Congestive Heart Failure

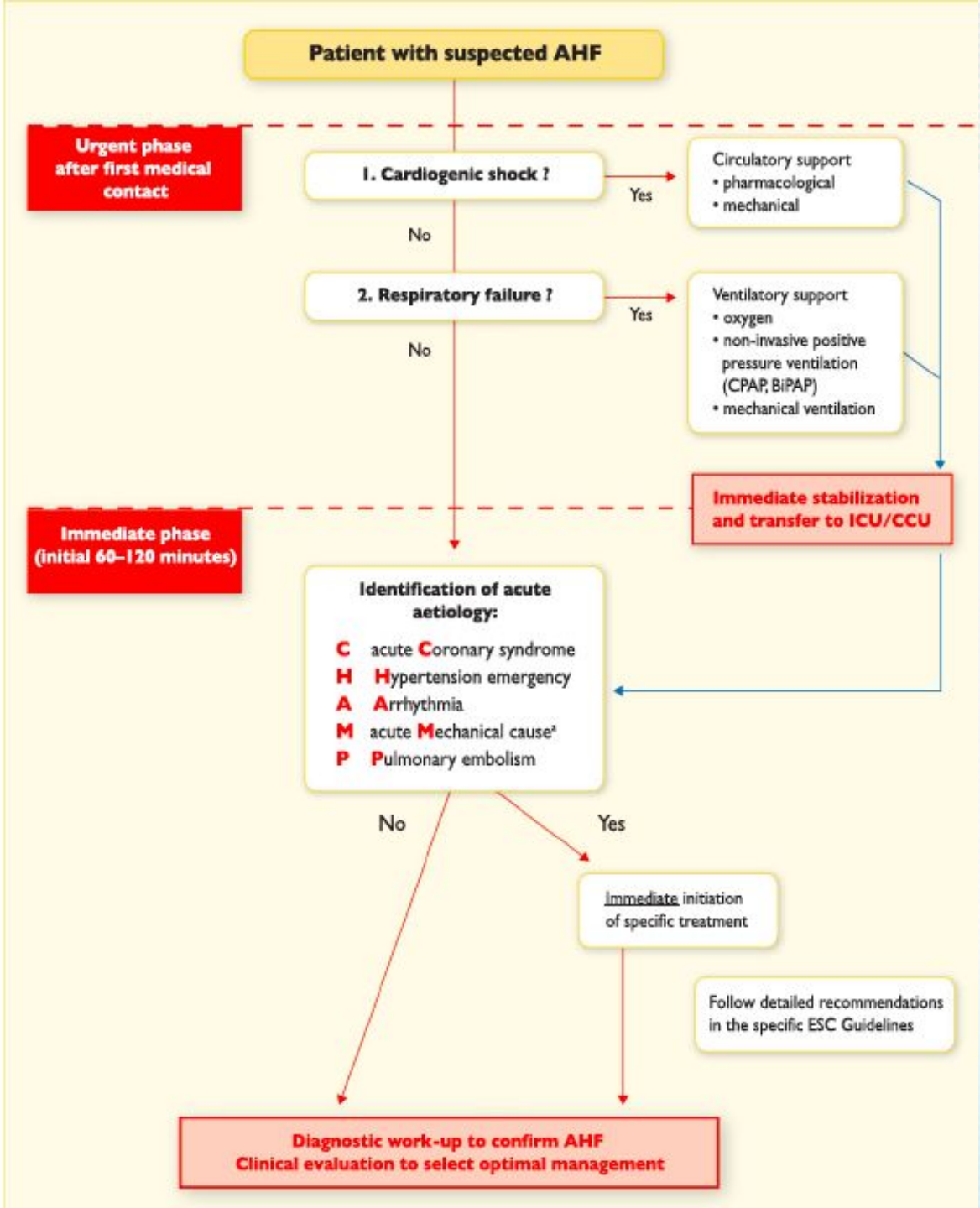
Diagnosis, Assessment and Treatment

Heart Failure: Epidemiology

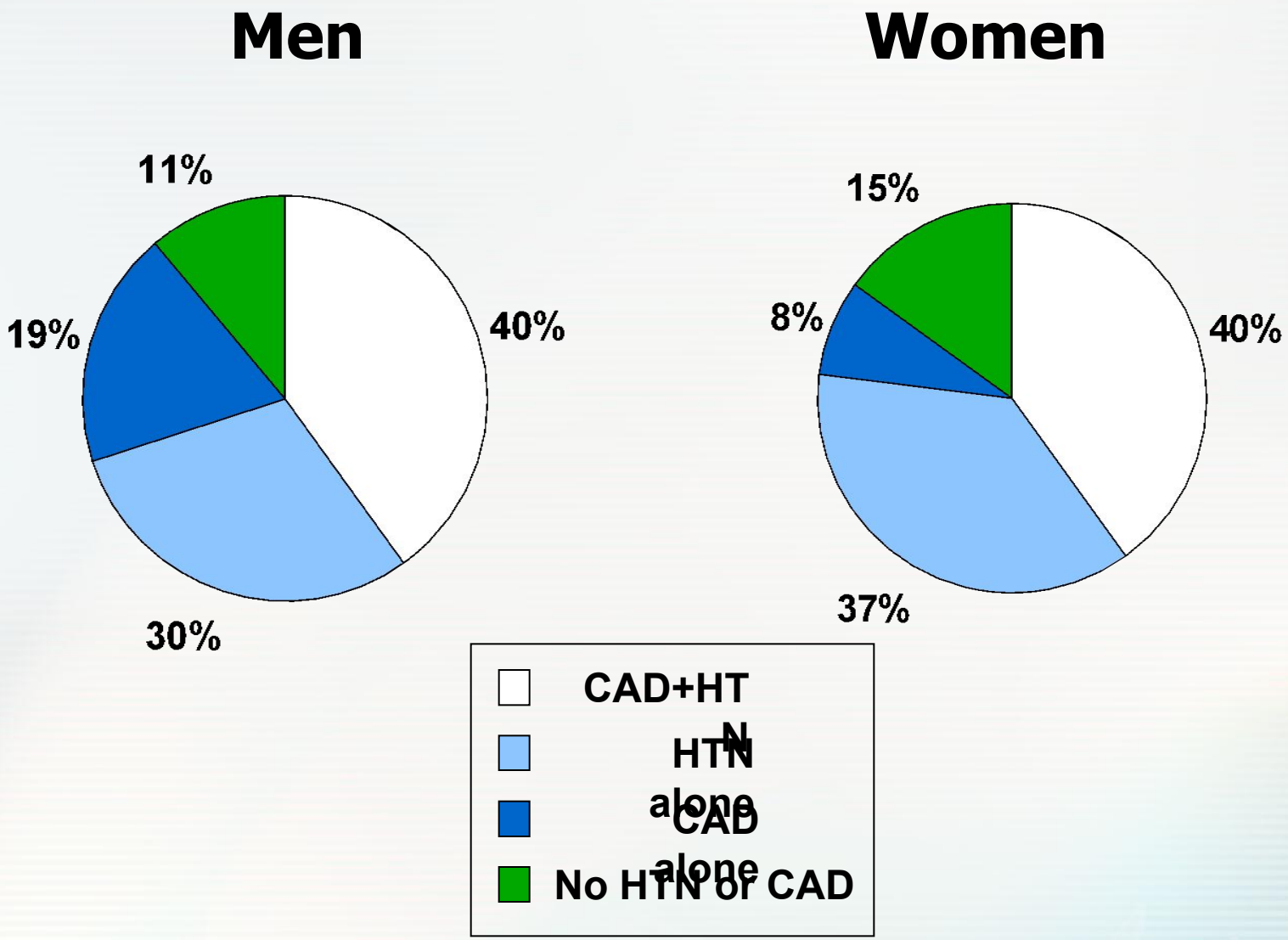
- **Burden of CHF is staggering**
  - **5 million in US (1.5% of all adults)**
  - **500.000 cases annually**
  - **In the elderly**
    - ✔ **6-10% prevalence**
    - ✔ **80% hospitalized with HF**
  - **250.000 death/year attributable to CHF**
  - **$38 billion (5.4% of healthcare cost)**

Definition

HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) 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.


Patient with suspected AHF
Urgent phase after first medical contact
1. Cardiogenic shock ?
Yes
Circulatory support
• pharmacological
• mechanical
No
2. Respiratory failure ?
Yes
Ventilatory support
• oxygen
• non-invasive positive pressure ventilation (CPAP, BiPAP)
• mechanical ventilation
No
Immediate stabilization and transfer to ICU/CCU
Immediate phase (initial 60–120 minutes)
Identification of acute aetiology:
C acute Coronary syndrome
H Hypertension emergency
A Arrhythmia
M acute Mechanical cause[a]
P Pulmonary embolism
No
Yes
Immediate initiation of specific treatment
Follow detailed recommendations in the specific ESC Guidelines
Diagnostic work-up to confirm AHF
Clinical evaluation to select optimal management

Etiologies of Chronic Heart Failure



Stages of Heart Failure

NYHA Class

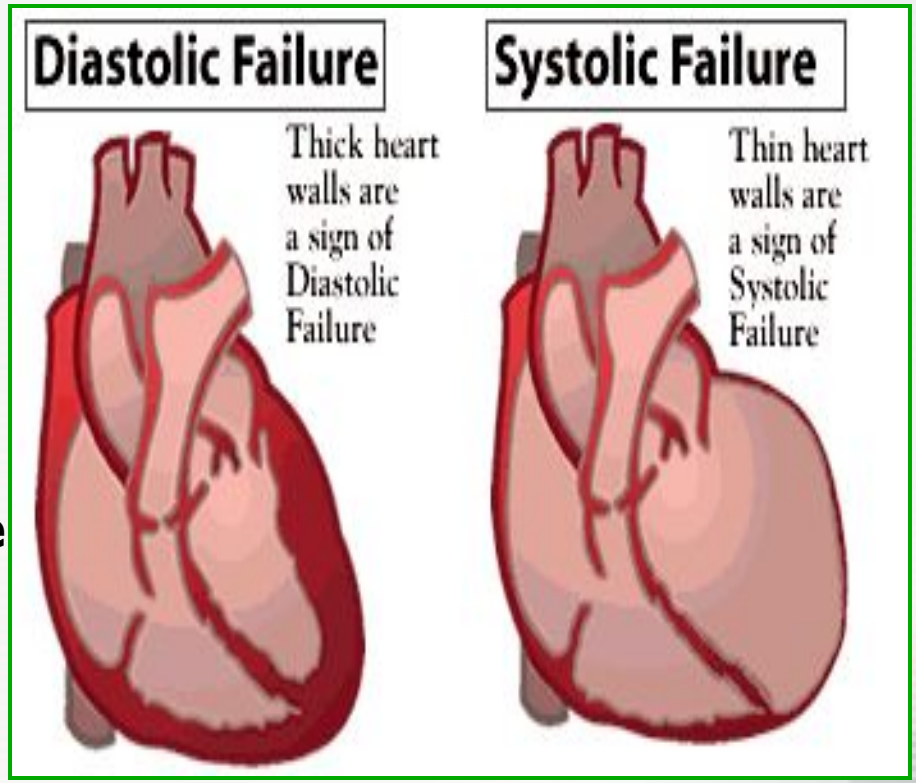
- Class I : Symptoms with more than ordinary activity
- Class II: Symptoms with ordinary activity
- Class III: Symptoms with minimal activity
- Class IV: Symptoms at rest

Types of HF

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).

Systolic vs. Diastolic HF (HFrEF vs. HFpEF)

- **Diastolic dysfunction**
  - **EF normal or increased**
  - **Hypertension**
  - **Due to chronic replacement fibrosis & ischemia-induced decrease in distensibility**
- **Systolic dysfunction**
  - **EF < 40%**
  - **Usually from coronary disease**
  - **Due to ischemia-induced decrease in contractility**
- **A combination of both**



Subtypes of Systolic Heart Failure

- Left Heart Failure
  - Pulmonary congestion
- Right Heart Failure
  - Peripheral edema
- Biventricular Failure
  - Systemic and pulmonary congestion

- Low cardiac output
- High output
  - Severe anemia
  - AV malformations
  - Hyperthyroidism

Principles of Treatment

Systolic HF

- ↓ Preload
- ↓ Afterload
- ↑ Inotropism
- ↓ Neurohumoral activity

- ACE-I, β-blockers, diuretics and aldosterone antagonist are the mainstay of treatment

Management of Heart Failure

- Therapies
  - ACE-Inhibitors
  - Beta Blockers
  - Aldactone
  - Diuretics
  - Digoxin
- Recent non-Pharmacological Advances
  - Sudden death and ICD's
  - Contractile dysynchrony and biventricular pacing
- Diastolic Dysfunction

Diagnosis of HF

- Anamnesis
- Chest X-Ray
- ECG
- Echocardiography
- Cardiac catheterization: coronary angiography and Rt heart catheterization
- CMR
- Myocardial biopsy
- Genetic testing

Recommendations
Upon presentation a measurement of plasma natriuretic peptide level (BNP, NT-proBNP or MR-proANP) is recommended in all patients with acute dyspnoea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnoea.
At admission in all patients presenting with suspected AHF, the following diagnostic tests are recommended: a. 12-lead ECG; b. chest X-ray to assess signs of pulmonary congestion and detect other cardiac or non-cardiac diseases that may cause or contribute to the patient's symptoms; c. the following laboratory assessments in the blood: cardiac troponins, BUN (or urea), creatinine, electrolytes (sodium, potassium), glucose, complete blood count, liver function tests and TSH.
Echocardiography is recommended immediately in haemodynamically unstable AHF patients and within 48 hours when cardiac structure and function are either not known or may have changed since previous studies.

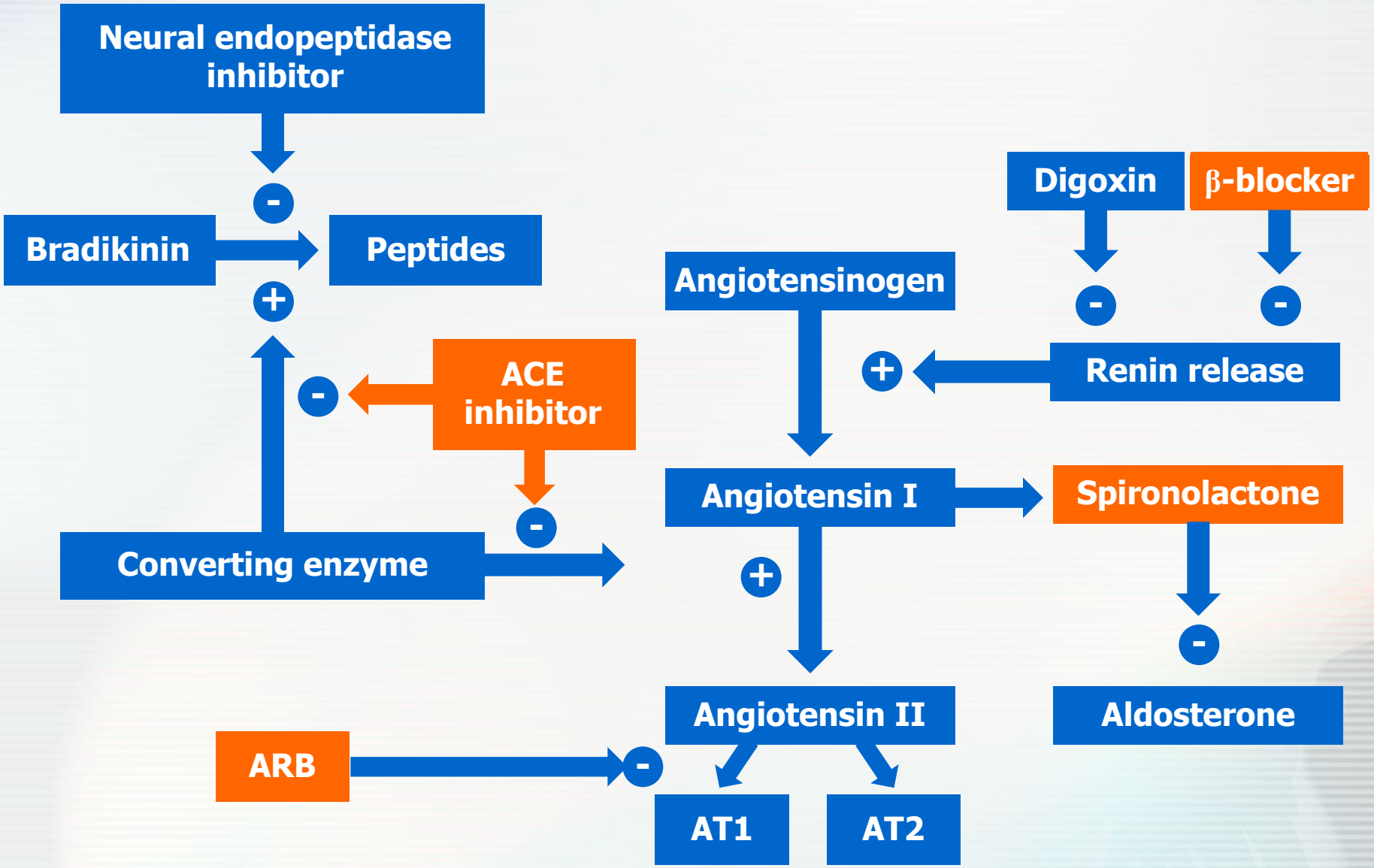
Aims of therapy

- Reduce symptoms & improve QOL
- Reduce hospitalization
- Reduce mortality
  - Pump failure
  - Sudden cardiac death

Targets for treatment: Neurohormonal responses to impaired cardiac performance

Physiological response	Short-term effects	Long-term effects
Salt and water retention	Augmented preload	Pulmonary congestion, anasarca
Vasoconstriction	Maintains BP for perfusion of vital organs	Exacerbates pump dysfunction (excessive afterload), increases cardiac energy expenditure
Sympathetic stimulation	Increase HR and ejection	Increases energy expenditure & risk of arrhythmias & sudden death

Renin-Angiotensin Cascade & β-blockers



SAVE: Survival and Ventricular Enlargement study

Purpose

To determine whether long-term therapy with the ACE inhibitor captopril reduces morbidity and mortality in patients with left ventricular dysfunction after MI

Reference

Pfeffer MA, Braunwald E, Moyé LA *et al*. on behalf of the SAVE Investigators. **Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival And Ventricular Enlargement trial. *N Engl J Med* 1992;**327**:669–77.**

SAVE: Survival and Ventricular Enlargement study

Design

Multicenter, randomized, double-blind, placebo-controlled

Patients

2231 patients, aged 21–80 years, with left ventricular dysfunction (ejection fraction ≤40%), but no overt heart failure or symptoms of myocardial ischemia, 3–16 days after MI

Follow up and primary endpoint

Average 3.5 years follow up. Primary endpoint all-cause mortality

Treatment

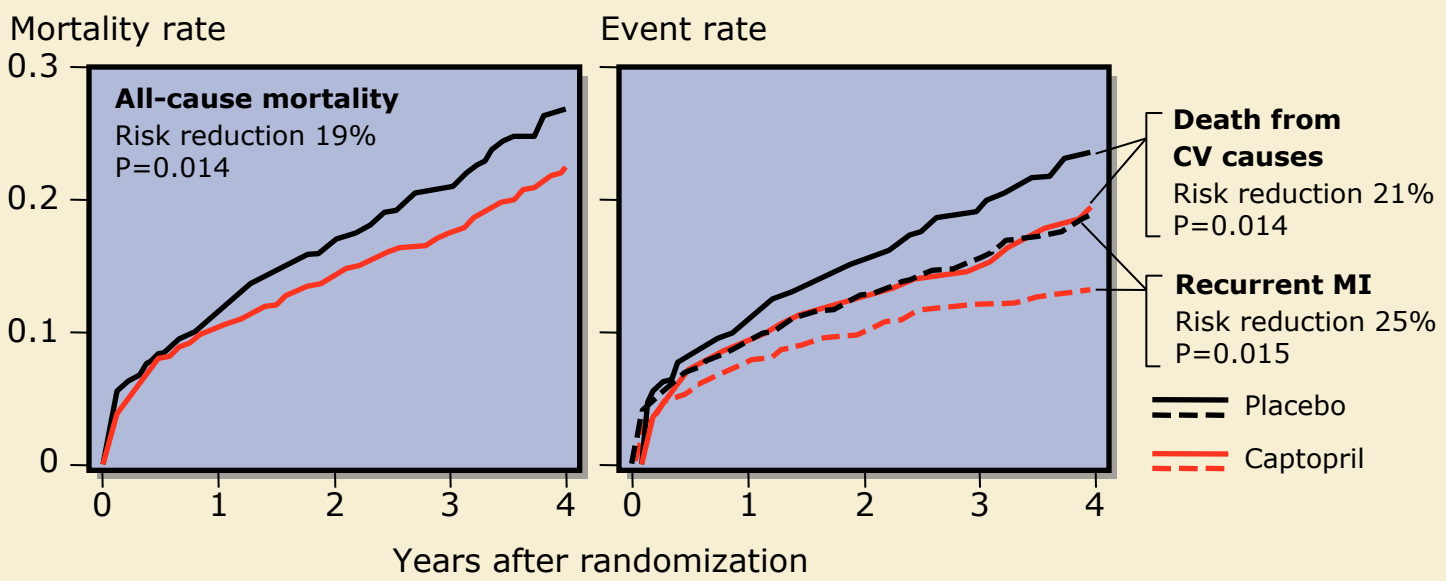
Placebo or captopril, initially titrated from 12.5 mg to 25 mg three-times daily before leaving hospital, increasing to maximum 50 mg three-times daily if tolerated

SAVE: Survival and Ventricular Enlargement study

In patients with left ventricular dysfunction after MI, long-term captopril over a mean 3.5-year period:

- **Significantly improved overall survival rates, including significant reduction in risk of death due to cardiovascular causes**
- **Reduced risk of recurrent MI, development of severe heart failure and CHF requiring hospitalization**

SAVE: Survival and Ventricular Enlargement study

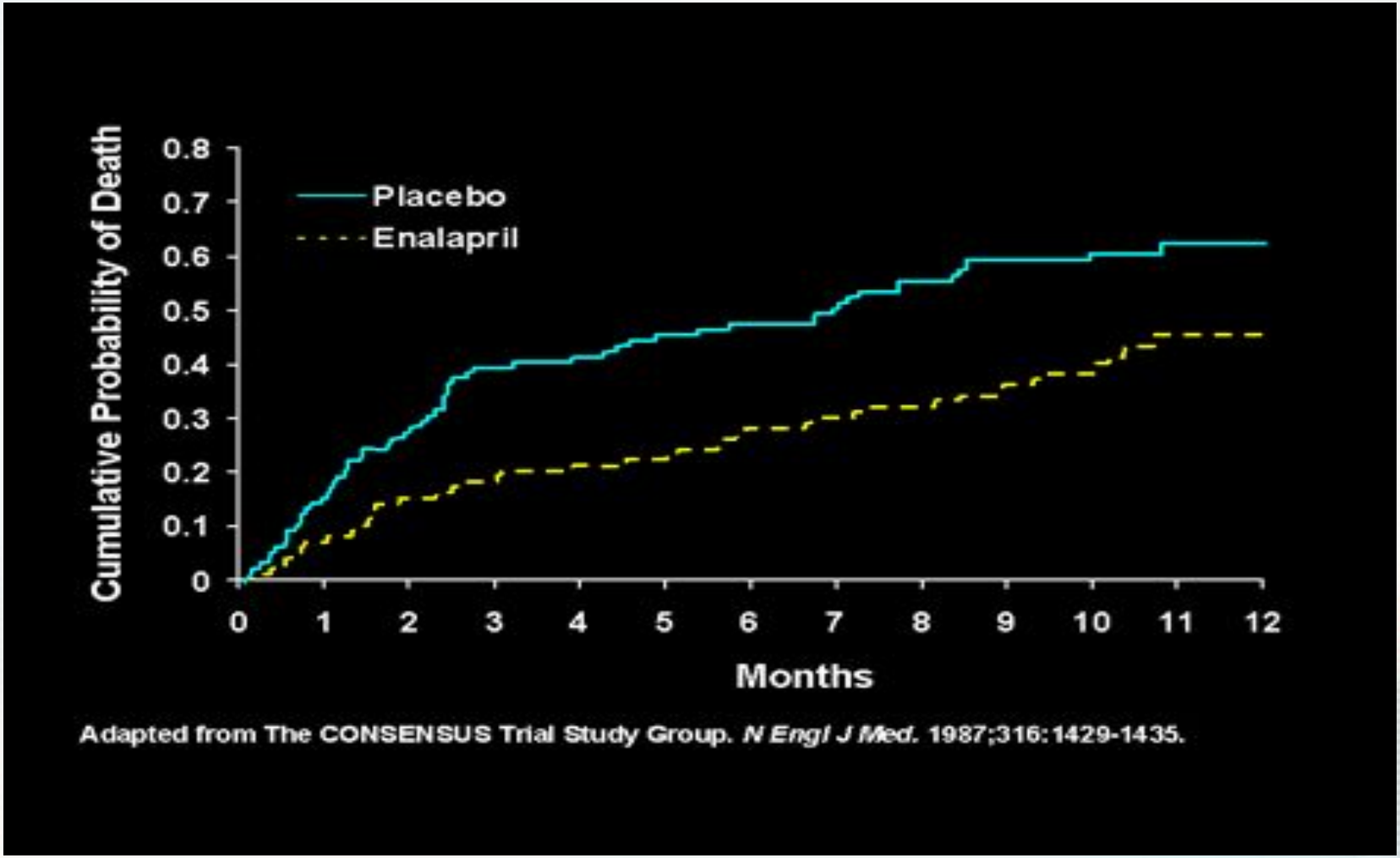


Pfeffer *et al*. *N Engl J Med* 1992;**327**:669–77.

!ACE-I: Use at Any Stage of CHF

- CONSENSUS trial -Enalapril 2.5-40mg (188 days) vs placebo
- Pts were already taking digoxin and diuretics
- 253 Patient with NYHA Class IV
- Dec mortality at:
  - 6 months -40%
  - 1 Year – 27%
- SOLVD trial - Enalapril 20mg/day (41 mo)
- 2569 Patients with and EF <35%
  - Earlier stages of HF even asymptomatic
  - NYHA Class II-III
- All cause mortality dec by 16%
- Morality rate from HF dec by 16%

Mortality as a Function of Tx



Adapted from The CONSENSUS Trial Study Group. *N Engl J Med.* 1987;316:1429-1435.

Angiotensin-Receptor Blockers

- Comparable to ACE inhibitors
- Reduce all-cause mortality
- Suitable alternative for patient with adverse events (angioedema, cough, hyperkalemia) occur with ACE-I

ACE + ARB

- CHARM trial
- 2548 NYHA II-IV; LVEF < 40%
  - Decrease in CV death, hospital admission
  - NNT=25
- But 23% discontinued due to side effects (increased SCr, hypotension, hyperkalemia)
- Currently ACE-I + ARB are not recommended

ACE Inhibitors Dosage - ATLAS Trial Results

Outcomes at 3y	High-dose	Low-dose	Hazard ratio (95% CI)	NNT (CI)
Mortality plus hospitalization	79.7%	83.8%	0.88 (0.82 to 0.96)	26 (16 to 82)
Mortality plus CV hospitalization	71.1%	74.1%	0.92 (0.84 to 0.99)	34 (17 to 284)
Mortality plus CHF hospitalization	55.1%	60.4%	0.85 (0.78 to 0.93)	17 (12 to 37)
CV mortality plus CV hospitalization	69.4%	72.7%	0.91 (0.84 to 0.99)	30 (16 to 281)

- No difference in primary endpoint
  - All-cause mortality (42.5% vs. 44.9, p=0.13)
  - CV mortality (37.2% vs. 40.2%, p=0.07)
- Reduction in combined endpoints

Conclusion

- High-dose lisinopril was more effective than low-dose lisinopril for reducing the combines end points of all-causes mortality combines with either all hospitalization, CV hospitalization, or CHF hospitalization and CV mortality plus CV hospitalization for patients with CHF

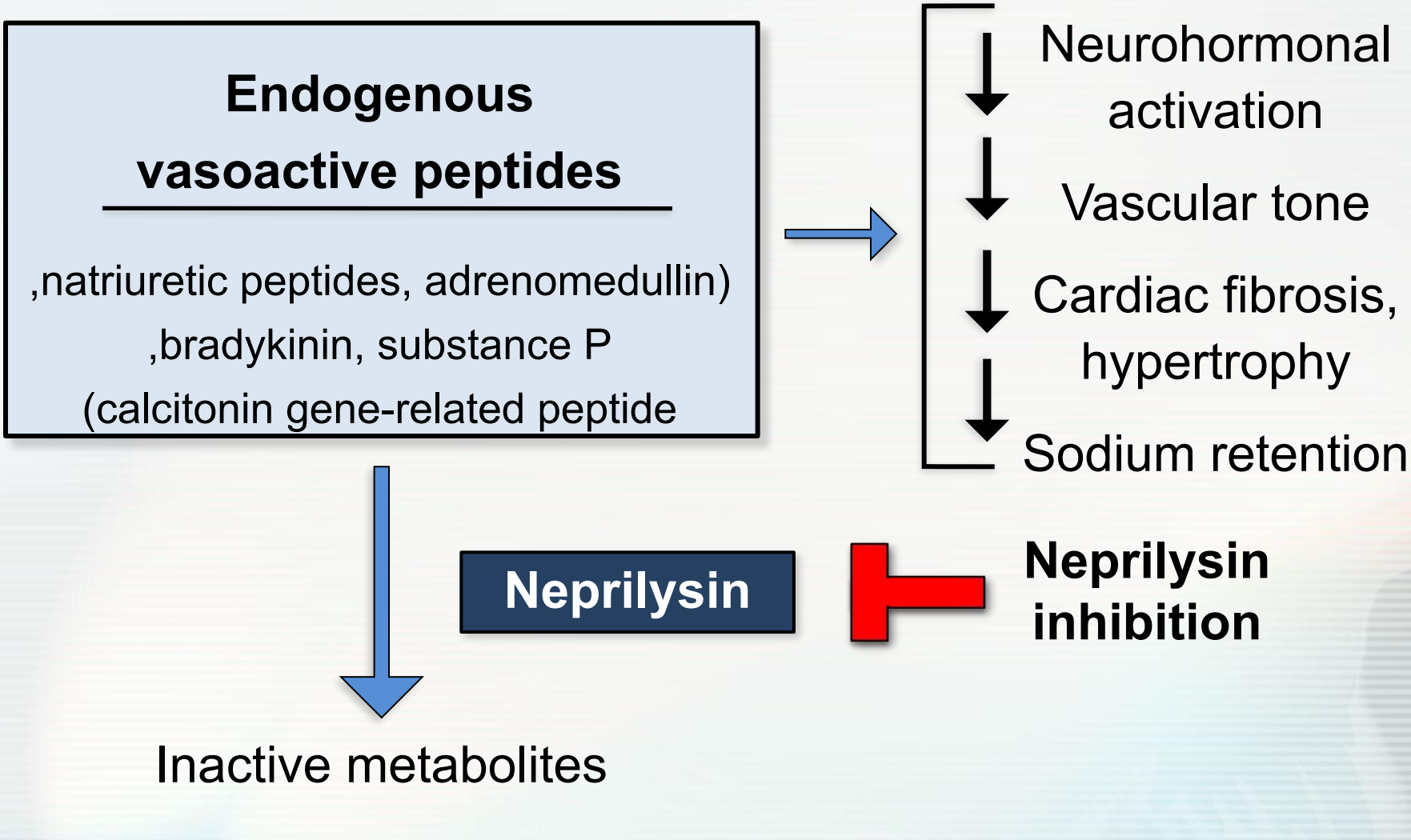
ACE-Inhibitors in CHF

- In patients with CHF total mortality and mortality combined with hospitalization from CHF are reduced with ACE-I
- In patients with asymptomatic left ventricular dysfunction ACE-I reduce the 3-year incidence of heart failure and related hospitalization
- High-dose lisinopril was more effective than low-dose lisinopril for reducing the combined end points of all-causes mortality combined with hospitalizations

Entresto® - Sacubitril/Valsartan Drug Facts

- **Pharmacology:**
  - **Sacubitril – prodrug metabolized to active metabolite (LBQ657), which inhibits neprilysin**
    - **Neprilisyn – neutral endopeptidase**
    - **Leads to increase in level of peptides, including natriuretic peptides**
  - **Valsartan – blocks the angiotensin II type-1 (AT1) receptor**

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



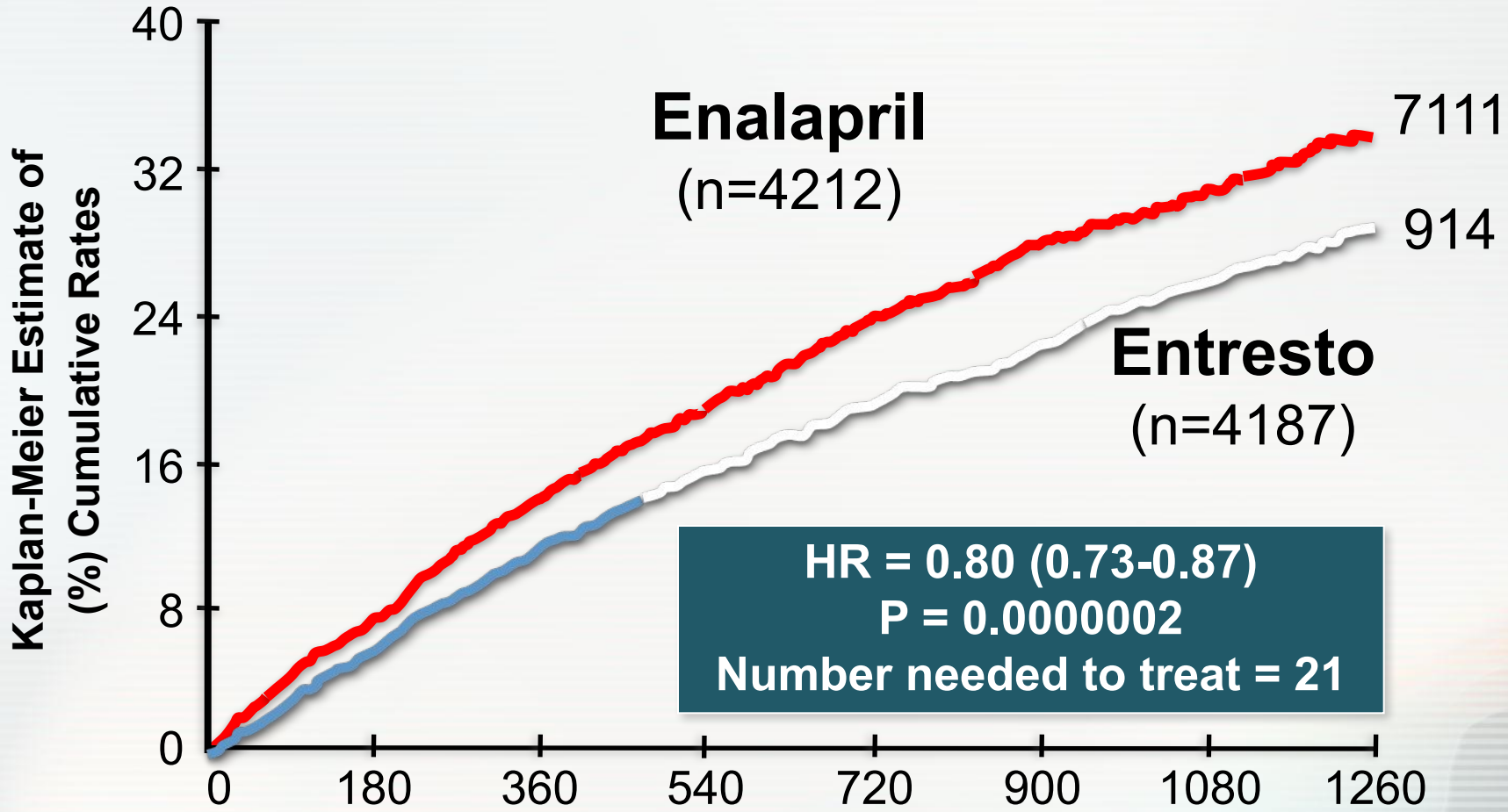
Aim of the PARADIGM-HF Trial

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

LCZ696 mg daily 400 ⟷ **Enalapril mg daily 20**

specifically designed to replace current use blockers of ACE inhibitors and angiotensin receptor as the cornerstone of the

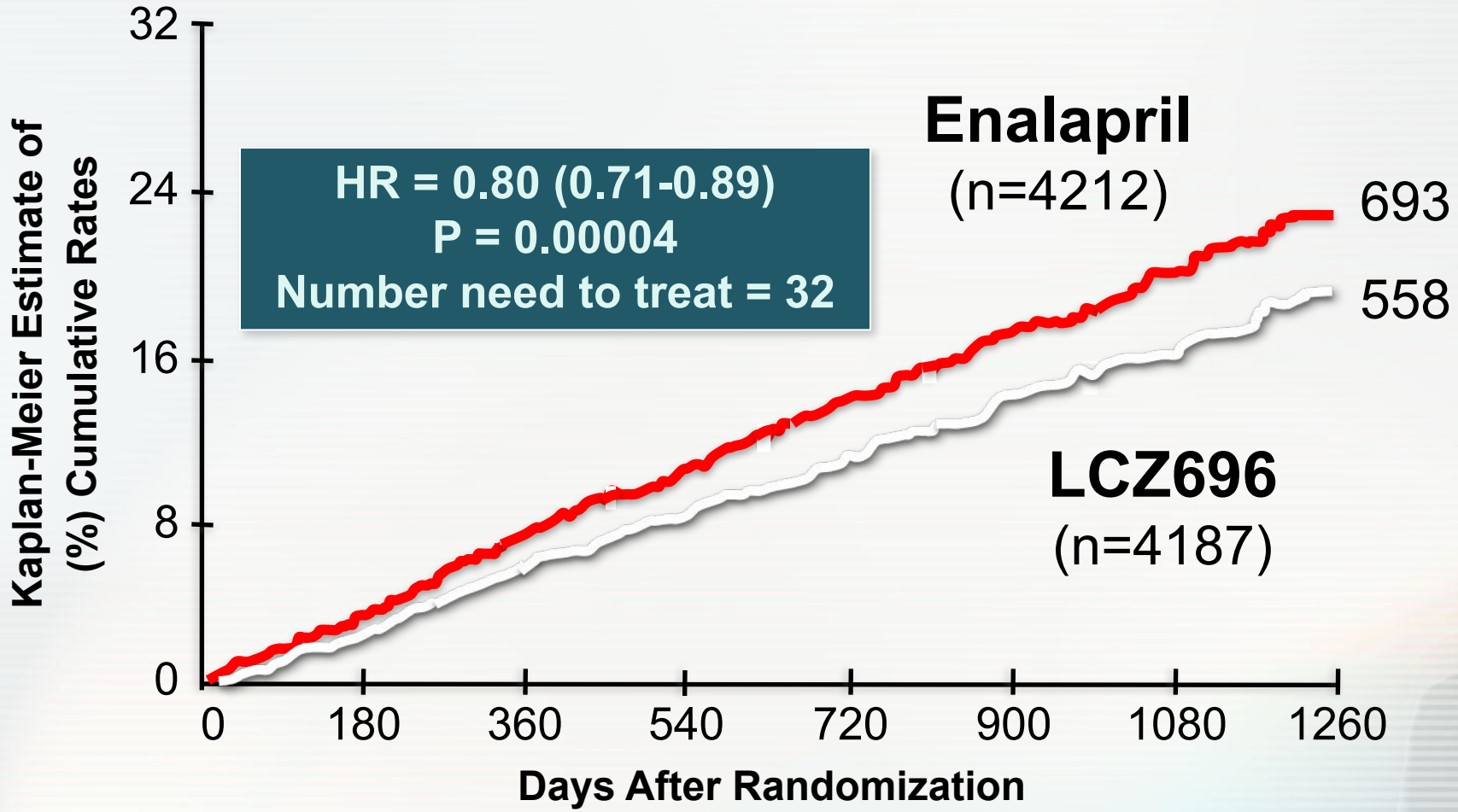
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)



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



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

Hydralazine (Apresoline) Plus Isosorbide Dinitrate (Sorbitrate)

- African-American Heart Failure Trial (A-HeFT)
- Hydralazine

  Reduces systemic vascular resistance by preferentially dilating arterioles
- Isosorbide dinitrate

  Preferential venodilator - reduces ventricular filling pressure and treat pulmonary congestion
- Reduces mortality – up to 28%
- Poor tolerability->30% drop out of study

  (flushing, headaches, GI upset, less frequently can cause positive ANA titers and lupus-like syndrome)

Beta-Blockers

- Decrease cardiac sympathetic activity
- 34% reduction in all mortality with use of β-blockers
- Use in stable, chronic disease (start as early as discharge-IMPACT-HF)
- Titrate slowly
- Contraindications-bradycardia, heart block or hemodynamic instability
- Mild asthma is not a contraindication
- Work irrespective of the etiology of the heart failure

?β-blocker - which to pick

Three beta-blockers :

- **Bisoprolol (Zebeta) -Trial CIBIS-II trial**
  Metoprolol (Toprol XL) –Trial MERIT-HF trial (sustained release)
  Carvedilol (Coreg) – COPERNICUS trial

- **6 RCT's with > 9,000 pts already taking ACE-I showed a significant reduction in total mortality and sudden death (NNT 24, and 35 over 1-2 years) regardless of severity**

- **Carvedilol vs. Metoprolol (COMET trial)**

  - **3029 pts; carvedilol 25mg bid vs. metoprolol 50 mg bid**
  - **Patient with NYHA Classes II-IV**
  - **Carvedilol – greater reduction in mortality (NNT, 18 over 5 years) and cardiovascular mortality (NNT, 16 over 5 years) than metoprolol but hypotension was greater in carvedilol (14 vs 11 percent)**

Initial and Target Doses of β-blockers for CHF

Medication	Starting Dose	Target Dosage
Bisoprolol	1.25mg daily	10mg daily
Carvedilol	3.125mg bid	25mg bid
Metoprolol	12.5-25mg daily	200mg daily

β-blockers in symptomatic Heat Failure: Meta-analysis Results

- 123 articles, 18 trials, 2986 patients
- 7 (n=562) of metoprolol, 4 (n=209) of bucindolol, 2 (n=1509) of carvedilol, 2 (n=36) of nebivolol, 1 (n=641) of bisoprolol, 1 (n=17) of acebutolol & 1 (n=12) of labetalol

Outcomes (mean FU)	β-blocker	Control	RRR (95% CI)	NNT (CI)
Mortality (13 mo)	8.2%	12.6%	25% (7 to 40)	32 (19 to 93)
Hospitalization (20 mo)	18.1%	28.8%	37% (24 to 48)	11 (8 to 18)
Heart transplantation (10 mo)	1.1%	2.7%	54% (13 to 75)	115 (53 to 580)

- Improved LVEF (p<0001) (11 trials)
- Higher rates of bradycardia, hypotension and dizziness (p<0.001) (13 trials)
- A decreased rate of worsening of heart failure (p<0.001) (13 trials)
- No difference existed between β-blockers and placebo for maximum exercise duration (9 trials)

Conclusion

- In patients with CHF, β-blockers reduce mortality, hospitalization and heart transplantation and improve left ventricular ejection fraction
- Subsequent large RCT: CIBIS II (bisoprolol) and MERIT-HF (metoprolol XL) verifies these findings in NYHA II-UV

b-blockers in symptomatic Heat Failure: Meta-analysis Design

β-blockers therapy for congestive heart failure: a systematic overwiew and critical appraisal of the published trails.

Avezum A, Tsuyuki RT, Pogue j, Yusuf S. Can J cardiol. 1998 Aug; 14:1045-53.[lb]

- **Question**
  - **In patients with congestive heart failure (CHF), what effect do β-blockers have on mortality and morbidity?**
- **Data sources**
  - **Studies were identified by searching MEDLINE (1966 to March 1997) using the terms beta adrenergic blocking agents and heart failure**
- **Study selection**
  - **PCRCT of β-blockers in patients with CHF and reduced LVEF**
  - **Treatment was >1 month**
  - **Follow-up was >95%**
  - **Analysis was by intention to treat**
- **Data extraction**
  - **β-blocker type and class (New York Heart Association)**
  - **Randomization ratio**
  - **Length of follow-up**
  - **Cause of CHF, mortality, hospitalization for CHF, heart transplantation, LVEF, maximum exercise duration and adverse effects**

Digoxin

- May relieve symptoms, does not reduce mortality
- Pts taking digoxin are less likely to be hospitalized (25% reduction)
- More admissions for suspected digoxin toxicity

Digoxin in symptomatic systolic dysfunction: RCT Design

The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure

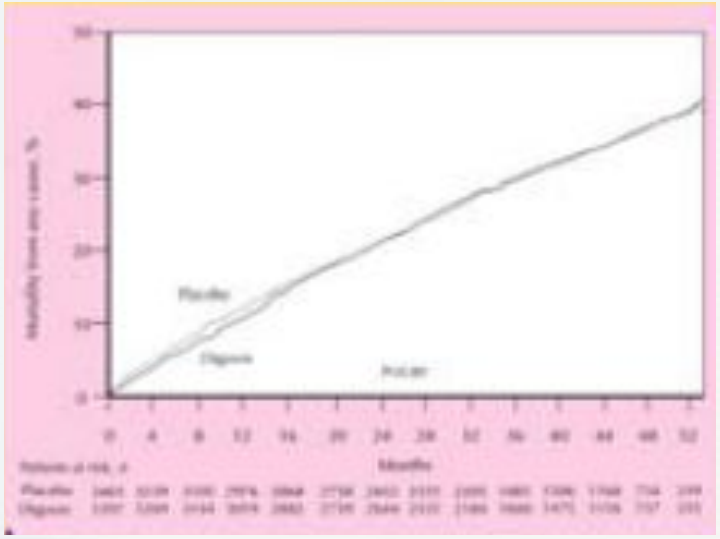
N Eng J Med, 1997 Feb 20, 336: 525-33

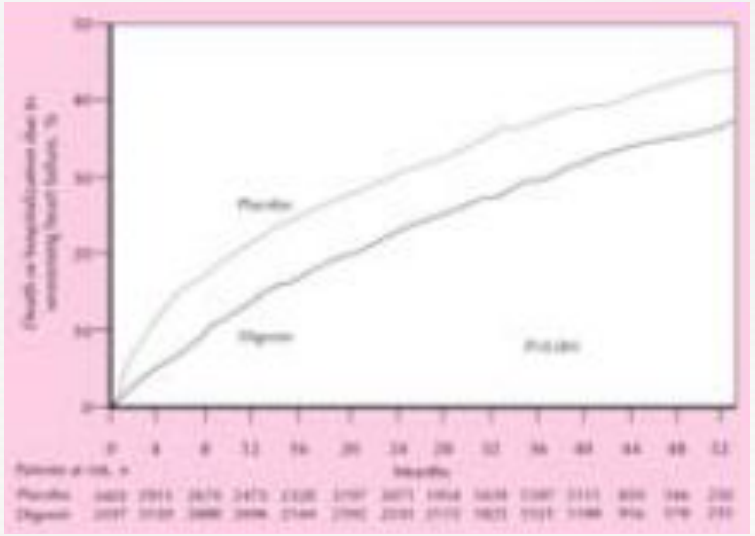
- **Objective**
  - To determine the effect of digoxin on mortality and hospitalization for heart failure in patients with heart failure and normal sinus rhythm
- **Design**
  - Randomized double-blind placebo-controlled trial
  - Mean follow-up 37 - month follow-up
- **Setting**
  - 302 clinical centers in the United States and Canada

Digoxin in symptomatic systolic dysfunction: RCT Design

- **Patients**
  - 6800 patients with heart failure, LVEF <0.45 & NSR
  - Most patients were receiving ACE-I & diuretics
  - 988 patients with heart failure and LVEF.0.45 were enrolled in an ancillary trial
  - Patients were included whether they had already been treated with digoxin
- **Intervention**
  - Stratified by center & LVEF
  - 3397 to digoxin & 3403 to placebo
  - Initial digoxin dose was based on the patient's age, sex, weight and renal function
  - Investigators allowed to modify dose and encouraged to give AC-I
  - Patients assessed at 4 & 16 weeks and 34 months thereafter
- **Main outcome measures**
  - Primary outcome: total mortality
  - Secondary outcomes:
    - ✔ Mortality from cardiovascular causes and worsening heart failure
    - ✔ Hospitalization for other causes, particularly digoxin toxicity

DIG :
Reduces Hospitalization but not Mortality Benefit





The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure *N Eng J Med, 1997 ;336: 525-533*

Digoxin in symptomatic systolic dysfunction: RCT Results

Hospitalization	Digoxin	Placebo	RRR (95% CI)	ARR	NNT (CI)
Total	64%	67%	4.1% (0.8 to 7.4)	3%	36 (20 to 196)
For worsening heart failure	27%	35%	23% (17 to 28)	8%	13 (10 to 18)
For cardiovascular causes	50%	54%	8% (4 to 12)	4%	22 (15 to 47)

- No differences in deaths 1181 vs 1194
- More patients in the digoxin group were hospitalized for digoxin toxicity then in the placebo group ($p<0.001$)
- Subgroup analyses suggested a greater benefit among patients at high risk patients

Conclusions

- Digoxin did not affect mortality but reduced hospitalizations in patients with heart failure and normal sinus rhythm
- May need to be cautious in female where overdosing may occur

Ivabradin

- **Specifically binds the Funny channel**
  - **Reduces the slope for diastolic depolarization**
    - ✔ **Prolongs diastolic duration**

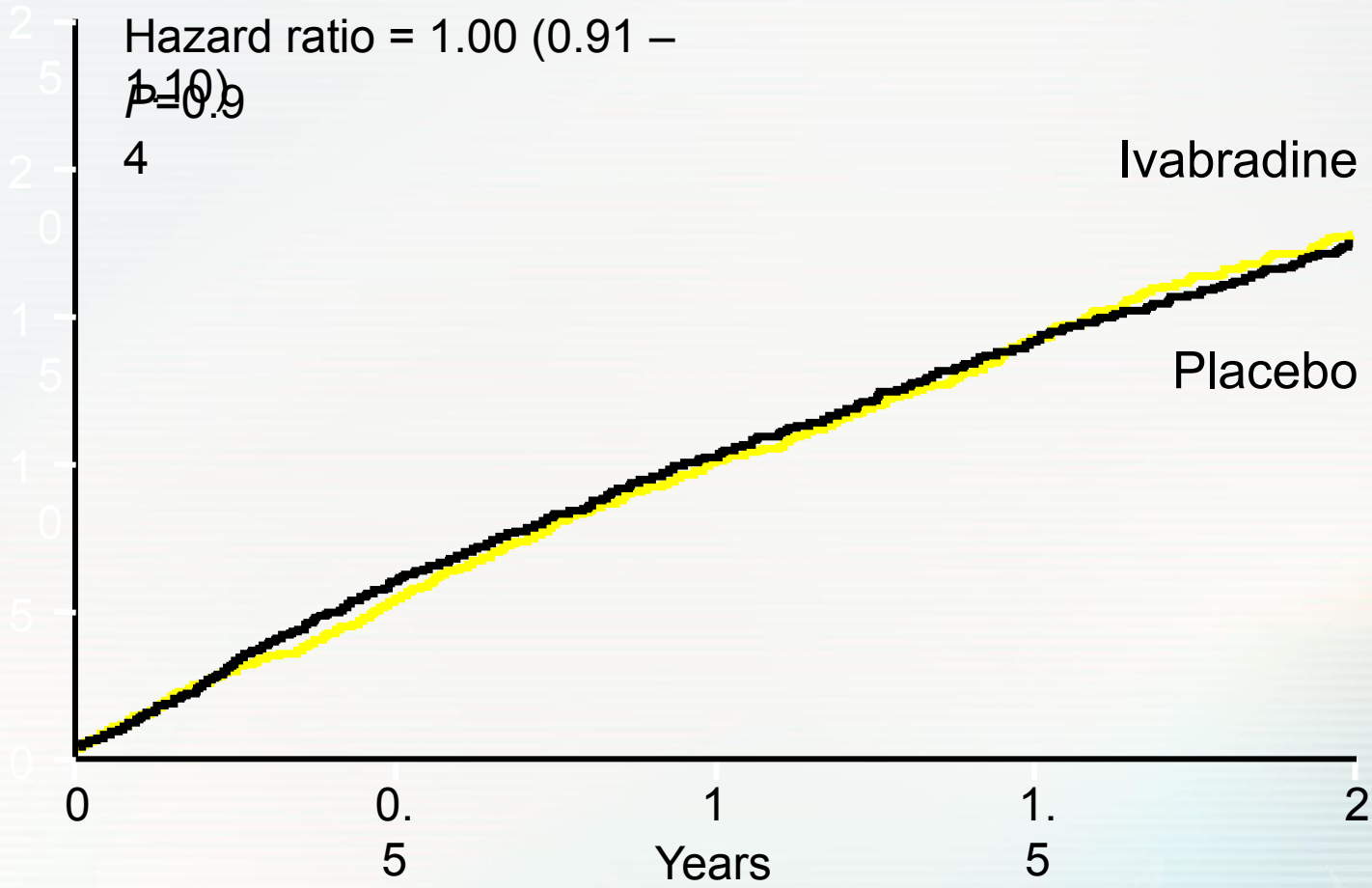
- **Does not alter…**
  - ✔ **Ventricular repolarization**
  - ✔ **Myocardial contractility**
  - ✔ **Blood pressure**

BEAUTIFUL Trial: Inclusion criteria

- Male or female
- Nondiabetic ≥55 years, diabetic ≥18 years
- Documented coronary artery disease
- Sinus rhythm and resting heart rate ≥60 bpm
- Documented left ventricular systolic dysfunction (<40%)
- Clinically stable for 3 months with regards to angina or heart failure symptoms or both
- Therapeutically stable for 1 month (appropriate or stable doses of conventional medications)

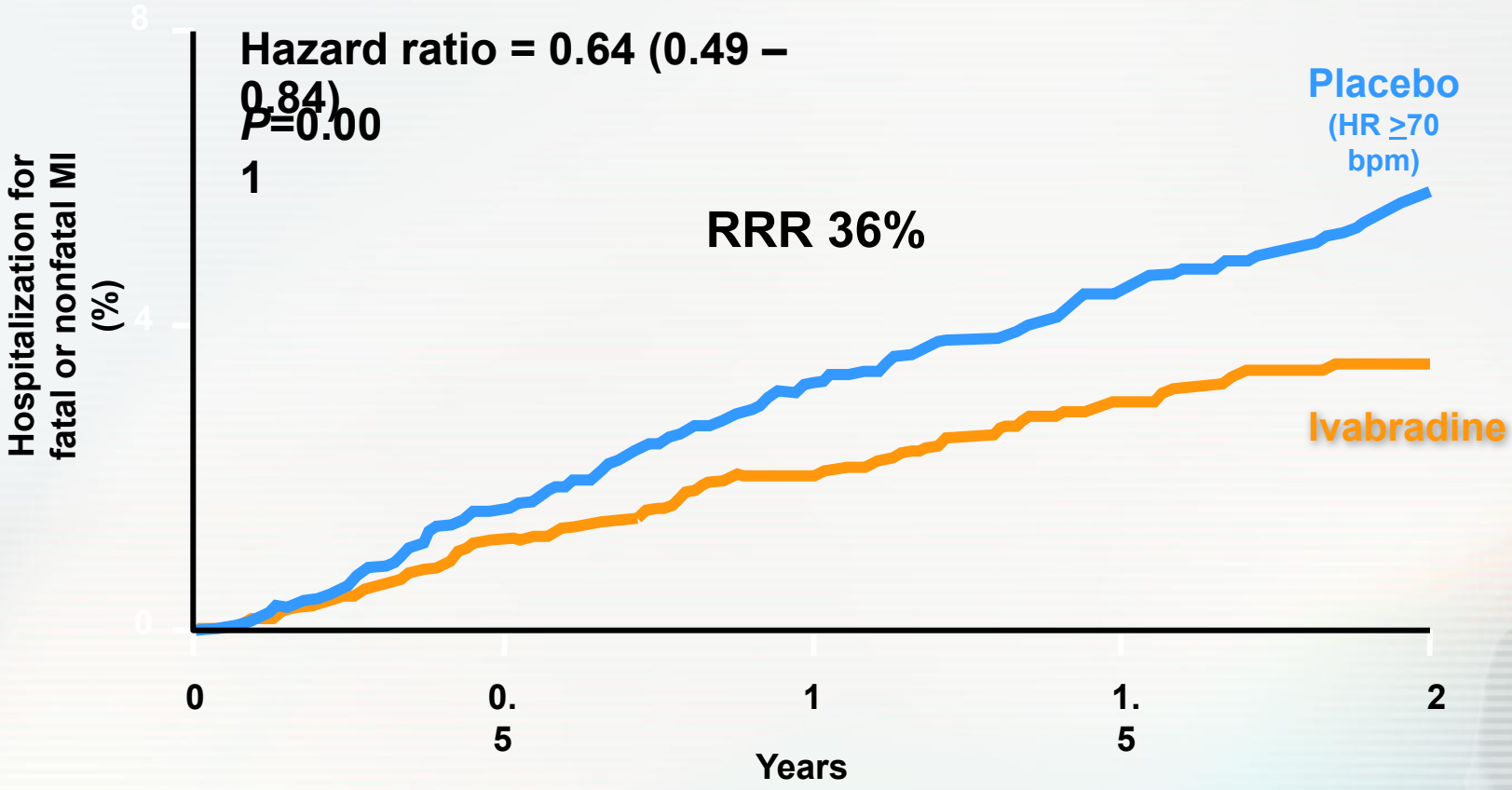
Effect of Ivabradine on primary endpoint (Overall population)

% with primary composite end point of CV death, hospitalization for acute MI, or for new-onset or worsening heart failure



Fox K et al. *Lancet.* 2008;372:807-816.

Ivabradine reduces fatal and nonfatal myocardial infarction (HR ≥70 bpm)



RRR: relative risk reduction

Fox K et al. *Lancet.* 2008;372:807-816

Ivabradine

- **In patients with coronary artery disease and left ventricular dysfunction, those with a heart rate ≥70 bpm have a higher risk of cardiovascular mortality, hospitalization for myocardial infarction, and heart failure.**
- **In patients with heart rate ≥70 bpm, ivabradine reduces the composite of fatal and nonfatal myocardial infarction and reduces the need for revascularisation.**

Spironolactone in Severe Heart Failure: RCT Design

Pitt B, Zannad F, Remme WJ, et al, for the Randomized Aldactone Evaluation Study Investigators The effect of spironolactone on morbidity and mortality in patients with severe heart failure

N Engl J Med. 1999 Sep 2;341:709-17 [lb]

- **Question**
  - In patients with severe congestive heart failure (CHF) does spironolactone combined with usual care reduce all- cause mortality?
- **Design**
  - Random zed (allocation concealed*), blinded (patients, clinicians, and outcome assessors)* placebo-controlled trial
  - Mean follow-up of 24 months with interim analyses
- **Setting**
  - 195 clinical centers in 15 countries

Spironolactone in Severe Heart Failure: RCT Design

Patients

- 1663 patients (mean age 65 y, 73% men, 87% white)
- Inclusion: NYHA III-IV, LVEF < 35%
- ACE-I (95%), Dig (75%), BB (11%)

Intervention

- Usual care vs spironolactone, 25 mg/d (x2 after 8wks)
- On the basis of evidence of worsening CHF without hyperkalemia
- Tx N = 822 or placebo n = 841
- 25 mg every other day if hyperkalemia occurred

Main outcome measures

- Primary outcome: All-cause mortality
- Secondary outcomes
  - ✔ Cardiac mortality
  - ✔ Hospitalization for cardiac causes
  - ✔ Change in NYHA
  - ✔ Adverse effects

Spironolactone in Severe Heart Failure: RCT Design

Outcome at mean 24 mo	Spironolactone	Placebo	RRR(95% CI)	NNT (CI)
All-cause mortality	35%	46%	25% (15 to 33)	9 (7to 16)
Cardiac mortality	28%	37%	26% (15 to 36)	11 (7 to 19)
CHF mortality	16%	23%	31% (16 to 44)	15 (10 to 31)
Hospitalization for cardiac causes	32%	40%	21% (10 to 31)	13 (8 to 27)

Main results

- Greater improvement in NYHA class (P<0.001)
- Did not differ for adverse effects: 82% of patients in the Spironolactone group had ≤1 event compared with 79% of patients in the placebo group (P = 0.17)
- "Serious hyperkalemia" 1% vs 2% (ns); no comment on mild-moderate
- Men in tx group had higher rate of gynecomastia or breast pain (10% vs 1%, P<0.001)

Conclusion

- Spironolactone reduced all-cause mortality, death, and hospitalization from cardiac causes and death from CHF and improved NYHA functional class in patients with severe CHF

EPHESUS Trial

Eplerenone Post-AMI Heart Failure Efficacy and Survival Study

EPHESUS Trial

6,632 patients with acute MI complicated by heart failure and systolic left ventricular dysfunction

- Acute MI in prior 3-14 days
- Left ventricular dysfunction (EF ≤40%)
- Heart failure (in non-diabetics but not required for diabetics)

Optimal medical therapy
(ACE inhibitors, angiotensin-receptor blockers, diuretics, and beta-blockers, coronary reperfusion therapy)

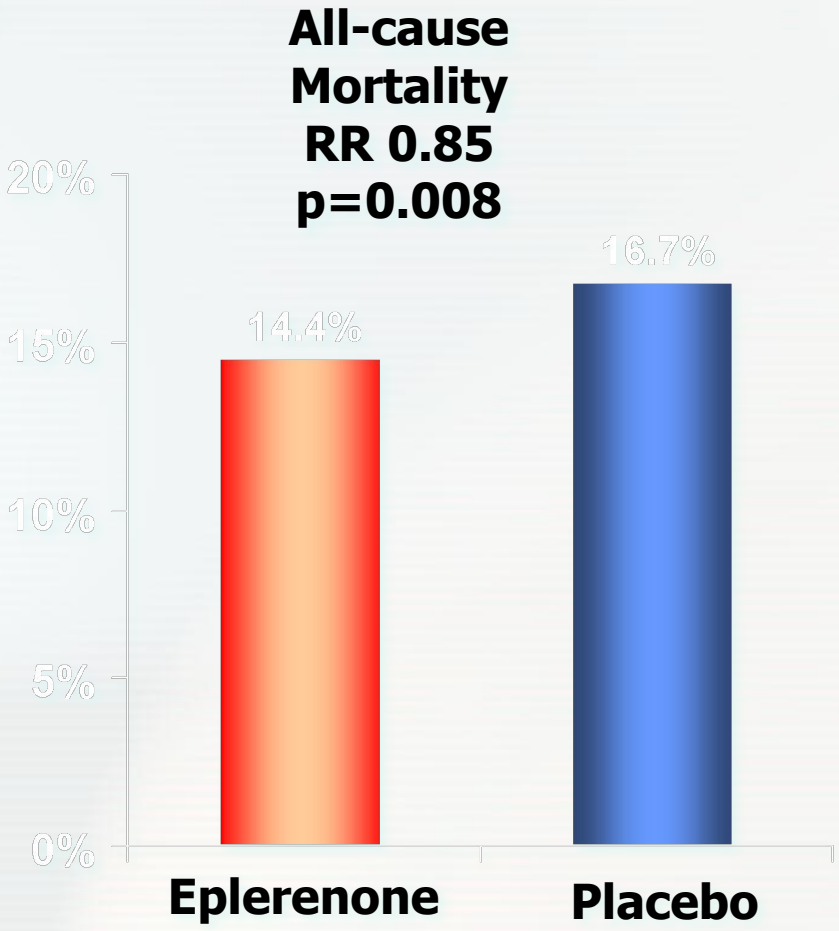
Eplerenone (n = 3,313)	Placebo (n = 3,319)

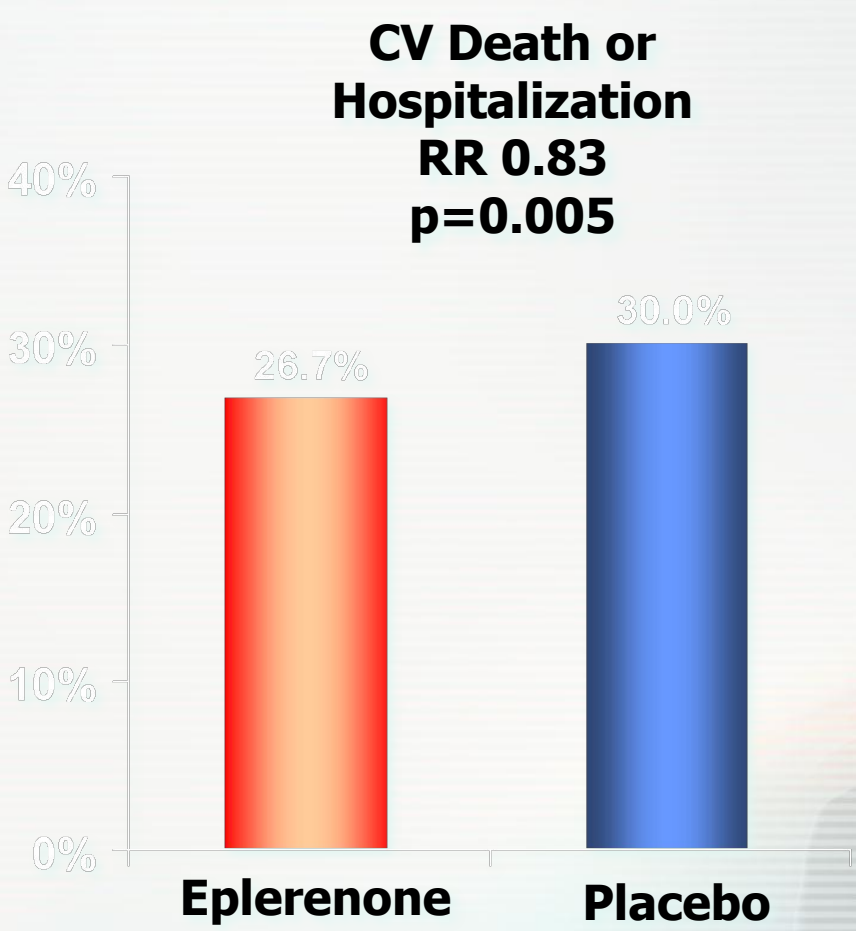
Endpoints (at mean of 16 month follow-up):

- Primary – 1) death from any cause and 2) death or hospitalization from CV causes

N Engl J Med 2003;348:1309-21

EPHESUS Trial: Primary Endpoints





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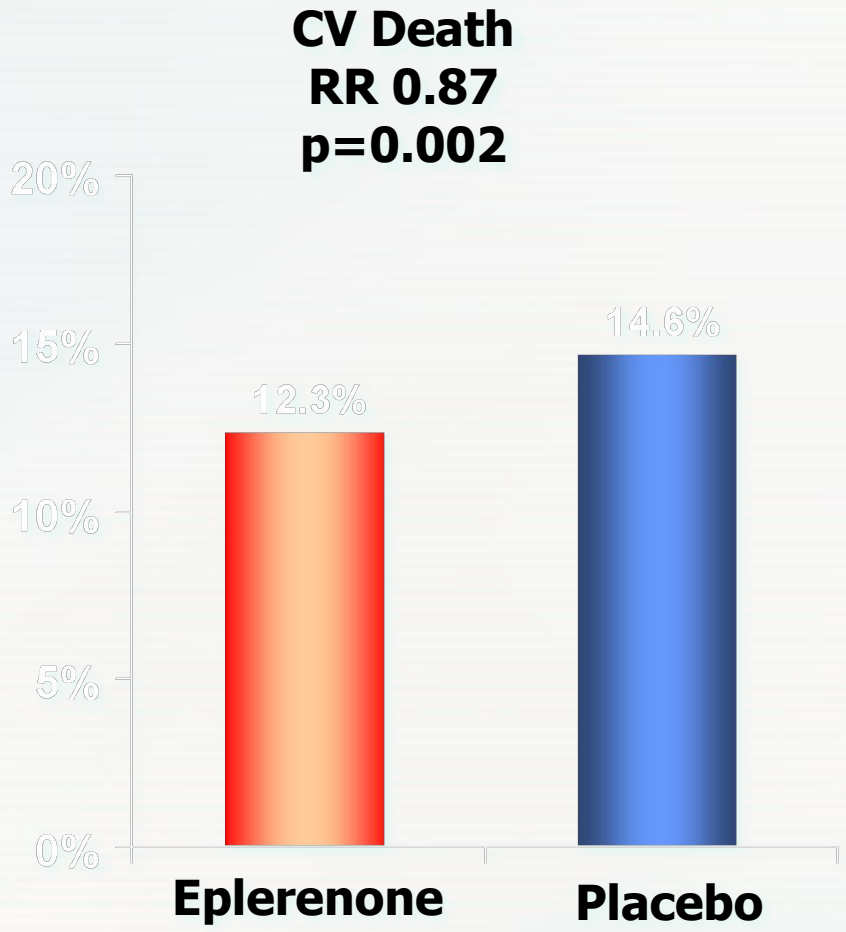
EPHESUS Trial: Secondary Endpoint



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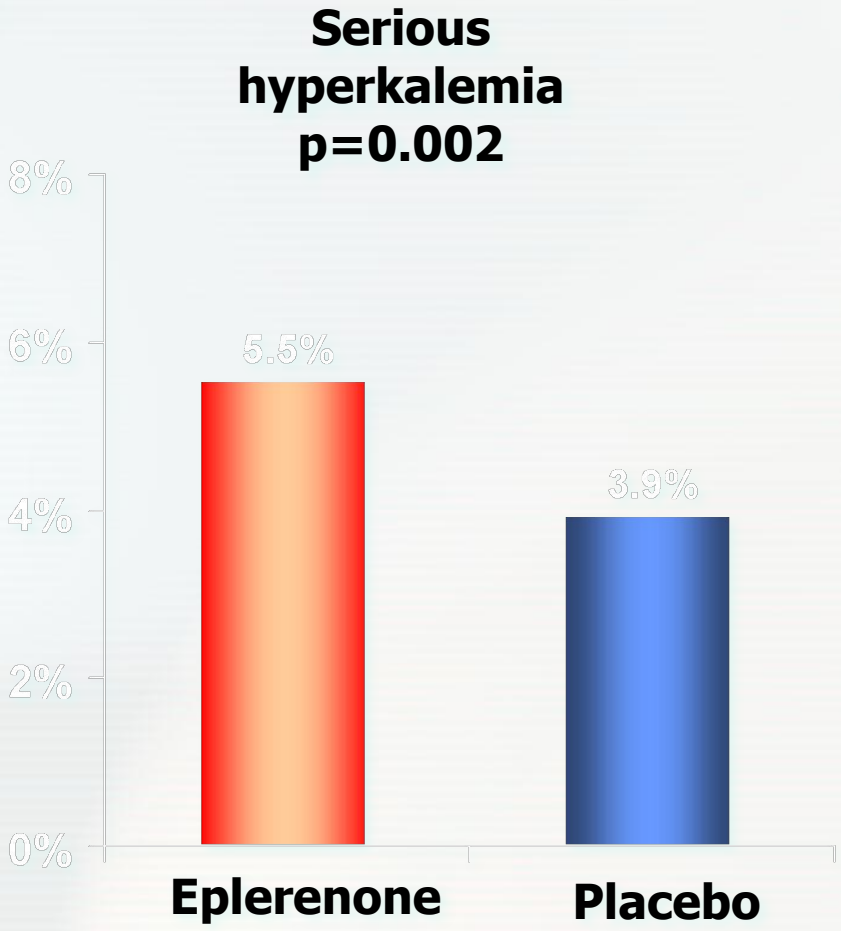
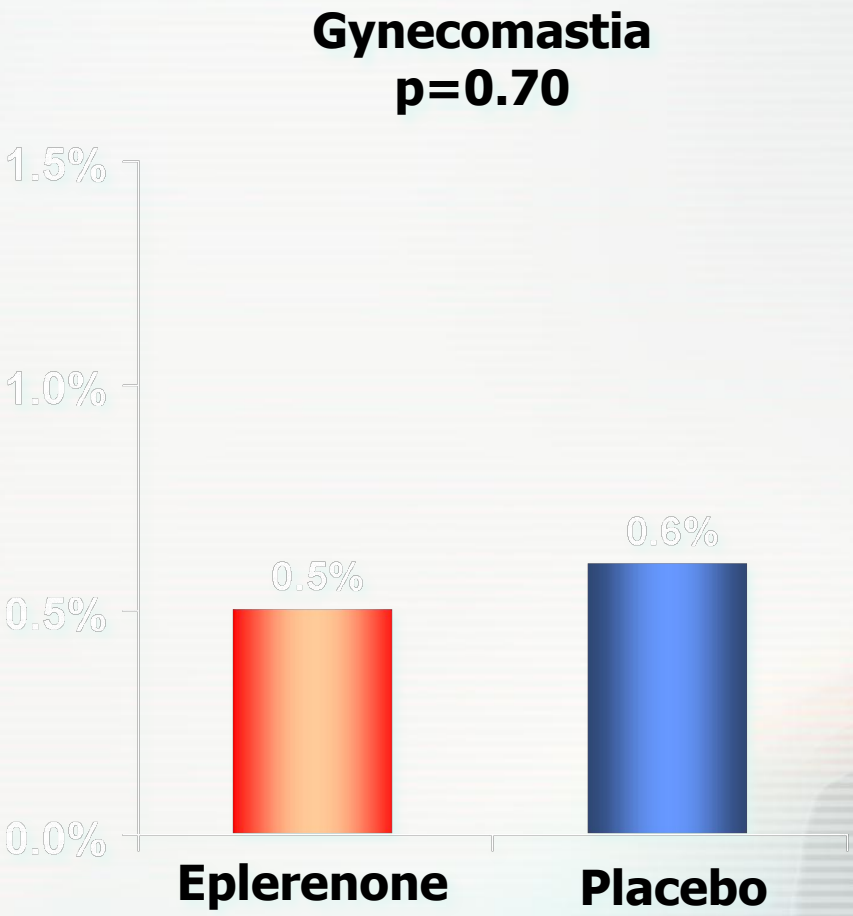
EPHESUS Trial: Serious Adverse Events





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Loop Diuretics

- **Mainstay of symptomatic treatment**
  - **Improve fluid retention**
  - **Increase exercise tolerance**
  - **No effects on morbidity or mortality**

Diuretics in Heart Failure

Benefits

- Improve symptoms of congestion
- Can improve cardiac output
- Improved neurohormonal milieu
- No inherit nephrotoxicity

Limitations

- Oral absorption unpredictable
- Excessive volume depletion
- Electrolyte disturbance
- Unknown effects on mortality
- Ototoxicity

Antiplatelet Therapy and Anticoagulation

- Increased risk of thromboembolic events, 1.6-3.2% per year
- Antiplatelet therapy (aspirin) in not useful in patient in sinus rhythm
- Coumadin for patient with atrial fibrillation or a previous thromboembolic event

Nesiritide (Natrecor)

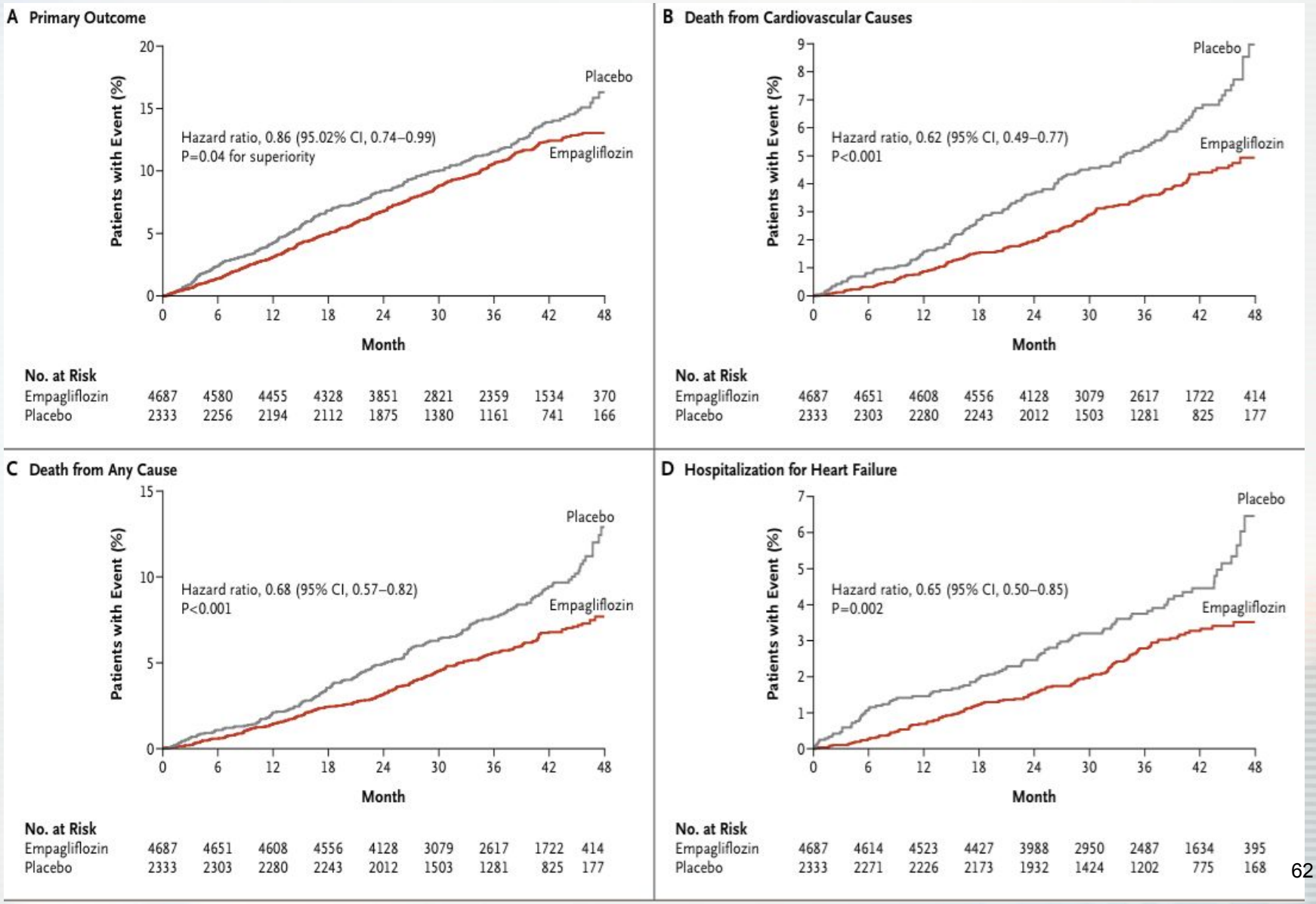
- Recombinant form of human BNP
- Causes venous and arterial vasodilation
  - Has been shown to improve dyspnea and global assessments at 3 hours after initiation in pts with Acute HF.
  - Risks- deleterious effect on renal function and decreased 30 day survival

Anti-Diabetic Drugs and Cardiovascular Outcomes

Drug	CV Effects
Biguanides	Significant reduction in CV events ◆ Reduces LDL; increases HDL ◆
Sulfonylureas	May increase risk of CV events ◆ May prevent protective ischemic cardiac preconditioning after MI ◆
Meglitinides	May increase ischemic events and LV dysfunction in patients with underlying CAD ◆ No effect on reducing CV outcomes ◆
Thiazolidinedones	Increased risk of MI, CHF, and mortality ◆
DPP-4 inhibitors	Does not increase risk of major CV events ◆ *Hospitalization for HF higher with saxagliptin ◆
GLP-1 agonists	Moderate decrease in risk of CVD and CVD-related hospitalizations ◆

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998.
The University Group Diabetes Program. *Diabetes* 1976.
Cioffi G, et al. *Diabetes Res Clin Pract* 2013.
Nissen SE, et al. *N Engl J Med* 2007.
Scirica BM, et al. *N Engl J Med* 2013.
Best JH, et al. *Diabetes Care* 2011.

Cardiovascular Outcomes EMPA-REG Trial



Not recommended

Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.
NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.
Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.
The addition of an ARB (or renin inhibitor) to the combination of an ACE-I and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia.

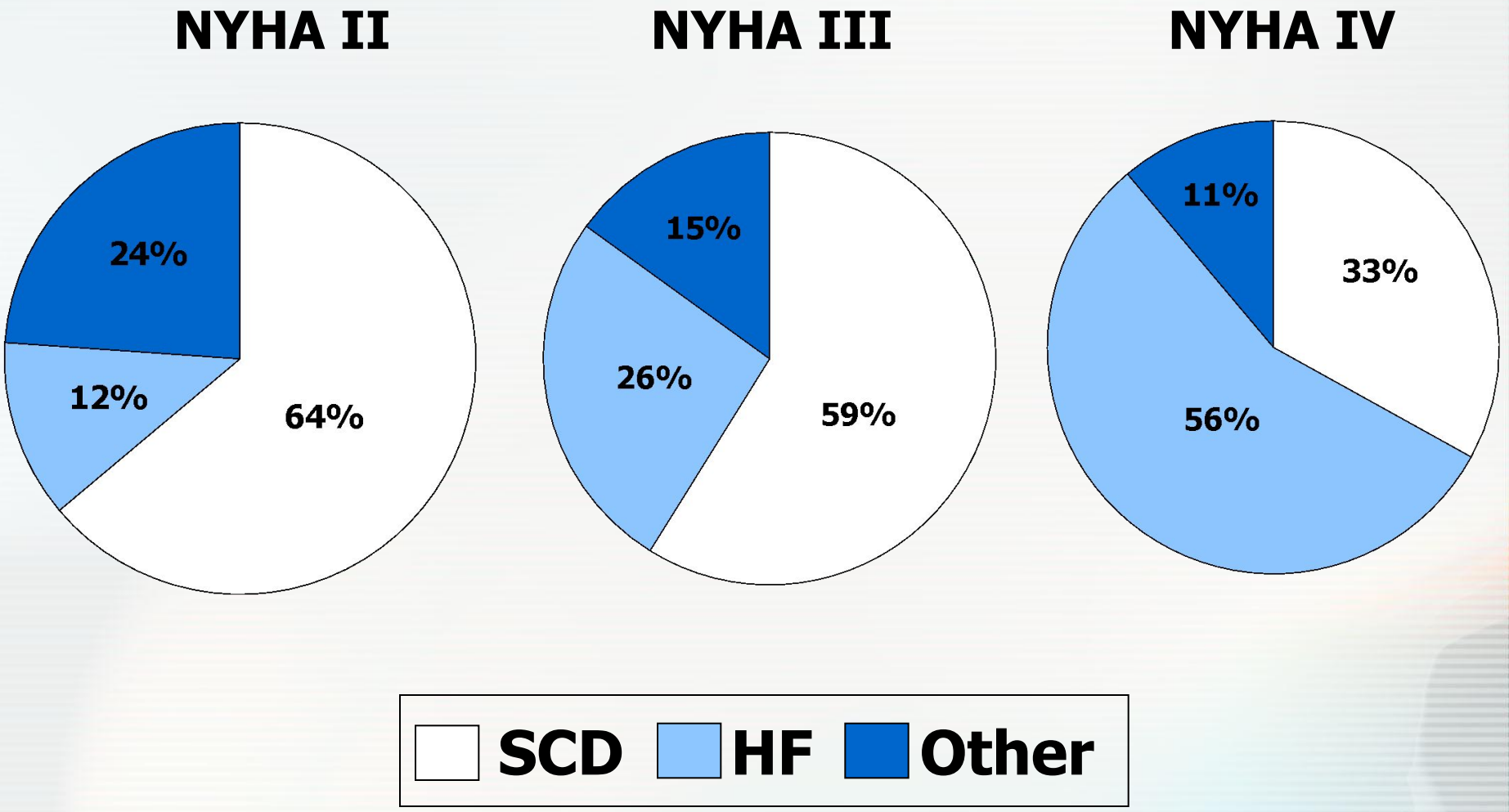
Pharmacological Therapies for Heart Failure: Conclusions

- **Symptomatic systolic dysfunction**
  - **ACE-I: reduce mortality & hospitalization for heart failure**
    - ✔ **High-dose lisinopril: more effective than low dose for reducing combined mortality and cardiovascular events in CHF**
  - **Beta blockers: reduce mortality & hospitalization in moderate to severe heart failure**
  - **Digoxin: reduces hospitalizations in patients with heart failure and normal sinus rhythm**
  - **Spironolactone: reduces mortality in severe heart failure**
- **Asymptomatic systolic dysfunction**
  - **ACE-I: reduces incidence of heart failure & hospitalization**

Device Therapy

- Implantable Cardioverter-Defibrillators (ICD)
- Cardiac Resynchronization Therapy (CRT)
- Left Ventricular Assist Devices (LVAD)

Rates of Sudden Cardiac Rate



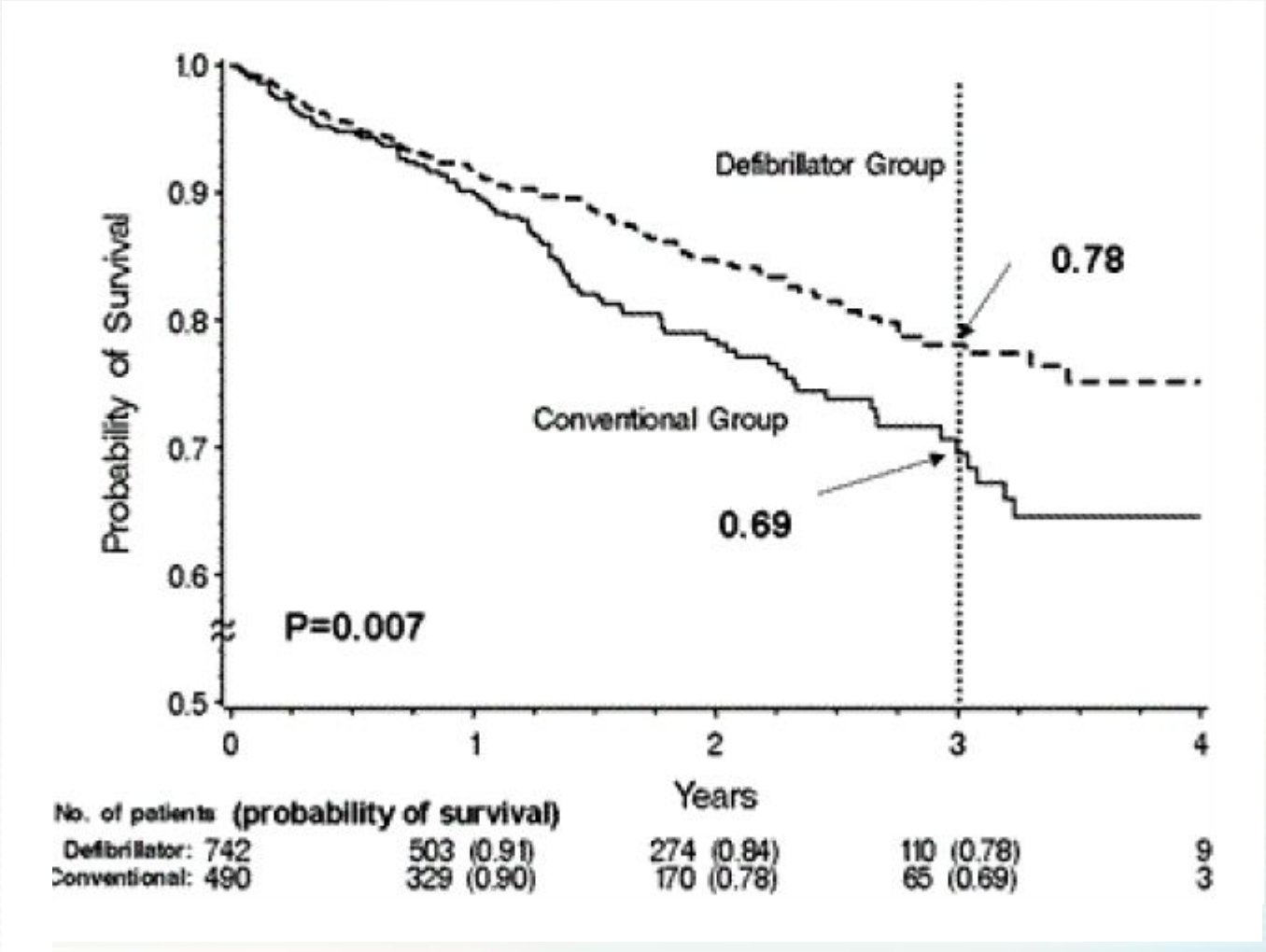
ICD

- SCD-HeFT (sudden cardiac death)
- 2521 patients with depressed LV systolic function and Class II-III HF
- Randomized to standard therapy vs. standard therapy plus ICD vs. standard therapy plus amiodarone
- 23% reduction in mortality with ICD
- No difference in mortality with amiodarone
- Results did not vary based on etiology of LV dysfunction

MADIT-II: Eligibility

- Chronic CAD with prior MI
- EF≤0.30
- No requirement for NSVT or EPS
- No upper age limitation

MADIT-II: Results



ICD

- Recommended in pts with EF<30% and mild to moderate symptoms of HF
- Survival with good functional capacity is anticipated for > 1 year

Cardiac Resynchronization Therapy

Patient Indications

- **CRT device:**
  - Moderate to severe HF (NYHA Class III/IV) patients
  - Symptomatic despite optimal, medical therapy
  - QRS $\geq$120 msec
  - LVEF $\leq$35%
- **CRT plus ICD:**
  - Same as above with ICD indication

CRT

- COMPANION trial
- 1520 patients, most with class III-IV HF, QRS duration >120 ms
- Randomized in 1:2:2 ratio to standard therapy vs. standard therapy plus CRT vs. standard therapy plus CRT with device that also defibrillated
- 34% reduction in death or any hospitalization with CRT
- 40% reduction when combined with ICD

Conclusions

- ACE inhibitors improve symptoms in CCF (CONSENSUS) and reduce mortality even in asymptomatic patients with low ejection fraction (SOLVD). Angiotensin receptor blockers also appear to share these benefits (CHARM, ValHEFT), though any benefit when added to ACEi is controversial (CHARM, .ValHEFT)

- Aldosterone antagonists do confer extra benefit when added to ACEi/ARBs in NYHA 3 (RALES) and .NYHA 2 CCF (EMPHASIS-HF)

- Beta-blockers also improve mortality and reduce hospitalisations (CIBIS-II) with some evidence of superiority between agents (COMET). If blockers such as Ivabradine is an alternative rate-controlling .agent that appears beneficial in some patients (BEAUTIFUL, SHIFT)

- Neither routine anticoagulation with warfarin (WARCEF) nor treatment with digoxin (DIG) appear beneficial on mortality

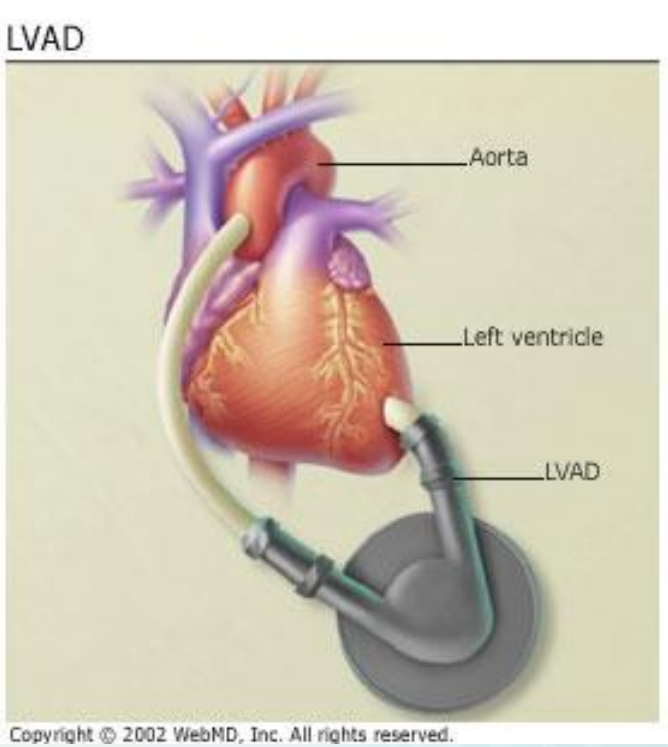
- Insertion of cardiac resynchronisation devices (CRT) adds further benefit (MADIT-CRT) above the .benefits of inserting an implantable cardiac defibrillatory (ICD) (SCD-HeFT)

- Statins do not add benefit in CCF in patients with no other indication (CORONA) and ultrafiltration appears inferior to stepped medical therapy in patients with acute cardio-renal syndrome

- Surgical revascularisation may be beneficial in some patients (STITCH) but the high crossover in this .trial makes interpretation very difficult

Left Ventricular Assist Devices (LVAD)

- **REMATCH trial-**
- **1 yr survival 52% (LVAD) vs 24% (medical Rx)**
- **2 yr survival 23% vs 8%**
- **End-Stage (Class IV)**
- **HF pts ineligible for transplant due to:**
  - **>65yo**
  - **DM with EOD**
  - **CRI**



Diastolic Dysfunction

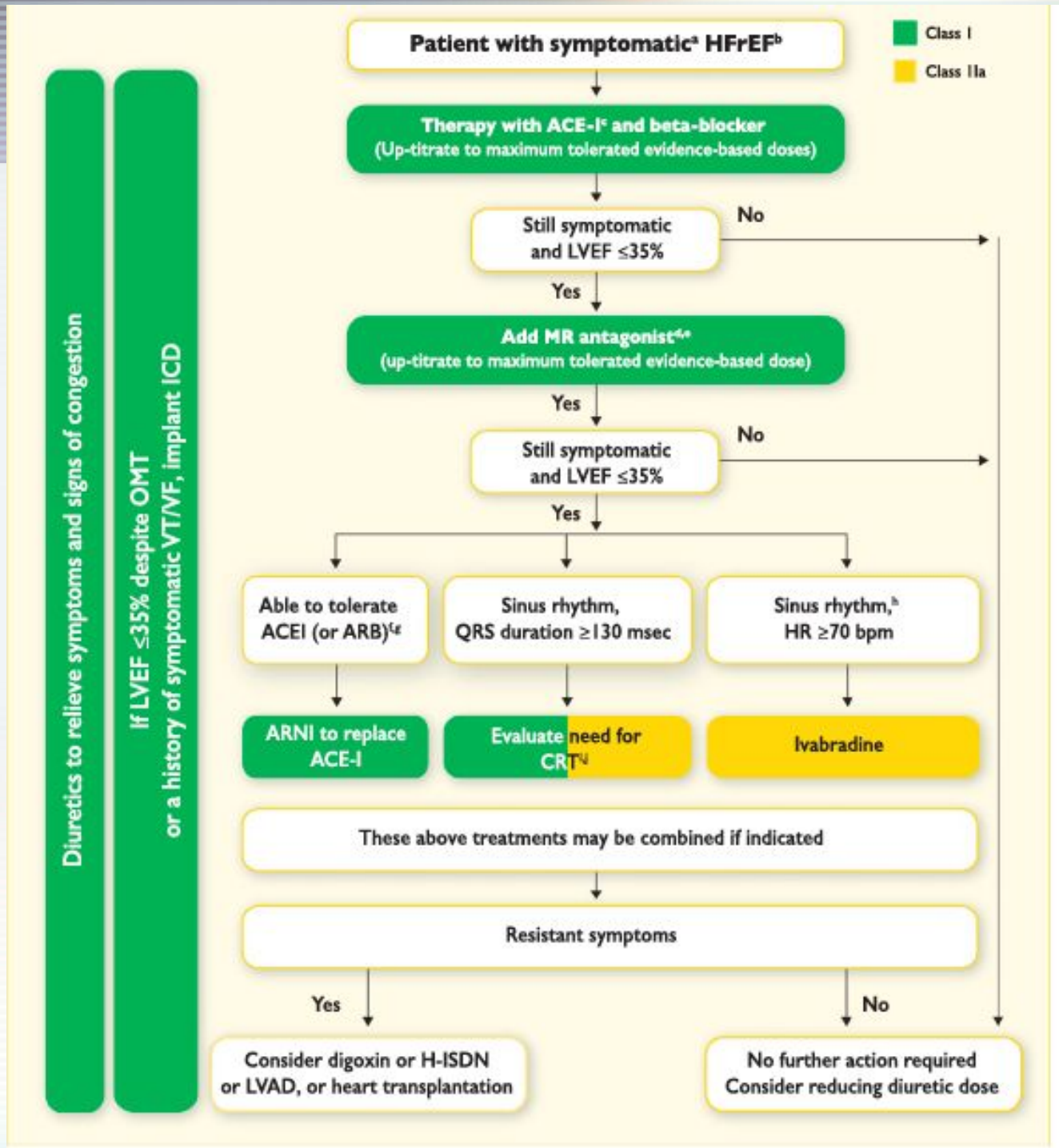
- 20-40% of presenting CHF syndrome
- Risk of death lower than systolic dysfunction
- Dx: Doppler echocardiography
- Lack of clear-cut definition = lack of trial data
- Treat symptomatically and prevent reversible causes

Diastolic Dysfunction

- Acute Management is the SAME
- Chronic Management is CONTROVERSIAL
  - Diuretics-dec fluid volume
  - CCB-promote left ventricular relaxation
  - ACE-I-promote regression of left ventricular hypertrophy
  - β-blockers/anti-arrhythmic agents-control heart rate or maintain atrial contraction

Heart Failure: More than just drugs

- Dietary counseling
- Patient education
- Physical activity
- Medication compliance
- Aggressive follow-up
- Sudden death assessment


Class I
Class IIa
Patient with symptomatic[a] HFrEF[b]
Therapy with ACE-I[c] and beta-blocker
(Up-titrate to maximum tolerated evidence-based doses)
Still symptomatic and LVEF ≤35%
No
Yes
Add MR antagonist[d,e]
(up-titrate to maximum tolerated evidence-based dose)
Yes
Still symptomatic and LVEF ≤35%
No
Yes
Able to tolerate ACEI (or ARB)[f,g]
Sinus rhythm, QRS duration ≥130 msec
Sinus rhythm,[h] HR ≥70 bpm
ARNI to replace ACE-I
Evaluate need for CRT[i,j]
Ivabradine
These above treatments may be combined if indicated
Resistant symptoms
Yes
No
Consider digoxin or H-ISDN or LVAD, or heart transplantation
No further action required
Consider reducing diuretic dose
Diuretics to relieve symptoms and signs of congestion
If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

Prevention of HF

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