Journal Club del Venerdì

I NUOVI FARMACI PER LO SCOMPENSO CARDIACO

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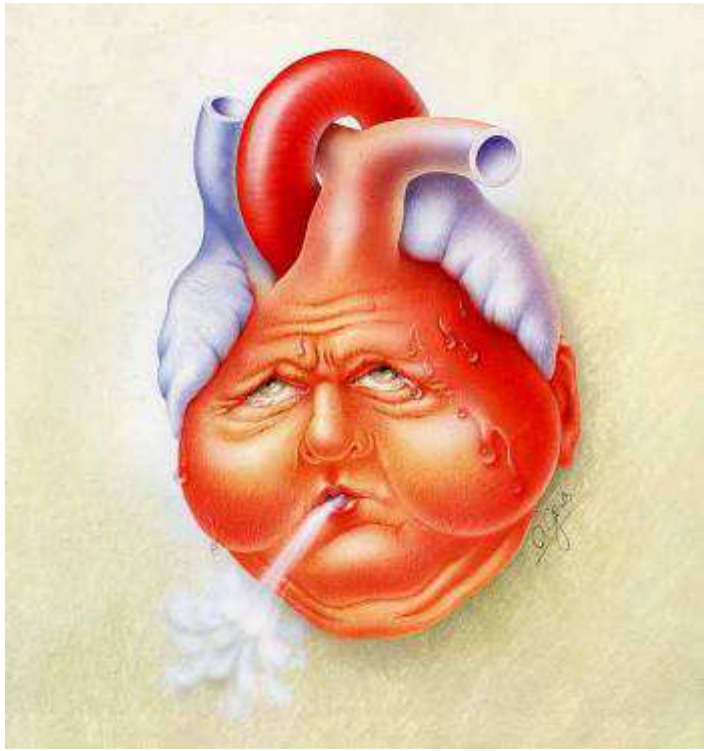
Brescia, 8 Settembre 2017



Highlights

- HF classification
- Chronic heart failure: epidemiology, pathophysiology, diagnosis
- Chronic heart failure: prevention
- Treatment guidelines of chronic heart failure with reduced ejection function
- Future treatment directions

Highlights

ACCF/AHA Practice Guideline

2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

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)

Yancy CW, et al
Heart Failure Focused Update on Pharmacological Therapy

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

Yancy et al
2017 ACC/AHA/HFSA Heart Failure Focused Update

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

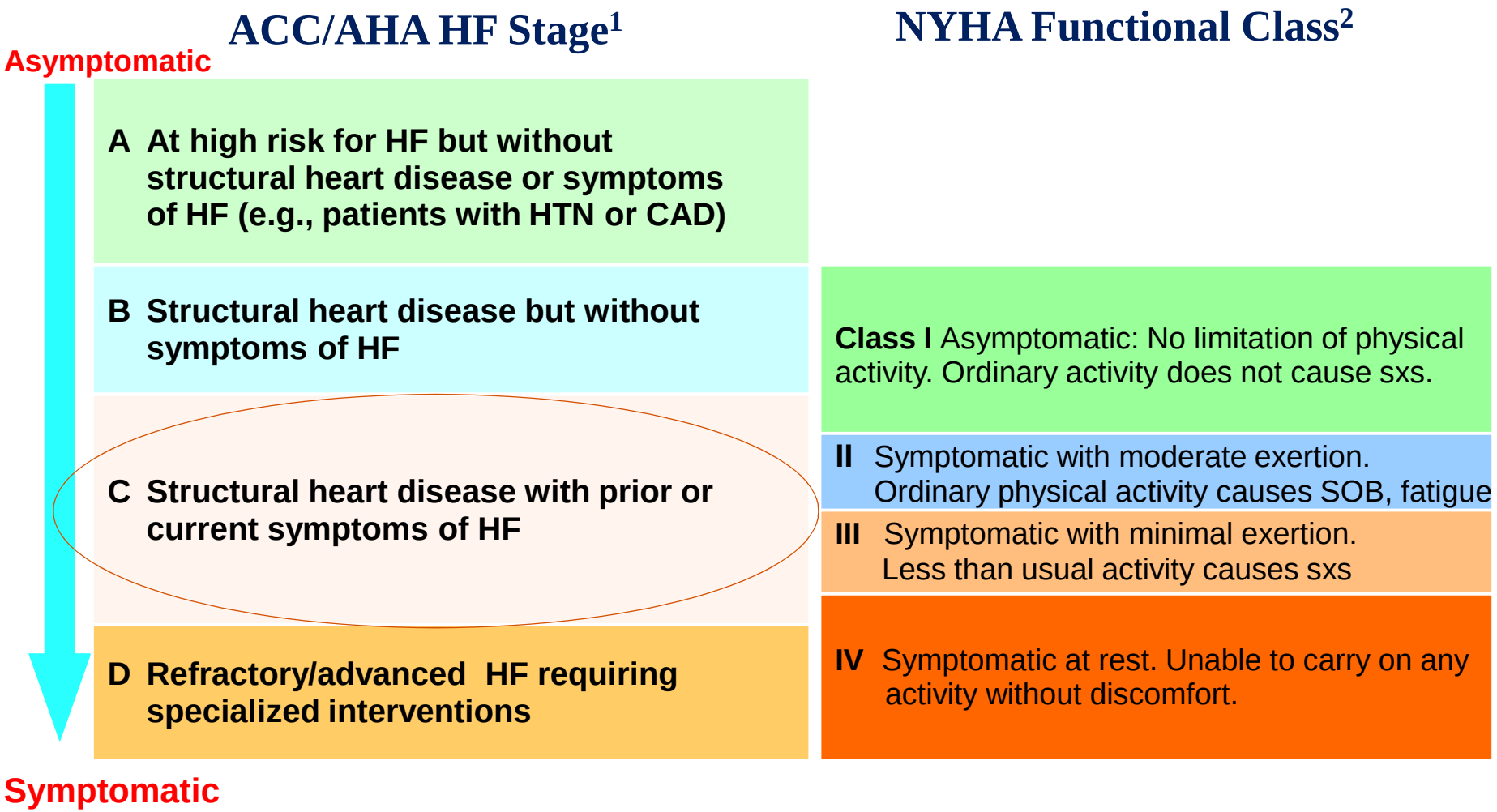
Classification

Many clinical classification systems

- based on symptom severity, as assessed by the New York Heart Association functional classification system
- on disease progression, as staged from A to D in the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines.

The Lancet, April 2017, S0140-6736(17)31071

Stages of Heart Failure



Classification

For practical purposes, the most important distinctions are those between acute and chronic heart failure and between patients with heart failure with reduced (≤40%) left ventricular ejection fraction and those with heart failure with preserved (≥50%) left ventricular ejection fraction.

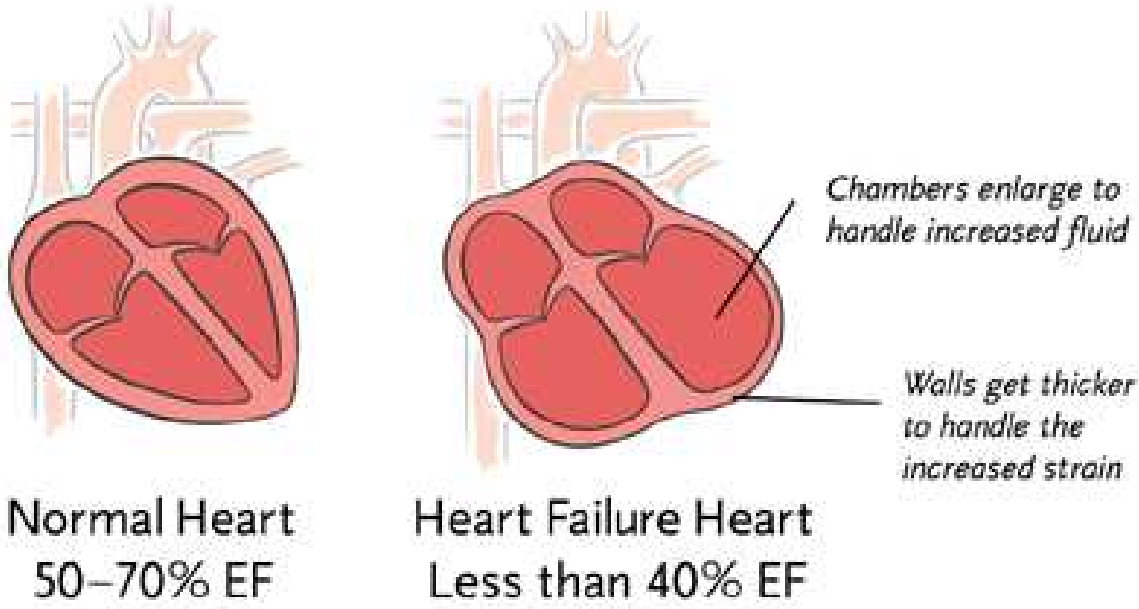
To date, almost every drug or device trial showing a beneficial treatment effect has enrolled patients with chronic heart failure with reduced ejection fraction.

The Lancet, April 2017, S0140-6736(17)31071

A Key Indicator for Diagnosing Heart Failure

Ejection Fraction (EF)

- Ejection Fraction (EF) is the percentage of blood that is pumped out of your heart during each beat



Classification

About 10–20% of patients with heart failure have intermediate ejection fraction values.

The term mid-range ejection fraction has been used for patients with an ejection fraction of 40–49%.

The mortality of these patients can be lower than that of patients with a reduced ejection fraction, whereas their rate of readmission to hospital might be similar

The Lancet, April 2017, S0140-6736(17)31071

European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

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).

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.
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.
[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL.

From: 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failureThe 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
Eur Heart J. 2016;37(27):2129-2200. doi:10.1093/eurheartj/ehw128

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Epidemiology

The prevalence of HF depends on the definition applied, but is approximately 1–2% of the adult population in developed countries, rising to ≥10% among people 70 years of age.

Among people 65 years of age presenting to primary care with breathlessness on exertion, one in six will have unrecognized HF (mainly HFpEF).

The lifetime risk of HF at age 55 years is 33% for men and 28% for women

European Heart Journal (2016) **37**, 2129–2200
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Epidemiology

Patients with heart failure have a poor prognosis, with high rates of hospital admission and mortality.

Implementation of evidence-based treatments (neurohormonal antagonists and implantable devices) has led to a reduction in the mortality rate of patients with heart failure, but rates remain high,

- 6–7% per year in patients with stable heart failure

- 25% or more per year in patients admitted to hospital with acute heart failure.

Pathophysiology

The pathophysiology of heart failure with reduced ejection fraction is that of a progressive condition;

risk factors lead to cardiac injury and then the development of myocardial dysfunction (initially asymptomatic), and then to worsening symptoms until the patient develops end-stage heart failure.

The Lancet, April 2017, S0140-6736(17)31071

Pathophysiology

European Heart Journal (2016) **37**, 2129–2200
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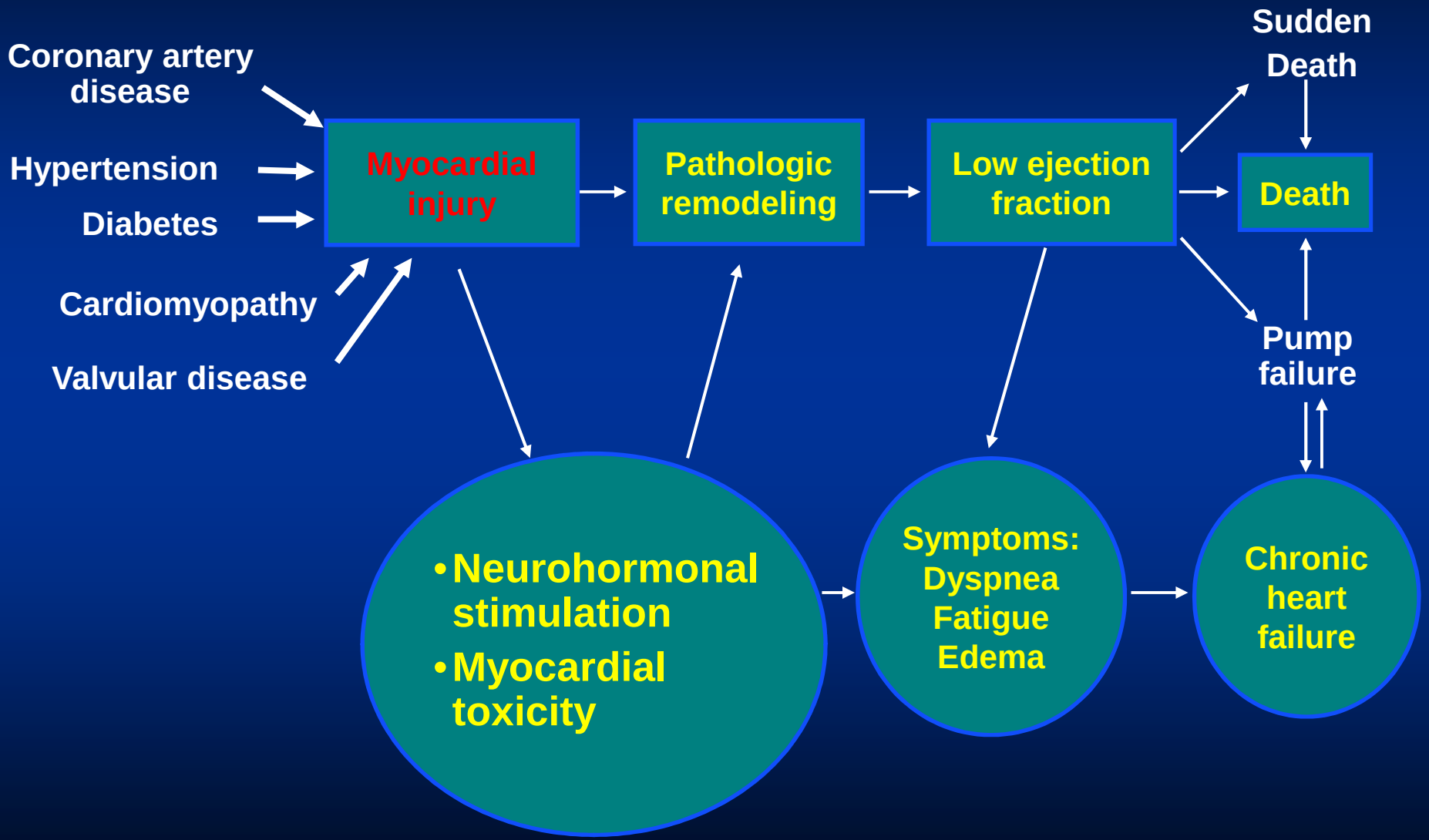
Table 3.4 Aetiologies of heart failure

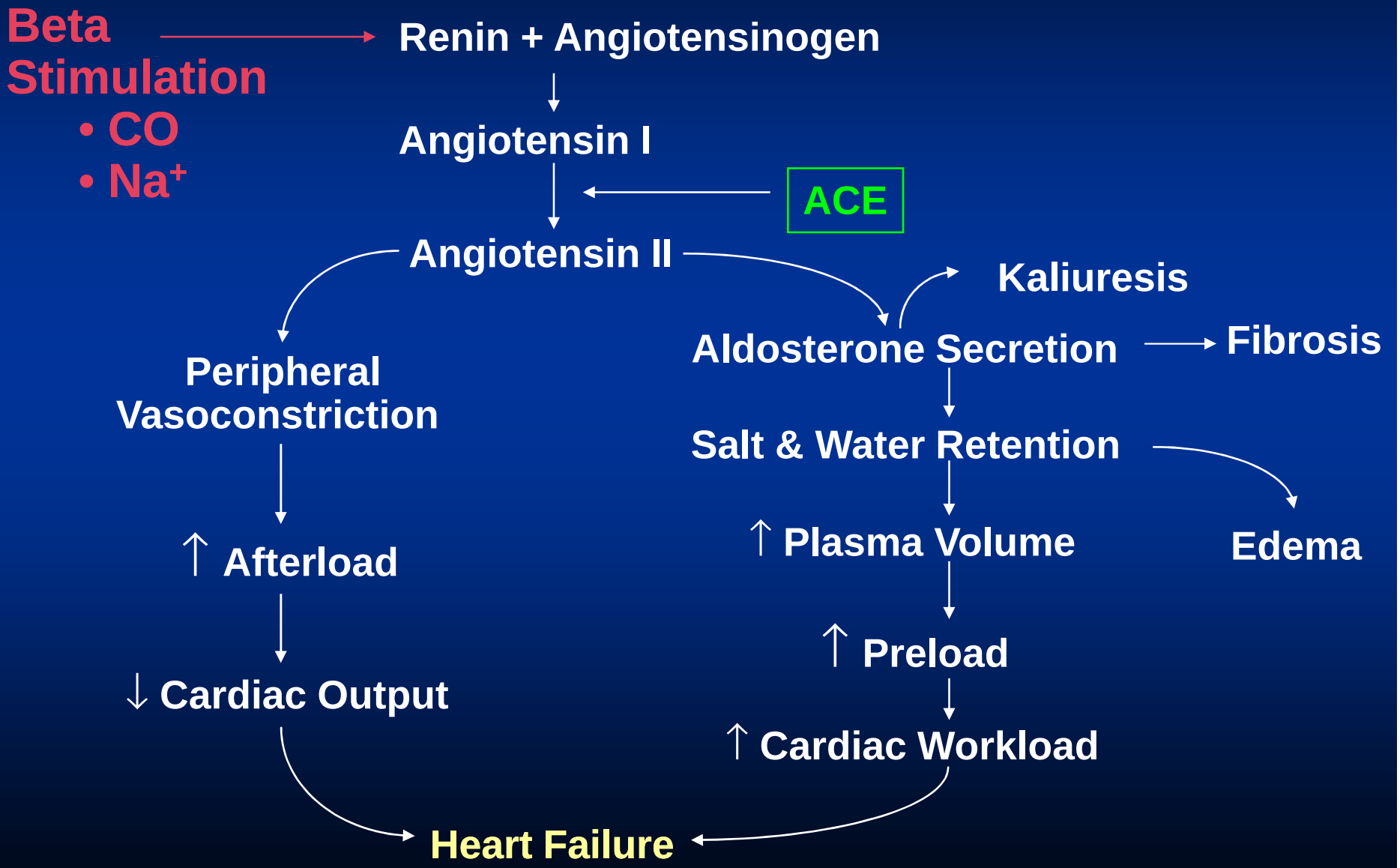
DISEASED MYOCARDIUM		
Ischaemic heart disease	Myocardial scar	
	Myocardial stunning/hibernation	
	Epicardial coronary artery disease	
	Abnormal coronary microcirculation	
	Endothelial dysfunction	
Toxic damage	Recreational substance abuse	Alcohol, cocaine, amphetamine, anabolic steroids.
	Heavy metals	Copper, iron, lead, cobalt.
	Medications	Cytostatic drugs (e.g. anthracyclines), immunomodulating drugs (e.g. interferons monoclonal antibodies such as trastuzumab, cetuximab), antidepressant drugs, antiarrhythmics, non-steroidal anti-inflammatory drugs, anaesthetics.
	Radiation	
Immune-mediated and inflammatory damage	Related to infection	Bacteria, spirochaetes, fungi, protozoa, parasites (Chagas disease), rickettsiae, viruses (HIV/AIDS).
	Not related to infection	Lymphocytic/giant cell myocarditis, autoimmune diseases (e.g. Graves' disease, rheumatoid arthritis, connective tissue disorders, mainly systemic lupus erythematosus), hypersensitivity and eosinophilic myocarditis (Churg–Strauss).
Infiltration	Related to malignancy	Direct infiltrations and metastases.
	Not related to malignancy	Amyloidosis, sarcoidosis, haemochromatosis (iron), glycogen storage diseases (e.g. Pompe disease), lysosomal storage diseases (e.g. Fabry disease).
Metabolic derangements	Hormonal	Thyroid diseases, parathyroid diseases, acromegaly, GH deficiency, hypercortisolaemia, Conn's disease, Addison disease, diabetes, metabolic syndrome, phaeochromocytoma, pathologies related to pregnancy and peripartum.
	Nutritional	Deficiencies in thiamine, L-carnitine, selenium, iron, phosphates, calcium, complex malnutrition (e.g. malignancy, AIDS, anorexia nervosa), obesity.
Genetic abnormalities	Diverse forms	HCM, DCM, LV non-compaction, ARVC, restrictive cardiomyopathy (for details see respective expert documents), muscular dystrophies and laminopathies.
ABNORMAL LOADING CONDITIONS		
Hypertension		
Valve and myocardium structural defects	Acquired	Mitral, aortic, tricuspid and pulmonary valve diseases.
	Congenital	Atrial and ventricular septum defects and others (for details see a respective expert document).
Pericardial and endomyocardial pathologies	Pericardial	Constrictive pericarditis Pericardial effusion
	Endomyocardial	HES, EMF, endocardial fibroelastosis.
High output states		Severe anaemia, sepsis, thyrotoxicosis, Paget's disease, arteriovenous fistula, pregnancy.
Volume overload		Renal failure, iatrogenic fluid overload.
ARRHYTHMIAS		
Tachyarrhythmias		Atrial, ventricular arrhythmias.
Bradyarrhythmias		Sinus node dysfunctions, conduction disorders.

Pathologic Progression of CV Disease



Adapted from Cohn JN. *N Engl J Med*. 1996;335:490–498.

Compensatory Mechanisms:
Renin-Angiotensin-Aldosterone System



Symptoms and Signs

	Mechanisms
Symptoms	
Breathlessness	Lung congestion due to raised left atrial pressure, respiratory muscle and chemoreceptor abnormalities
Orthopnoea	Increased venous return and lung congestion in the supine position
Paroxysmal nocturnal dyspnoea	The same as above plus respiratory centre depression
Fatigue	Skeletal muscle hypoperfusion and metabolic abnormalities
Palpitations	Tachyarrhythmias, reduced effort tolerance
Ankle swelling	Fluid retention
Early satiety; abdominal bloating	Fluid retention, increased right atrial pressure
Anorexia, depression, confusion	Fluid retention, cerebral hypoperfusion
Cachexia	Intestinal congestion, chronic cytokine and inflammatory pathway activation

The Lancet, April 2017, S0140-6736(17)31071

Symptoms and Signs

Signs	
Elevated jugular venous pressure*	Increased right atrial pressure
Displaced apex beat	Left ventricular dilatation
Cardiac holosystolic murmur	Mitral or tricuspid regurgitation
Third heart sound, gallop rhythm	Increased left atrial pressure
Pulmonary crackles*	Increased left atrial pressure, lung congestion
Pleural effusion*	Fluid retention, increased left or right atrial pressure
Hepatomegaly	Increased right atrial pressure
Hepatojugular reflux	Increased right atrial pressure
Ascites	Fluid retention, increased right atrial pressure
Peripheral oedema	Fluid retention

*These signs are assessed with the patient in the sitting position.

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Diagnosis

European Heart Journal (2016) **37**, 2129–2200
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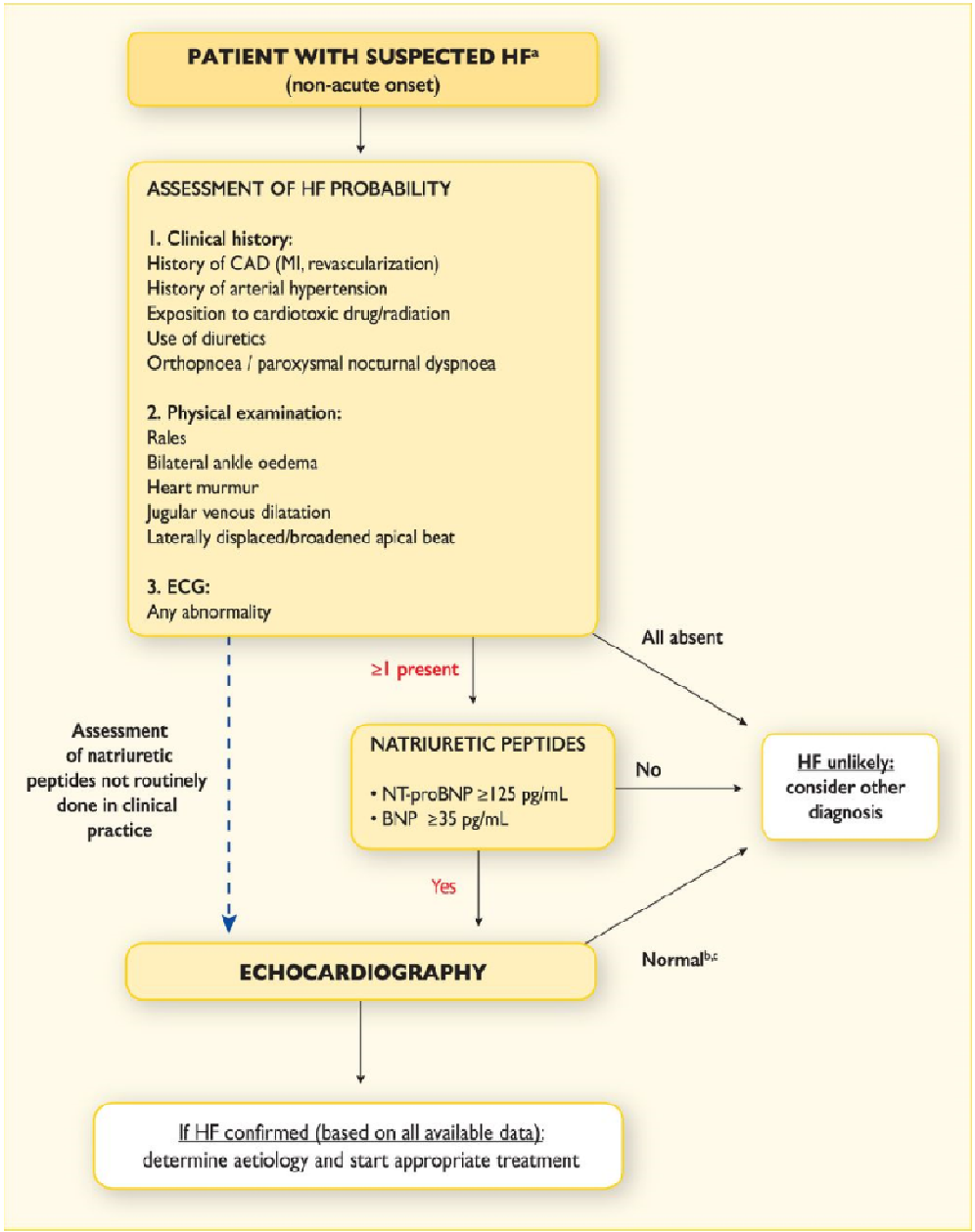


Diagnosis

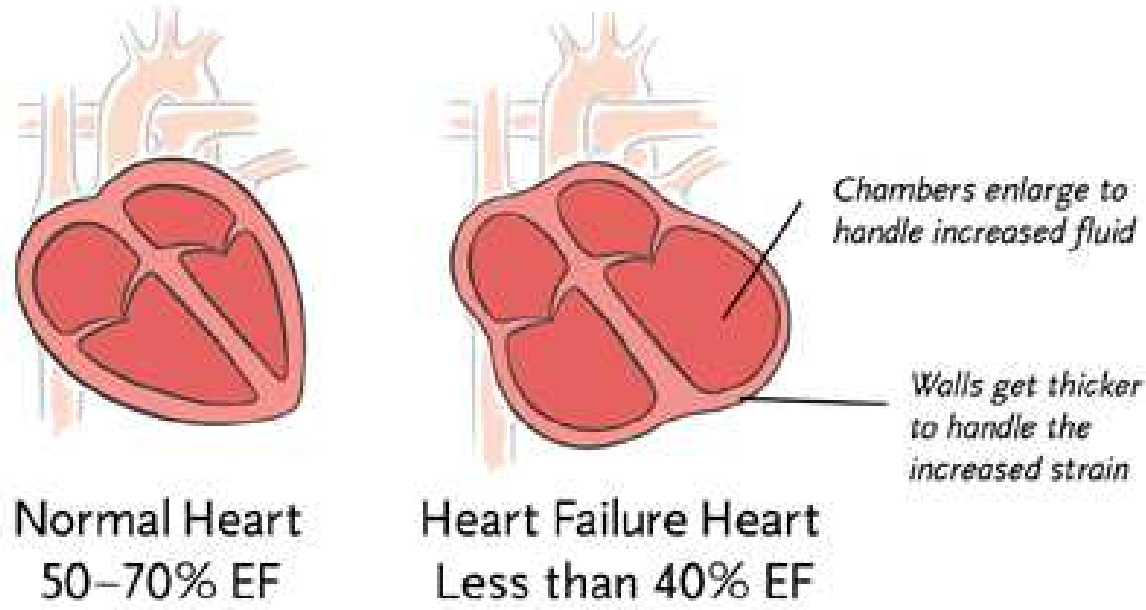
Cardiac MRI has better tissue characterisation and spatial resolution that help in the diagnosis of inflammatory and infiltrative conditions. However, use of cardiac MRI is limited by its cost and incompatibility with some devices, including many implantable cardioverter defibrillators (ICDs) and pacemakers.

Single-photon emission **CT and PET** are useful to assess myocardial ischaemia and viability.

Coronary angiography and cardiac CT are used to diagnose coronary artery disease. Angiography is indicated in patients with angina or a medium-to-high pre-test probability of coronary artery disease and in those who are suitable for coronary revascularisation.

The Lancet, April 2017, S0140-6736(17)31071

Prevention of Heart Failure



Prevention

European Heart Journal (2016) **37**, 2129–2200
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Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Recommendations	Class [a]	Level [b]	Ref [c]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A	126, 129, 150, 151
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A	137–140, 152
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C	131–134
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C	130, 141, 153–155
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B	130
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A	5, 144, 145
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B	5
ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	IIa	A	142
Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.	I	B	146
ICD is recommended in patients: a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction, b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy, in order to prevent sudden death and prolong life.	I	B	149, 156–158

Prevention

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Inhibitors of sodium–glucose cotransporter 2 reduce rates of hyperglycemia in patients with type 2 diabetes by decreasing renal glucose reabsorption, thereby increasing urinary glucose excretion.

Empagliflozin is a selective inhibitor of sodium glucose cotransporter 2 that has been approved for type 2 diabetes. Given as either monotherapy or as an add-on therapy, the drug is reported to reduce glycated hemoglobin levels in patients with type 2 diabetes, including those with stage 2 or 3a chronic kidney disease.

Furthermore, empagliflozin is associated with weight loss and reductions in blood pressure without increases in heart rate.

The most common side effects of empagliflozin are urinary tract infection and genital infection.

Prevention

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

In the EMPA-REG OUTCOME trial, 7020 patients with a high cardiovascular risk were randomly assigned to either a placebo group or an empaglifozin group.

Empaglifozin reduced the primary outcome of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke by 14%, as well as the number of cardiovascular-related deaths, hospital admissions due to heart failure, and all cause deaths.

The effects were consistent across different categories (a history of heart failure or not) and among those taking different heart failure or antidiabetic medications.

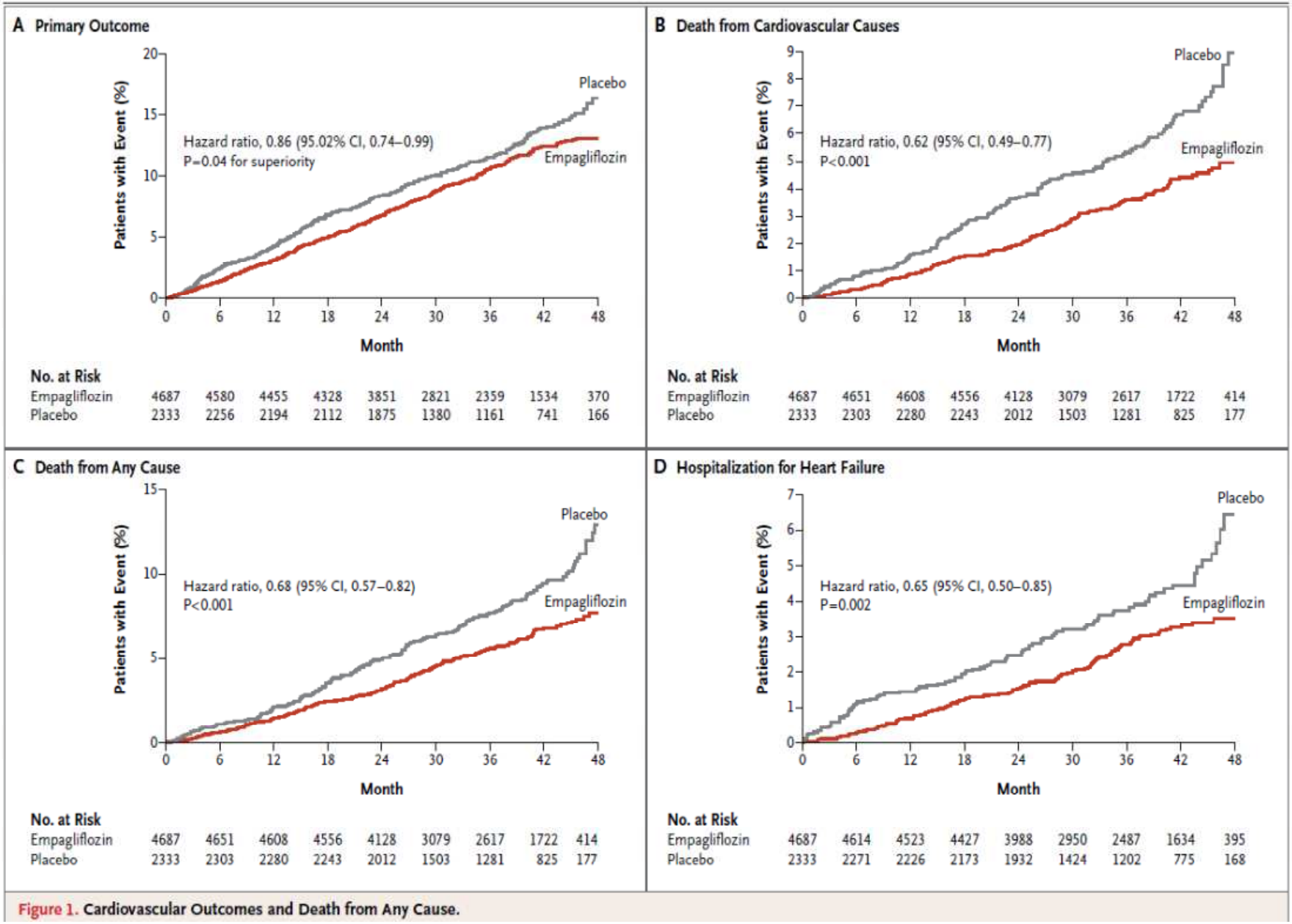


Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Prevention

Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction:

A Randomized Clinical Trial

In the LEADER study of 9340 patients with cardiovascular disease,

chronic kidney disease, or both, liraglutide (glucagon-like peptide-1 agonist) reduced the primary outcome of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke and the secondary outcome of cardiovascular death.

Additionally, liraglutide reduced the number of hospital admissions due to heart failure, although not significantly.

In the FIGHT study, 300 patients with heart failure with reduced ejection fraction who had been recently admitted to hospital were randomly assigned to liraglutide or placebo groups.

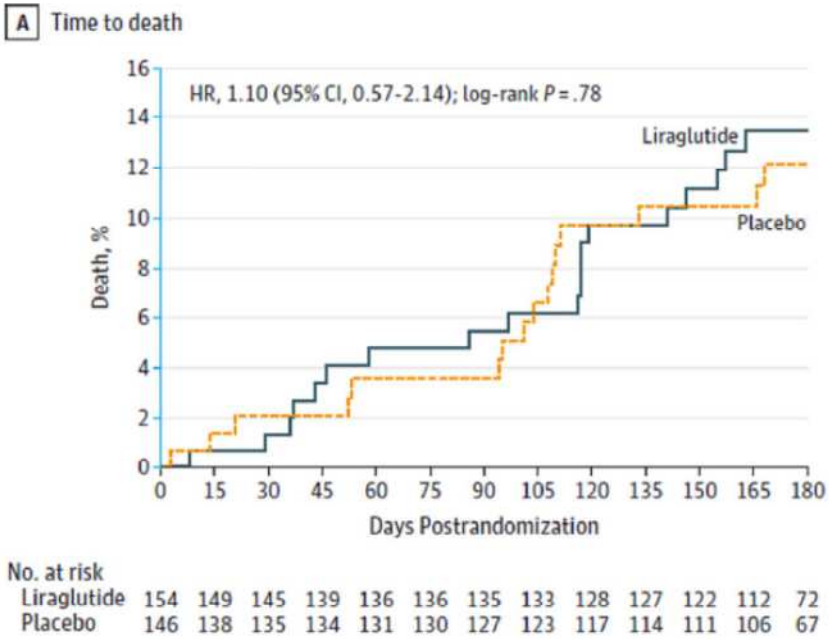
During the 6 months of follow-up in that study, there was no difference between the groups in the primary outcome or in its single components of death, readmission to hospital, and decrease in NT-proBNP concentrations, or in the other secondary endpoints.

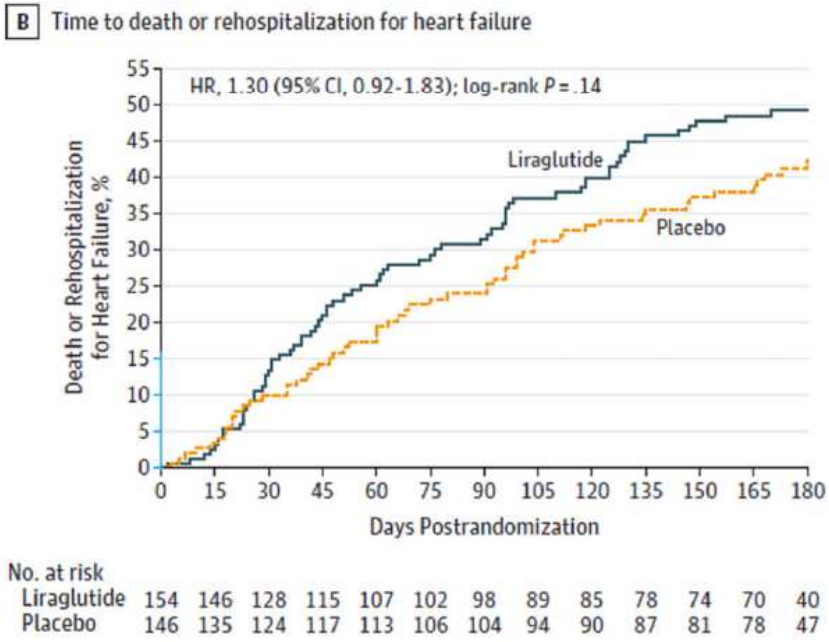
JAMA. 2016 August 2; 316(5): 500–508. doi:10.1001/jama.2016.10260.

Prevention

Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction:

A Randomized Clinical Trial





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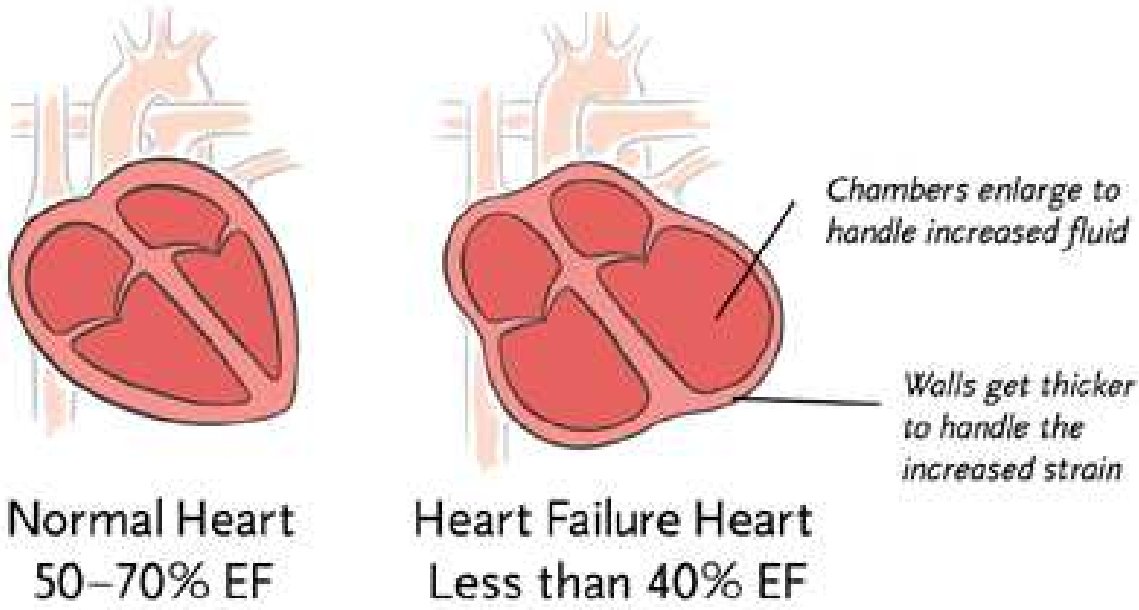
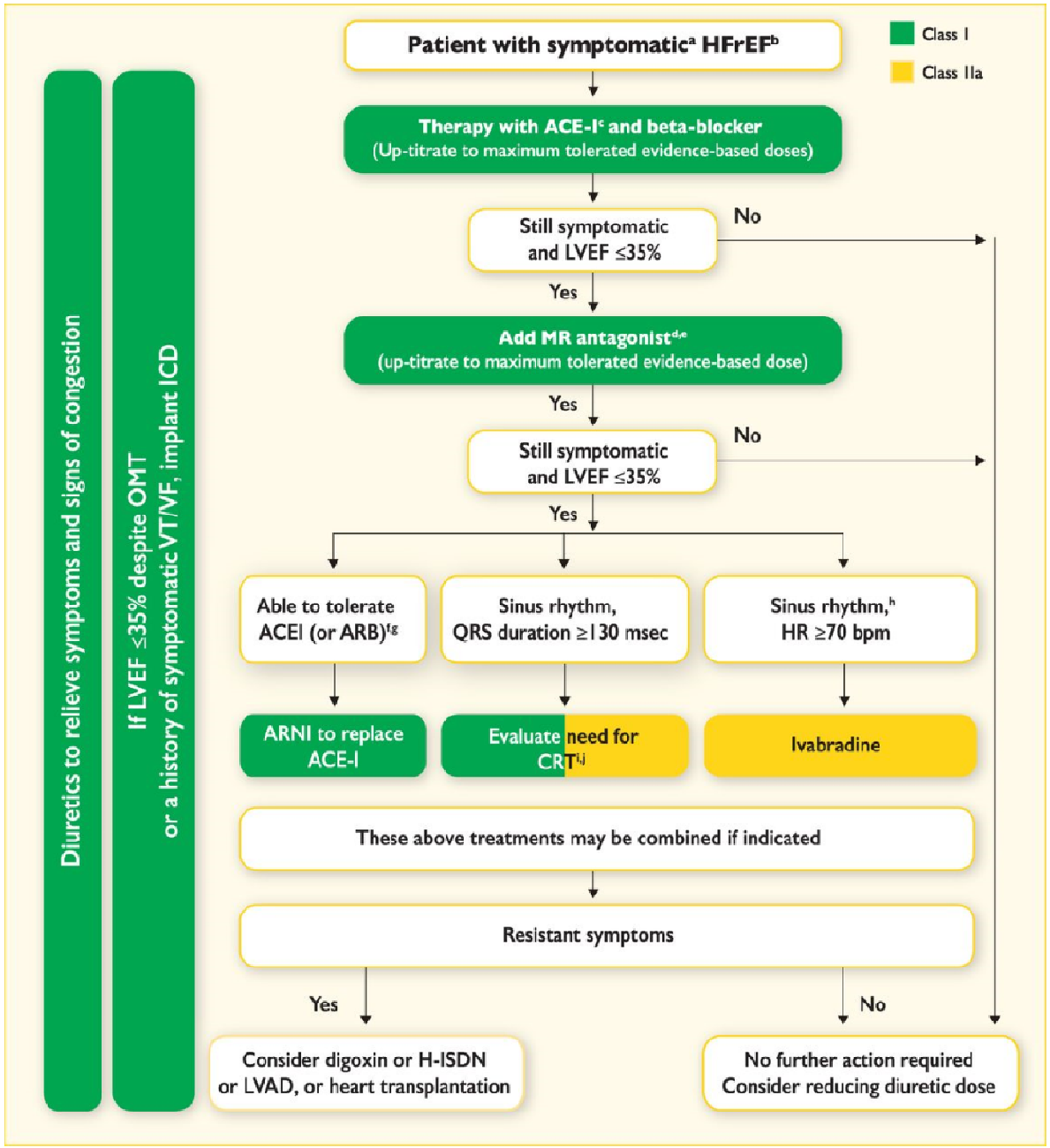
Treatment of Heart Failure with reduced Ejection Fraction (HFrEF)





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Treatment

European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
An ACE-I[d] is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A	2, 163–165
A beta-blocker is recommended, in addition an ACE-I[d], for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A	167–173
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I[d] and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A	174, 175

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ACEIs have been shown to reduce mortality and morbidity in patients with HFrEF and are recommended unless contraindicated or not tolerated in all symptomatic patients.

ACEIs should be up-titrated to the maximum tolerated dose in order to achieve adequate inhibition of the renin–angiotensin–aldosterone system (RAAS).

There is evidence that in clinical practice the majority of patients receive suboptimal doses of ACEI.

Treatment

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- There is consensus that beta-blockers and ACEIs are complementary, and can be started together as soon as the diagnosis of HFrEF is made.
- There is no evidence favouring the initiation of treatment with a beta-blocker before an ACEI has been started.
- Betablockers should be initiated in clinically stable patients at a low dose and gradually up-titrated to the maximum tolerated dose.

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- In patients admitted due to acute HF (AHF) beta-blockers should be cautiously initiated in hospital, once the patient is stabilized.
- Beta-blockers should be considered for rate control in patients with HFrEF and AF, especially in those with high heart rate

European Heart Journal (2016) **37**, 2129–2200
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	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril[a]	6.25 *t.i.d.*	50 *t.i.d.*
Enalapril	2.5 *b.i.d.*	10–20 *b.i.d.*
Lisinopril[b]	2.5–5.0 *o.d.*	20–35 *o.d.*
Ramipril	2.5 o.d.	10 *o.d.*
Trandolapril[a]	0.5 *o.d.*	4 *o.d.*
Beta-blockers		
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*[d]
Metoprolol succinate (CR/XL)	12.5–25 *o.d.*	200 o.d.
Nebivolol[c]	1.25 *o.d.*	10 *o.d.*
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

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- MRAs (spironolactone and eplerenone) block receptors that bind aldosterone and, with different degrees of affinity, other steroid hormone (e.g. corticosteroids, androgens) receptors.
- Spironolactone or eplerenone are recommended in all symptomatic patients (despite treatment with an ACEI and a beta-blocker) with HFrEF and LVEF ≤35%, to reduce mortality and HF hospitalization

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- ARBs are recommended only as an alternative in patients intolerant of an ACEI.
- Candesartan has been shown to reduce cardiovascular mortality.
- Valsartan showed an effect on hospitalization for HF (but not on all-cause hospitalizations) in patients with HFrEF receiving background ACEIs

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	Starting dose (mg)	Target dose (mg)
ACE-I		
ARBs		
Candesartan	4–8 *o.d.*	32 *o.d.*
Valsartan	40 *b.i.d.*	160 *b.i.d.*
Losartan[b,c]	50 *o.d.*	150 *o.d.*
MRAs		
Eplerenone	25 *o.d.*	50 *o.d.*
Spironolactone	25 *o.d.*	50 *o.d.*
Eplerenone	25 *o.d.*	50 *o.d.*
Spironolactone	25 *o.d.*	50 *o.d.*
ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*
If-channel blocker		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

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- Diuretics are recommended to reduce the signs and symptoms of congestion in patients with HFrEF, but their effects on mortality and morbidity have not been studied in RCTs.
- Loop diuretics produce a more intense and shorter diuresis than thiazides, although they act synergistically and the combination may be used to treat resistant oedema.
- However, adverse effects are more likely and these combinations should only be used with care.

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Treatment

- The aim of diuretic therapy is to achieve and maintain euvolaemia with the lowest achievable dose.
- The dose of the diuretic must be adjusted according to the individual needs over time.
- In selected asymptomatic euvolaemic/ hypovolaemic patients, the use of a diuretic drug might be (temporarily) discontinued.
- Patients can be trained to self-adjust their diuretic dose based on monitoring of symptoms/signs of congestion and daily weight measurements.

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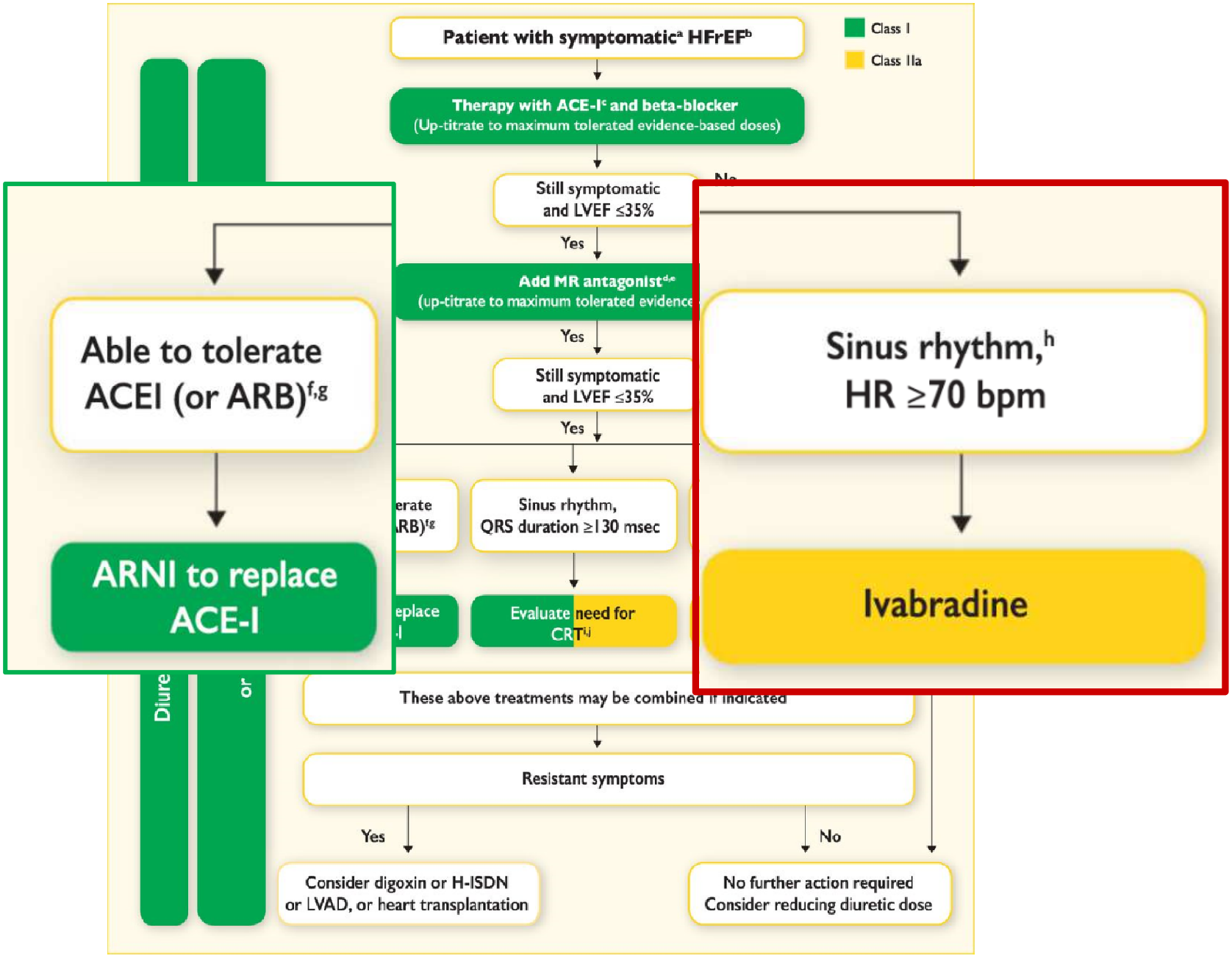
Table 7.3 Doses of diuretics commonly used in patients with heart failure

Diuretics	Initial dose (mg)		Usual daily dose (mg)	
Loop diuretics[a]				
Furosemide	20–40		40–240	
Bumetanide	0.5–1.0		1–5	
Torasemide	5–10		10–20	
Thiazides[b]				
Bendroflumethiazide	2.5		2.5–10	
Hydrochlorothiazide	25		12.5–100	
Metolazone	2.5		2.5–10	
Indapamide[c]	2.5		2.5–5	
Potassium-sparing diuretics[d]				
	+ACE-I/ ARB	-ACE-I/ ARB	+ACE-I/ ARB	-ACE-I/ ARB
Spironolactone/ eplerenone	12.5–25	50	50	100–200
Amiloride	2.5	5	5–10	10–20
Triamterene	25	50	100	200



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Treatment

European Heart Journal (2016) **37**, 2129–2200
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Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
Diuretics			
Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.	I	B	178, 179
Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion	IIa	B	178, 179

Angiotensin receptor neprilysin inhibitor

Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B

Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker	IIa	B	180

I_f-channel inhibitor

Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).	IIa	B
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).	IIa	C

Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.	IIa	B	183
Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.	IIb	B	184
Other treatments with less-certain benefits			
Digoxin			
Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).	IIb	B	185
N-3 PUFA			
An n-3 PUFA[e] preparation may be considered in symptomatic HF patients to reduce the risk of cardiovascular hospitalization and cardiovascular death.	IIb	B	186

Treatment

European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril[a]	6.25 *t.i.d.*	50 *t.i.d.*
Enalapril	2.5 *b.i.d.*	10–20 *b.i.d.*
Lisinopril[b]	2.5–5.0 *o.d.*	20–35 *o.d.*
Ramipril	2.5 o.d.	10 *o.d.*
Trandolapril[a]	0.5 *o.d.*	4 *o.d.*
Beta-blockers		
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*[d]

ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*
If-channel blocker		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*
If-channel blocker		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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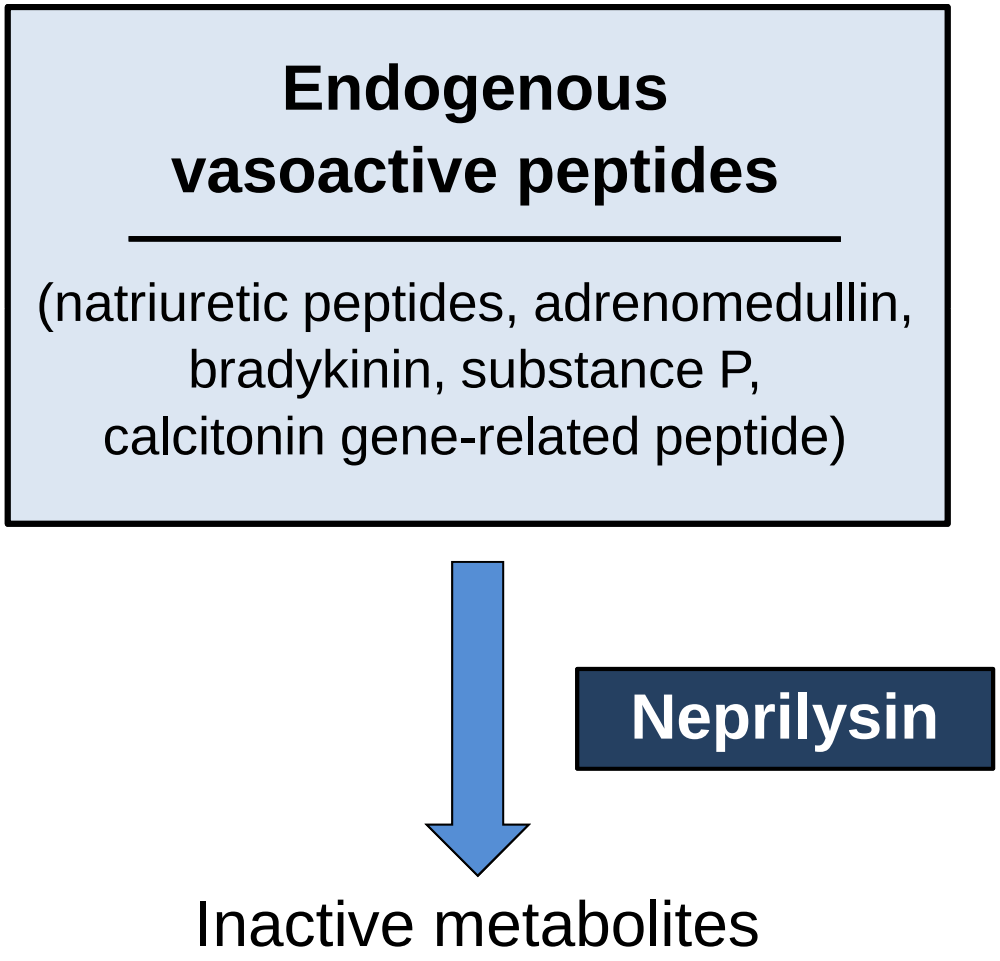
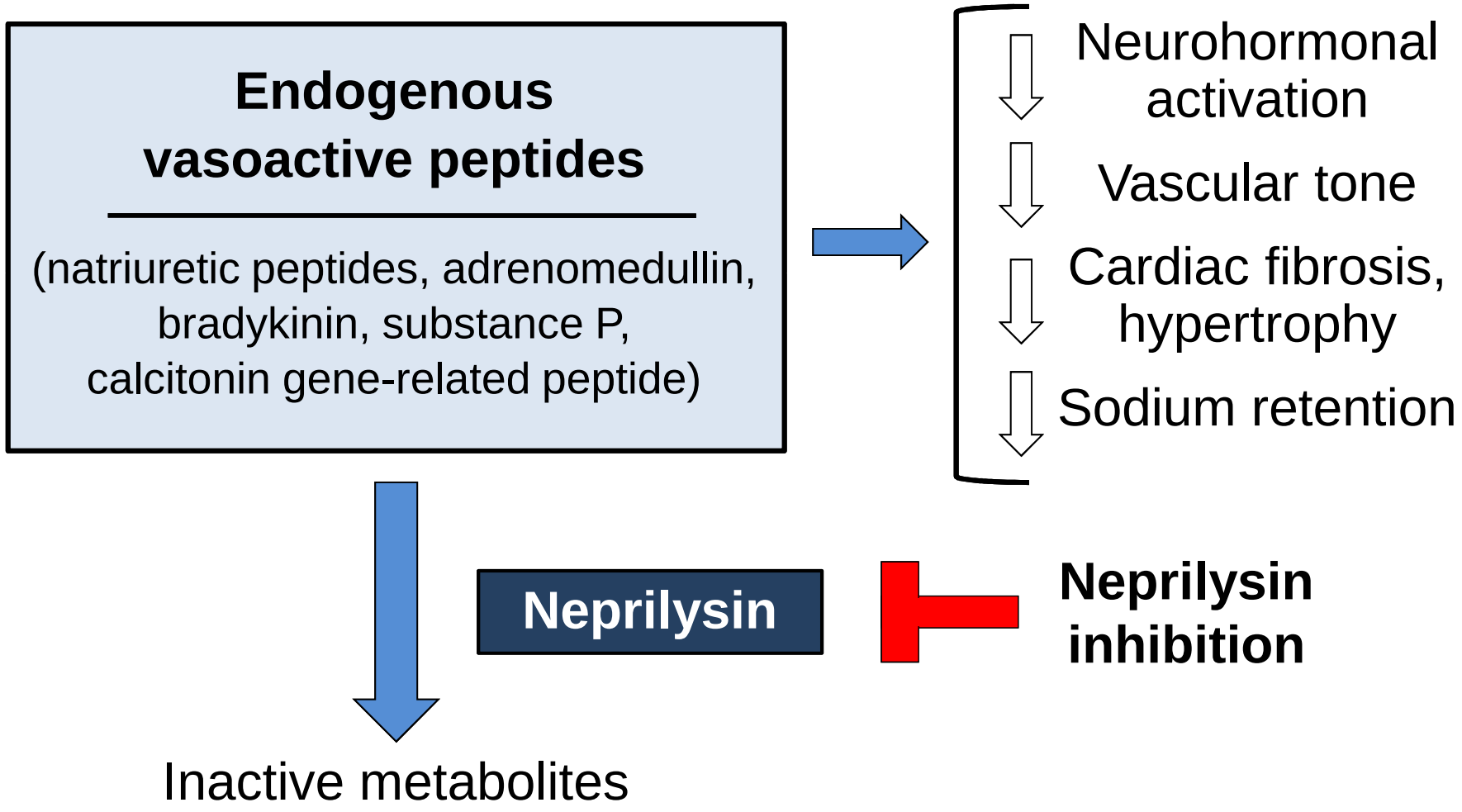
Sucubitril-Valsartan

PARADIGMHF

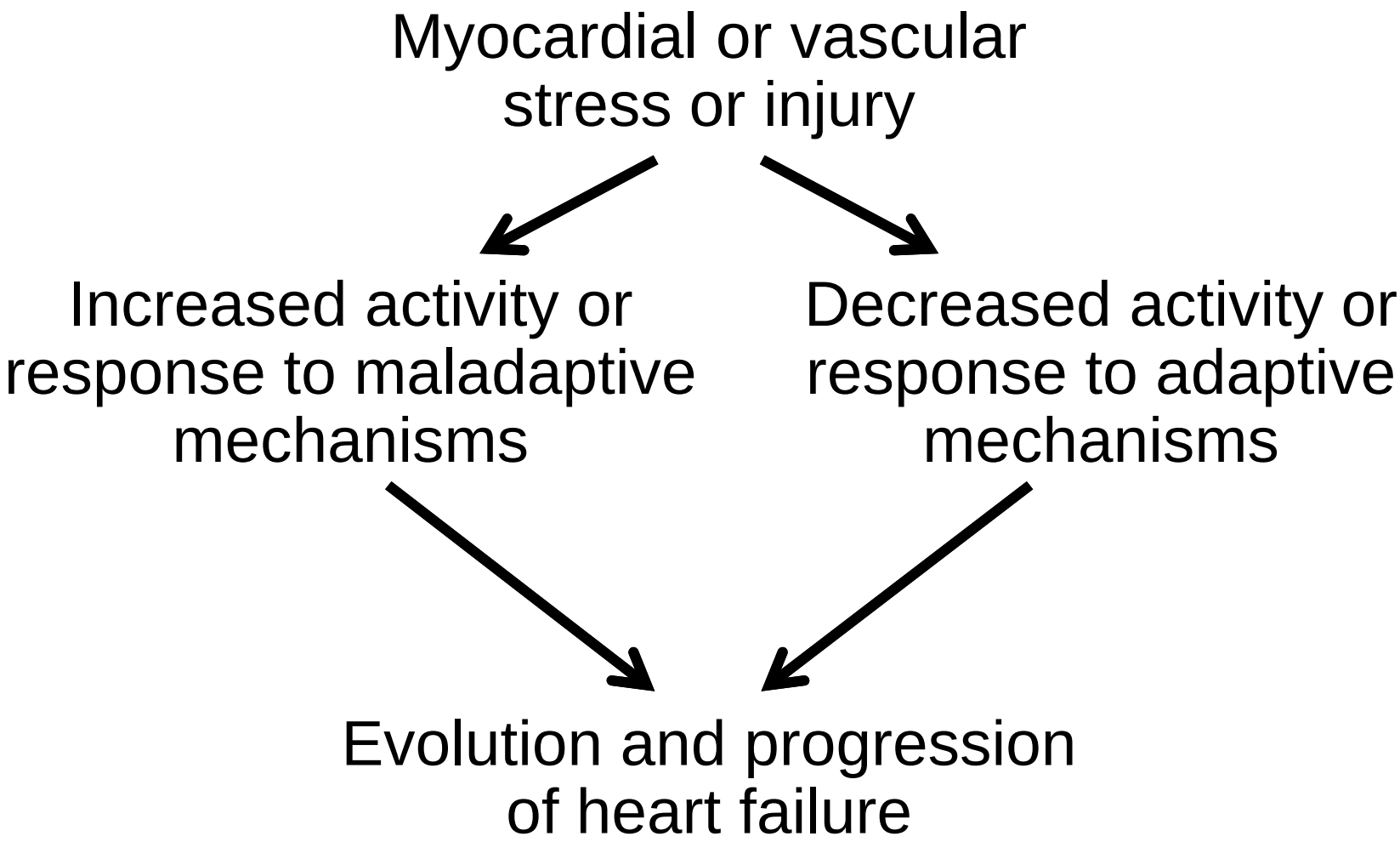
One Enzyme — Neprilysin — Degrades Many Endogenous Vasoactive Peptides



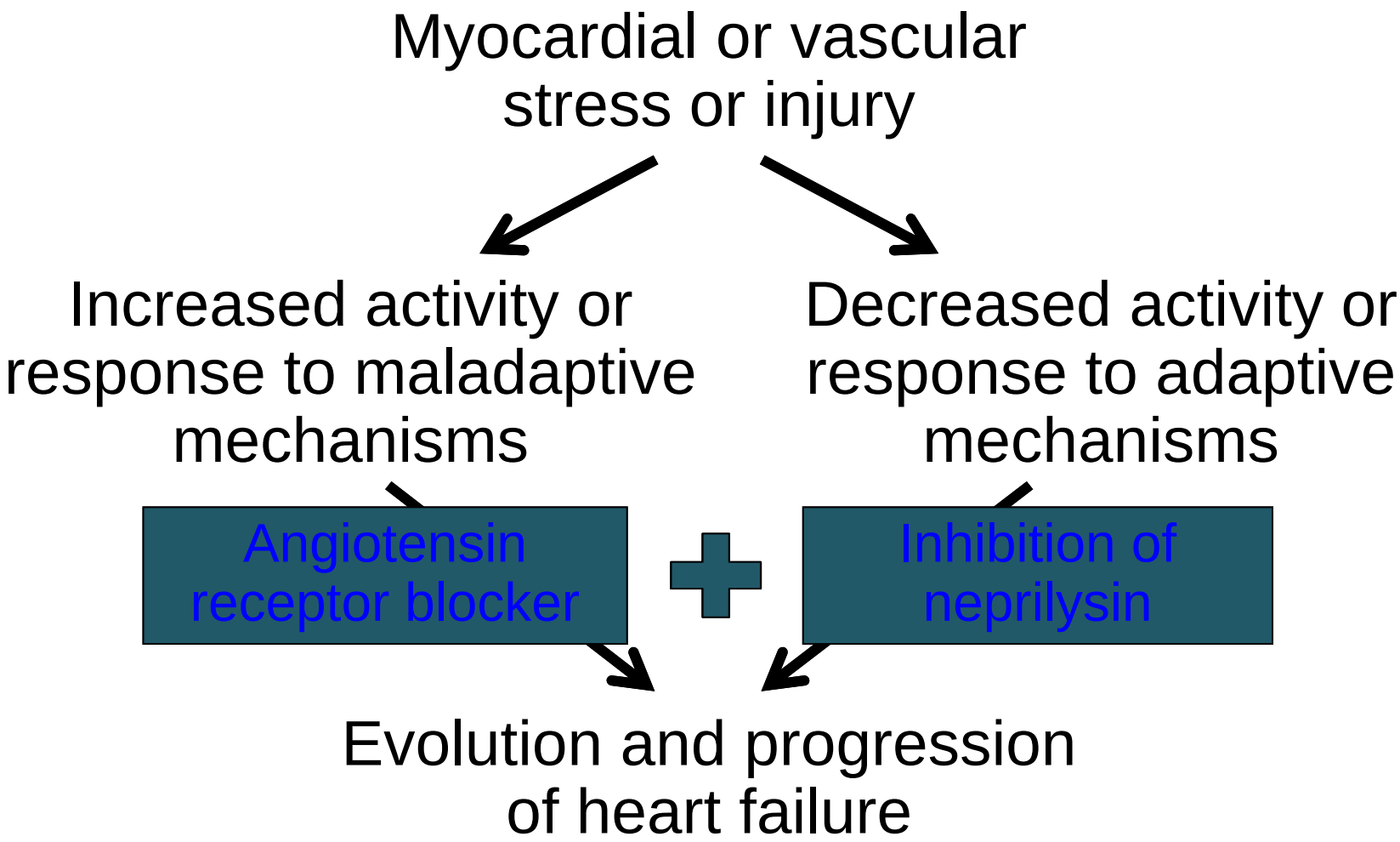
Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure



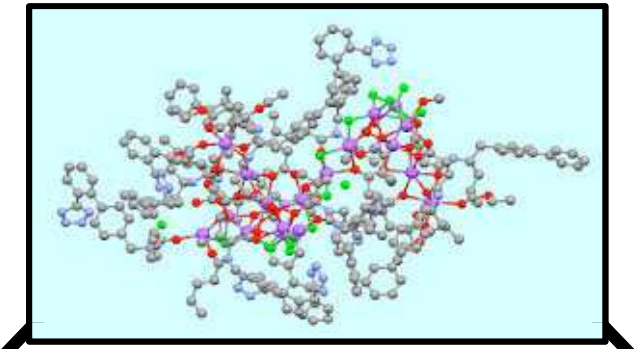
Mechanisms of Progression in Heart Failure



Mechanisms of Progression in Heart Failure



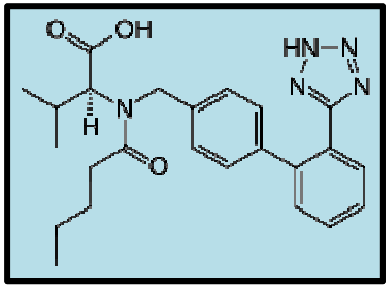
LCZ696: Angiotensin Receptor Neprilysin Inhibition

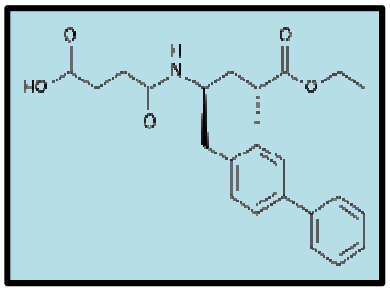


Angiotensin receptor blocker

+

Inhibition of neprilysin





Aim of the PARADIGM-HF Trial

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

LCZ696
400 mg daily

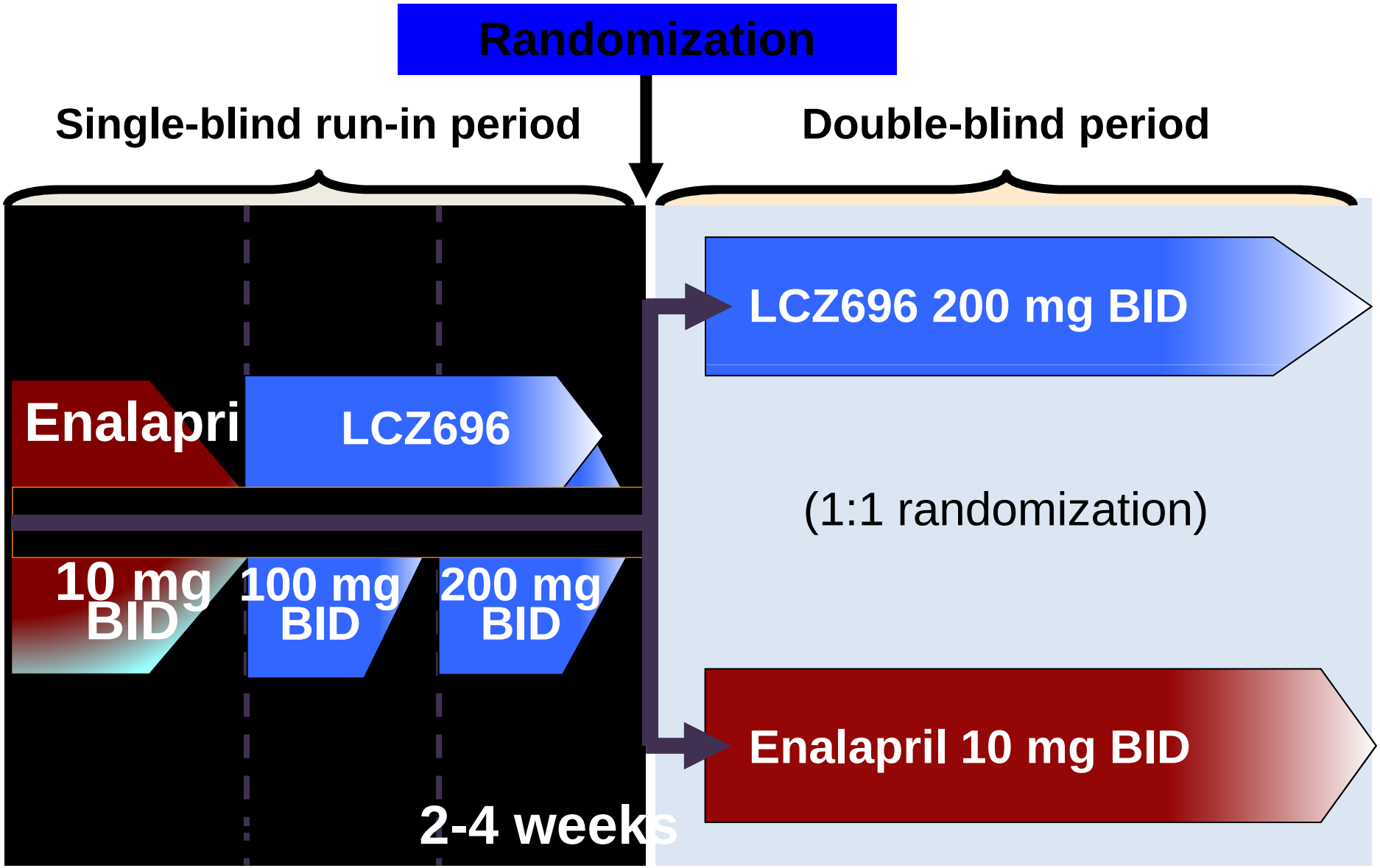
Enalapril
20 mg daily

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE

PARADIGM-HF: Entry Criteria

- NYHA class II-IV heart failure
- LV ejection fraction ≤ 40% ➔ 35%
- BNP ≥ 150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months
- Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks
- Guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists
- Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m^2 and serum K ≤ 5.4 mEq/L at randomization

PARADIGM-HF: Study Design



PARADIGM-HF Was Designed to Show Incremental Effect on Cardiovascular Death

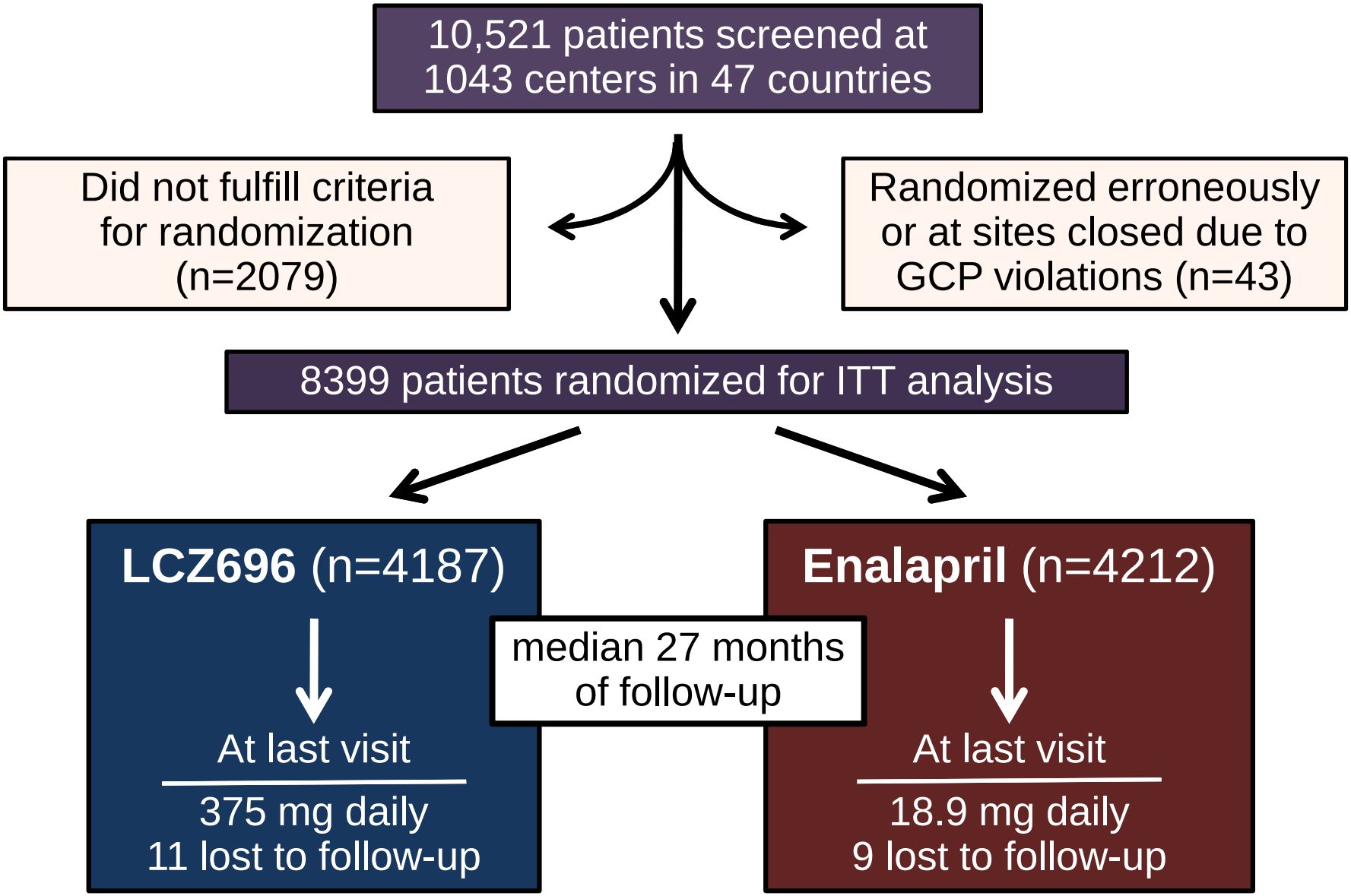
Primary endpoint was cardiovascular death or hospitalization for heart failure, but PARADIGM-HF was designed as a cardiovascular mortality trial

The sample size of the trial was determined by effect on **cardiovascular mortality**, not the primary endpoint

The Data Monitoring Committee was allowed to stop the trial only for a compelling effect on **cardiovascular mortality** (in addition to the primary endpoint)

Difference in cardiovascular mortality of 15% between LCZ696 and enalapril was prospectively identified as being clinically important (n=8000 yielded 80% power)

PARADIGM-HF: Patient Disposition



PARADIGM-HF: Baseline Characteristics

	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 12
N-terminal pro-BNP (pg/ml)	1631 (885-3154)	1594 (886-3305)
B-type natriuretic peptide (pg/ml)	255 (155-474)	251 (153-465)
History of diabetes	35%	35%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
ICD and/or CRT	16.5%	16.3%

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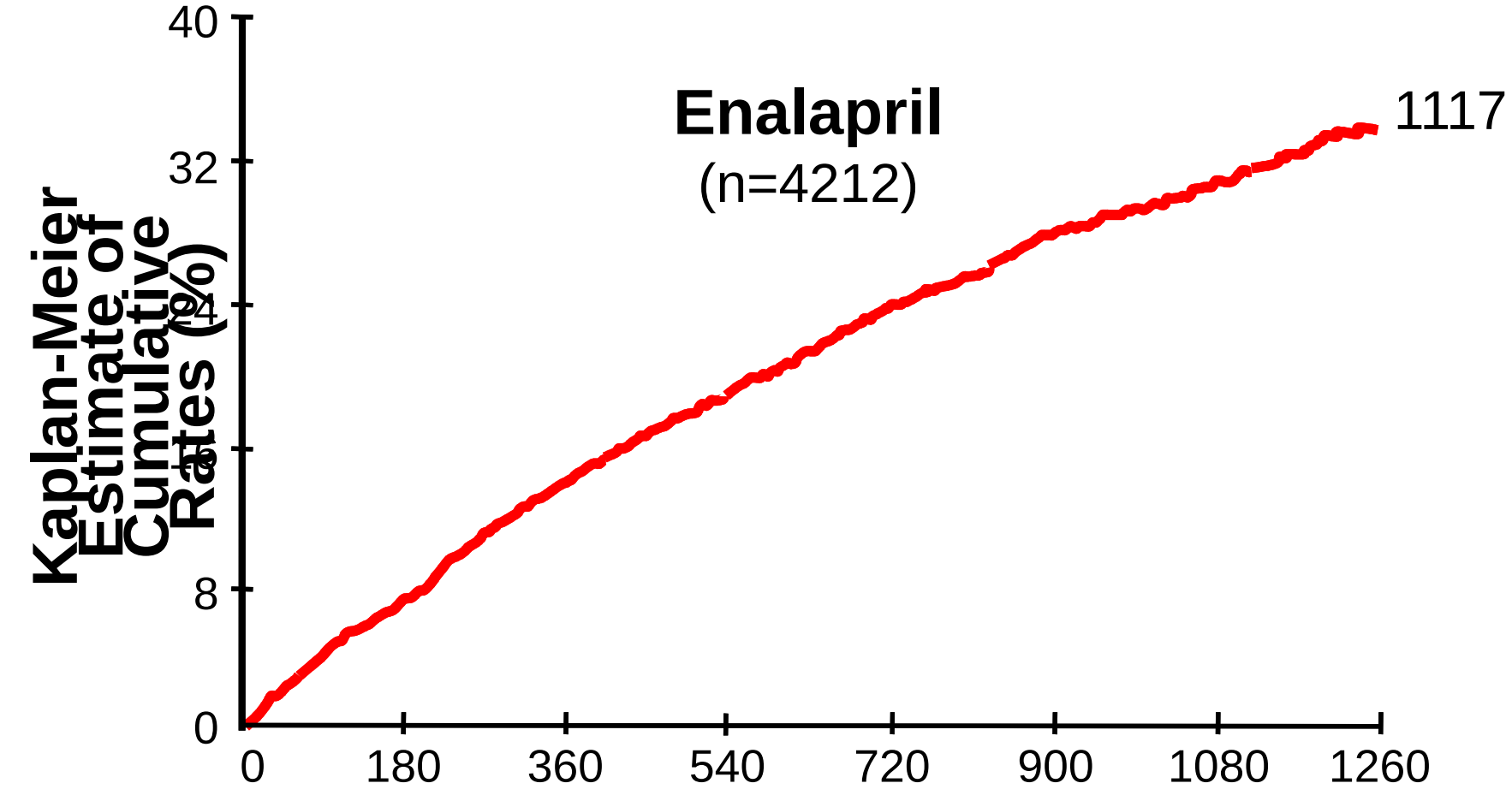
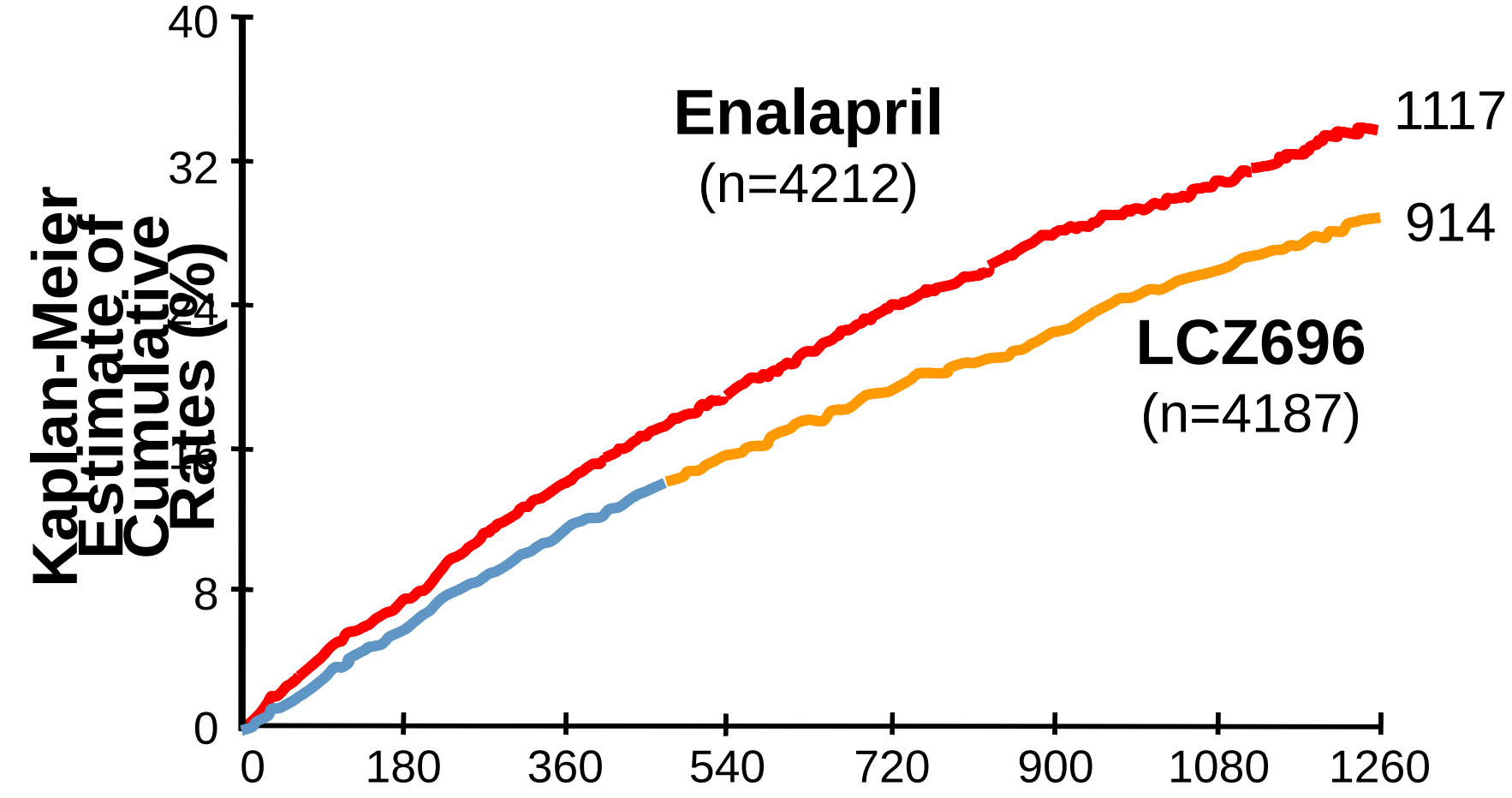
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)



Patients at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)



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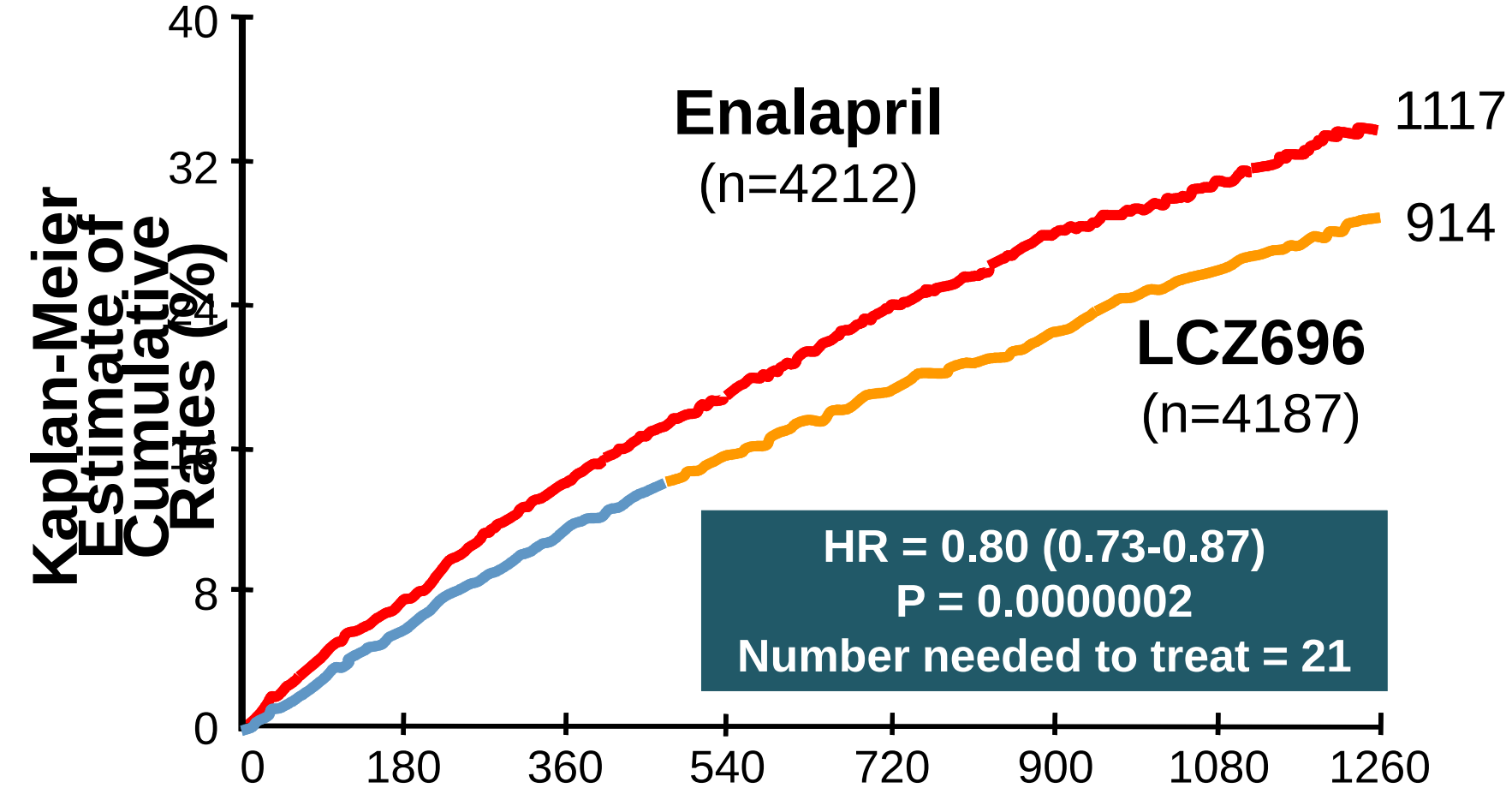

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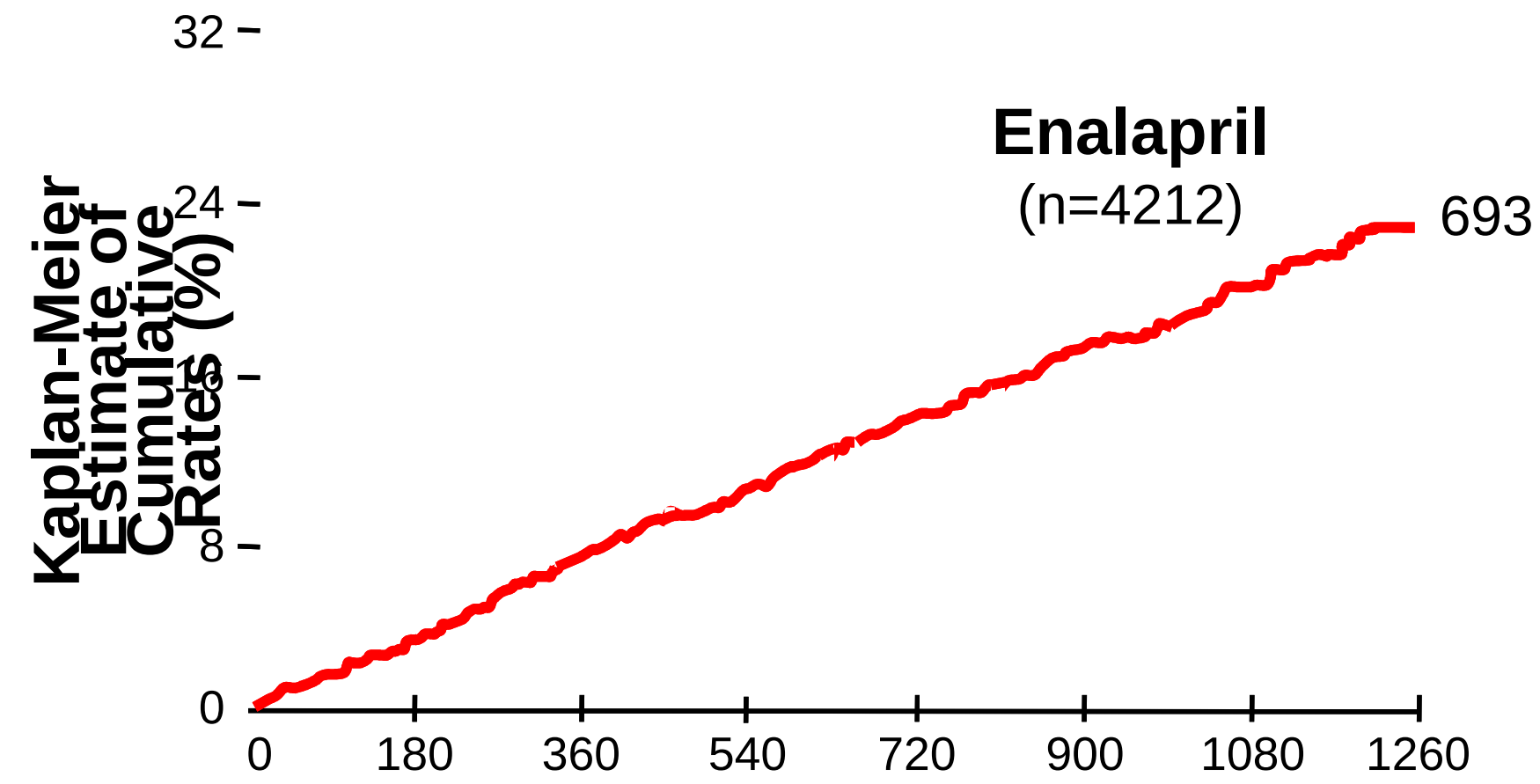
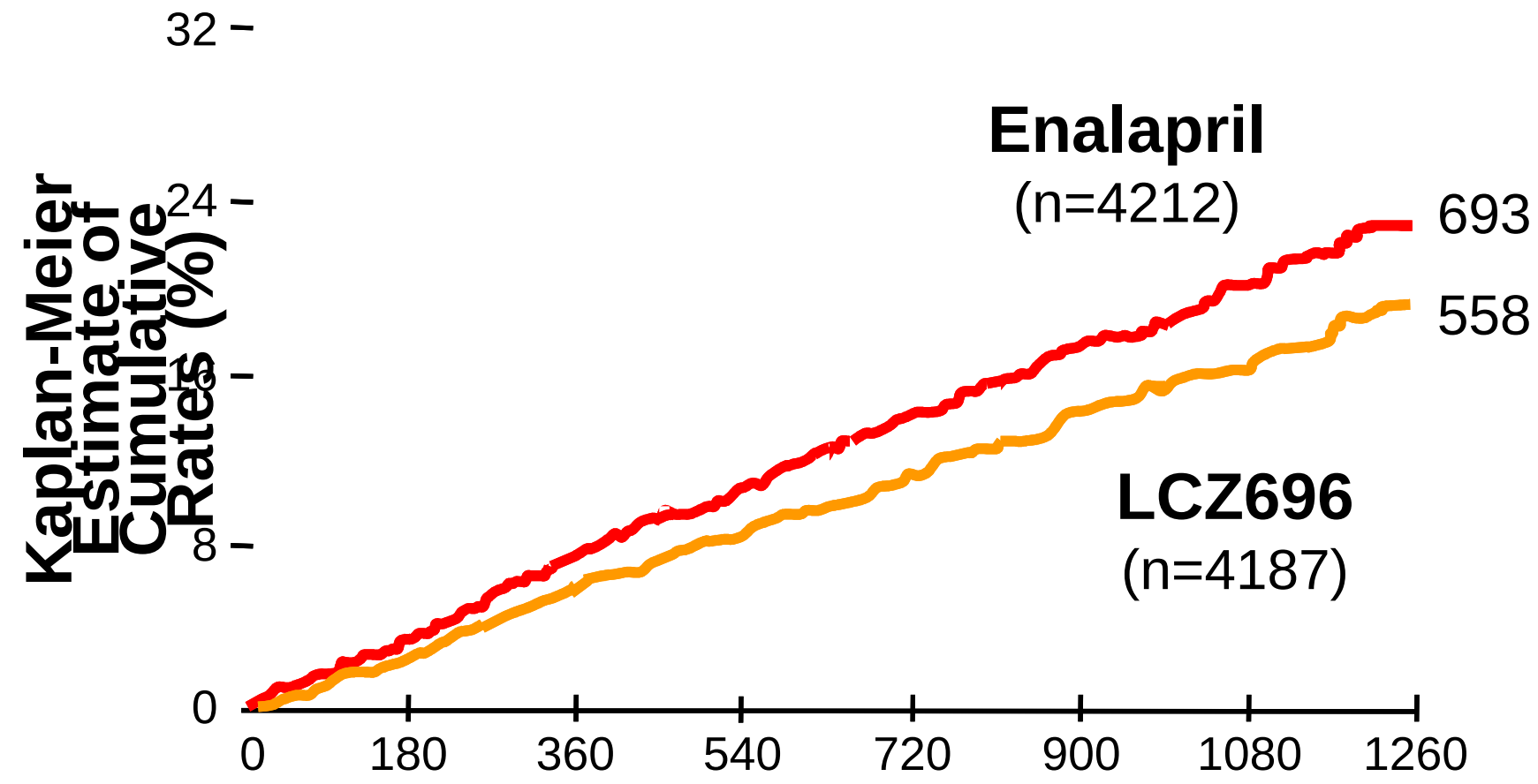
PARADIGM-HF: Cardiovascular Death



Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

PARADIGM-HF: Cardiovascular Death



Patients at Risk

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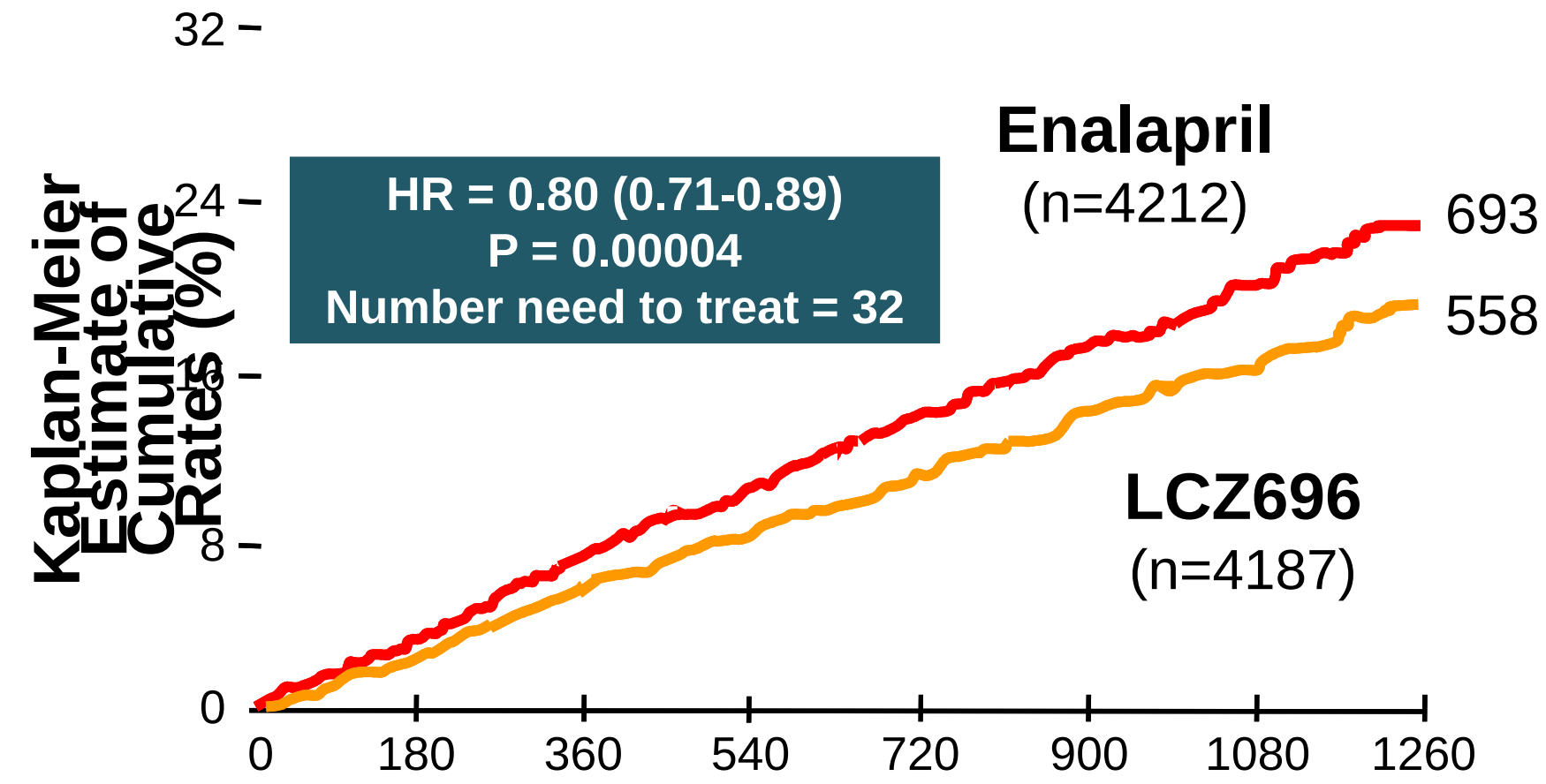
PARADIGM-HF: Cardiovascular Death



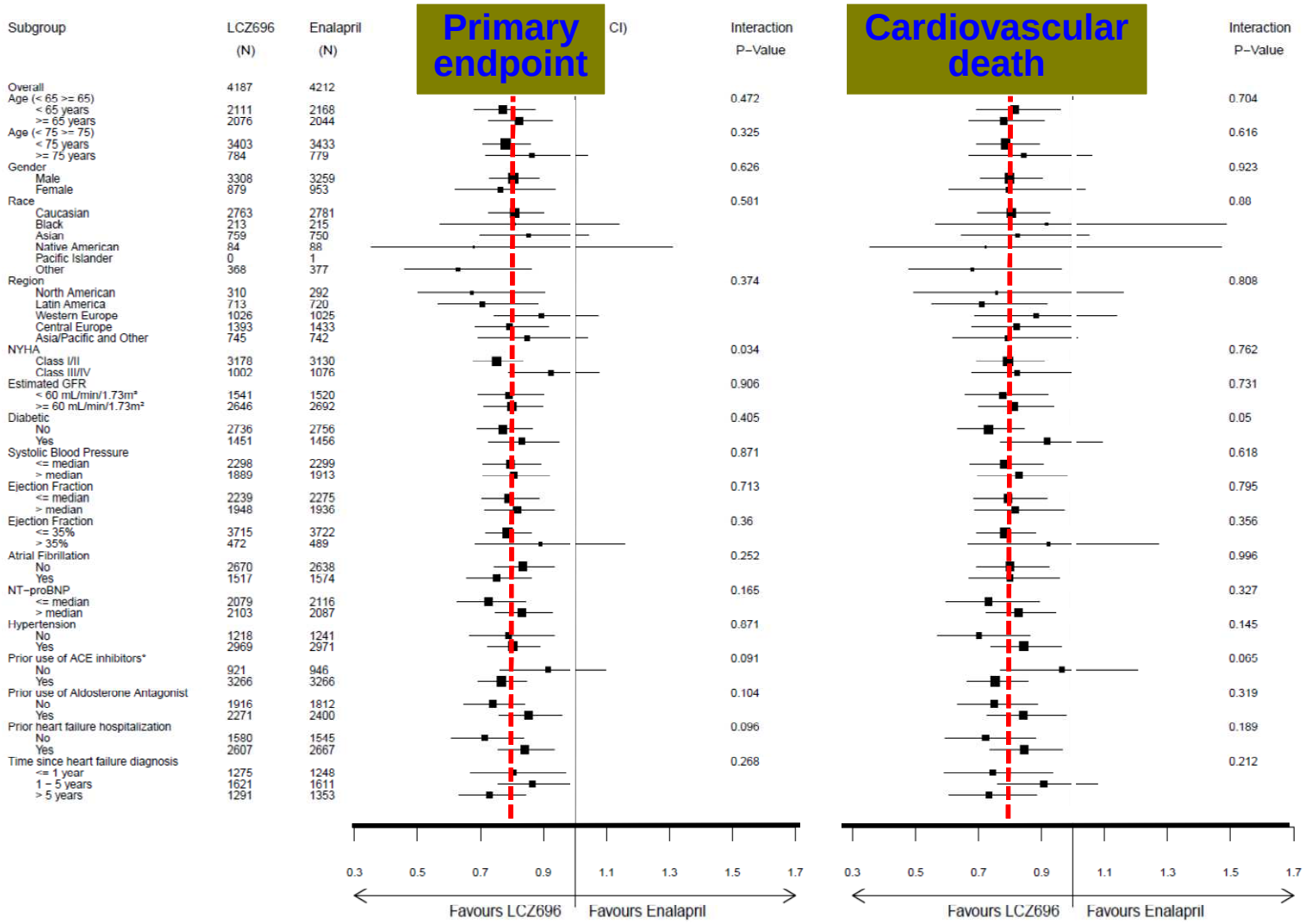
Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

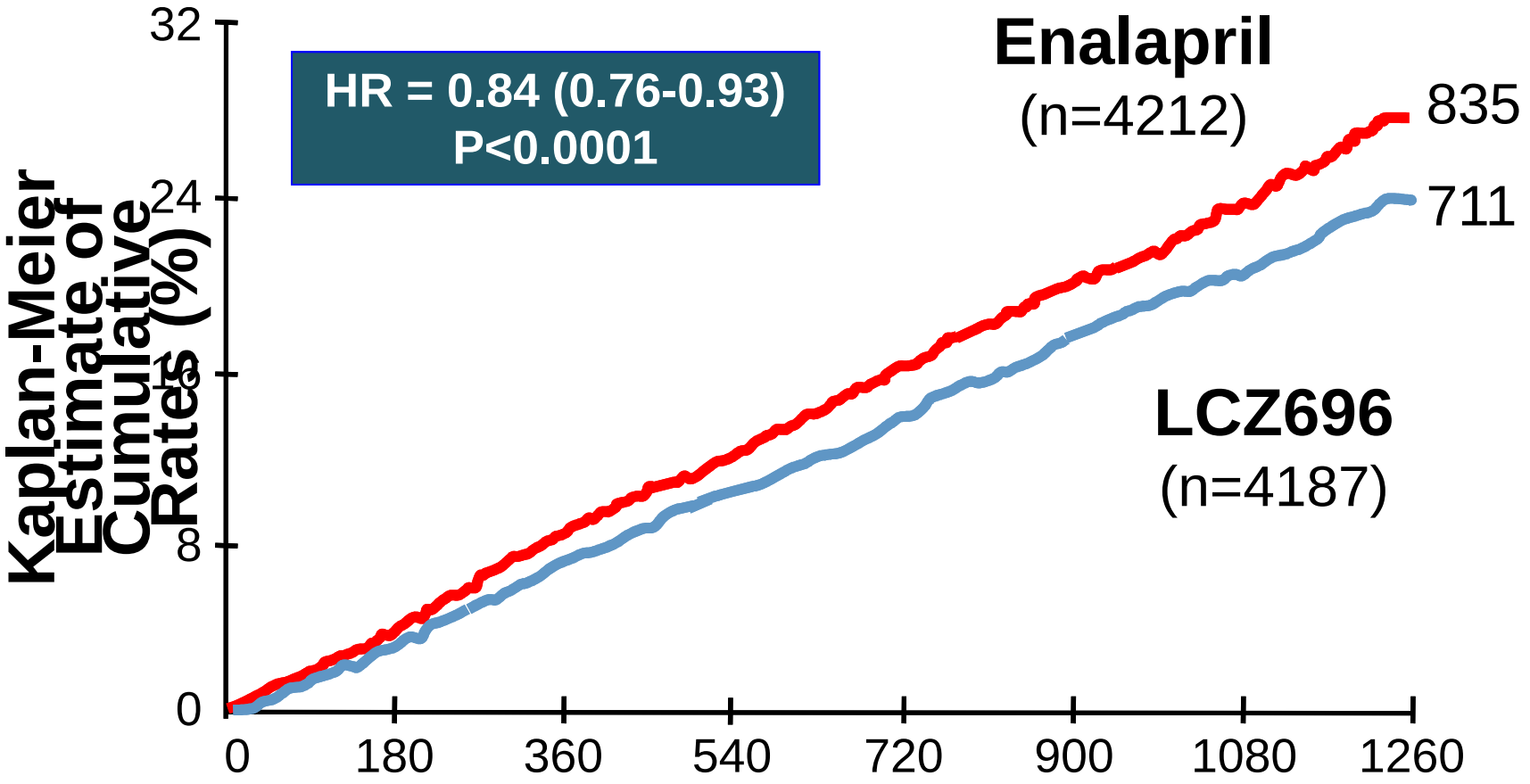
PARADIGM-HF: Effect of LCZ696 vs Enalapril on Primary Endpoint and Its Components

	LCZ696 (n=4187)	Enalapril (n=4212)	Hazard Ratio (95% CI)	P Value
Primary endpoint	914 (21.8%)	1117 (26.5%)	0.80 (0.73-0.87)	0.0000002
Cardiovascular death	558 (13.3%)	693 (16.5%)	0.80 (0.71-0.89)	0.00004
Hospitalization for heart failure	537 (12.8%)	658 (15.6%)	0.79 (0.71- 0.89)	0.00004

LCZ696 vs Enalapril on Primary Endpoint and on Cardiovascular Death, by Subgroups



PARADIGM-HF: All-Cause Mortality



Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

PARADIGM-HF: Adverse Events

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine ≥ 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001
Discontinuation for adverse event	**449**	**516**	**0.02**
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	----

PARADIGM-HF: Summary of Findings

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

LCZ696 was *more effective* than enalapril in . . .

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by *incremental* 20%
- Reducing the risk of HF hospitalization by *incremental* 21%
- Reducing all-cause mortality by *incremental* 16%
- *Incrementally* improving symptoms and physical limitations

LCZ696 was *better tolerated* than enalapril . . .

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

Treatment

European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

- A new compound (LCZ696) that combines the moieties of an ARB (valsartan) and a neprilysin (NEP) inhibitor (sacubitril) has recently been shown to be superior to an ACEI (enalapril) in reducing the risk of death and of hospitalization for HF in a single trial with strict inclusion/ exclusion criteria.
- Sacubitril/valsartan is therefore recommended to replace ACEIs in ambulatory HFrEF patients who remain symptomatic despite optimal therapy and who fit these trial criteria.
- To decrease the risk of angio-oedema, a washout period for the ACE inhibitor of at least 36 h is essential.

PARADIGM-HF: Entry Criteria

- NYHA class II-IV heart failure
- LV ejection fraction ≤ 40% ➔ 35%
- BNP ≥ 150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months
- Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks
- Guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists
- Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m^2 and serum K ≤ 5.4 mEq/L at randomization

Treatment

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.687

Dementia-related adverse events in PARADIGM-HF and other trials in heart failure with reduced ejection fraction

Jane A. Cannon[1†], Li Shen[1†], Pardeep S. Jhund[1], Søren L. Kristensen[2], Lars Køber[2], Fabian Chen[3], Jianjian Gong[3], Martin P. Lefkowitz[3], Jean L. Rouleau[4], Victor C. Shi[3], Karl Swedberg[5], Michael R. Zile[6], Scott D. Solomon[7], Milton Packer[8], and John J.V. McMurray[1*], on behalf of the PARADIGM-HF Investigators and Committees

- Previous concerns about neprilysin inhibition, including increasing β-amyloid protein concentration in the central nervous system—a possible risk factor for Alzheimer's dementia—have been partially addressed, although further investigations will be done in other trials (eg, NCT01920711 and NCT02884206)

Treatment

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.687

Dementia-related adverse events in PARADIGM-HF and other trials in heart failure with reduced ejection fraction

Table 2 Number and rate of cognition-related adverse events in trials analysed

	Broad SMQ *n* (rate[a])	Narrow SMQ *n* (rate[a])
PARADIGM-HF		
Enalapril (*n* = 4212)	97 (0.91, 0.73–1.12)	15 (0.16, 0.10–0.27)
Sacubitril/valsartan (*n* = 4187)	104 (0.92, 0.75–1.14)	12 (0.12, 0.07–0.21)
Hazard ratio (95% CI)	1.01 (0.75–1.37)	0.73 (0.33–1.59)
Val-HeFT		
Placebo (*n* = 2494)	139 (3.03, 2.57–3.56)	5 (0.11, 0.04–0.26)
Valsartan (*n* = 2506)	102 (2.20, 1.82–2.67)	6 (0.13, 0.06–0.28)
Hazard ratio (95% CI)	0.73 (0.56–0.94)	1.12 (0.37–3.93)
CORONA		
Placebo (*n* = 2497)	115 (1.62, 1.33–1.97)	19 (0.31, 0.20–0.48)
Rosuvastatin (*n* = 2514)	120 (1.74, 1.44–2.10)	28 (0.45, 0.31–0.65)
Hazard ratio (95% CI)	1.07 (0.82–1.41)	1.46 (0.82–2.62)
ATMOSPHERE		
Enalapril (*n* = 2336)	52 (0.65, 0.48–0.85)	17 (0.21, 0.12–0.33)
Aliskiren (*n* = 2340)	81 (1.01,0.81–1.26)	20 (0.25, 0.15–0.38)
Combination (*n* = 2340)	85 (1.05, 0.84–1.30)	16 (0.20, 0.11–0.32)
Hazard ratio (95% CI)[b]	1.57 (1.11–2.22)	1.18 (0.62–2.26)
Hazard ratio (95% CI)[c]	1.63 (1.15–2.30)	0.93 (0.47–1.85)

CI, confidence interval; SMQ, Standardized Medical Dictionary for Regulatory Activities Query.

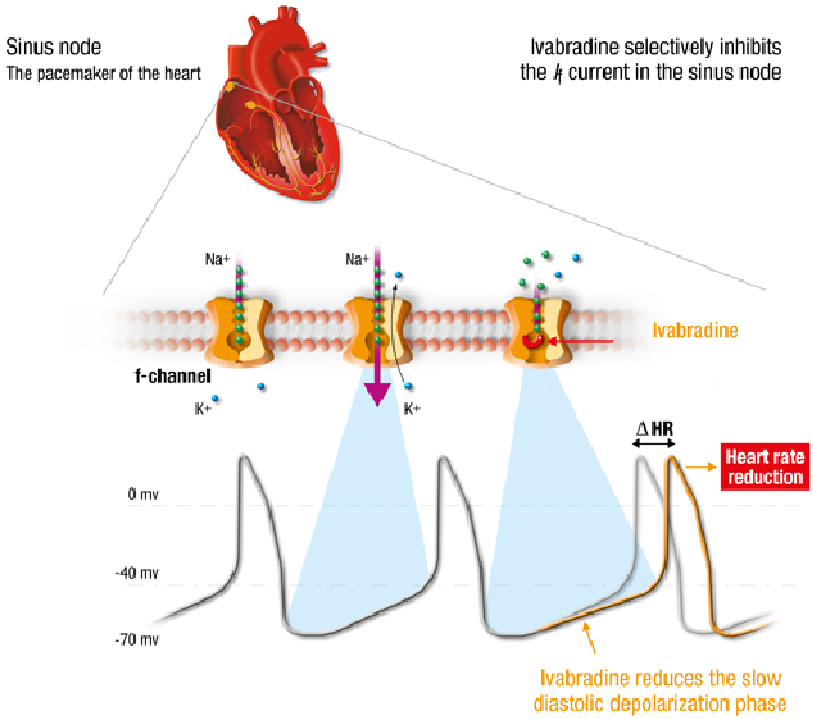
[a]Rates were calculated per 100 patient-years (crude rate with 95% confidence interval). Rate for broad SMQ includes narrow SMQ terms.

[b]Aliskiren vs. enalapril.

[c]Combination vs. enalapril.

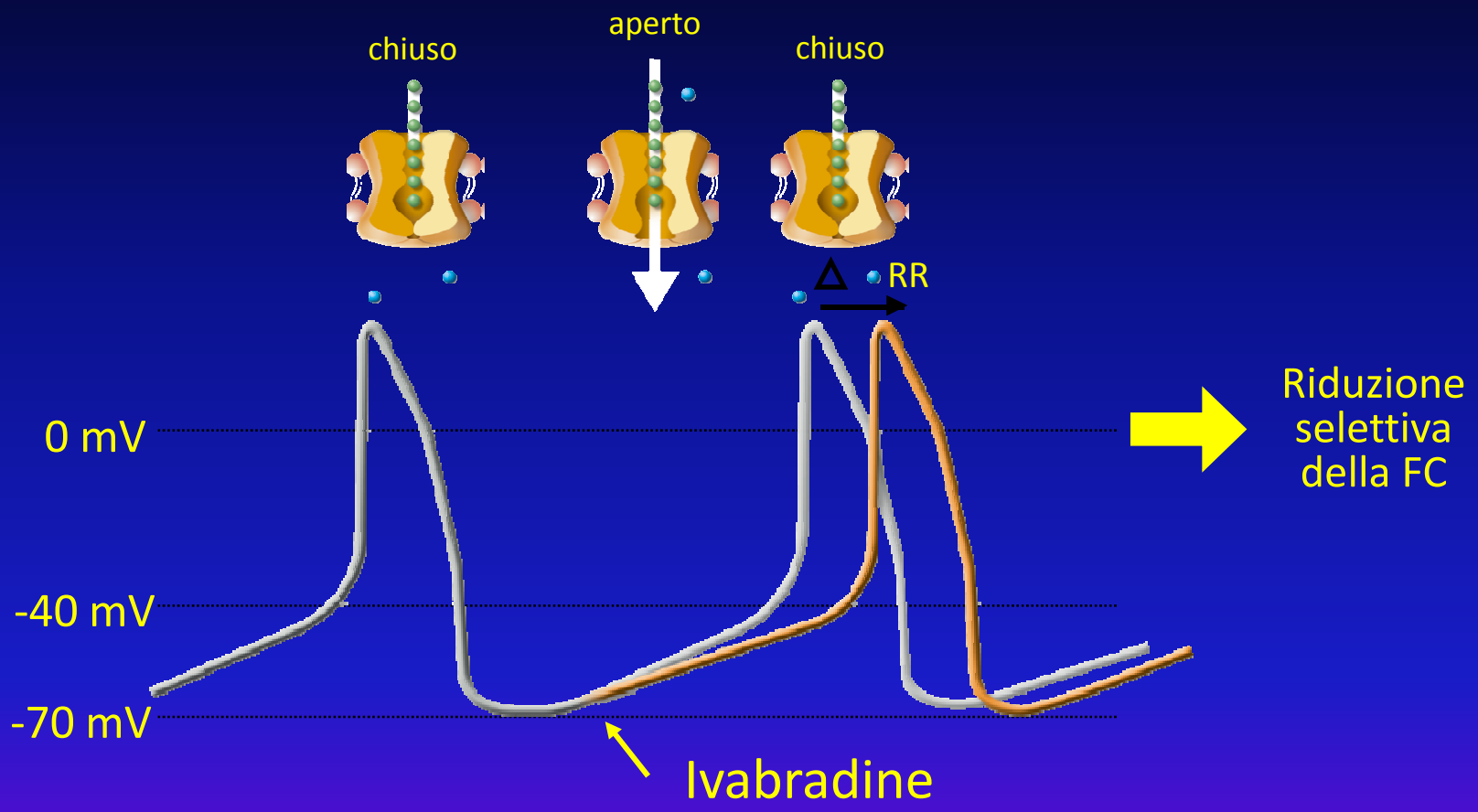
Treatment

Ivabradine and Outcomes in Chronic Heart Failure (SHIFT): a Randomised Controlled Placebo Study



The Lancet, 2010, 376: 875-85

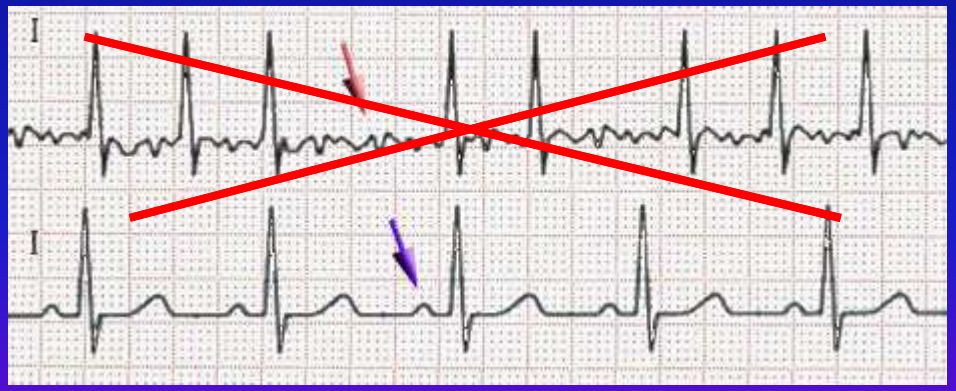
Ivabradina
riduzione selettiva della FC



L'inibizione dei canali If controlla la FC riducendo la pendenza di depolarizzazione diastolica

Thollon C, et al. *Brit J Pharmacol*. 1994;112:37-42.

NB : l'EFFETTO DEL FARMACO SI HA SOLO SE IL PAZIENTE E' IN RITMO SINUSALE

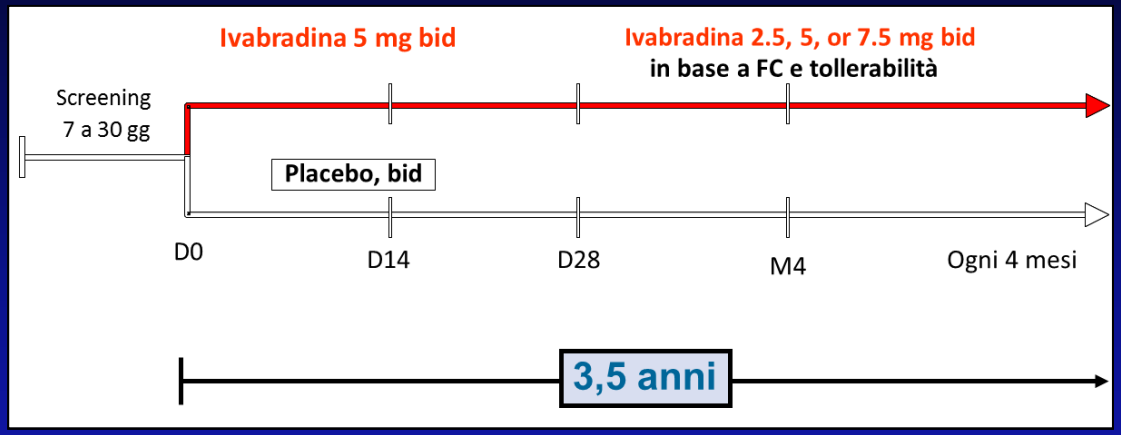


Azione selettiva sulla FC

	β-bloccanti	Verapamil Diltiazem	Ivabradina
Frequenza cardiaca	↓↓	↓	↓↓
Contrattilità cardiaca	↓	↓	ø
Conduzione cardiaca	↓	↓	ø
Eccitabilità cardiaca	↓	ø	ø
Pressione arteriosa	↓	↓	ø

SHIFT

Disegno



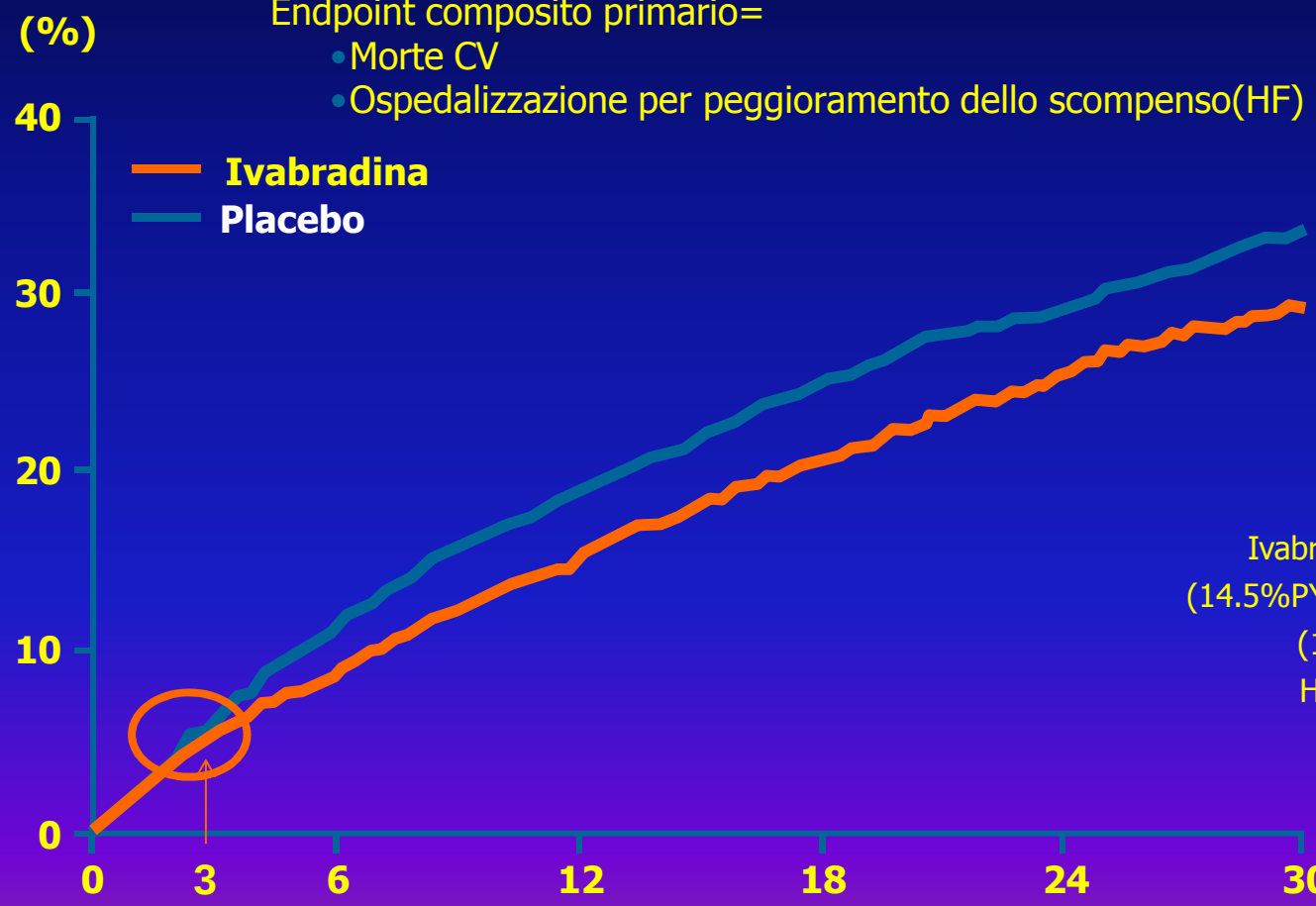
Popolazione

	Ivabradina 3.241	Placebo 3.264
Età media (anni)	60,7	60,1
Maschi, %	76	77
Eziologia ischemica, %	68	67
NYHA II, %	49	49
NYHA III/IV, %	51	51
Precedente IM, %	56	56
Diabete, %	30	31
Ipertensione, %	67	66

Swedberg K, et al. Lancet 2010;376:875-85

Benefici sull'endpoint composito primario

Endpoint composito primario=
- Morte CV
- Ospedalizzazione per peggioramento dello scompenso(HF)



- 18%

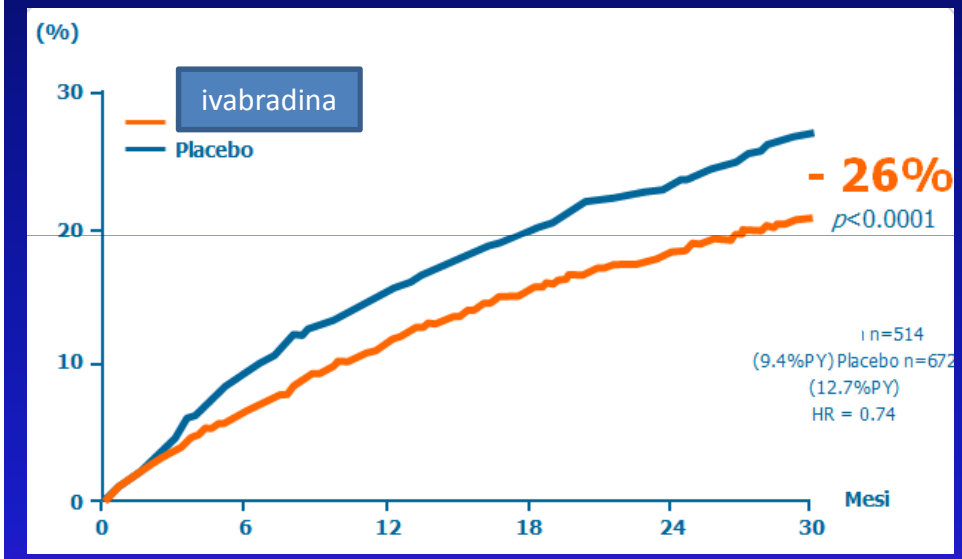
p<0.0001

Ivabradina n=793
(14.5%PY) Placebo n=937
(17.7%PY)
HR = 0.82

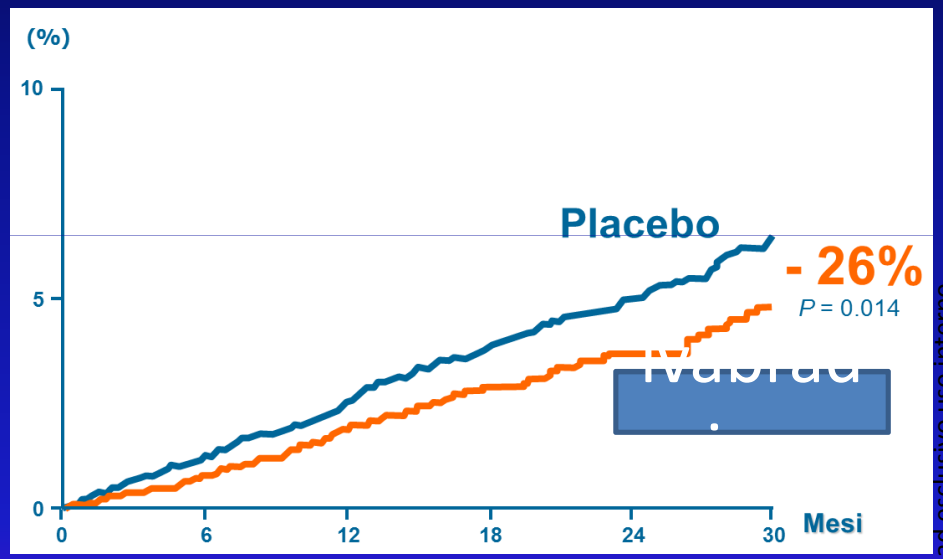
Swedberg K, et al. Lancet 2010;376:875-85

SHIfT

Ospedalizzazione per scompenso



Morte per scompenso

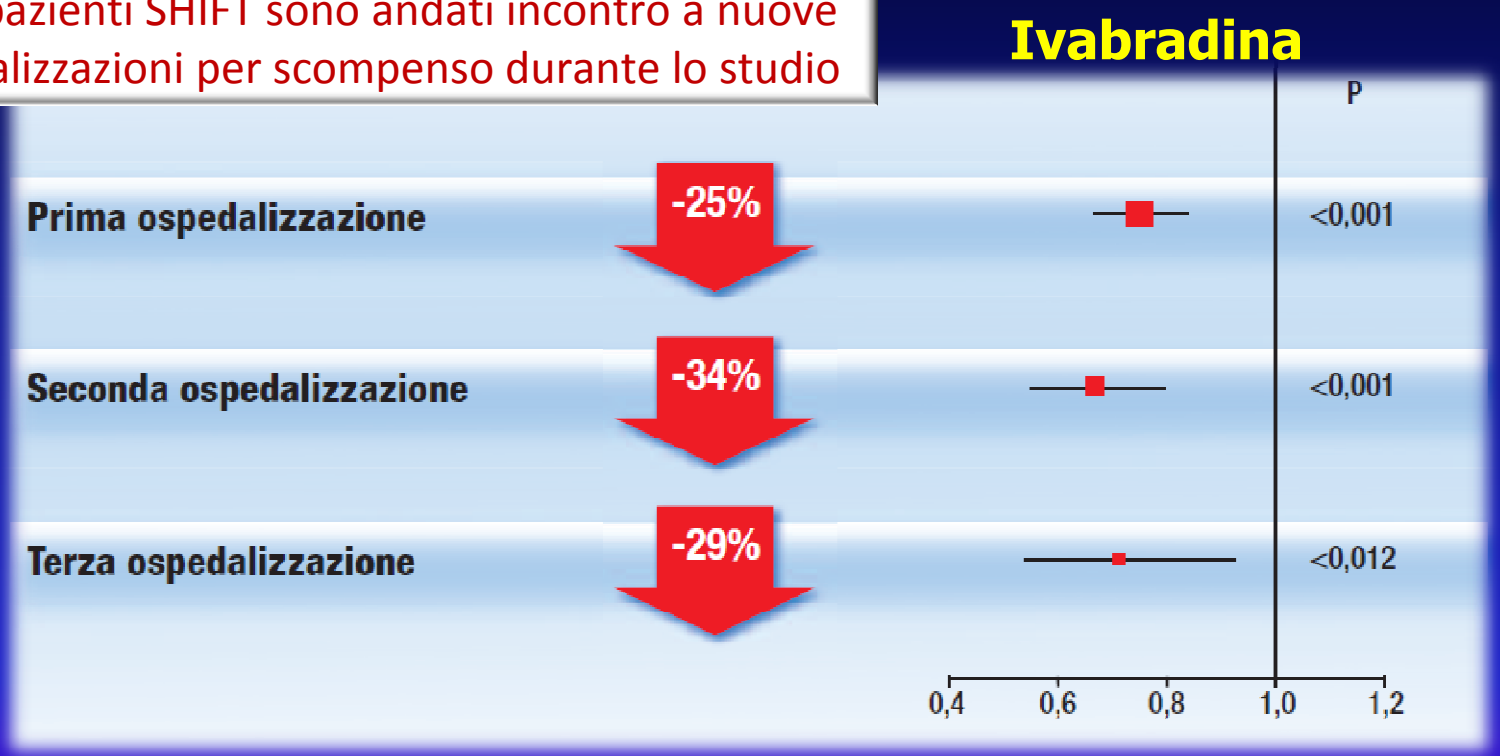


Benefici ottenuti con Ivabradina «on Top» alla normale terapia per il paziente con scompenso

Swedberg K, et al. Lancet 2010;376:875-85

SHIFT hospitalization

1186 pazienti SHIFT sono andati incontro a nuove ospedalizzazioni per scompenso durante lo studio



Il trattamento con Ivabradina è stato associato significativamente a minori ospedalizzazioni

Borer et al. Eur Heart J 2012; doi:10. 1093/eurheartj/ehs259

Treatment

European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
Diuretics			
Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.	I	B	178, 179
Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion.	IIa	B	178, 179
Angiotensin receptor neprilysin inhibitor			
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B	162
I*f*-channel inhibitor			
Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-	IIa	B	180

I*f*-channel inhibitor

Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).	IIa	B
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).	IIa	C

Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.	IIa	B	183
Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.	IIb	B	184
Other treatments with less-certain benefits			
Digoxin			
Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).	IIb	B	185
N-3 PUFA			
An n-3 PUFA[e] preparation may be considered in symptomatic HF patients to reduce the risk of cardiovascular hospitalization and cardiovascular death.	IIb	B	186

European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

Treatment

- Ivabradine slows the heart rate through inhibition of the If channel in the sinus node and therefore should only be used for patients in sinus rhythm.
- The European Medicines Agency (EMA) approved ivabradine for use in Europe in patients with HFrEF with LVEF ≤35% and in sinus rhythm with a resting heart rate ≥75 bpm, because in this group ivabradine conferred a survival benefit based on a retrospective subgroup analysis requested by the EMA.

Future Directions for Treatment

Future directions

Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial

John R Teerlink, G Michael Felker, John J V McMurray, Scott D Solomon, Kirkwood F Adams Jr, John G F Cleland, Justin A Ezekowitz, Assen Goudev, Peter Macdonald, Marco Metra, Veselin Mitrovic, Piotr Ponikowski, Pranas Serpytis, Jindrich Spinar, János Tomcsányi, Hans J Vandekerckhove, Adriaan A Voors, Maria Laura Monsalvo, James Johnston, Fady I Malik, Narimon Honarpour, for the COSMIC-HF Investigators

Omecamtiv mecarbil, a cardiac myosin activator that directly improves cardiac function, has shown favourable results in initial studies.

In a study of 450 patients with heart failure with reduced ejection fraction (COSMIC-HF), 20 weeks of oral omecamtiv mecarbil decreased ventricular dimensions and volumes, increased stroke volume and ejection fraction, and reduced heart rate and NT-proBNP concentrations.

Omecamtiv mecarbil is being investigated in an outcomes trial of 8000 patients (GALACTIC-HF; NCT02929329).

Lancet 2016; 388: 2895–903

Future directions

European Heart Journal (2017) **38**, 1119–1127
doi:10.1093/eurheartj/ehw593

Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF (SOCRATES-PRESERVED) study

Vericiguat is a soluble guanylate cyclase stimulator that augments nitric oxide production.

Vericiguat has been studied in phase 2 trials of patients with heart failure with reduced or preserved ejection fraction, and is being evaluated in a large phase 3 trial of patients with reduced ejection fraction (VICTORIA; NCT02861534).

Future directions

European Heart Journal (2017) **38**, 1119–1127
doi:10.1093/eurheartj/ehw593

Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF (SOCRATES-PRESERVED) study

Vericiguat was well tolerated, did not change NT-proBNP and LAV at 12 weeks compared with placebo but was associated with improvements in quality of life in patients with HFpEF.

Given the encouraging results on quality of life, the effects of vericiguat in patients with HFpEF warrant further study, possibly with higher doses, longer follow-up and additional endpoints

Gruppo di ricerca geriatrica

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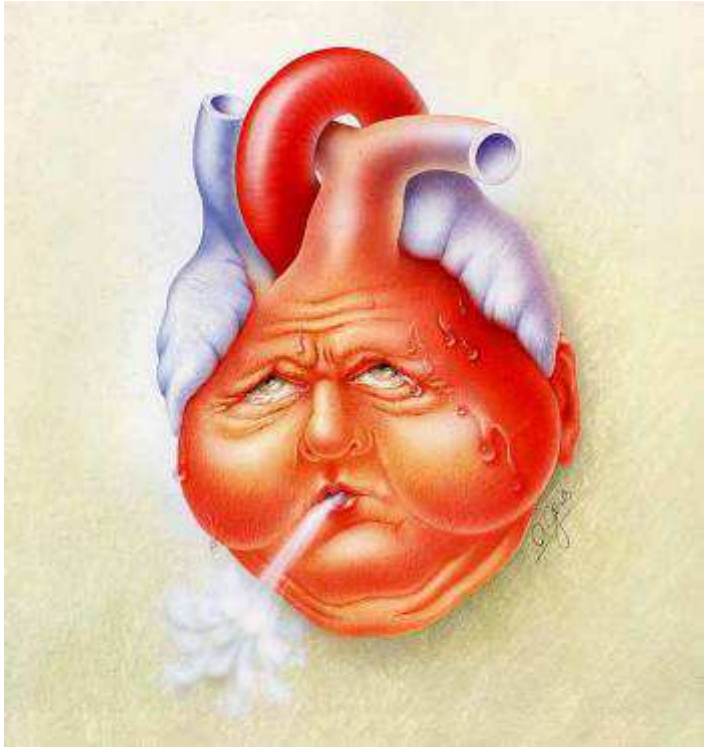

GRAZIE