



# Impacts des nouvelles recommandations sur l'optimisation du traitement.

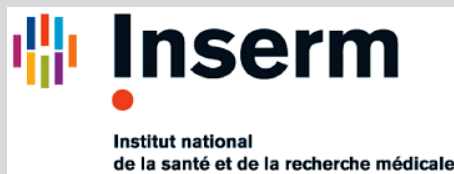
Pr Atul PATHAK

Clinique Pasteur

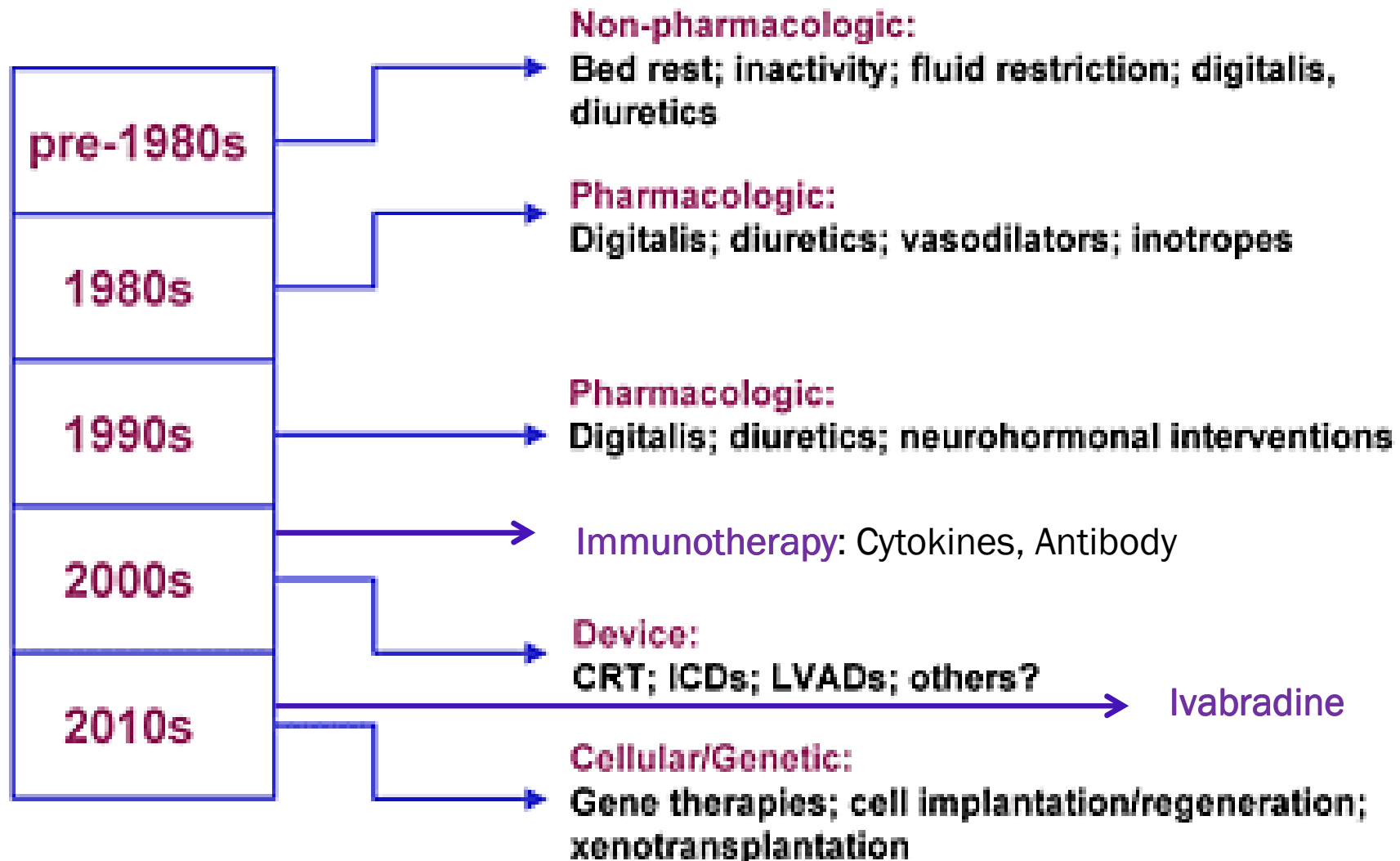
INSERM 1048

Biomedical Engineering Department de l'Ecole Polytechnique

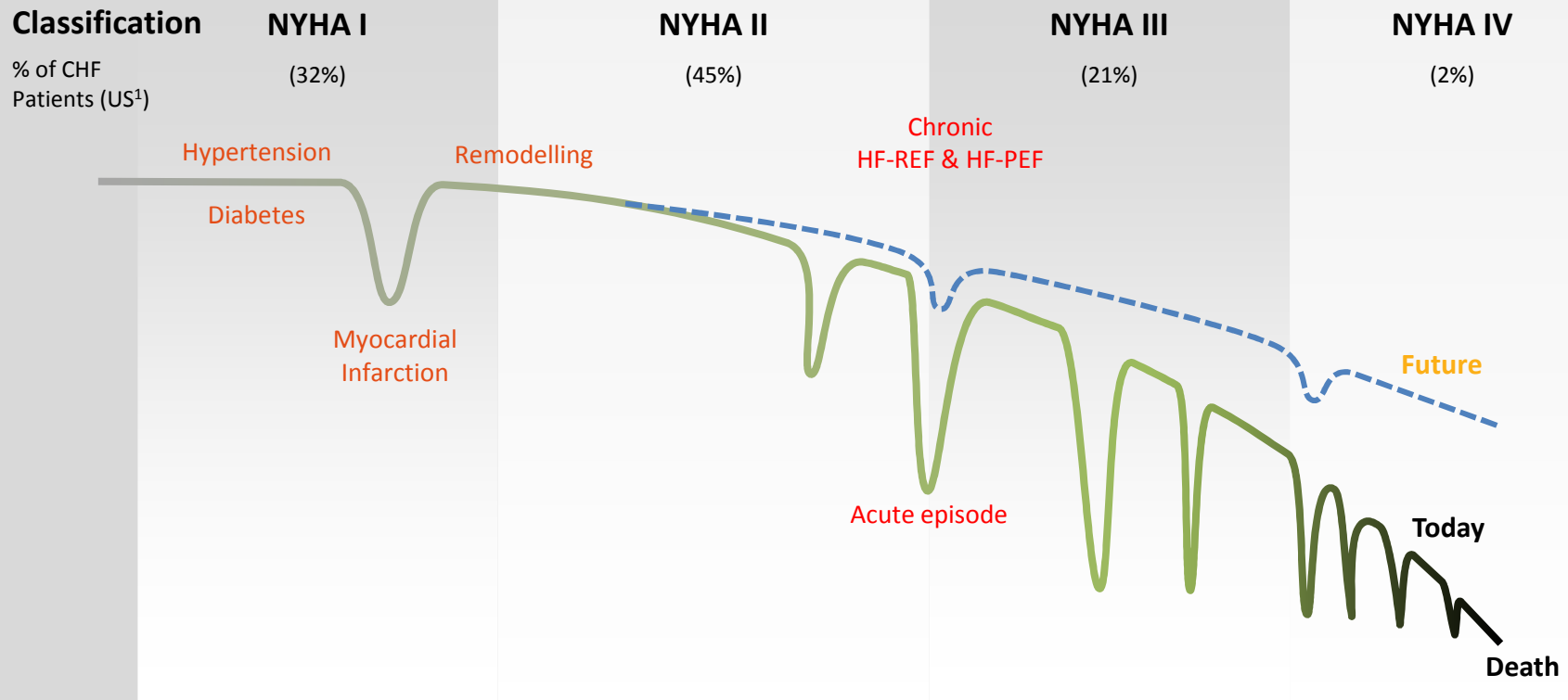
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# Heart Failure Therapy Timeline



# Natural history of our patient



# 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

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# Les grands changements

1. **A new term « HF with mid range ejection fraction » (HFmrEF).**
2. **A new algorithm for the diagnosis of HF.**
3. **Recommendations on prevention of HF.**
4. **Indications for the use of Sacubitril / Valsartan in HF with reduced ejection fraction (HFrEF).**
5. **Indications for cardiac resynchronisation therapy.**
6. **A new algorithm for the diagnosis and the management of acute HF.**
7. **A list of drugs contra-indicated in HFrEF.**

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7. A list of drugs contra-indicated in HFrEF.

# Nouvel algorithme pour le diagnostic de l'IC

- **Based on clinical probability of HF**
- **Based on the assessment of circulating natriuretic peptides, and on transthoracic echocardiography.**

# Diagnostic algorithm

**PATIENT WITH SUSPECTED HF<sup>a</sup>**  
(non-acute onset)



## **ASSESSMENT OF HF PROBABILITY**

### **1. Clinical history:**

- History of CAD (MI, revascularization)
- History of arterial hypertension
- Exposition to cardiotoxic drug / radiation
- Use of diuretics
- Orthopnoea / paroxysmal nocturnal dyspnoea

### **2. Physical examination:**

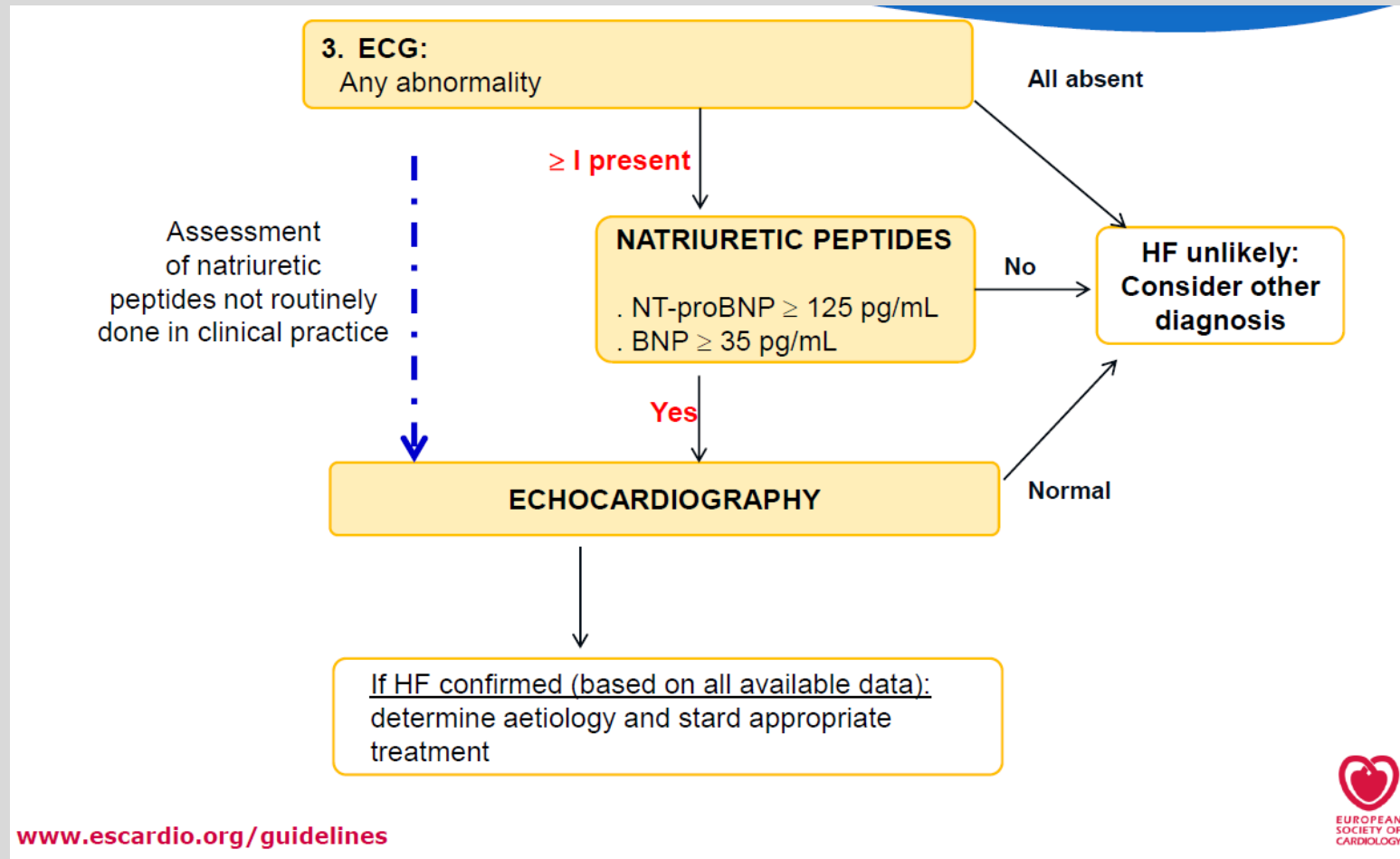
- Rales
- Bilateral ankle oedema
- Heart murmur
- Jugular venous dilatation
- Laterally displaced/broadened apical beat

### **3. ECG:**

- Any abnormality



# Algorithme Diagnostic



# Prevention de l'IC

- \* **Treatment of risk factors** (hypertension, diabetes, obesity, smoking cessation).
- \* Use of **statins** in patients with or at high risk of **coronary artery disease**.
- \* Use of **ACE-I** in patients with asymptomatic left ventricular dysfunction /stable CAD.
- \* **Use of beta-blockers** in those with asymptomatic left ventricular dysfunction and a history of myocardial infarction.

# Quels objectifs pour un traitement de l'IC

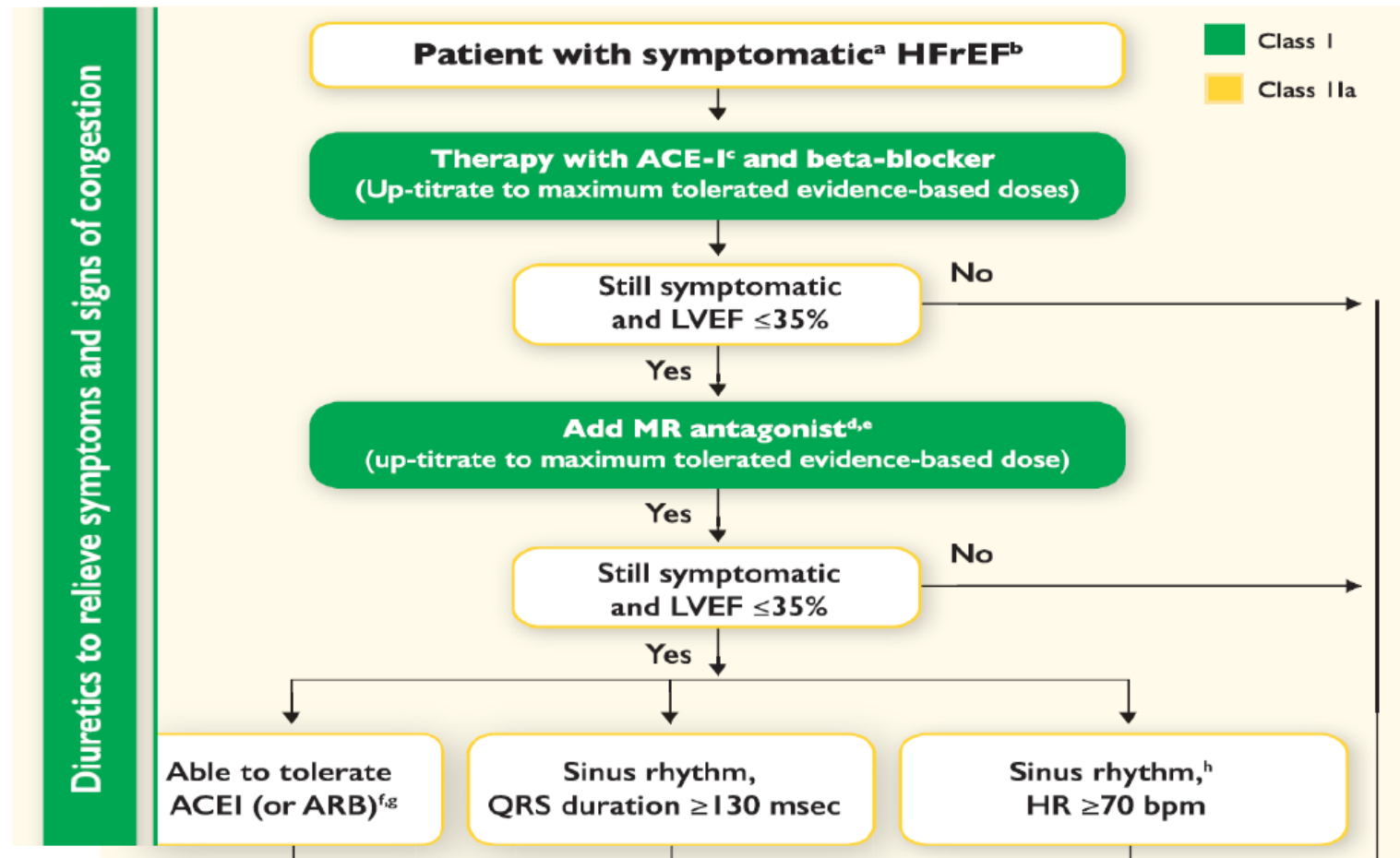
## ➤ Reduce mortality

## ➤ Improve

- clinical status
- functional capacity
- quality of life, prevent hospital admission

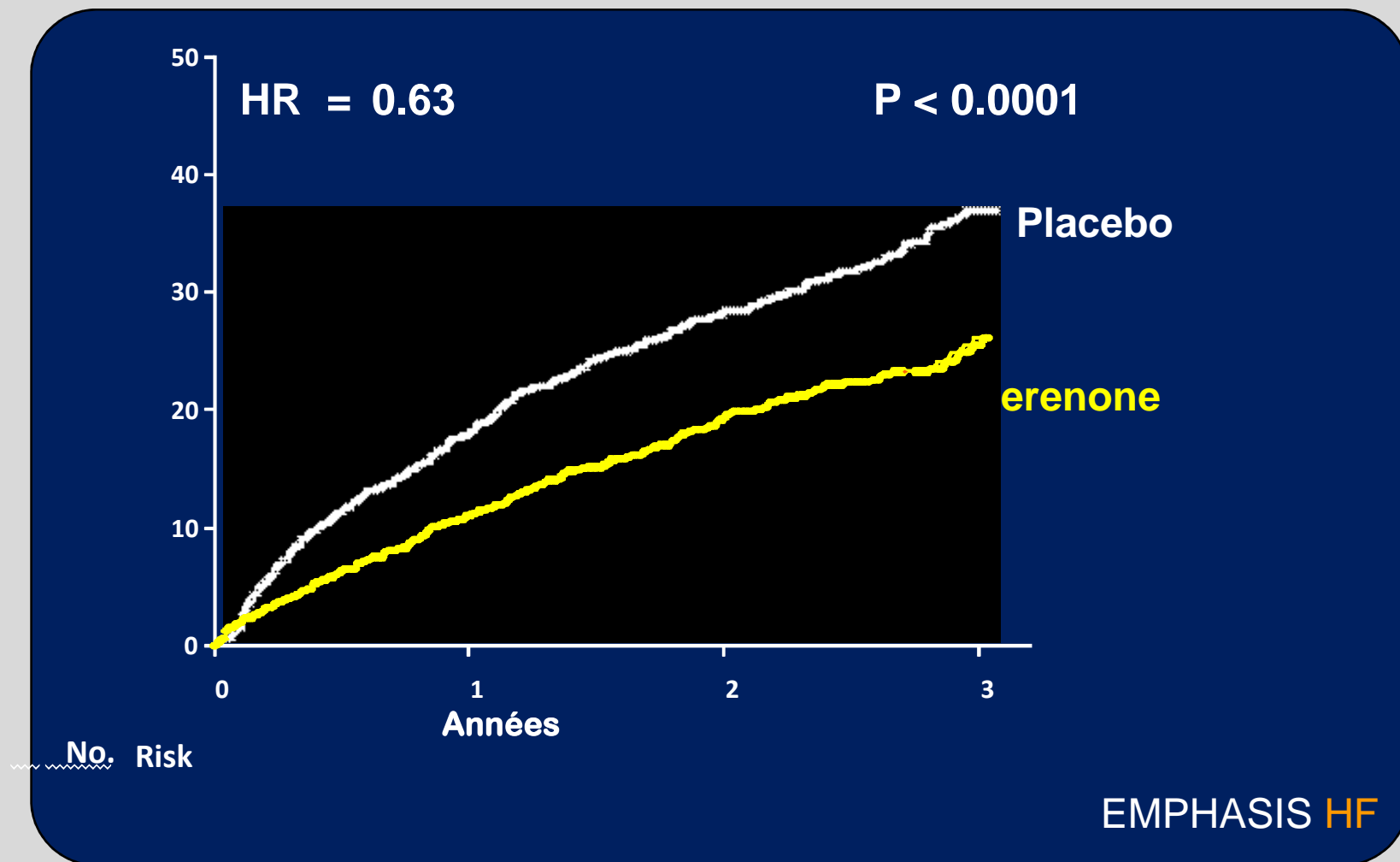
## ➤ Preventing HF hospitalizations and improving functional capacity.

# Prise en charge initiale



# Eplerenone

## CV mortality /HF hospitalisation



Diuretics to relieve symptoms and signs of congestion

Able to tolerate  
ACEI (or ARB)<sup>f,g</sup>

ARNI to replace  
ACE-I

Sinus rhythm,<sup>h</sup>  
HR  $\geq 70$  bpm

Ivabradine

These above treatments may be combined if indicated

Resistant symptoms

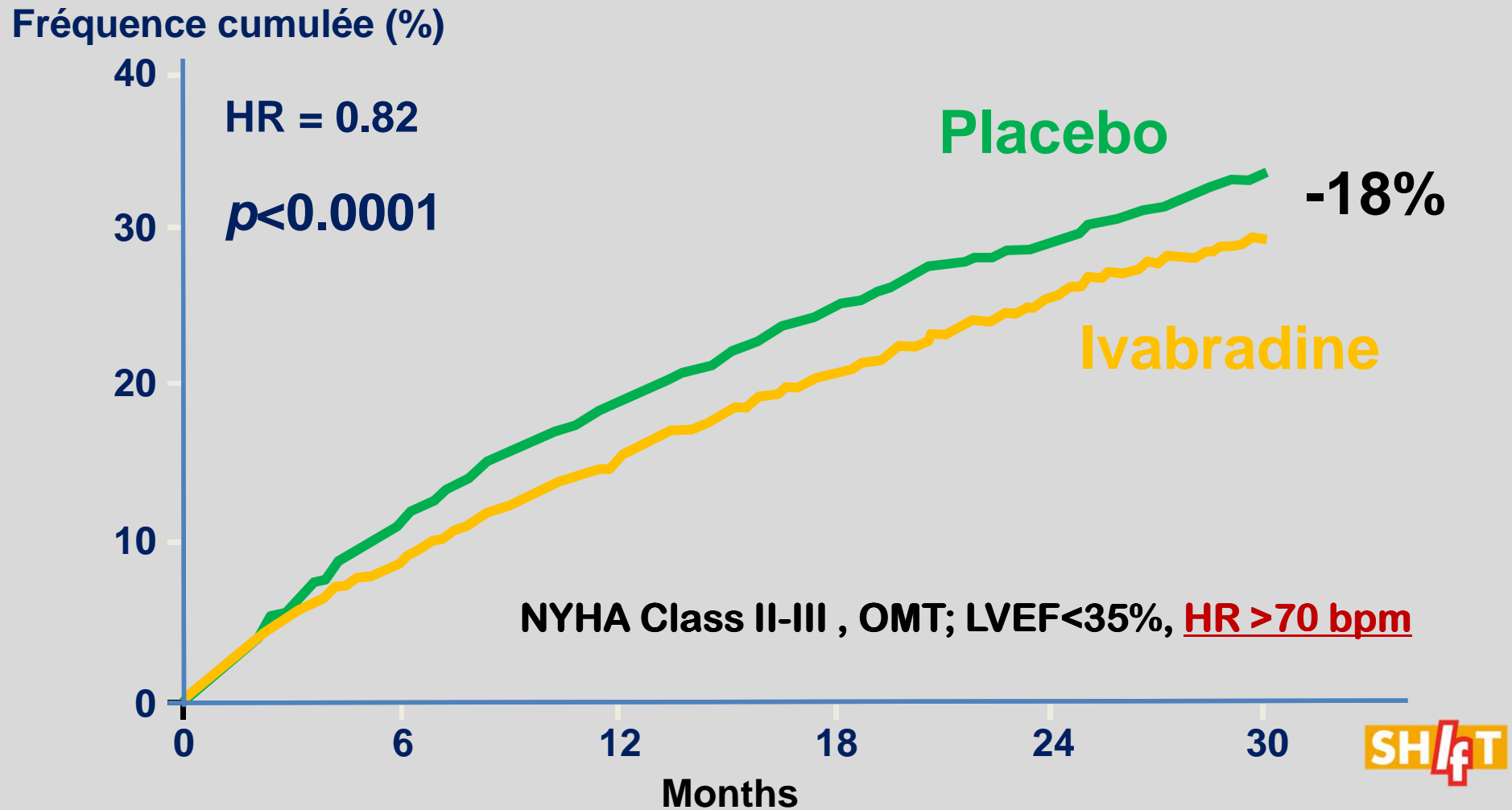
Yes

Consider digoxin or H-ISDN  
or LVAD, or heart transplantation

No

No further action required  
Consider reducing diuretic dose

# Ivabradine: Primary Outcome



➤ **Ivabradine is indicated in patients with:**

- symptomatic HFrEF and LVEF  $\leq 35\%$
- **in sinus rhythm and with a heart rate  $\geq 70$  bpm**
- who had been hospitalized for HF within the previous 12 months.

➤ **The European Medicines Agency (EMA)** approved ivabradine for use in Europe in patients with HFrEF with LVEF  $\leq 35\%$  and in sinus rhythm with a resting heart rate  $\geq 75$  bpm, because in this group ivabradine conferred a survival benefit.

➤ **Main side effects :bradycardia, blurred vision**



Diuretics to relieve symptoms and signs of congestion

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ACEI (or ARB)<sup>f,g</sup>

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# Physiopathologie de l'insuffisance cardiaque

Quête de modulateurs des systèmes capables d'être *diurétiques, vasodilatateurs, inhibant hypertrophie et fibrose.*

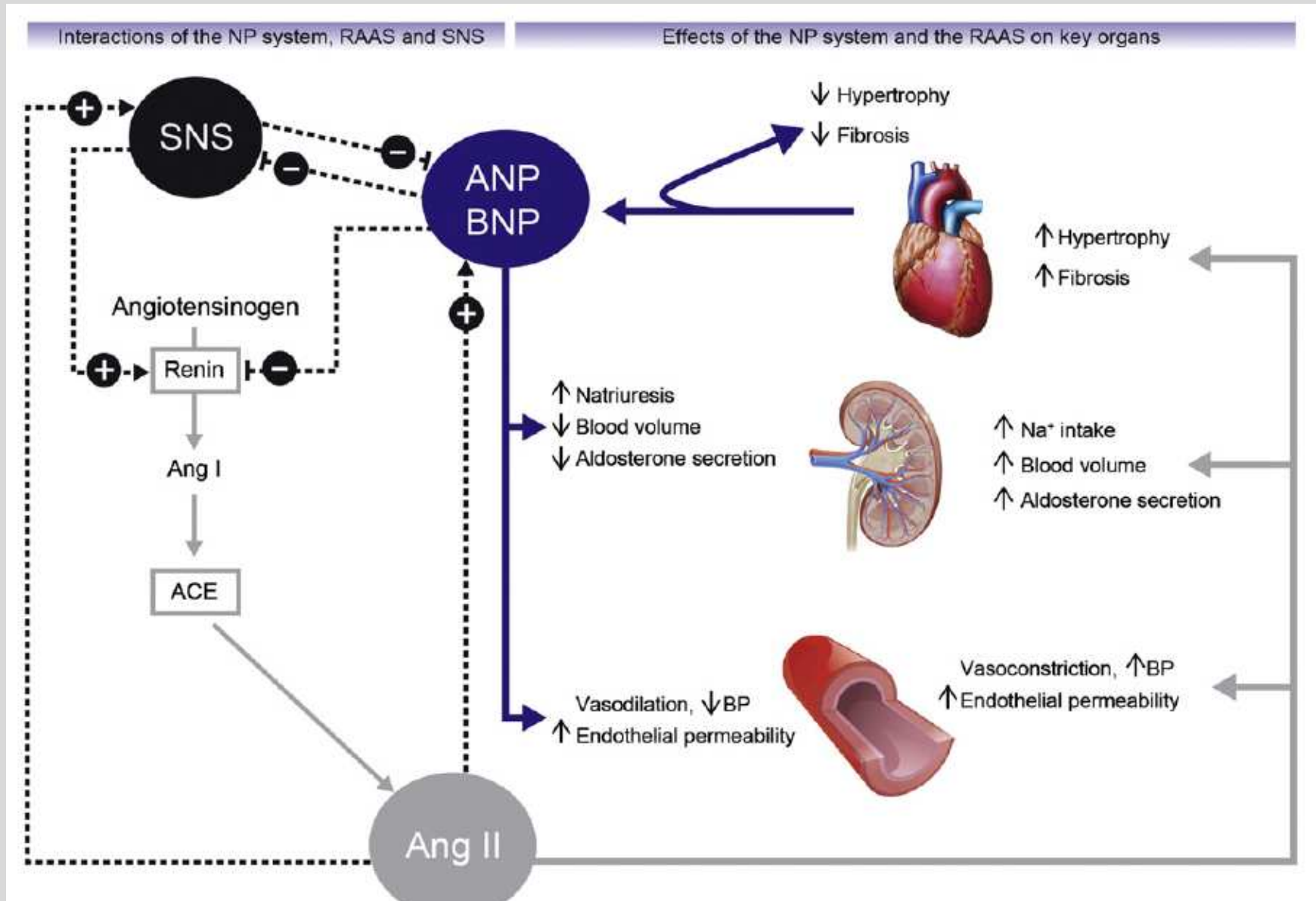
Stratégie complémentaire des approches inhibitrices

Injection de BNP (nesiritide)

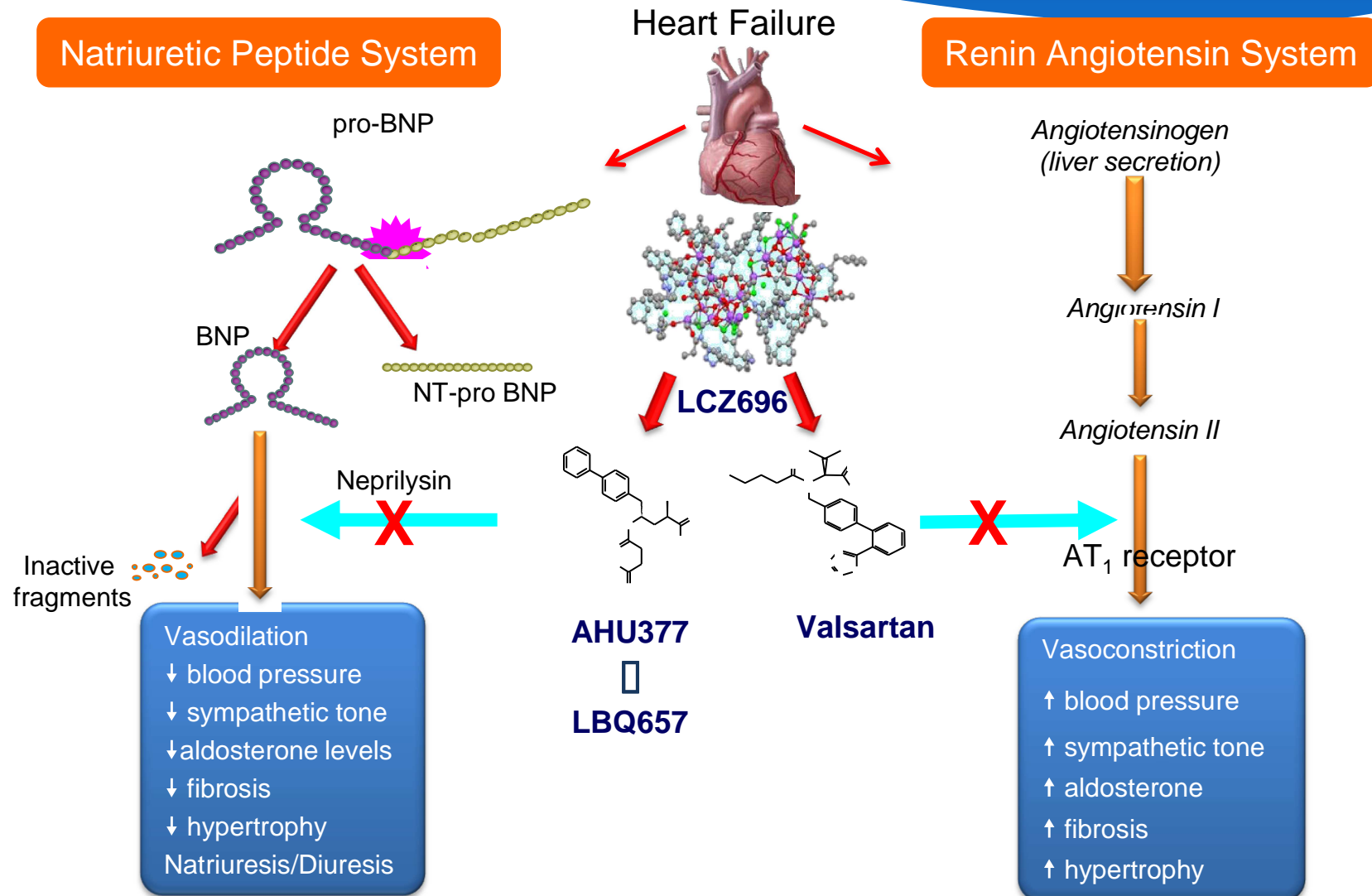
Injection sous cutanée d'ANP (Japon)

***Limites*** pharmacodynamiques ou pharmacocinetiques

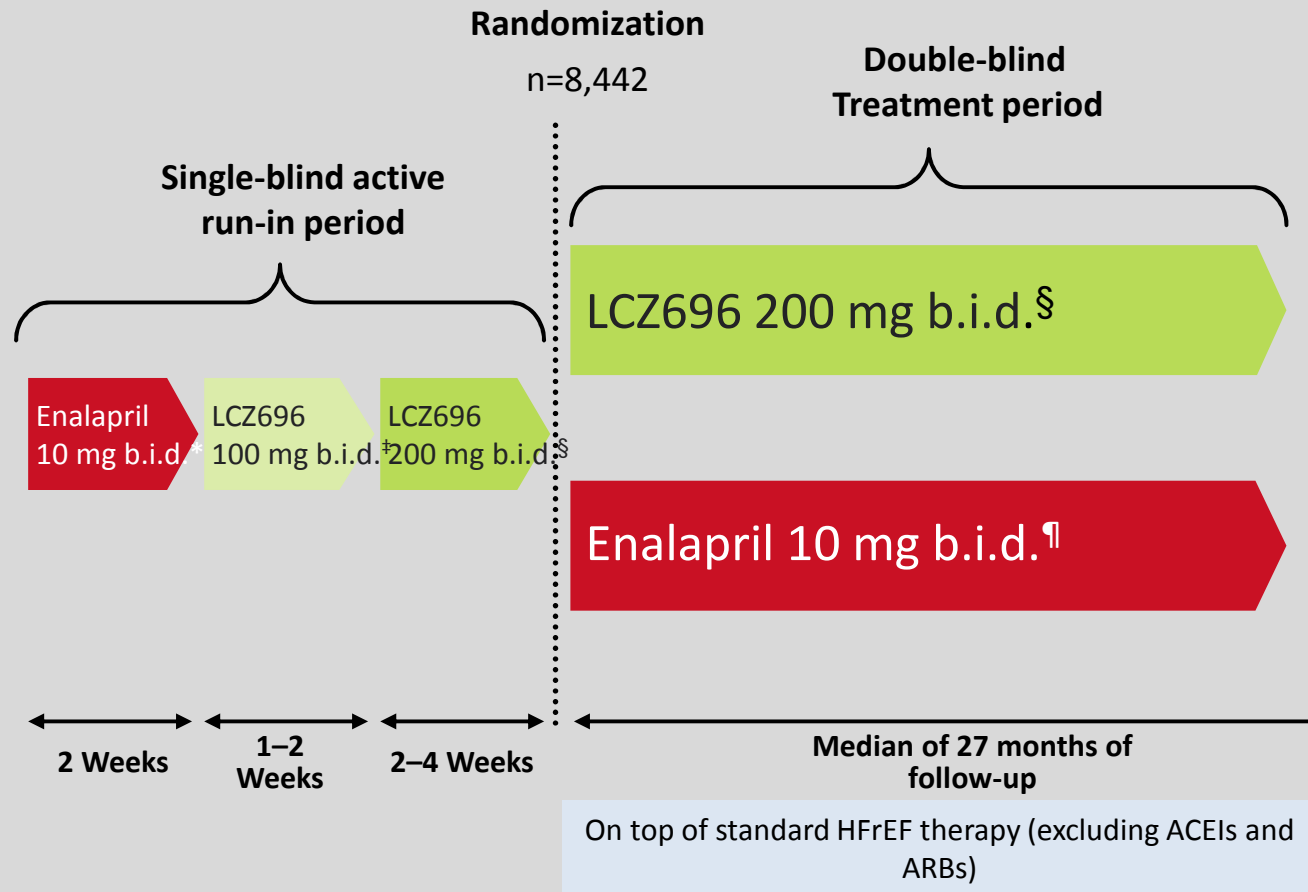
# Effets sur des organes et des systemes



# LCZ 696: Angiotensin Receptor Neprilysin Inhibitor



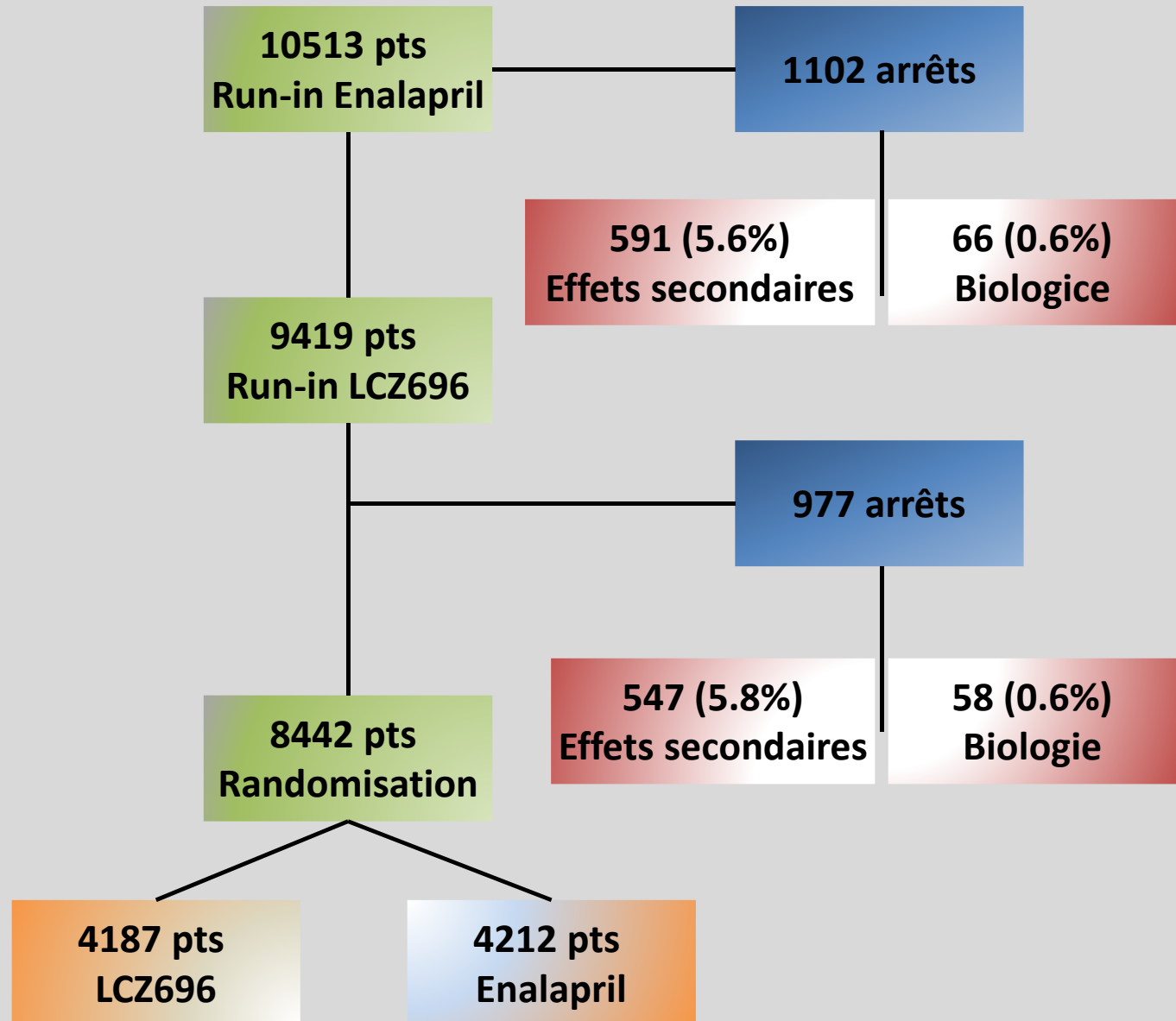
# PARADIGM-HF: Study design



\*Enalapril 5 mg b.i.d. (10 mg TDD) for 1-2 weeks followed by enalapril 10 mg b.i.d. (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEi; †200 mg TDD; ‡200 mg TDD; §20 mg b.i.d.=twice daily; TDD=total daily dose

McMurray et al. Eur J Heart Fail. 2013;15:1062-73;  
 McMurray et al. Eur J Heart Fail. 2014;16:817-25;  
 McMurray et al. N Engl J Med 2014;371:993-1004

# Patients

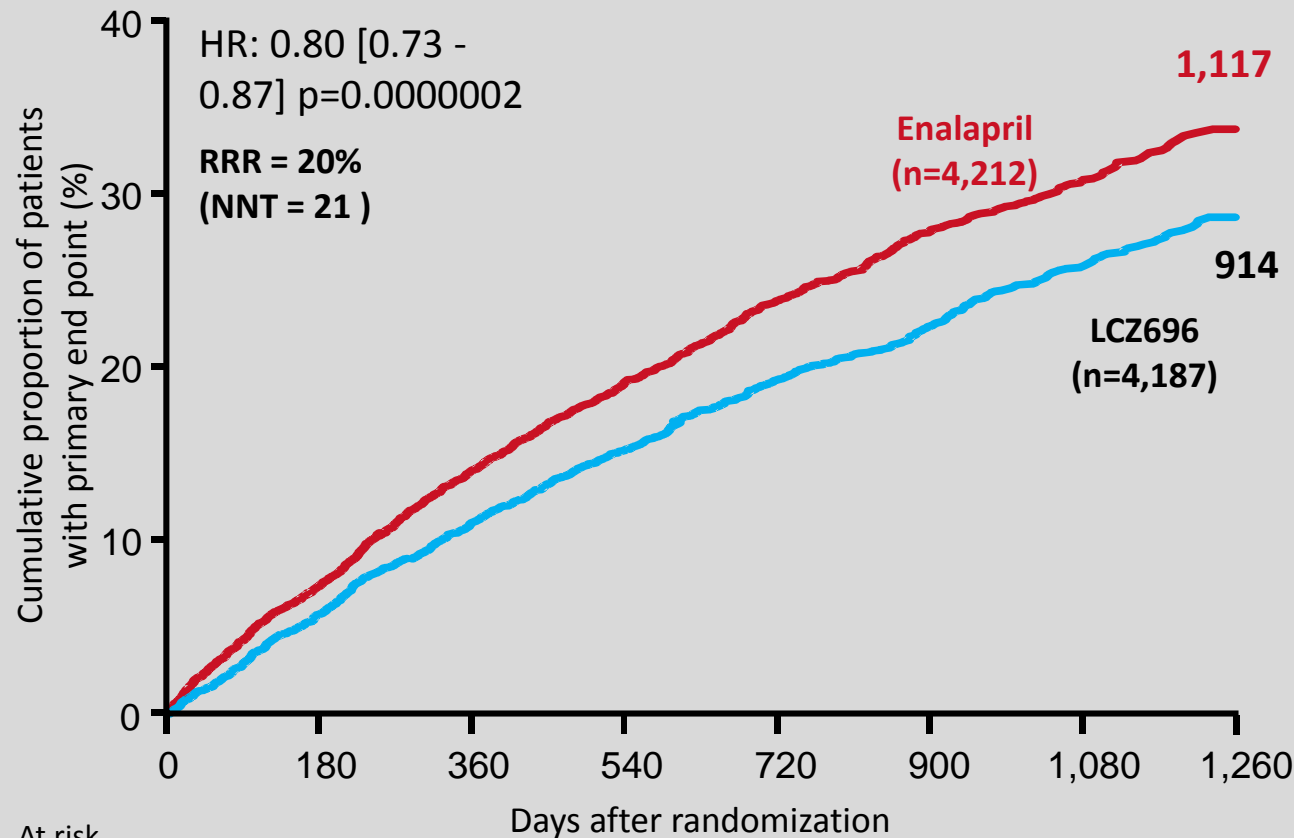


# Results

Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	-2.99±0.36	-4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

- Number of patient to treat during 27 months
  - To prevent one primary event is 21
  - To prevent one cardio-vascular death is 32

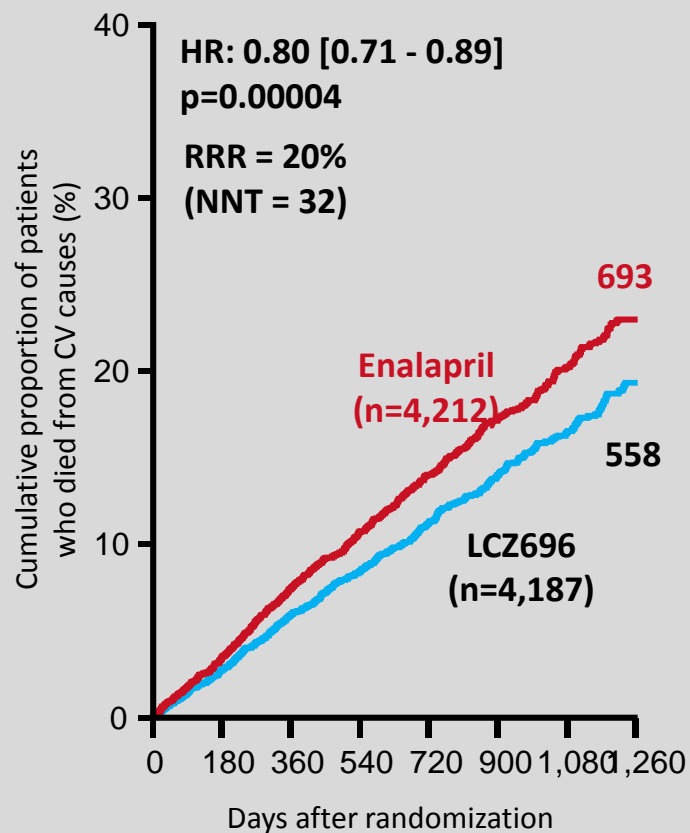
# Primary Outcome: Cardiovascular death or HF hospitalisation



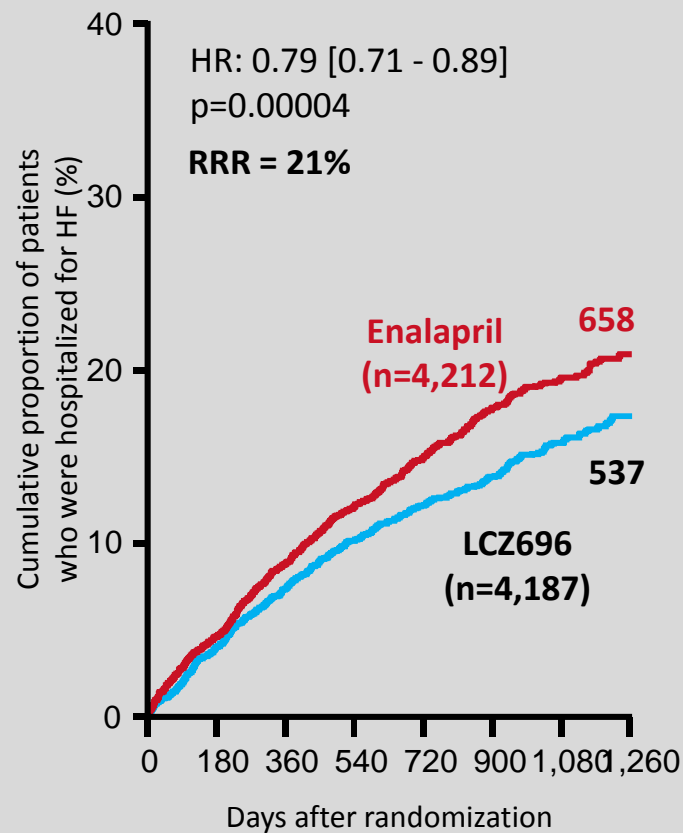
At risk	0	180	360	540	720	900	1,080	1,260
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236
LCZ696	4,187	3,922	3,663	3,018	2,257	1,544	896	249



## Cardiovascular death



## First HF hospitalization

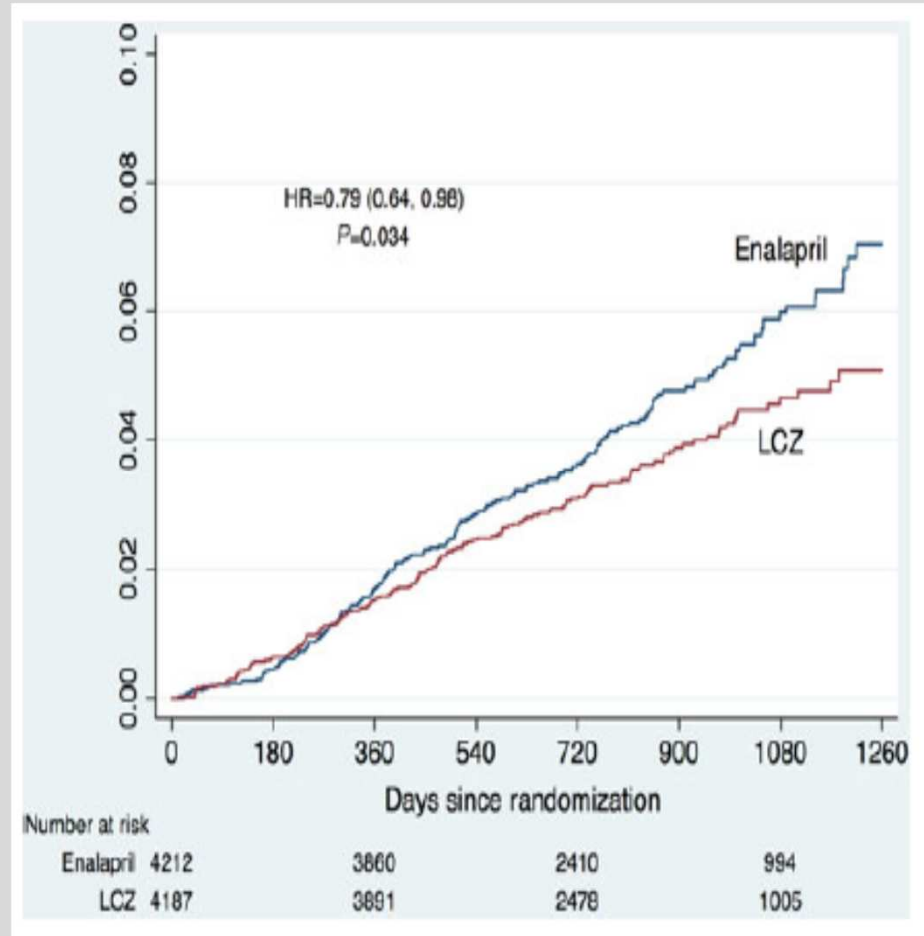
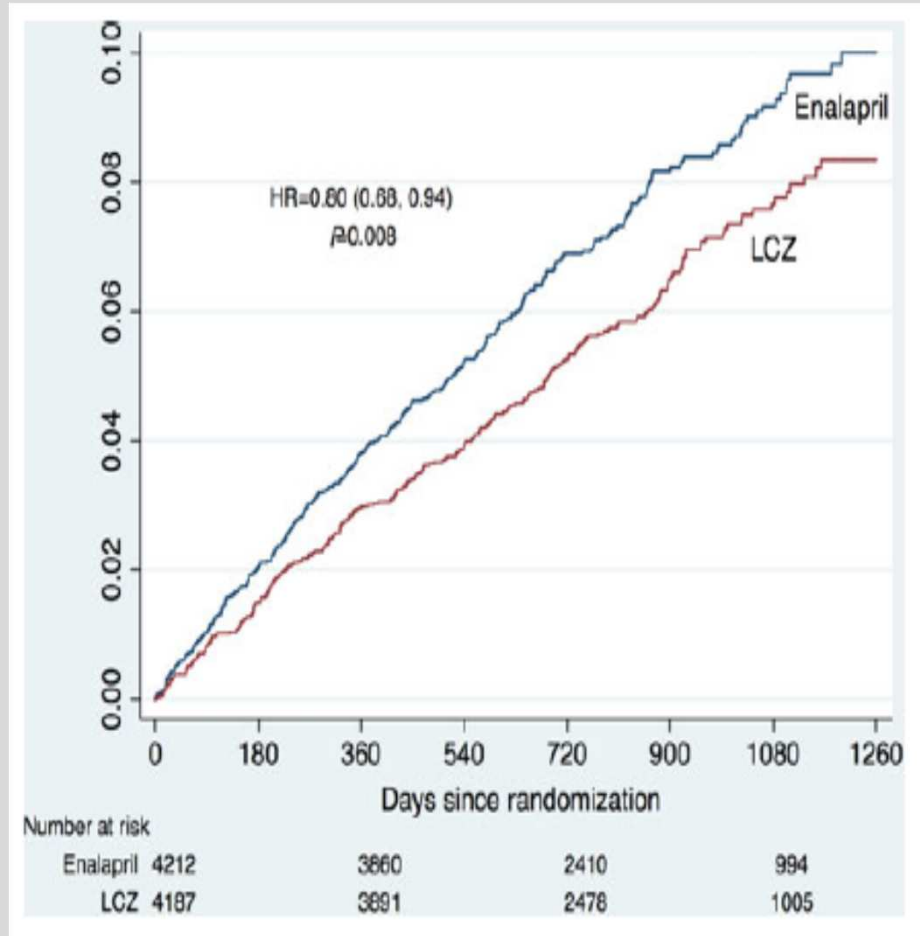


Sudden death and HF death also

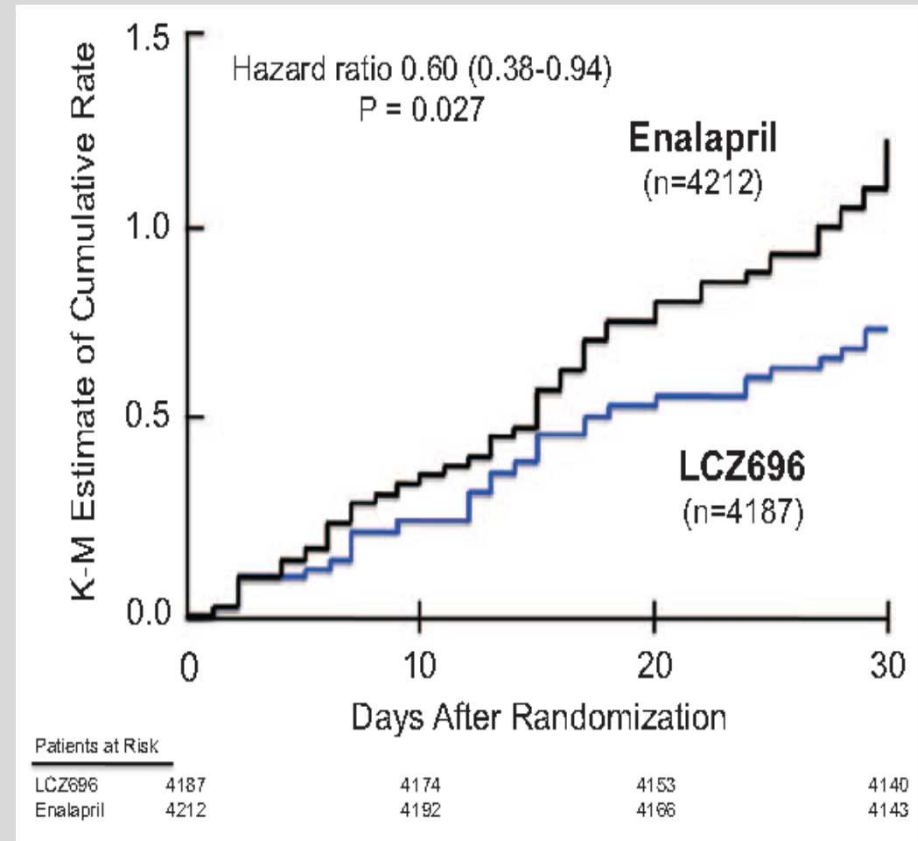
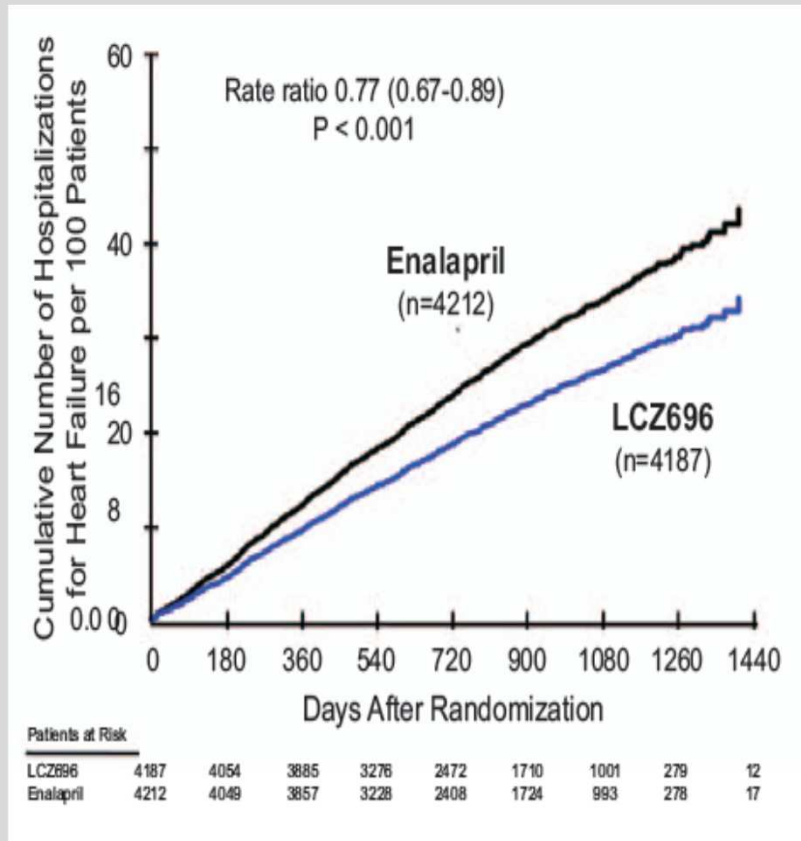
# Mode of death

## Sudden death

## Heart failure death



# Hospitalizations

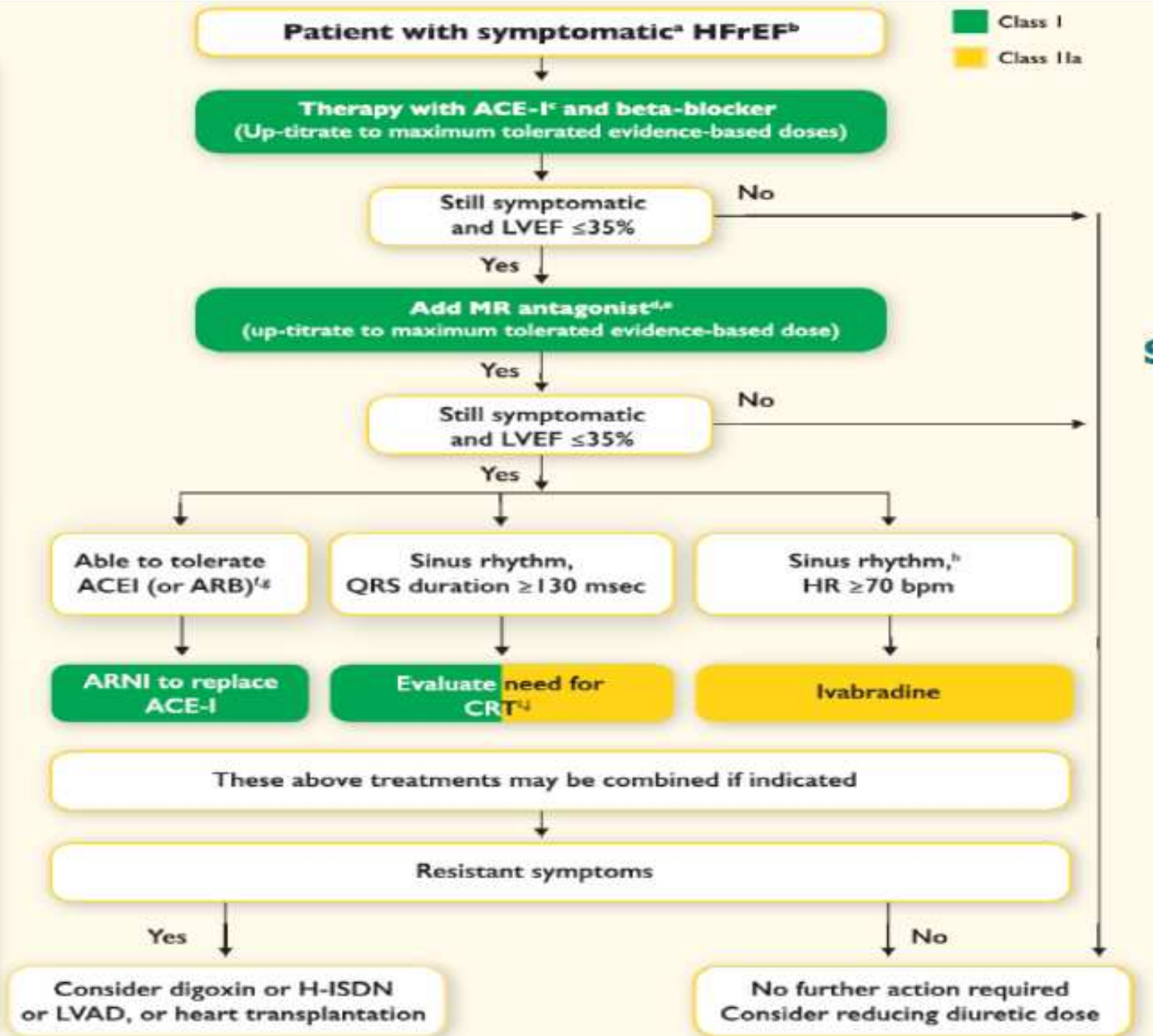


# Adverse events

Event	LCZ696 (N= 4187)	Enalapril (N= 4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

Diuretics to relieve symptoms and signs of congestion

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



### ➤ **Angiotensin II type I receptor blockers**

- ARBs are recommended only as an alternative in patients intolerant of an ACEI.
- The combination of ACEI/ARB should be restricted to symptomatic HFrEF patients receiving a beta-blocker who are unable to tolerate an MRA, and must be used under strict supervision.

### ➤ **Combination of hydralazine and isosorbide dinitrate**

- There is no clear evidence to suggest the use of this fix-dose combination therapy in all patients with HFrEF.
- This combination may be considered in patients who can tolerate neither ACEi nor ARB.

## **Digoxin and other digitalis glycosides**

- Digoxin may be considered in patients in sinus rhythm to reduce the risk of hospitalisation in symptomatic patients with HFrEF
- It is only recommended for the treatment of patients with HFrEF and AF with rapid ventricular rate when other therapeutic options cannot be pursued
- Digitalis should always be prescribed under specialist supervision. Caution should be exerted in females, in the elderly and in patients with reduced renal function.



## Statins

### Oral anticoagulants and antiplatelet therapy

- ✓ Except in patients with atrial fibrillation
- ✓ There is no evidence on the benefits of antiplatelet drugs in patients with HF without accompanying CAD, whereas there is a substantial risk of GI bleeding.

### Renin inhibitors

- ✓ It is not presently recommended as an alternative to an ACEI or ARB

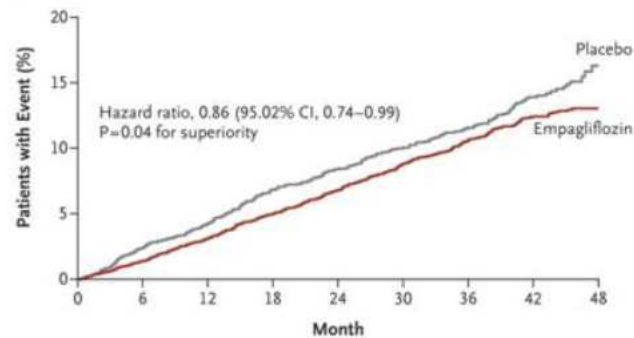


Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Thiazolidinediones (glitazones)</b> are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A
<b>NSAIDs or COX-2 inhibitors</b> are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	B
<b>Diltiazem or verapamil</b> are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.	III	C
The addition of an <b>ARB</b> (or renin inhibitor) to the combination of an <b>ACE-I</b> and an <b>MRA</b> is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia.	III	C

**Manage HF co-morbidities in all heart failure patients.**

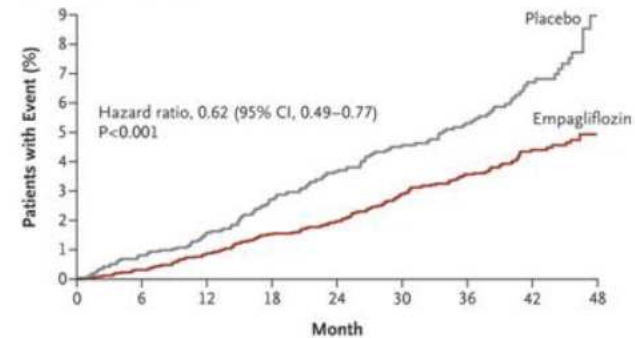
# EMPAREG Outcome

**A Primary Outcome**



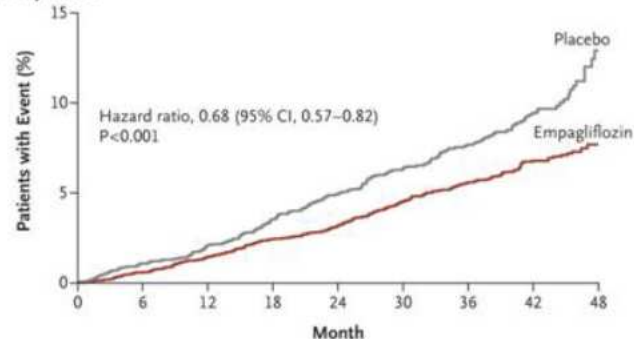
No. at Risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

**B Death from Cardiovascular Causes**



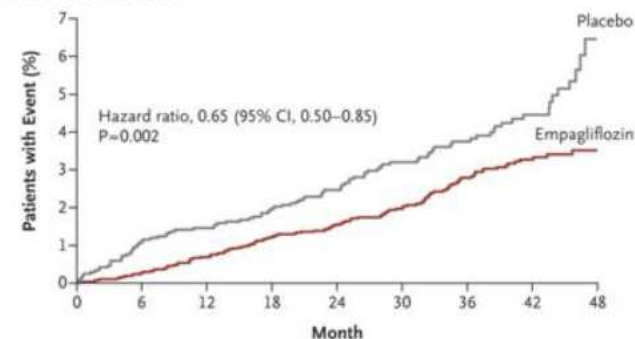
No. at Risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

**C Death from Any Cause**



No. at Risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

**D Hospitalization for Heart Failure**



No. at Risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

# BENEFIT / RISK OF DRUGS IN HF



	Major clinical benefit perceived	ADRs	Hard Outcome
Diuretics	<b>YES : relief of symptoms</b>	Renal failure Hypokaliemia	<b>NO</b>
Nitrates	<b>YES : relief of symptoms</b>	Hypotension Headache	<b>NO</b> Except A-HeFT trial
Oxygen	<b>Oxygen content</b>	PAH	<b>NO</b>
ACE i / ARB / BB	<b>NO</b>	Hypotension, Renal Failure, Hyperkaliemia	<b>YES</b>
MRA	<b>NO</b>	Renal Failure Hyperkaliemia	<b>YES</b>
Ivabradine	<b>YES : relief of non CHF symptoms</b>	Bradycardia Blurred vision	<b>NO in IHD (angina)</b>
Entresto	<b>YES : relief of symptoms</b>	Like ARB	<b>YES</b>

# Des digitalo-diurétiques à la prise en charge d'aujourd'hui

- Traitement symptomatique
- Réduction de la morbi-mortalité avec les IEC , BB et MRA
- Intérêt de l'ivabradine
- Apport du traitement électrique: CRT, DAI
- Avènement de l'ETP
- Importance du réentraînement à l'effort
- Approche e-santé
- Changement de paradigme avec SACUBITRIL – VALSARTAN et identification d'une nouvelle cible commune: la voie des peptides natriuretiques?