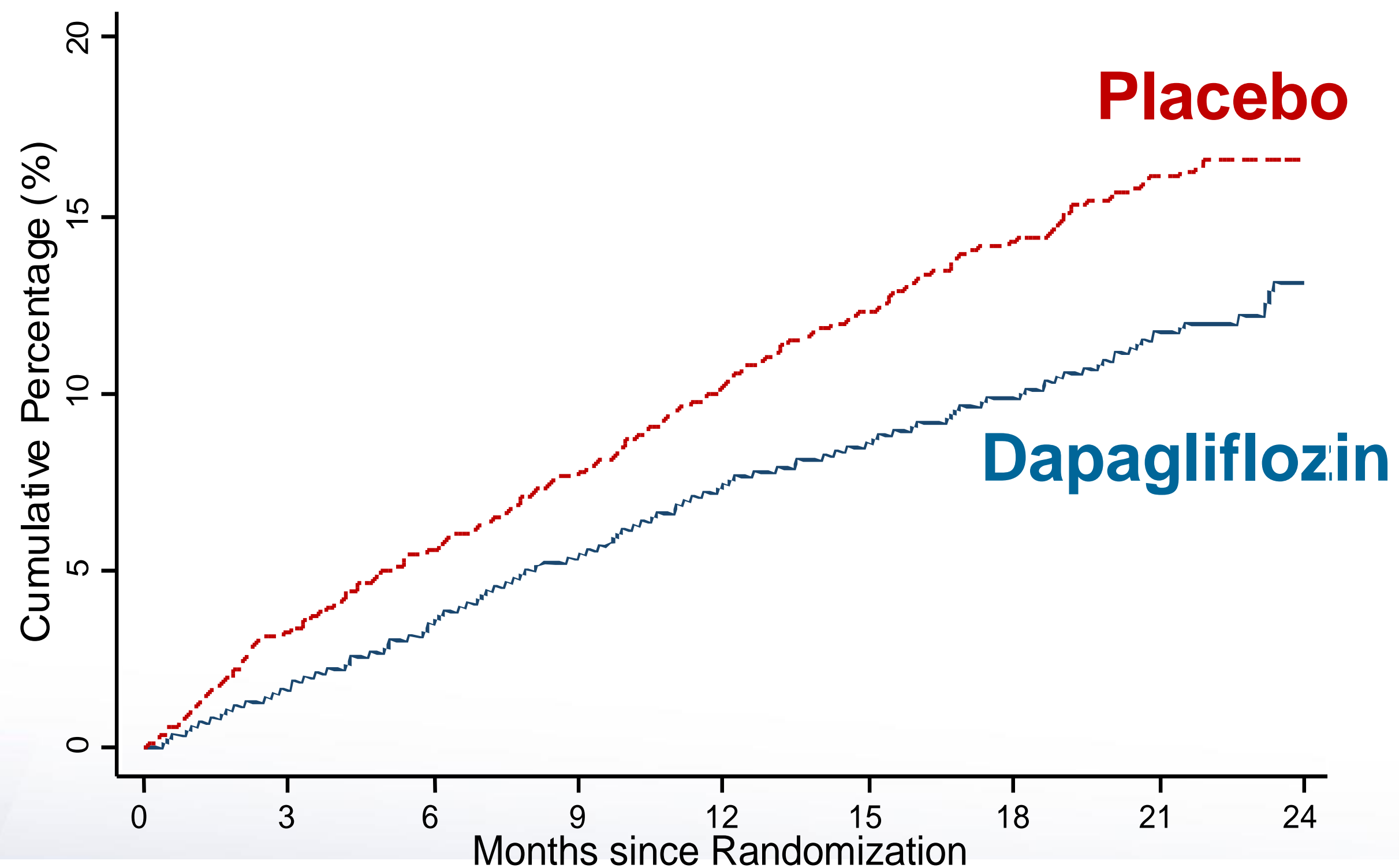




# Components of primary outcome

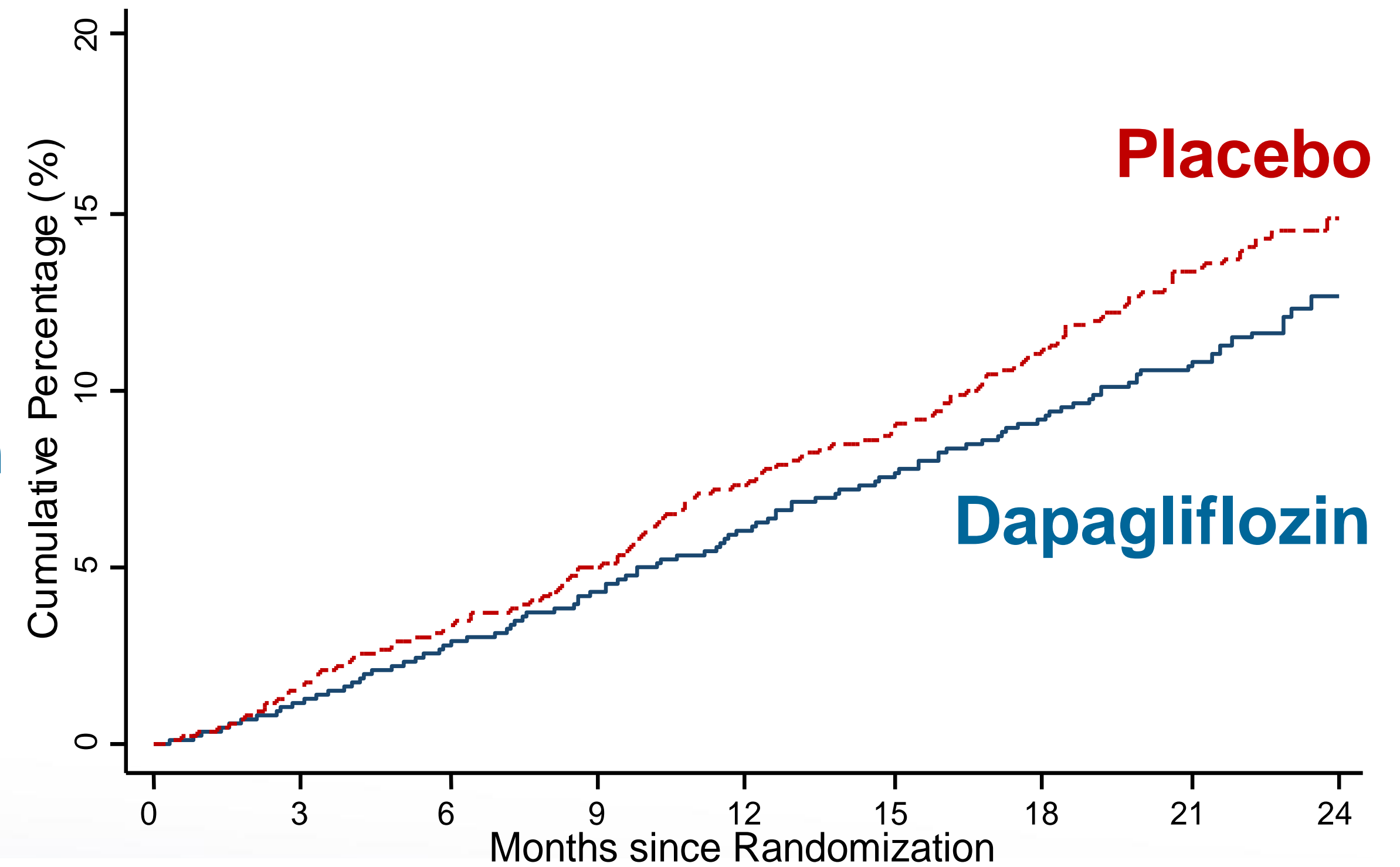
## Worsening HF event

HR 0.70 (0.59, 0.83); p=0.00003



## Cardiovascular death

HR 0.82 (0.69, 0.98); p=0.029

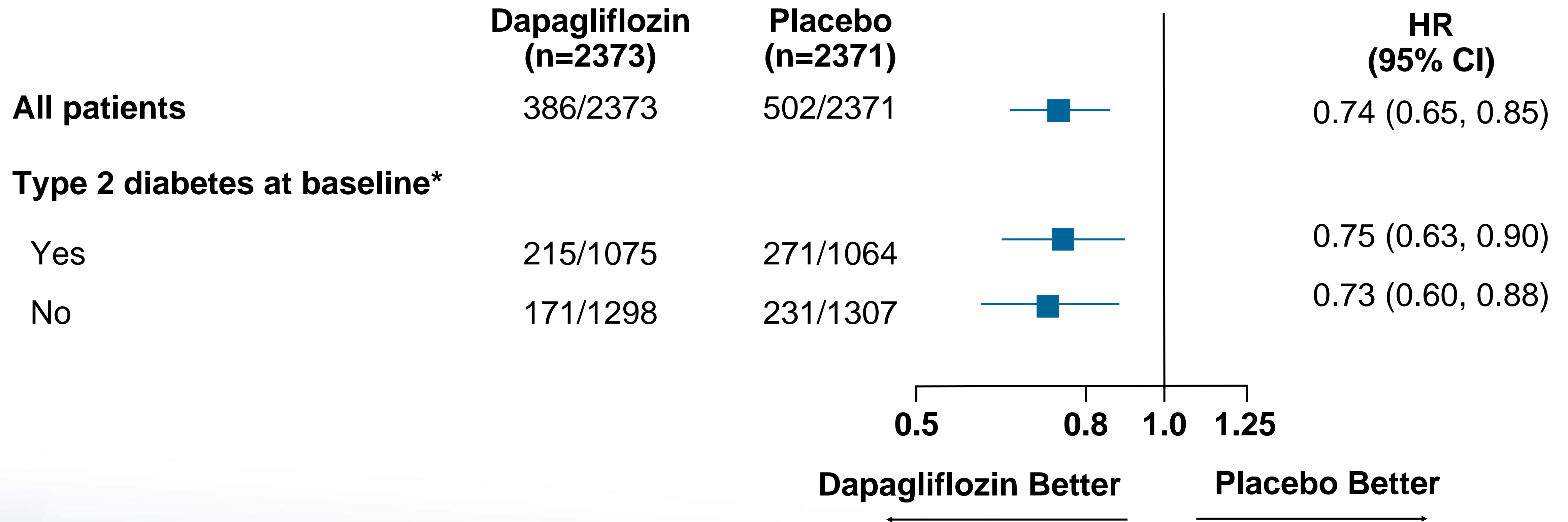


Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

2373	2339	2293	2248	2127	1664	1242	671	232
2371	2330	2279	2230	2091	1636	1219	664	234

# No diabetes/diabetes subgroup: Primary endpoint



\*Defined as history of type 2 diabetes or HbA1c  $\geq 6.5\%$  at both enrollment and randomization visits.



# Guidelines

**2019 ESC Guidelines on diabetes, pre-diabetes,  
and cardiovascular diseases developed in  
collaboration with the EASD**

# Recommendations for the treatment of patients with diabetes to reduce HF risk

SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) are associated with a lower risk of HF hospitalization in patients with DM, and are recommended.<sup>306,311,496</sup>

**I**

**A**

Metformin should be considered for DM treatment in patients with HF, if the eGFR is stable and  $>30 \text{ mL/min/1.73 m}^2$ .<sup>484,485</sup>

**IIa**

**C**

GLP1-RAs (lixisenatide, liraglutide, semaglutide, exenatide, and dulaglutide) have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF.<sup>158,176,297,299,300,303,498,499</sup>

**IIb**

**A**

The DPP4 inhibitors sitagliptin and linagliptin have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF.<sup>293,294</sup>

**IIb**

**B**

Insulin may be considered in patients with advanced systolic HFrEF.<sup>500</sup>

**IIb**

**C**

Thiazolidinediones (pioglitazone and rosiglitazone) are associated with an increased risk of incident HF in patients with DM, and are not recommended for DM treatment in patients at risk of HF (or with previous HF).<sup>279,491–493</sup>

**III**

**A**

The DPP4 inhibitor saxagliptin is associated with an increased risk of HF hospitalization, and is not recommended for DM treatment in patients at risk of HF (or with previous HF).<sup>291</sup>

**III**

**B**

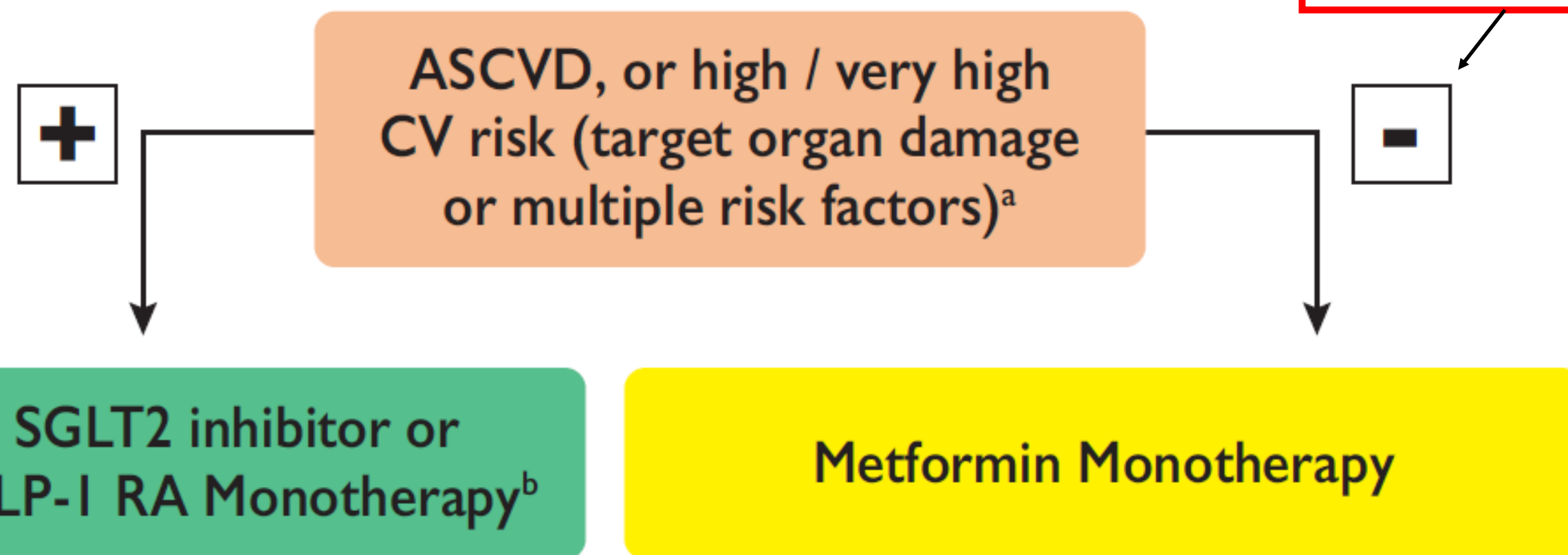




# 2019 ESC Guidelines on diabetes, pre-diabetes and cardiovascular diseases developed in collaboration with the EASD

## A Type 2 DM - Drug naïve patients

Moderate risk - Young patients (T2DM aged <50 years) with DM duration <10 years, without other risk factors



If HbA<sub>1c</sub> above target

Add Metformin

If HbA<sub>1c</sub> above target

DPP-4i

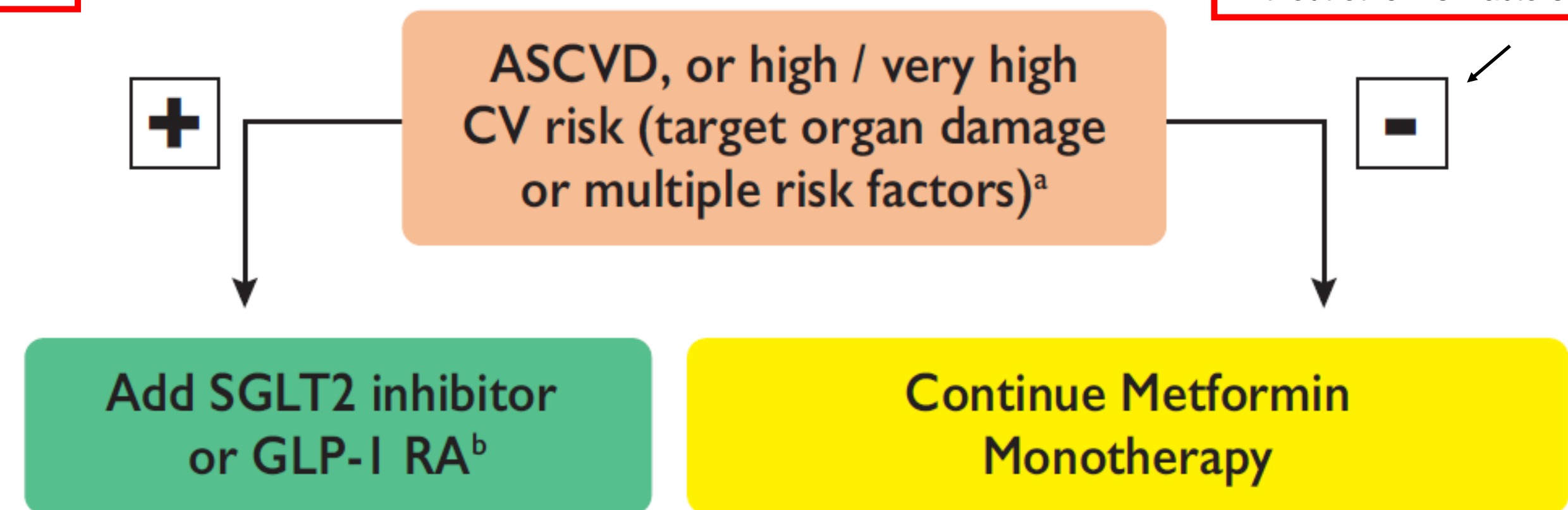
GLP-1 RA

SGLT2i if eGFR adequate

TZD

## B Type 2 DM - On metformin

Moderate risk - Young patients (T2DM aged <50 years) with DM duration <10 years, without other risk factors



If HbA<sub>1c</sub> above target

• Consider adding the other class (GLP-1 RA or SGLT2i) with proven CV benefit

If HbA<sub>1c</sub> above target

DPP-4i

GLP-1 RA

SGLT2i if eGFR adequate

TZD

# Recommendations for glucose-lowering treatment for patients with diabetes

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>SGLT2 inhibitors</b>		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk, <sup>c</sup> to reduce CV events. <sup>306,308,309,311</sup>	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death. <sup>306</sup>	I	B
<b>GLP1-RAs</b>		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk, <sup>c</sup> to reduce CV events. <sup>176,299–300,302–303</sup>	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk, <sup>c</sup> to reduce the risk of death. <sup>176</sup>	I	B
<b>Biguanides</b>		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk. <sup>146,149</sup>	IIa	C
<b>Insulin</b>		
Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/L or >180 mg/dL), with the target adapted according to comorbidities. <sup>260–262</sup>	IIa	C
<b>Thiazolidinediones</b>		
Thiazolidinediones are not recommended in patients with HF.	III	A
<b>DPP4 inhibitors</b>		
Saxagliptin is not recommended in patients with T2DM and a high risk of HF. <sup>291</sup>	III	B



# Conclusions

- Diabetes is increasing globally with dramatic increases in Asia
- DM increases the risk of HF and vice versa
- When DM and HF are present together, patients:
  - Feels worse
  - End up in hospital more
  - Die earlier
- We should screen for DM in all HF patients
- We should screen for HF in select diabetic patients:  
*Increasing Age; symptoms; IHD; BMI; displaced apex beat*
- **Treatment**
  - *SGLT2/Metformin*
  - *GLP1*
  - *Avoid – TZDs and Saxagliptin*

# Thank you



# Overview of heart failure therapies and case studies

**Dr. Reginald Liew**

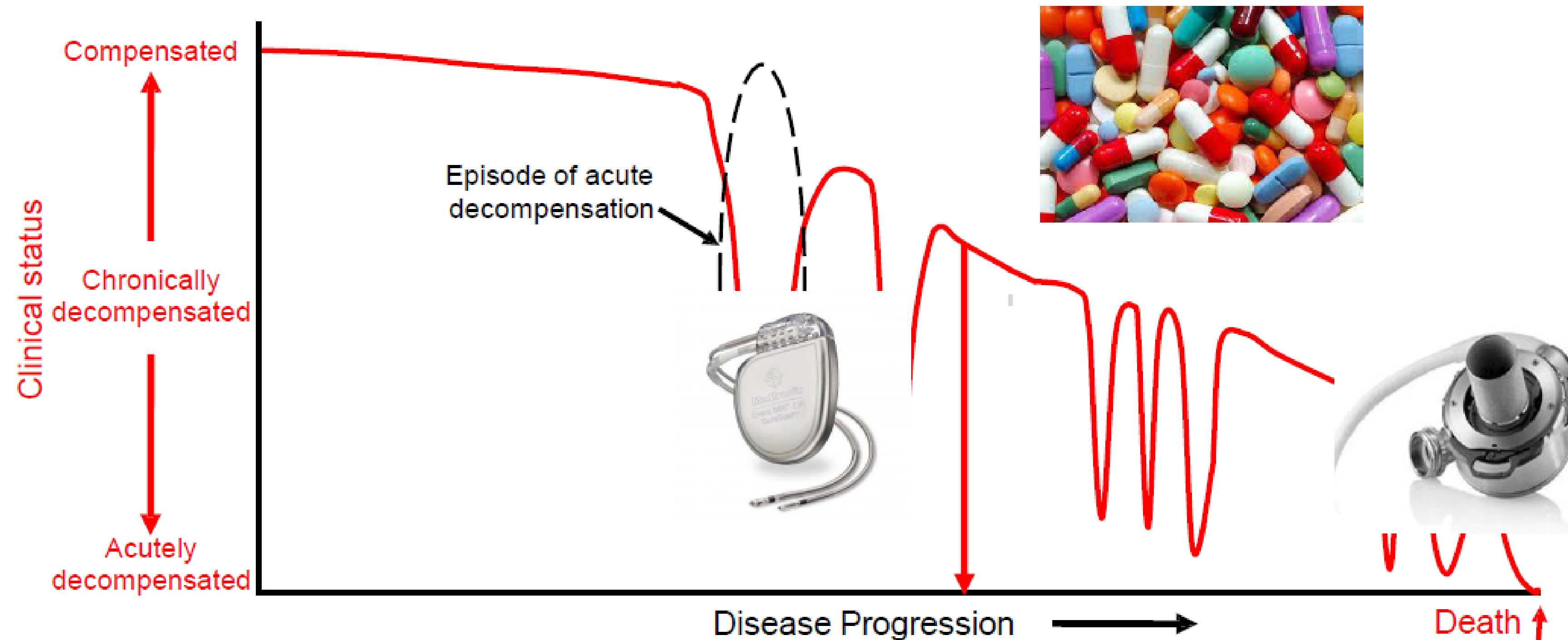
*MA (Camb), MBBS (Hons), PhD (Lond), FRCP (UK),*

*FESC, FACC, FAsCC, FAMS*

**Senior Consultant Cardiologist**

# Heart failure is a progressive disease whereby cardiac structure and function continue to deteriorate

- Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality<sup>1-7</sup>

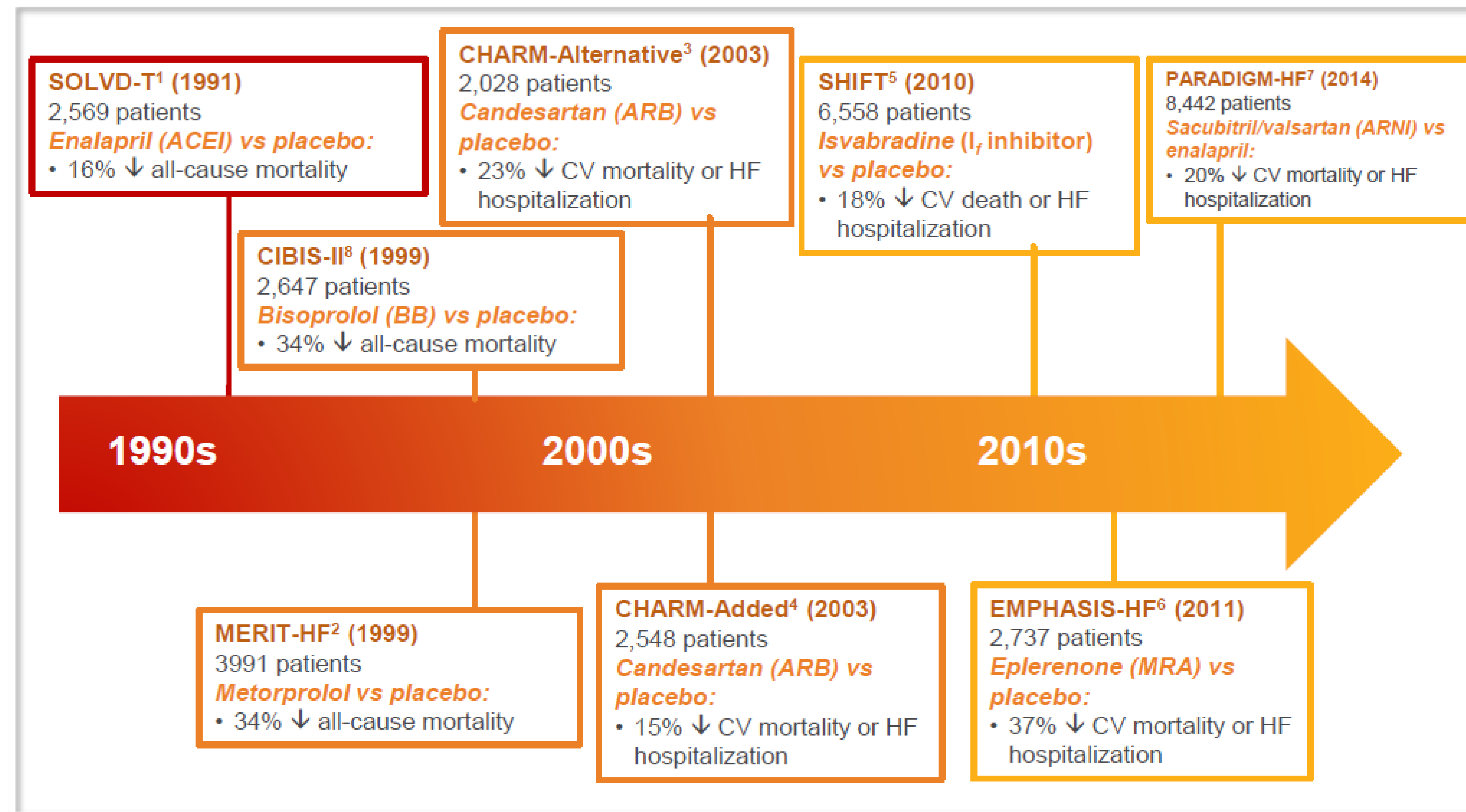


Adapted from Gheorghiade et al. 2005<sup>2</sup>





# Landmark trials in patients with HFrEF



# **2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure**

**The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)**

**Developed with the special contribution of the Heart Failure Association (HFA) of the ESC**

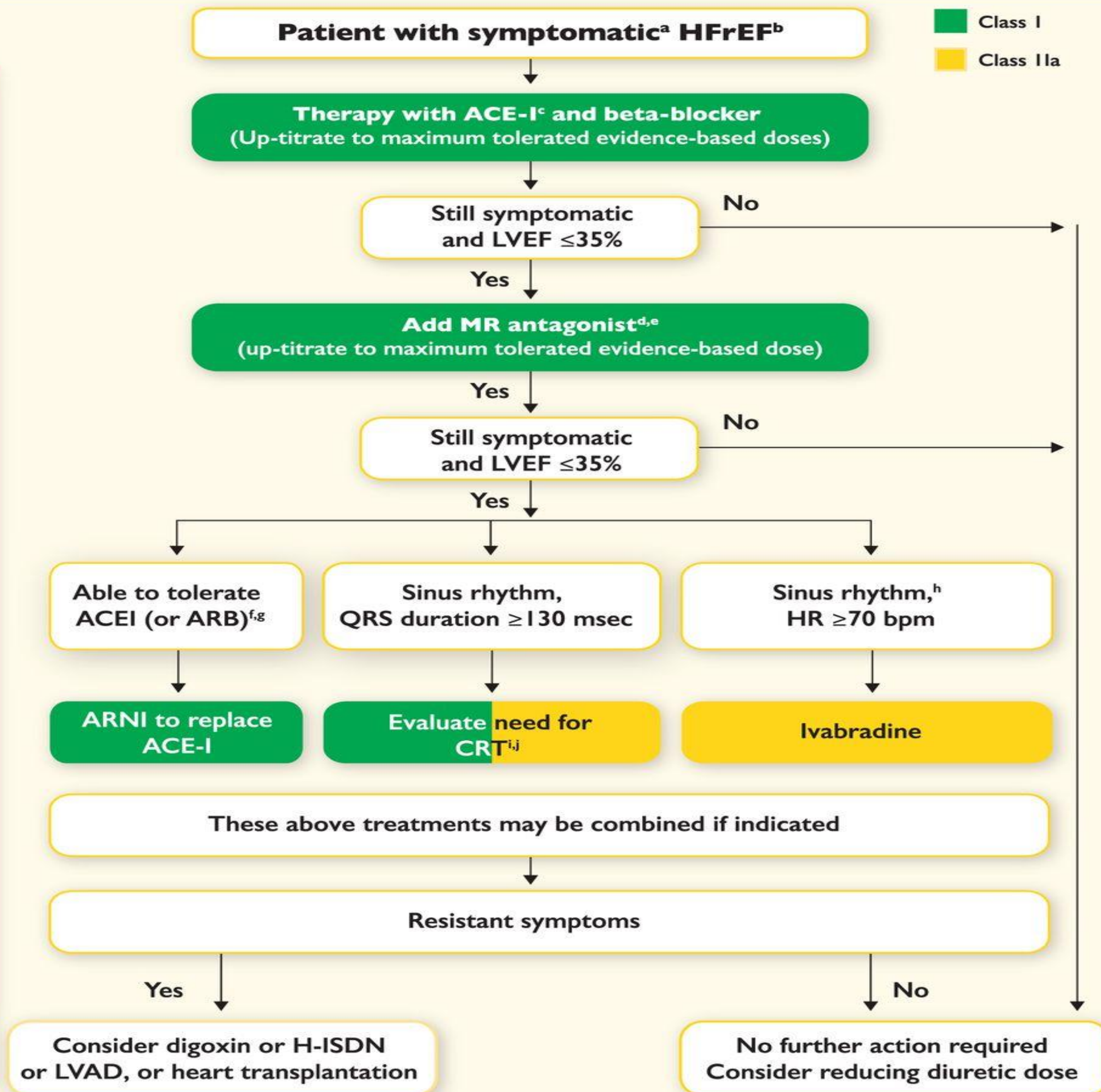
## **2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure**

**A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America**



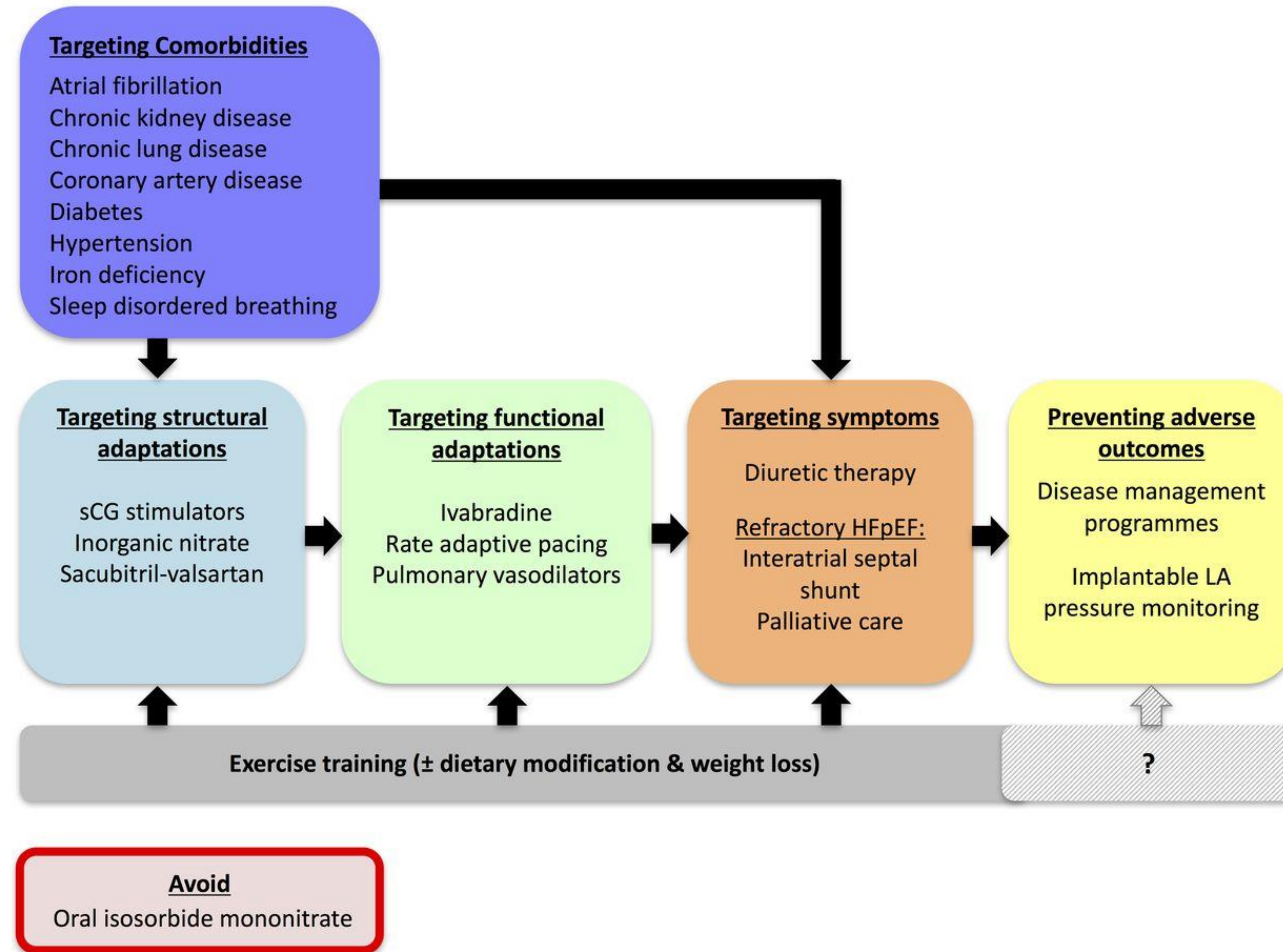
Diuretics to relieve symptoms and signs of congestion

If LVEF  $\leq 35\%$  despite OMT  
or a history of symptomatic VT/VF, implant ICD





# HFpEF treatment strategies

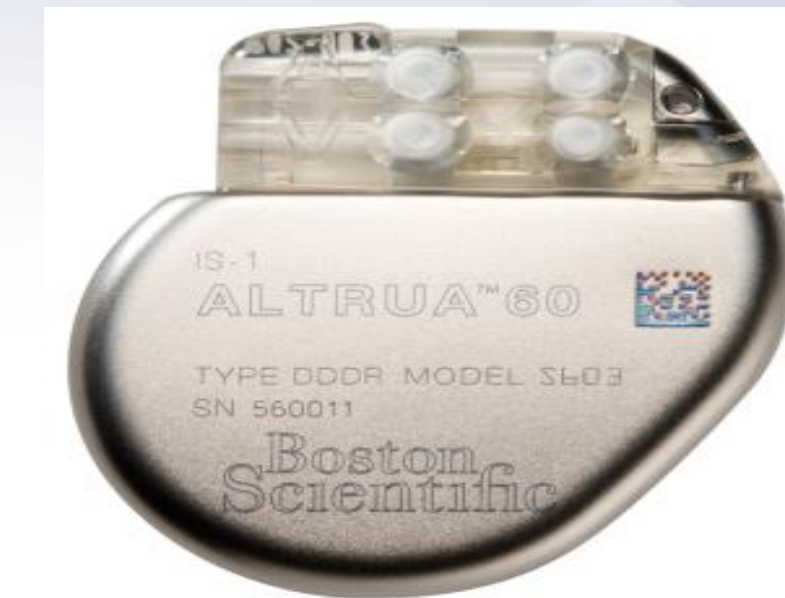




# Use of implantable devices in heart failure

## Permanent pacemakers

- Bradycardia 2ry to SN disease, conducting tissue disease, drugs
- AF with pauses
- AVN ablation + PPM



## Implantable cardioverter defibrillators (ICDs)

- 1ry prevention
- 2ry prevention
- No benefit on HF symptoms (shocks may be detrimental)



## Cardiac resynchronization therapy (CRT)

- Resynchronization therapy
- May improve HF symptoms and survival
- Currently indicated for pts with NYHA class III-IV symptoms with wide QRS complex
- May be combined with ICD (CRT-D)



## **Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology.**

Specific new recommendations have been made based on the evidence from major trials published since 2016, including SGLT2 inhibitors in type 2 diabetes mellitus; MitraClip for functional mitral regurgitation; atrial fibrillation ablation in HF; tafamidis in cardiac transthyretin amyloidosis; rivaroxaban in HF; ICD's in non-ischaemic HF; and telemedicine for HF. In addition, new trial evidence from smaller trials and updated meta-analyses have given us the chance to provide refined recommendations in selected other areas.



# Dapagliflozin reduces death and hospitalisation in patients with heart failure

**DAPA-HF trial presented in a Hot Line Session today at ESC Congress 2019 together with WCC**

01 Sep 2019

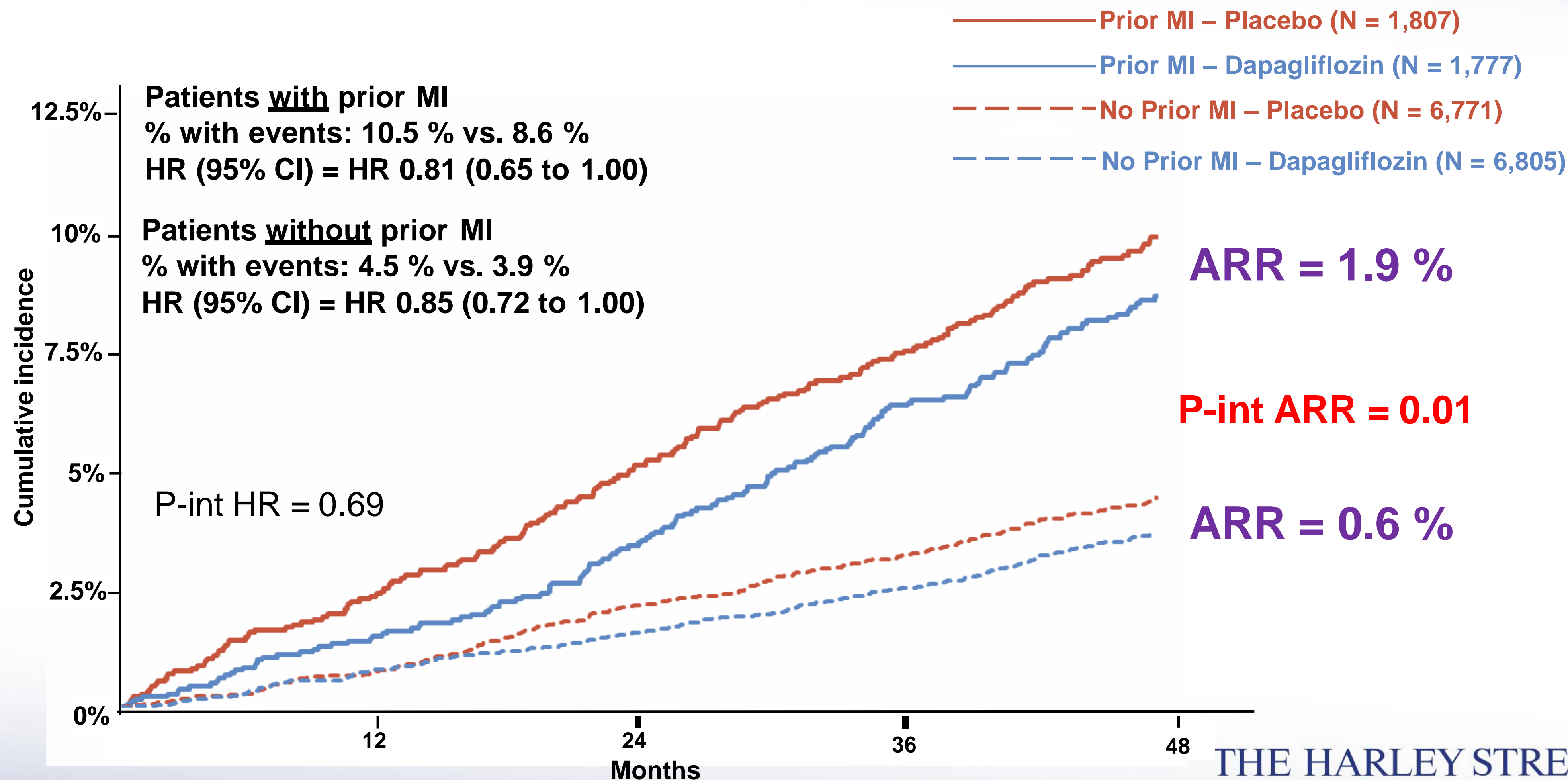
**Topic(s):** *Diabetes and the Heart; Heart Failure;*

**Paris, France – 1 Sept 2019:** Dapagliflozin reduces death and hospitalisation in patients with heart failure and reduced ejection fraction with and without diabetes. The late breaking results of the DAPA-HF trial are presented in a Hot Line Session today at ESC Congress 2019 together with the World Congress of Cardiology(1).

Principal investigator Professor John McMurray of the University of Glasgow, UK said: "The most important finding of all is the benefit in patients without diabetes. This is truly a treatment for heart failure and not just a drug for diabetes."

# CV outcomes with dapagliflozin

## CVD or HF hospitalization





# DECLARE results are key to the updated ACC/AHA CV Disease Primary Prevention Guideline in T2D in 2019

## ACC/AHA Guideline on Primary Prevention of CV Disease

***“Three RCTs have shown a significant reduction in ASCVD events and HF with the use of an SGLT2 inhibitor. Although most patients studied had established ASCVD at baseline, the reduction in heart failure has been shown to extend to primary prevention populations.”***

- Recommendations are expanding from secondary prevention to primary prevention
- HF prevention benefit is acknowledged in primary prevention population, citing DECLARE data to support this statement
- SGLT2 inhibitors and GLP-1 receptor agonists may be initiated in patients with T2D and additional ASCVD risk factors requiring glucose-lowering therapy despite initial metformin therapy

# ABCs of heart failure drugs

**A**- ACEIn/ ARB/ ARNI

**B**- Beta- blockers

**C**- Cholesterol meds (for CAD)

**D**- Digoxin/ Diuretics/ Dilators (Hydralazine/ Nitrates)

**E**- Eplerenone (MRA)/ Spironolactone

**F**- If funny channel blocker (ivabradine/ coralan)

**G**- SGLT2 inhibitors (recent evidence with dapagliflozin)



# Case 1

- 52 year old Chinese man presented to GP with cough and mild breathlessness for two weeks
- History of type II diabetes, smoker (2 packs a day)
- Works in construction industry- usually fit and active
- Medication- metformin, plavix
- Examination – BMI 26.3, HR 72 regular; BP 130/80mmHg
  - Heart sounds normal; JVP not elevated, lungs clear, no pitting oedema

• How would you manage this patient?

# Case 1- initial assessment

- **Differential diagnoses for cause of symptoms:**

- Chest infection
- COPD/ asthma
- Coronary artery disease
- Heart failure

- **Investigations-**

- Useful initial tests that can be done in primary care:
  - Bloods- FBC, renal and thyroid function, NT-proBNP
  - Chest X-ray/ spirometry
- More specialised tests: Echo, stress test, CT coronary angiogram or diagnostic angiogram



# Case 1- results and diagnosis

## Initial tests (done in primary care):

- FBC –normal Hb, increased WCC; renal and thyroid function normal
- Fasting glucose 7.3mmol/L, HbA1c 6.8%
- Chest Xray- mild venous congestion; old areas of lung fibrosis

•**NT proBNP 850ng/L**

## Specialised tests:

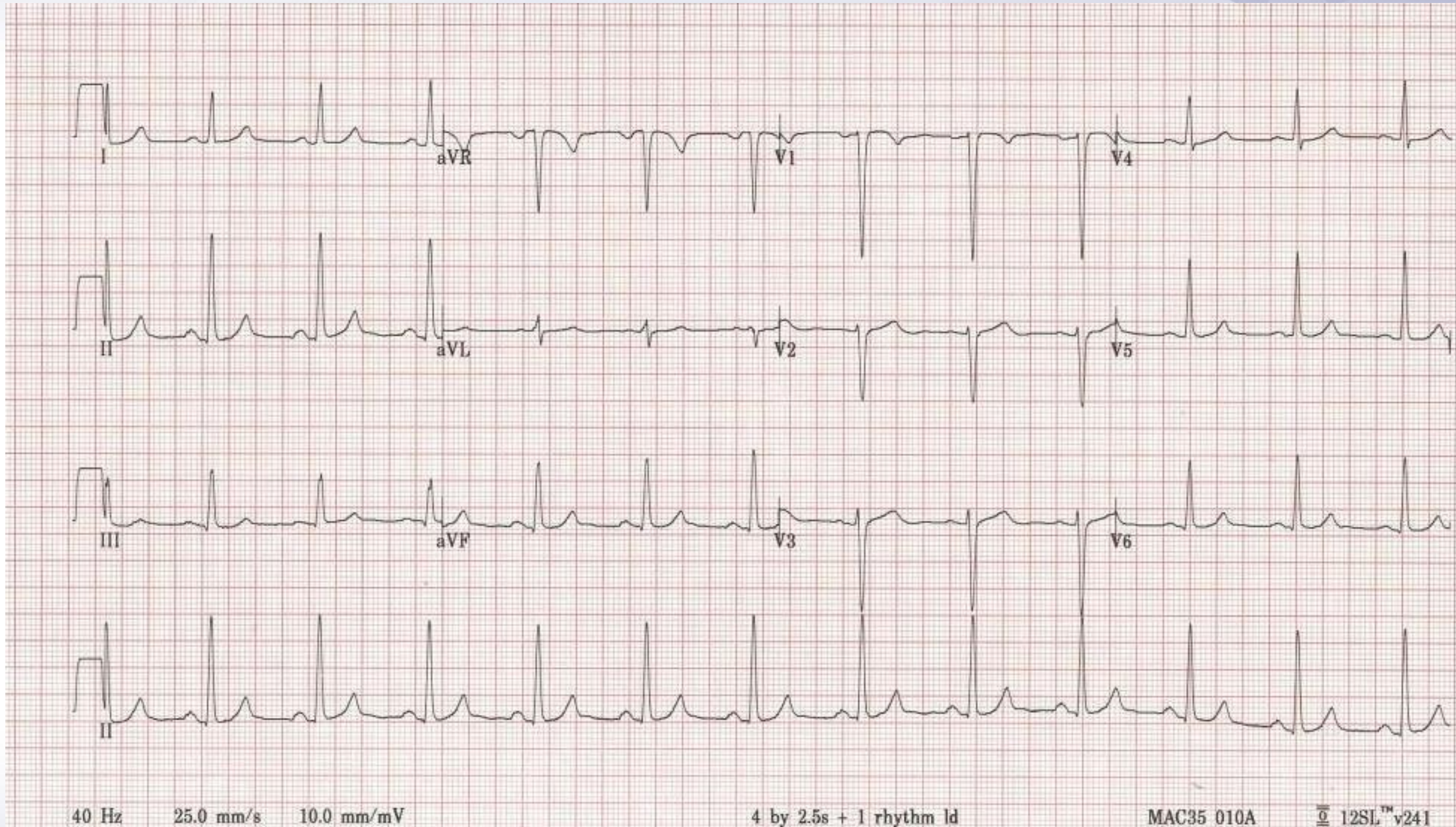
- Echo- Severely impaired cardiac function (LVEF 30-35%), diastolic dysfunction, mild MR, normal PASP, anterior hypokinesia
- Diagnostic coronary angiogram- mild coronary artery disease; no significant stenoses
- CT lung- patchy ground glass densities in both lower lobes; likely pneumonitis

## Diagnoses:

Chest infection ; HFrEF secondary to dilated cardiomyopathy



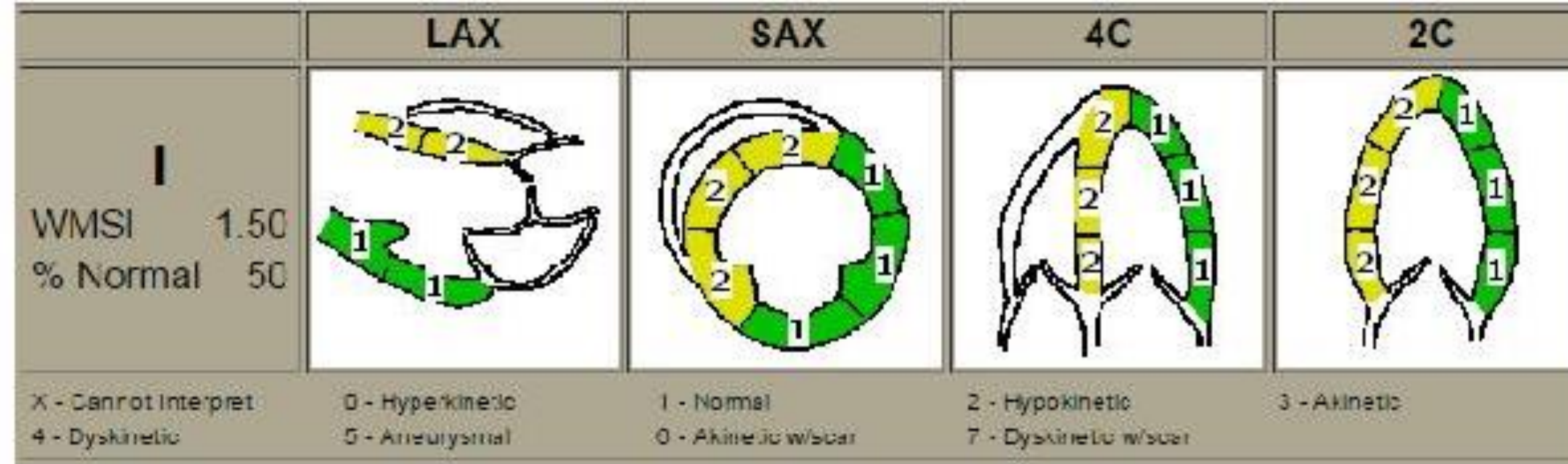
# Case 1 - ECG





# Case 1- initial echo

- Normal LV size with severely impaired systolic function (LVEF 30-35%); + RWMA
- LVIDD 5.7cm
- Dilated LA size
- Trivial MR and TR; PASP 21 + 5mmHg



# Case 1- management

- Given course of antibiotics
- Started oral heart failure medication as outpatient as clinically stable:
  - Lasix, concor, entresto
  - Dapagliflozin added to Metformin
  - Heart failure medication slowly uptitrated over next 2-3 months
- Review 4 months later:
  - Patient well with no further SOB; able to do usual activities
  - Echo showed markedly improved LVEF to 50-55%
  - LA normal size
  - NT proBNP 158

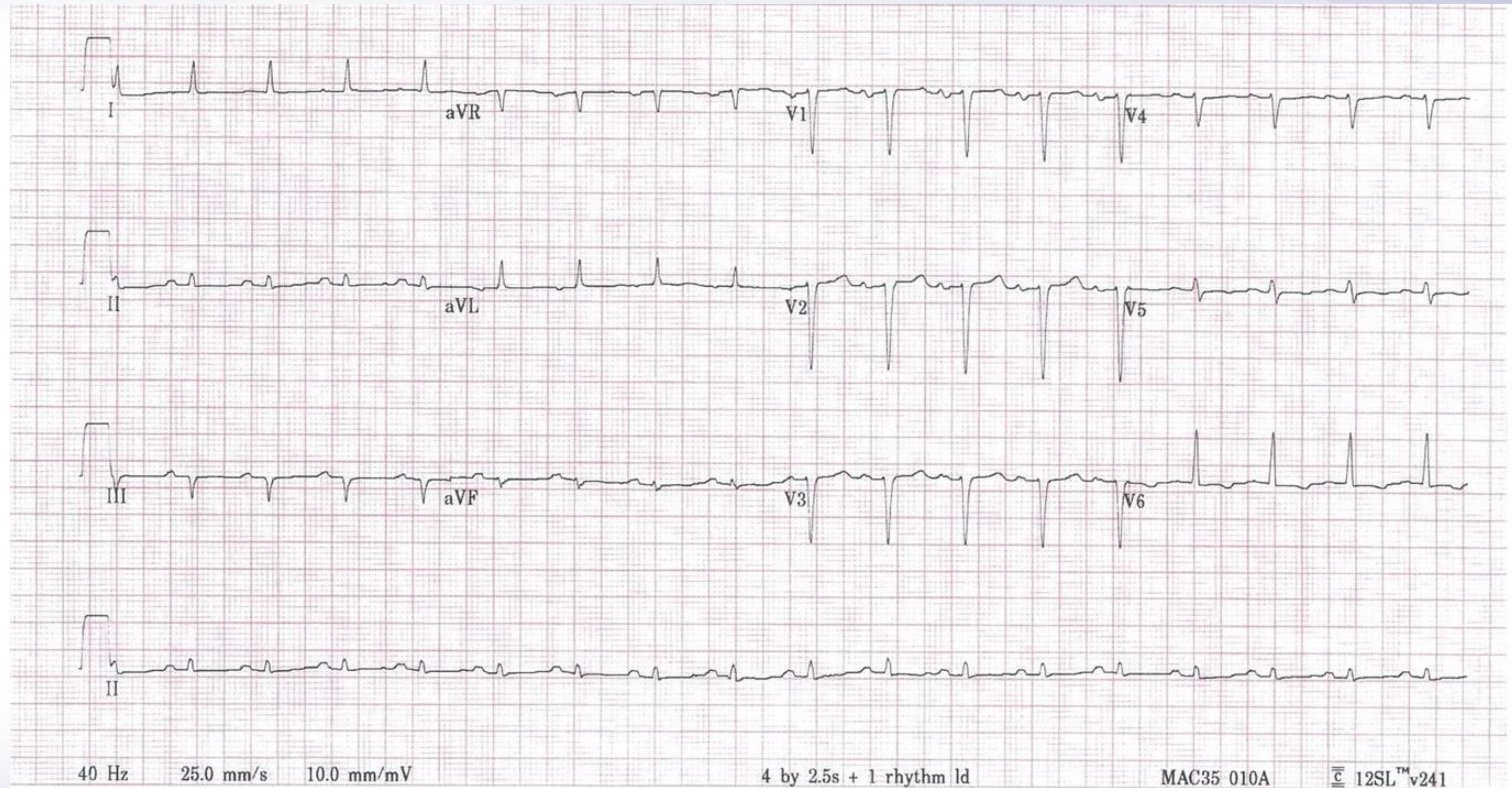


# Case 2

- 49 year old Australian woman presented to her GP with 6 week history of tiredness, shortness of breath, cough and reduced appetite
  - Treated with 2 courses of antibiotics (azithromycin and doxycycline) with no improvement
  - Father died of a cardiomyopathy in his 70s and mother underwent CABG surgery
  - Usually fit and active, travels regularly
- How would you manage this patient?



# Case 2 - ECG





## Case 2

- Chest X-ray (requested by GP): showed an enlarged heart and signs of cardiac decompensation
- Examination:
  - BP 100/60mmHg
  - Heart rate 105bpm
  - Heart sounds – normal first and second sounds, gallop rhythm
  - Lung fields clear, no ankle oedema

# Case 2- blood tests

- FBC, renal function, thyroid function –normal
- Increased liver function tests (ALT 227, AST 80, GGT 158)





**NT-proBNP : 7022ng/L**

NT-proBNP Reference	
Range	: 0 – 125 ng/L
<b>Age Dependent</b>	
125 ng/L under 75 years	
450 ng/L 75 years + over	



# Case 2- initial echo

- Moderately dilated LV size with severely impaired systolic function (LVEF 20%); mildly impaired RV function
- Mild to moderately dilated LA
- Moderate MR and mild TR; PASP 47mmHg

	LAX	SAX	4C	2C
<b>I</b> WMSI 2.00 % Normal 0				
X - Cannot Interpret 4 - Dyskinetic	0 - Hyperkinetic 5 - Aneurysmal	1 - Normal 8 - Akinetic w/scar	2 - Hypokinetic 7 - Dyskinetic w/scar	3 - Akinetic



# Case 2- management

- Admitted for diuresis and to start heart failure medication:  
Lasix, concor, digoxin, coralan aldactone, entresto (started later as BP improved)
- Diagnostic coronary angiogram- normal coronaries
- Cardiac MRI scan- severe LV systolic dysfunction (LVEF 19.8%) with global hypokinesia, no evidence of myocardial scar or intracardiac thrombus; moderate MR
- Good diuresis after 3 days of iv lasix and oral medication
- ICD inserted prior to discharge

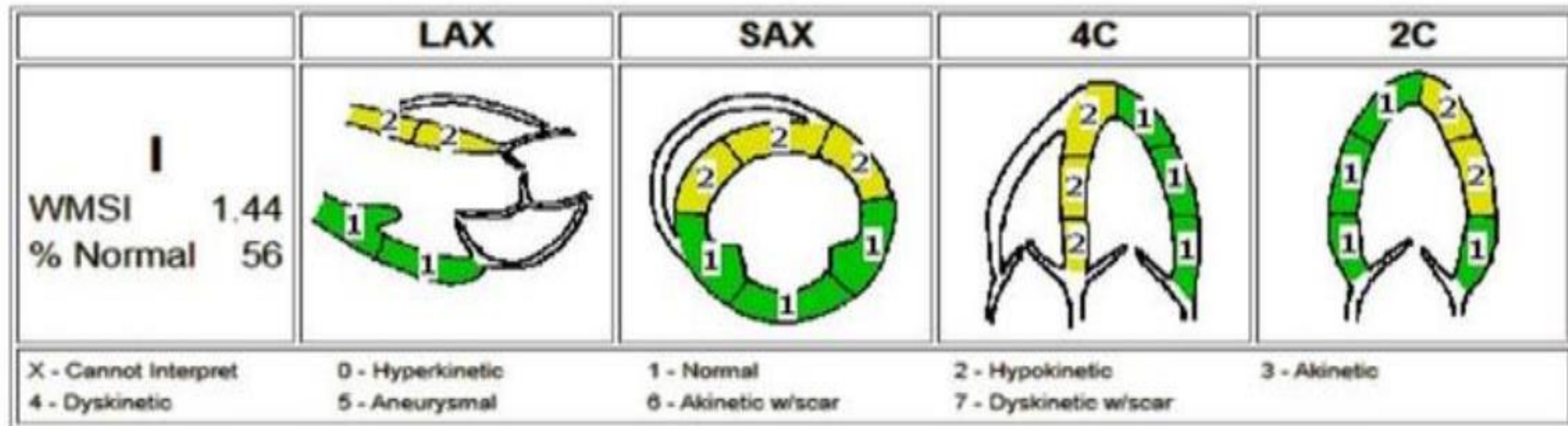


# Case 2- progress

- Marked symptomatic improvement over next few months- able to do regular exercise 3 times a week
- Not SOB or tired
- Weight decreased, appetite improved
- Last reviewed in clinic 2 weeks ago- BP 115/60mmHg, HR 56bpm
- Patient felt very well- no cardiac symptoms (NYHA class 0), travelling and back to normal exercise/ activity
- LFTs back to normal
- NT pro BNP 233 pg/mL

# Case 2- latest echo (Sept 2019)

- Normal LV size with mildly impaired systolic function (LVEF 46%); normal RV size and function
- Normal LA size
- Trivial MR and TR; PASP 21mmHg





# Case 3

- 78 year old woman presenting with palpitations, breathlessness, increasing weight and ankle swelling
- History of aortic valve replacement, hypertension, minor coronary artery disease and chronic AF
- Last echo 2 years ago showed normal ejection fraction
- Not usually very active at home
- Medication- concor, pradaxa, Lipitor, micardis, digoxin, nexium
- Examination – BMI 27.2, HR 90- 100bpm in AF; BP 140/80mmHg
- Soft systolic murmur lower left sternal edge; mild basal creps in lungs; mild pitting oedema in ankles
- ECG – AF; inferolateral T wave flattening
- How would you diagnose and manage this patient?

# Case 3- initial assessment

- **Differential diagnoses for cause of symptoms:**

- Worsening AF with poor rate control
- Ischaemic heart disease
- Valvular heart disease
- Heart failure
- Non-cardiac cause- e.g. anaemia, renal dysfunction, thyroid disease

- **Investigations-**

- Useful initial tests that can be done in primary care:
  - Bloods- FBC, renal and thyroid function, NT-proBNP
  - Chest X-ray
- More specialised cardiac tests (done by cardiologist):
  - Echo, Holter monitor, CT coronary angiogram



# Case 3- results and diagnosis

## Tests done in primary care:

- FBC, renal and thyroid function normal
- Mild renal impairment
- Chest Xray- prominent venous congestion, mild cardiomegaly, mild bilateral pleural effusions

## Cardiac tests:

- Echo- preserved LV function (EF 50-55%), bioprosthetic AV functioning well, mild MR, biatrial dilatation, evidence of diastolic dysfunction
- 24 hour Holter- AF throughout- heart rate range 58- 140bpm (average 94bpm)
- CT coron- mild coronary artery disease; no significant stenoses

## Diagnoses:

1. HFPEF
2. AF with poorly controlled ventricular rate

NT-proBNP : **1365** ng/L

NT-proBNP Reference	
Range	: 0 – 125 ng/L
<b>Age Dependent</b>	
125 ng/L under 75 years	
450 ng/L 75 years + over	

# Case 3- management

- Oral Lasix to reduce oedema (target optimal weight)
- Home weight chart
- Fluid and salt restrict
- Started spironolactone
- Improve AF rate control- AF nodal ablation with pacemaker if required



# Take home points in the management of heart failure patients in primary care

- Consider heart failure in patients at risk (hypertensives, diabetics, history of coronary artery disease) presenting with typical or atypical symptoms
- Arrange for diagnostic tests, e.g. blood tests (NT-proBNP), ECG, echocardiogram, chest X ray
- Identify precipitating causes or related co-morbidities (e.g. anaemia, diabetes, renal dysfunction, arrhythmias, CAD)
- Start appropriate pharmacotherapy (admit if unstable)
- Refer to cardiologist for further specialist assessment (especially for more advanced stages of heart failure)
- Monitor for progression of condition and need for escalation of medication or care

Co-management is key: patients may need initial specialist assessment; can be managed in 1ry care when stable

# Thank you



# Q & A