La terapia farmacologica secondo le linee guida

European Heart Journal (2008) **29**, 2388–2442
doi:10.1093/eurheartj/ehn309

ESC GUIDELINES

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM)

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Objectives of treatment in chronic heart failure (ESC guidelines 2008)

1. **Prognosis**
   - Reduce mortality
2. **Morbidity**
   - Relieve symptoms and signs
   - Improve quality of life
   - Eliminate oedema and fluid retention
   - Increase exercise capacity
   - Reduce fatigue and breathlessness
   - Reduce need for hospitalization
   - Provide for end of life care

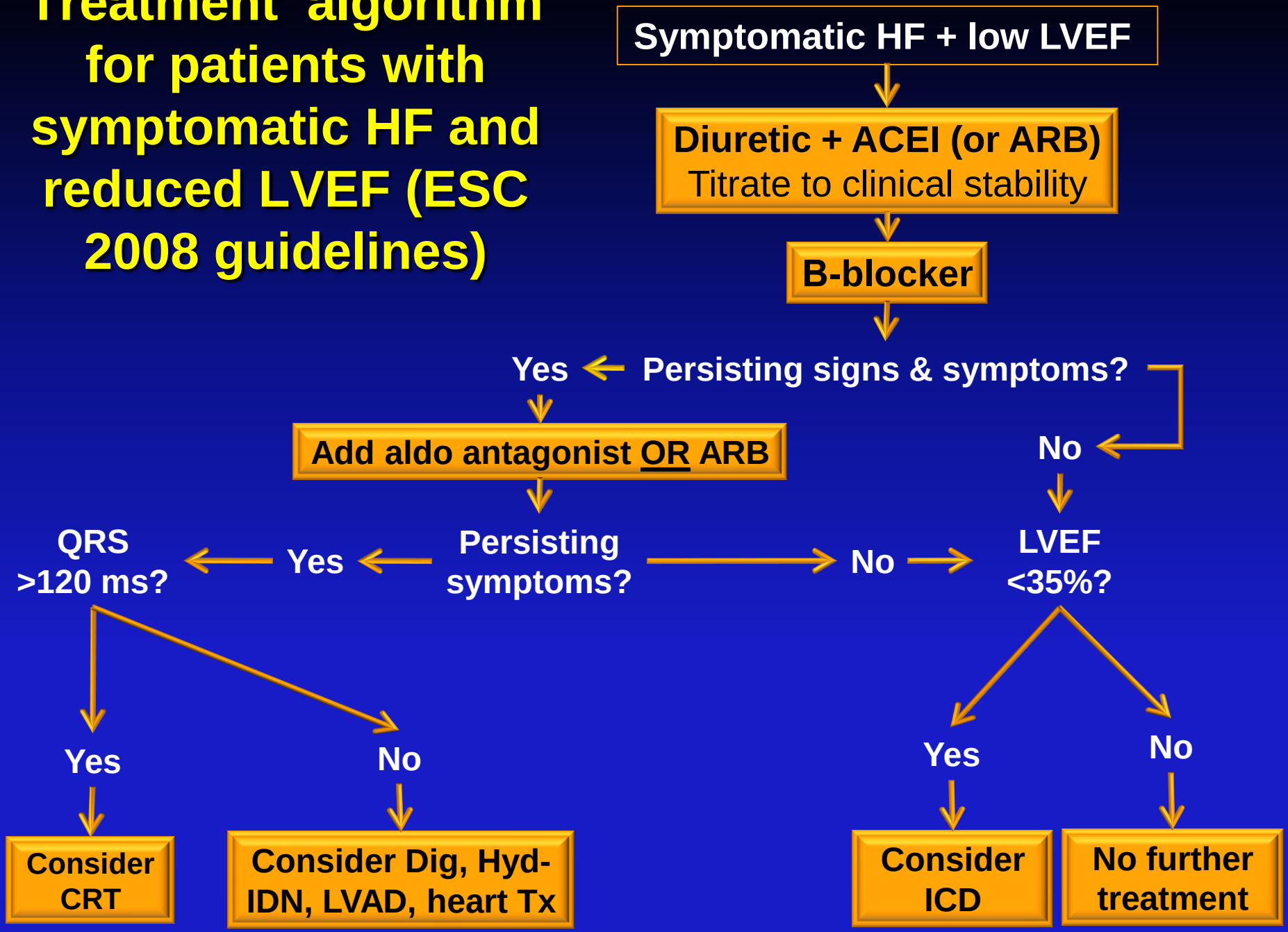
Objectives of treatment in chronic heart failure (ESC guidelines 2008)

3. **Prevention**
   - Occurrence of myocardial damage
   - Progression of myocardial damage
   - Remodelling of the myocardium
   - Recurrence of symptoms and fluid accumulation
   - Hospitalization

Non-pharmacologic management of HF

- Adherence to treatment
- Symptoms recognition
- Weight monitoring
- Sodium and fluid restriction
- Alcohol intake
- Weight reduction (obese) or unintentional weight loss
- Physical activity & exercise training
- Sexual activity
- Contraception
- Sleep disorders
- Depression and mood disorders

Treatment algorithm for patients with symptomatic HF and reduced LVEF (ESC 2008 guidelines)



Diuretics. ESC Guidelines 2008

- Provide relief from the symptoms and signs of pulmonary and systemic venous congestion (class I, level of evidence B)
- Cause activation of the RAA system and should be used in combination with an ACEI/ARB
- Dose requirement must be tailored to the individual's patient 's need and requires careful clinical monitoring
- A loop diuretic is generally required in moderate to severe HF
- A thiazide may be used in combination with loop diuretics for resistant oedema but with caution (dehydration, hypovolaemia, hyponatremia, hypokalaemia)
- Essential to monitor K, Na, and creatinine levels

Indications and dosing of diuretics in acute HF (ESC 2008 guidelines)

Fluid retention	Diuretic	Daily dose (mg)	Comments
Moderate	Furosemide or torasemide	20-40	Oral or iv symptoms
Severe	Furosemide Furosemide infusion Torasemide	40-100 5-40 mg/h 20-100	i.v., increase dose Better than high bolus doses Oral
Refractory to loop diuretic	Add metolazone Add spironolactone	2.5-10 25-50	More potent than HCTZ at CrCl<30 ml/m Best if no renal failure & normal/low K
Refractory to loop diuretics and thiazides	Add dopamine or dobutamine		Consider UF or haemodyalisis

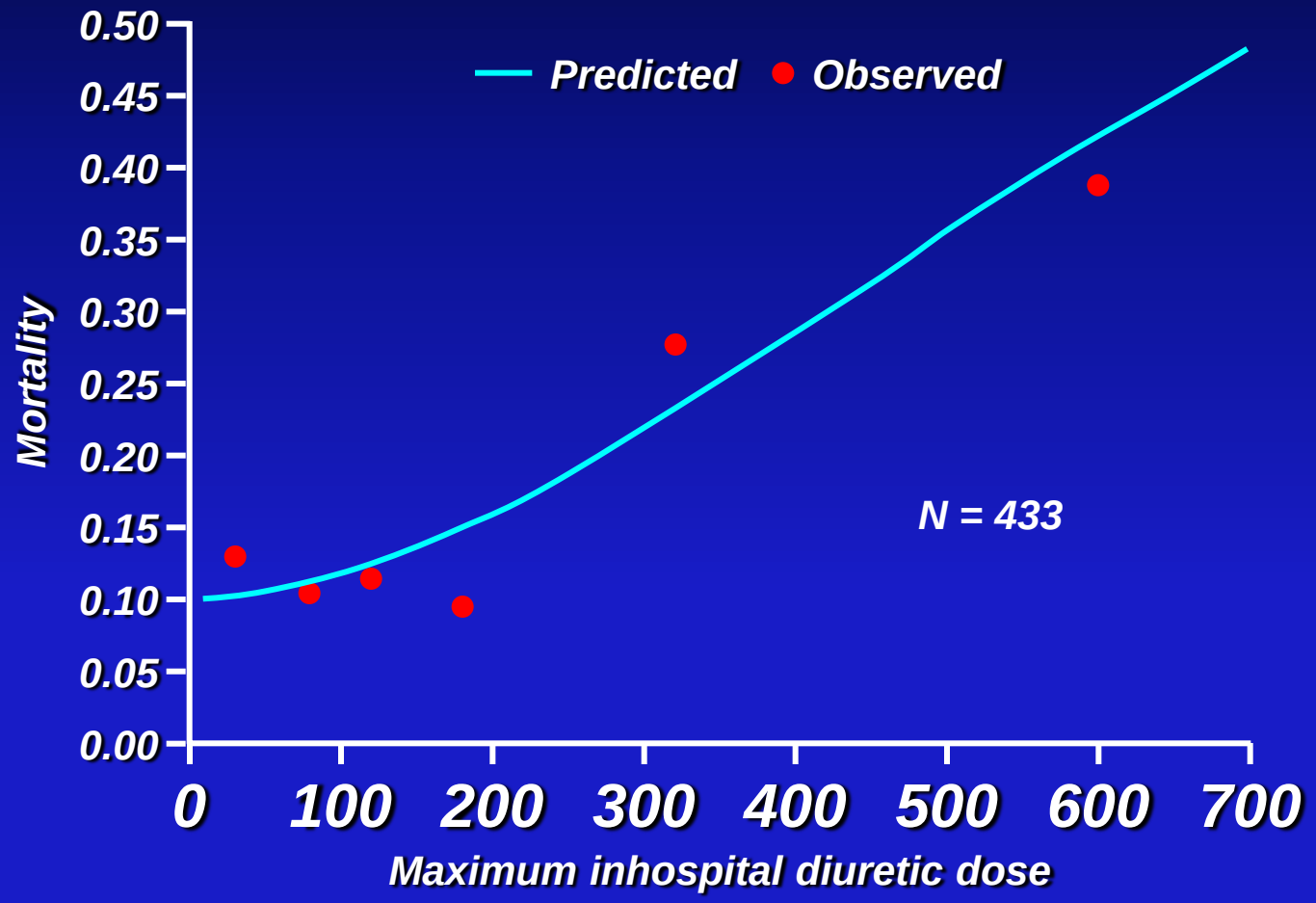
Diuretics in AHF. ESC Guidelines 2008

- IV administration recommended in AHF patients with symptoms secondary to congestion or volume overload. Class I, LoE B
- Symptomatic benefit and universal clinical acceptance has precluded formal evaluation in RCTs
- Patients with hypotension (SBP<90 mmhg), severe hyponatremia or acidosis are unlikely to respond to diuretics
- High doses of diuretics may lead to hypovolaemia & hyponatremia and increase likelihood of hypotension with ACEI/ARB
- Alternative treatments (e.g. vasodilators) may reduce the need of iv diuretics

Untoward effects of furosemide treatment in heart failure

- Resistance
- Side effects
  - Electrolyte abnormalities
  - Neurohormonal activation
  - Worsening renal function
- Independently associated with a worse outcome
  - Cause? Epiphenomenon?

ESCAPE: High-Dose Loop Diuretics in HF Associated With Increased 6-Month Mortality



Hasselblad V, et al. Eur J Heart Fail. 2007;9:1064-1069.

Predictors of Worsening Renal Failure Among 318 Patients Hospitalized for AHF

Results of Multivariable Analysis

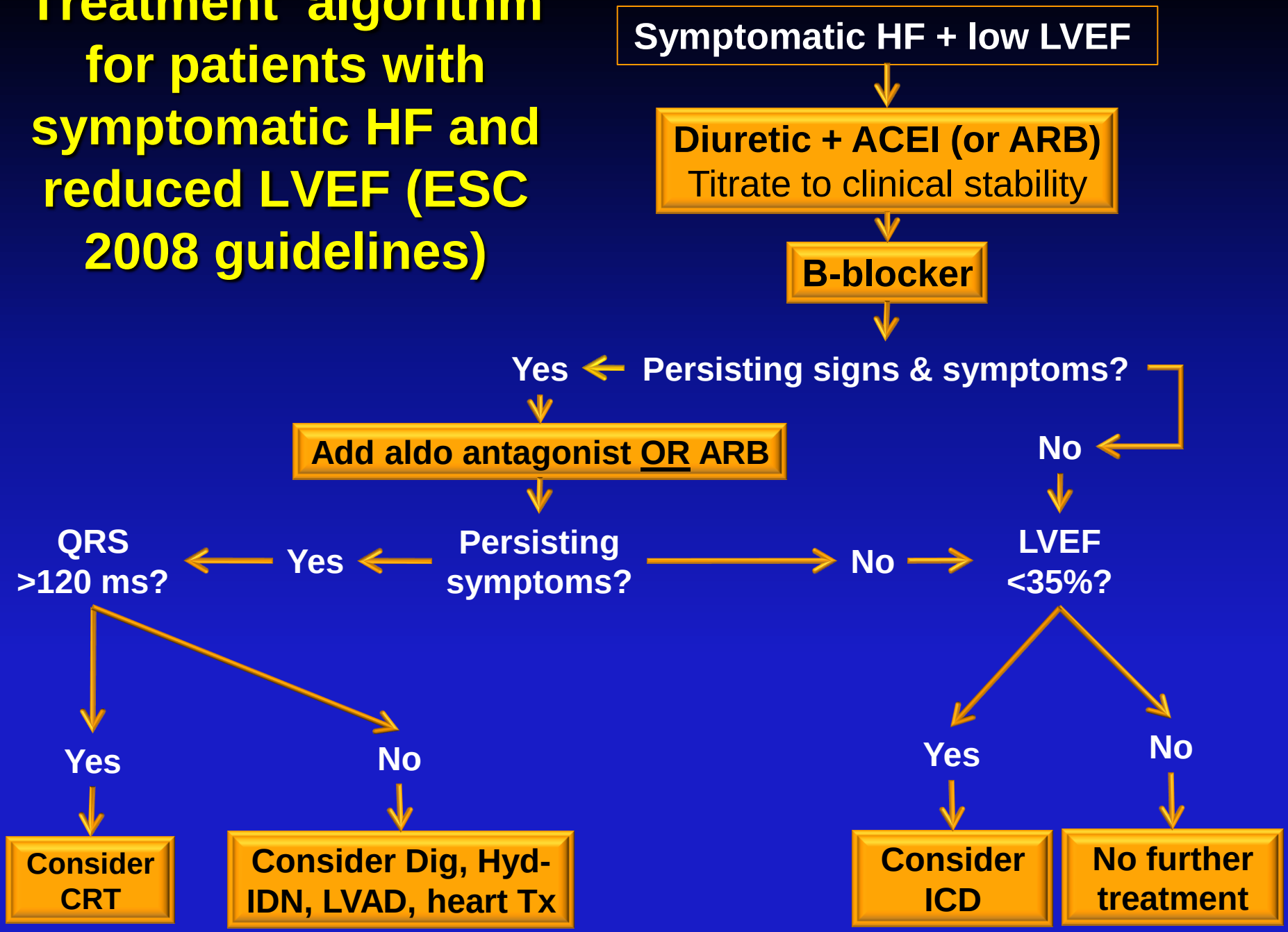
Predictor	Odds ratio (95% CI)	*P*
History of chronic kidney disease	1.84 (1.04 – 3.27)	< 0.0001
IV furosemide dose > 100 mg/d	2.18 (1.27 – 3.73)	0.004
NYHA class (IV vs. III)	2.07 (1.24 – 3.45)	0.005
LV ejection fraction < 30%	1.66 (1.01 – 2.75)	0.047

Metra … Dei Cas. Eur J Heart Fail. 2008;10:188-195.

Management of diuretic resistance (ESC guidelines 2008)

- Check compliance and fluid intake
- Increase dose of diuretic
- Consider switching from furosemide to torasemide or bumetanide
- Add aldosterone antagonist
- Combine loop diuretic and thiazide/ metolazone
- Administer loop diuretic twice daily or on empty stomach
- Consider short-term iv infusion of loop diuretic

Treatment algorithm for patients with symptomatic HF and reduced LVEF (ESC 2008 guidelines)



ACEI in HF: Key evidence

Trial	Drug	Relative risk reduction	Absolute risk reduction	NNT to save 1 life
CONSENSUS	Enalapril	27%	14.6%	7
SOLVD Treatment	Enalapril	16%	4.5%	22
SOLVD Prevention	Enalapril	20% death or hospital.		
SAVE, AIRE, TRACE	Captopril, trandolapril, ramipril	26% death 27% HF hosp		

ESC guidelines for the diagnosis and treatment of HF, 2008

ACEI in HF

- **Indications**
  - LVEF ≤40%, irrespective of symptoms
- **Contraindications**
  - History of angioedema
  - Bilateral renal artery stenosis
  - Serum potassium >5.0 mmol/L
  - Serum creatinine > 2.5 mg/dl
  - Severe aortic stenosis
- **Doses**
  - Titrate to target doses (uptitration every 2-4 ws)
  - Check s-electrolytes & creatinine 1 and 4 ws after dose increase

Side effects of ACEI

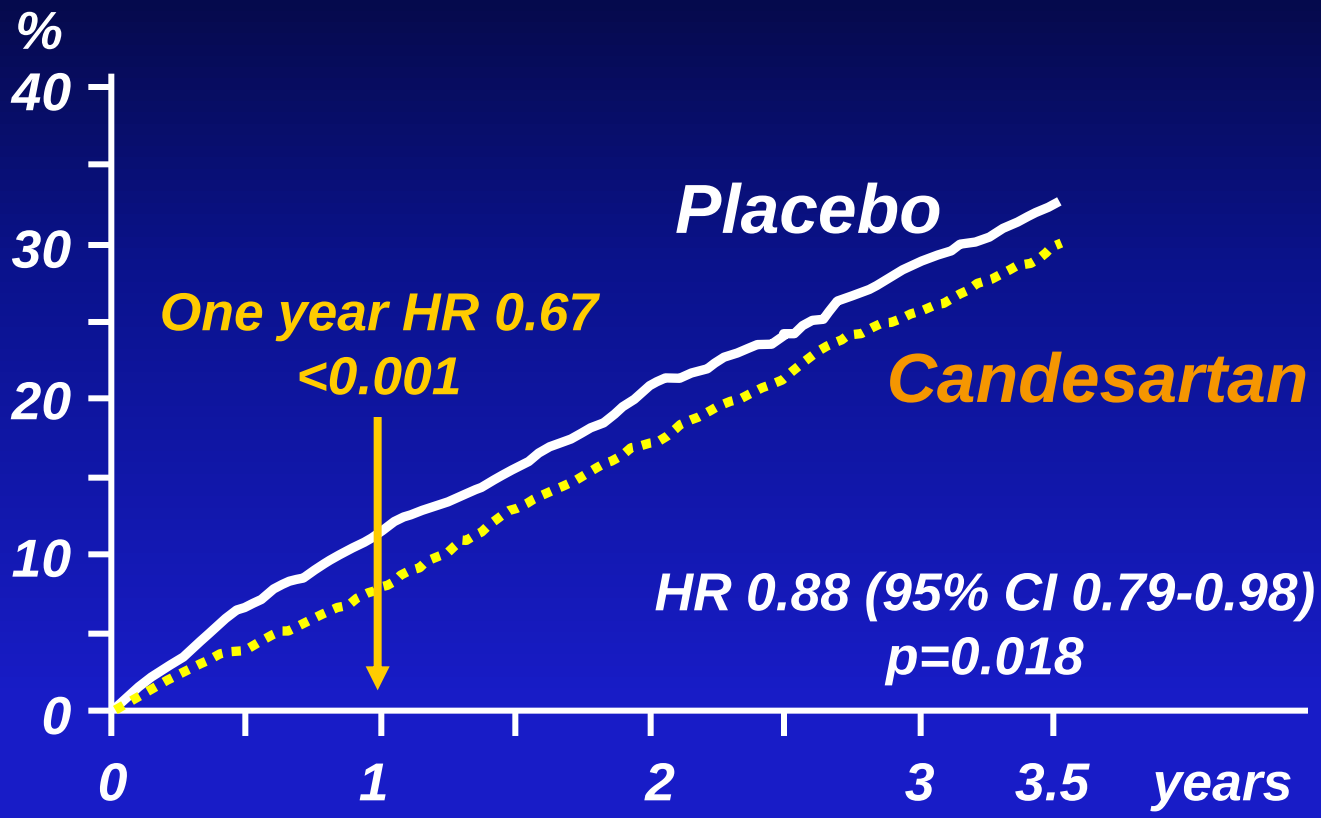
- Worsening renal function
  - Acceptable: ↑s-Creat <50% or <3 mg/dl
  - Moderate (s-Creat, 3 to 3.5 mg/dl):
    - half the ACEI dose & monitor blood chemistry
  - Severe (s-Creat >3.5)
    - Stop ACEI & monitor blood chemistry
- Hyperkaliemia
- Symptomatic hypotension
  - Common, often improves with time, reassure pts.
  - Consider dose ↓ diuretics and other hypotensive agents
  - No intervention if asymptomatic
- Cough
  - Switch to ARB

Angiotensin Receptor Blockers in HF: Key evidence

Trial	drug	Relative risk reduction	Absolute risk reduction	Number needed to treat
CONSENSUS	Enalapril	27%	14.6%	7
SOLVD -Treatment	Enalapril	16%	4.5%	22
SOLVD Prevention	Enalapril	20%*		
CIBIS, MERIT-HF*	Bisoprolol metoprolol	34%	4.3%	23
COPERNICUS*	carvedilol	35%	7.1%	14
RALES	Spironol.	30%	11.4%	9
ValHeFT	Valsartan	24% HF hosp	3.3%*	30*
CHARM-Added	Candesartan	16%	4.4%*	23*
CHARM-alternative	Candesartan	23%*	7%*	14*

** Death or HF hospitalizations*

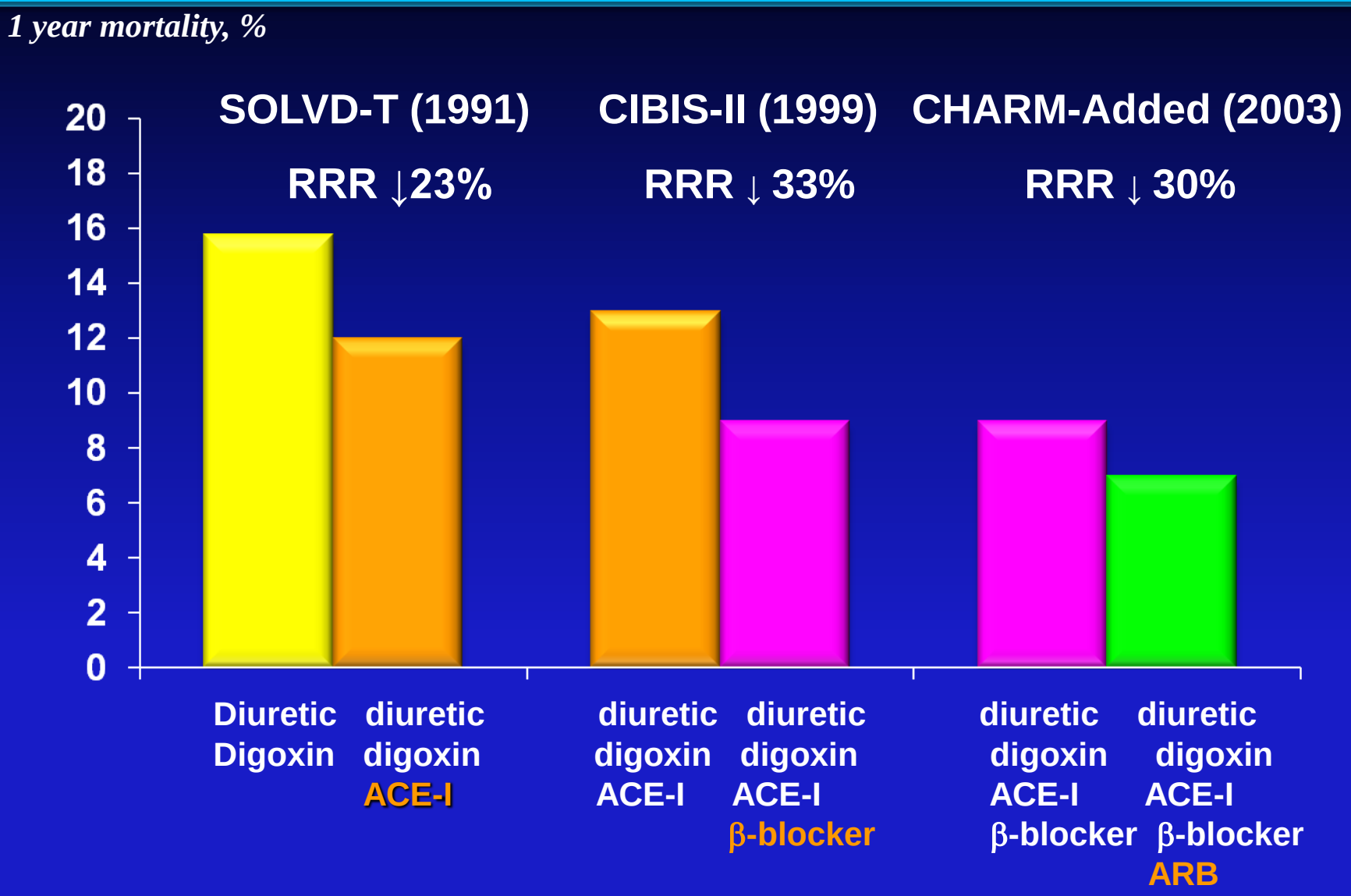
CHARM - Low EF (Alternative+Added):
All-cause death



Number at risk				
Candesartan	2289	2105	1894	1382
Placebo	2287	2023	1811	1333

Young et al Circ 2004

Improving Survival in CHF

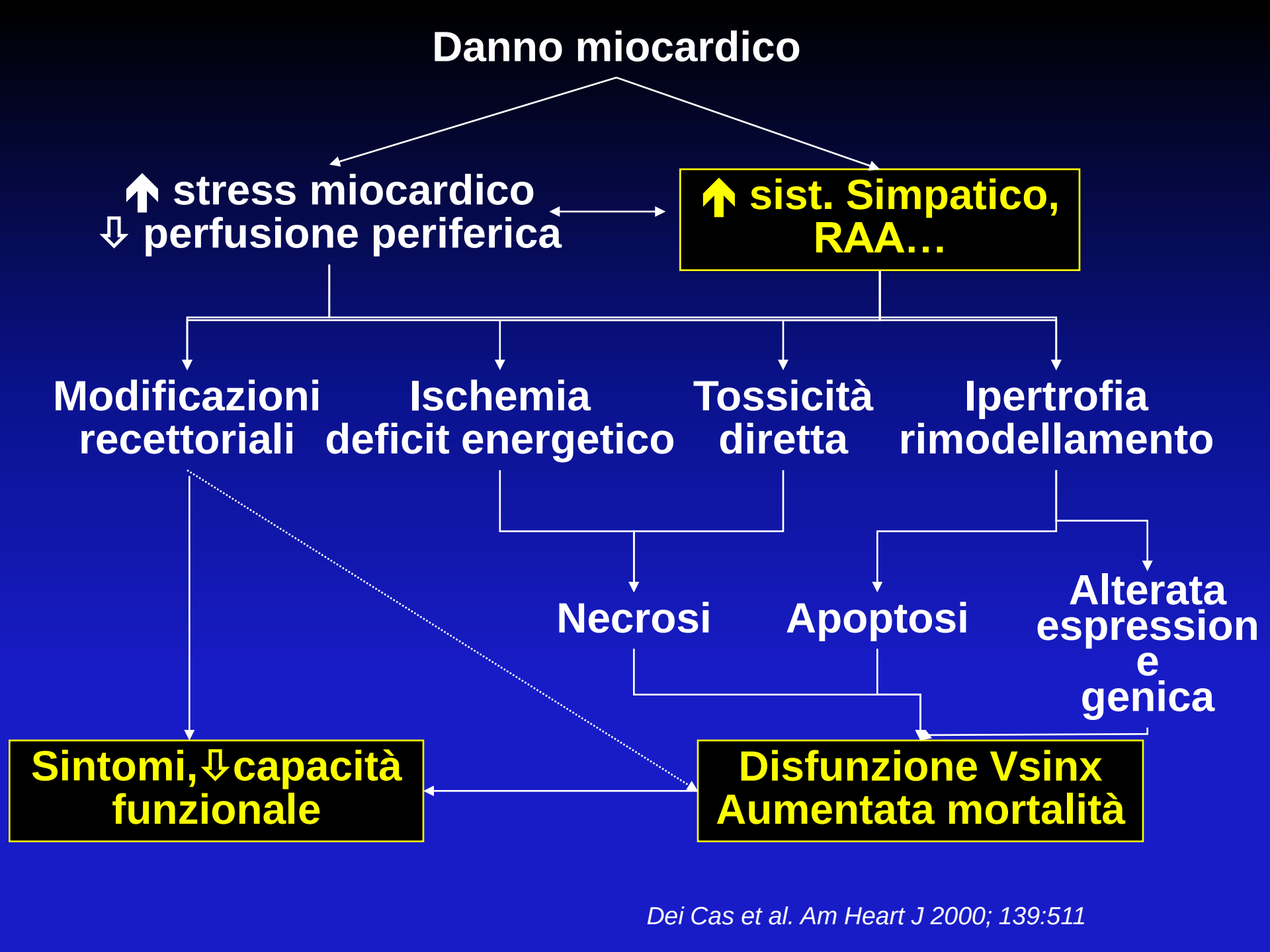


McMurray , Pfeffer, Swedberg, Dzau. Circulation 2004; 110: 3281

ACEI and BBs: Key evidence in ESC 2008 HF guidelines

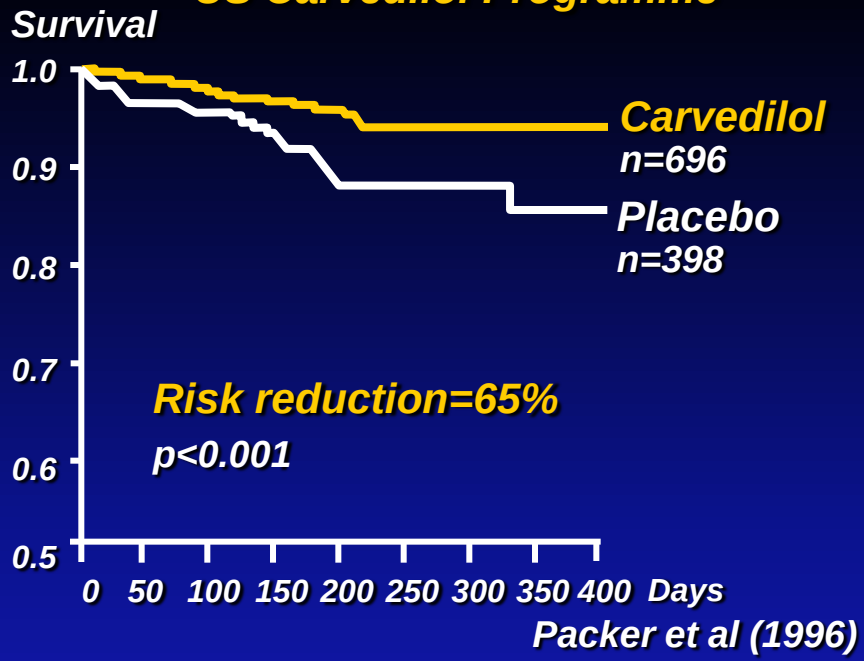
Trial	Drug	Relative risk reduction	Absolute risk reduction	Number needed to treat
CONSENSUS	Enalapril	27%	14.6%	7
SOLVD -Treatment	Enalapril	16%	4.5%	22
SOLVD Prevention	Enalapril	20%*		
SAVE, AIRE, TRACE	Captopril, trandolapril, ramipril	26%		
CIBIS, MERIT-HF*	Bisoprolol, metoprolol	34%	4.3%	23
COPERNICUS*	carvedilol	35%	7.1%	14
SENIORS	nebivolol	14%**	3.8%	
RALES	Spironolactone	30% death 35% HF hosp.	11.4%	9

* 90% of patients on ACEi **Death or HF hospitalizations in SENIORS



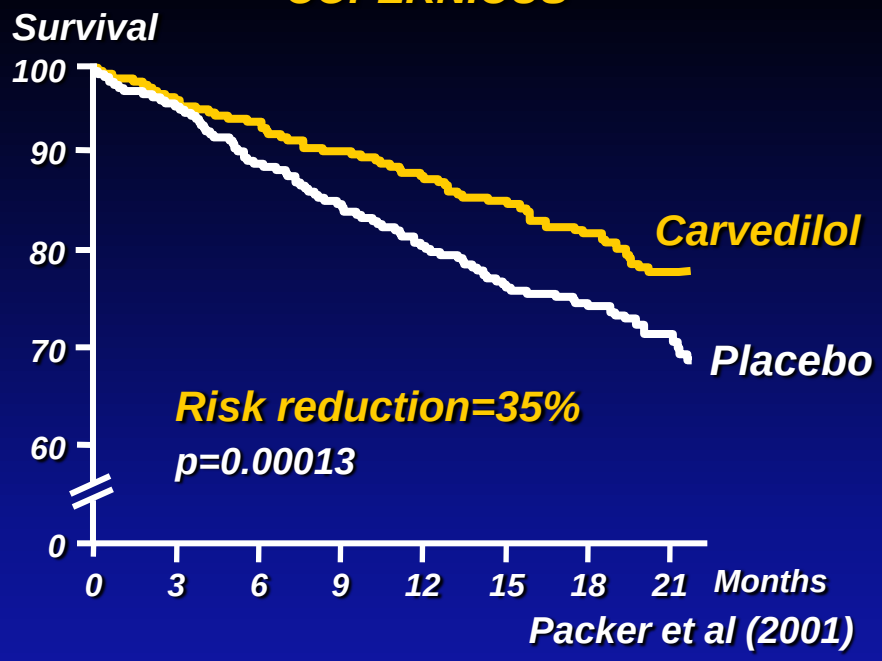
Dei Cas et al. Am Heart J 2000; 139:511

US Carvedilol Programme



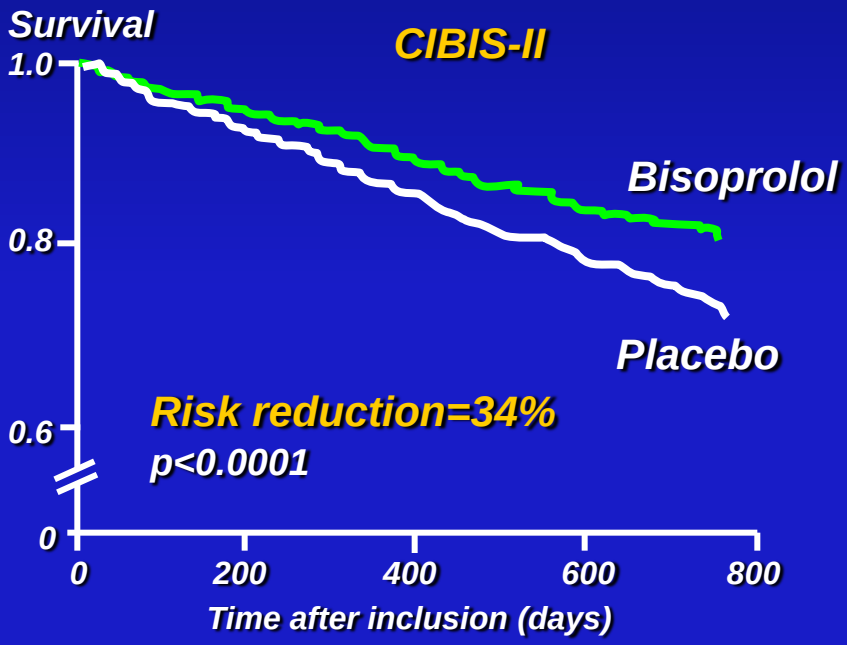
Packer et al (1996)

COPERNICUS



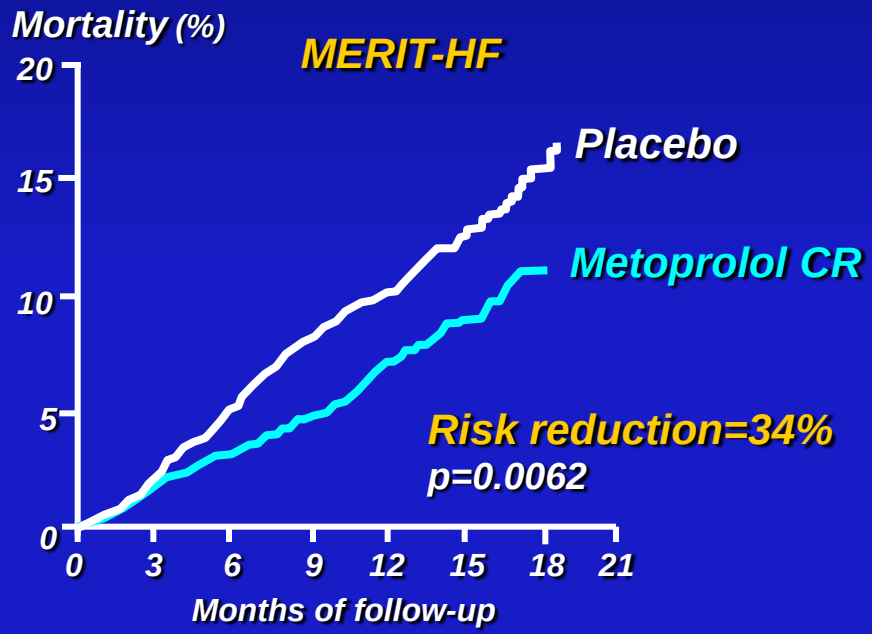
Packer et al (2001)

CIBIS-II



CIBIS-II Investigators (1999)

MERIT-HF



The MERIT-HF Study Group (1999)

Use of beta-blockers in HF

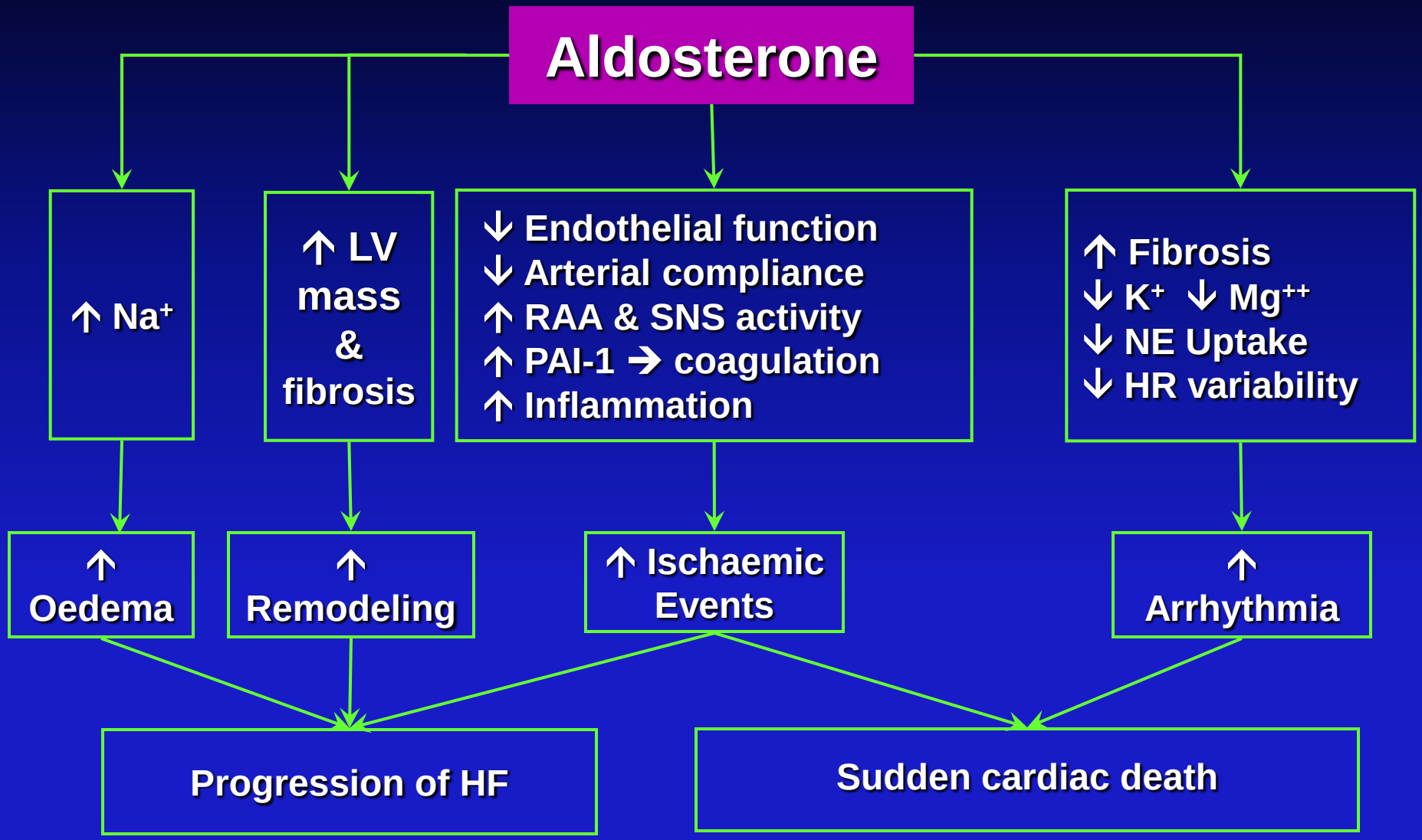
- **Indications**
  - LVEF ≤40%
  - NYHA class II-IV or asymptomatic postMI LVSD
  - Optimal dosage of ACEI/ARB and Aldo antagonist, if indicated
  - Clinically stable but predischarge initiation is possible
- **Contraindications**
  - Asthma (not COPD)
  - 2nd – 3rd degree AV block, sinus bradycardia (<50 bpm)

ESC guidelines for the diagnosis and treatment of HF, 2008

Beta-blockers in patients hospitalised for HF

- In patients admitted to hospital due to worsening HF, a reduction in the b-blocker dose may be necessary. In severe situations, temporary discontinuation can be considered.
- Low-dose therapy should be re-instituted and up-titrated as soon as the patient’s clinical condition permits, preferably prior to discharge.

Aldosterone and Cardiovascular Damage



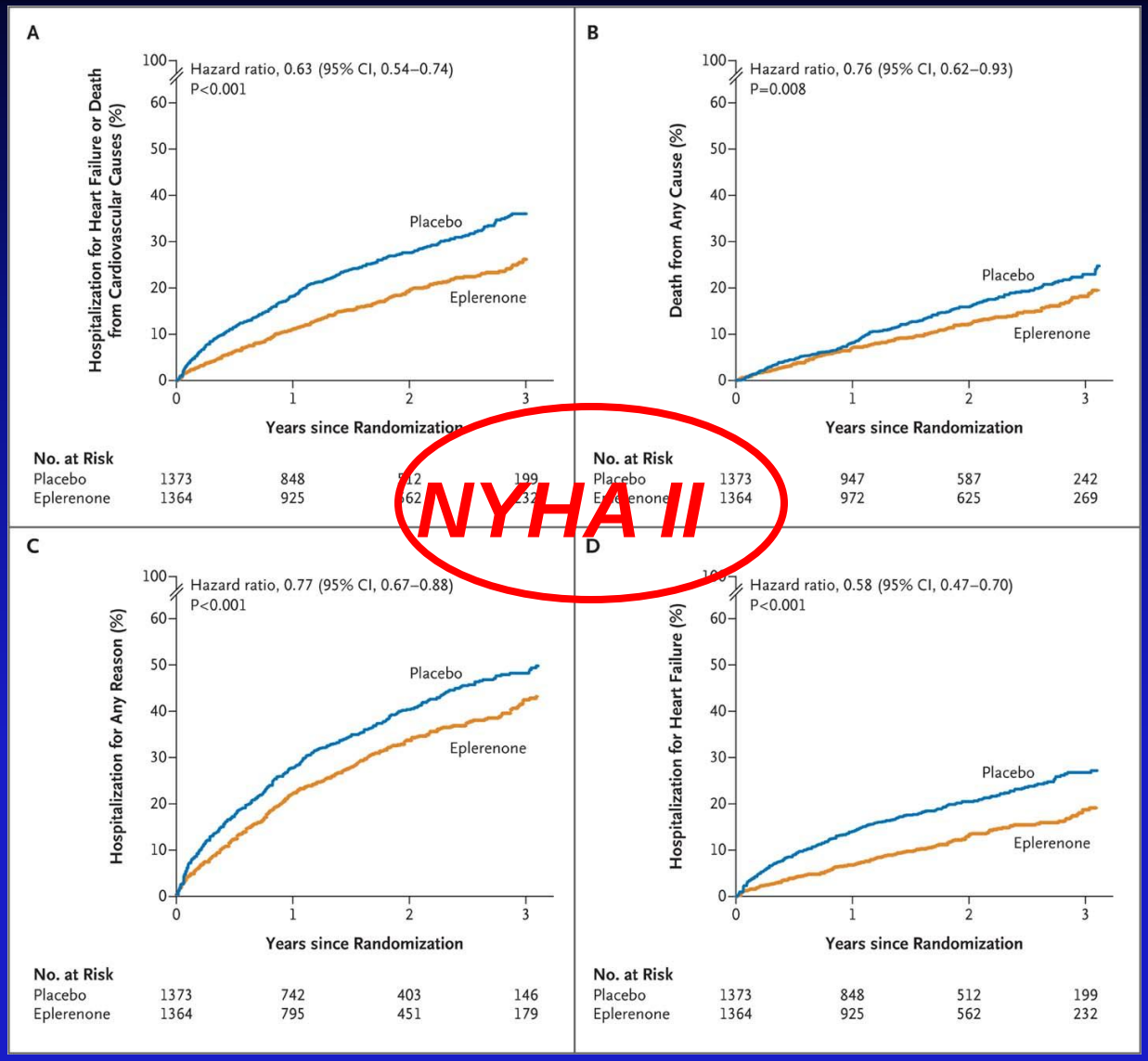
Use of aldosterone antagonists in HF

- **Indications**
  - LVEF ≤35%
  - Severe symptomatic HF, NYHA class III-IV
  - Optimal doses of ACEI or ARB but not both

- **Contraindications**
  - Hyperkaliemia (s-q/L)K>5.5 me
  - Renal dysfunction
    - S-Creat 2.5 → spiro 25 mg on alternate days
    - S-Creat >3.0 mg/dl: stop spironolactone

ESC guidelines for the diagnosis and treatment of HF, 2008

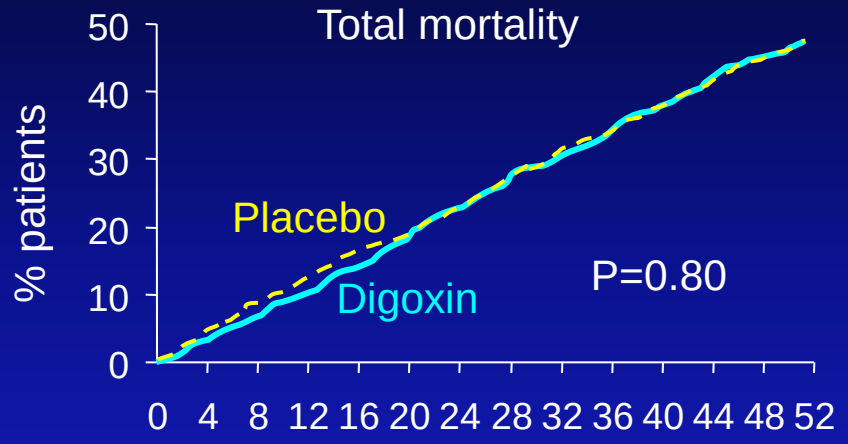
EMPHASIS: Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

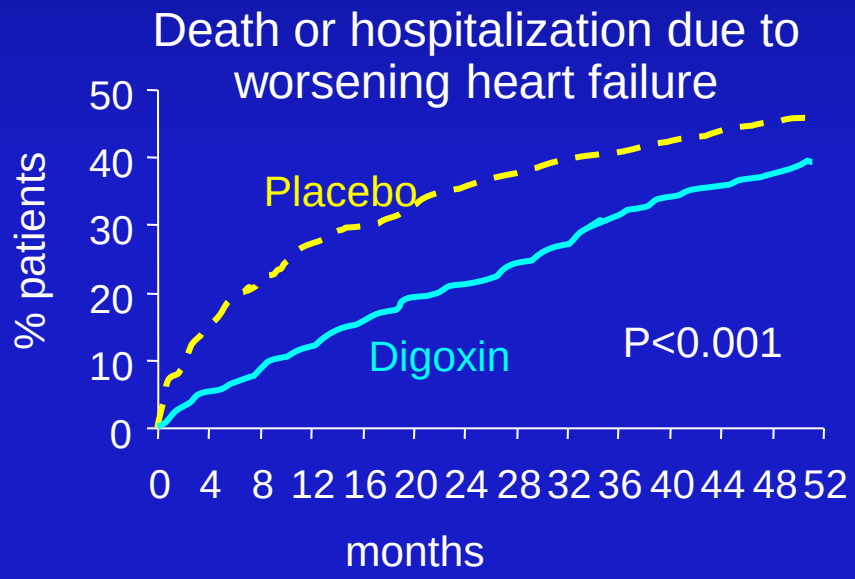


Zannad F et al. N Engl J Med 2011;364:11-21

Effetti della Digossina sulla Mortalità e Morbilità dei Pazienti con Insufficienza Cardiaca (DIG trial)

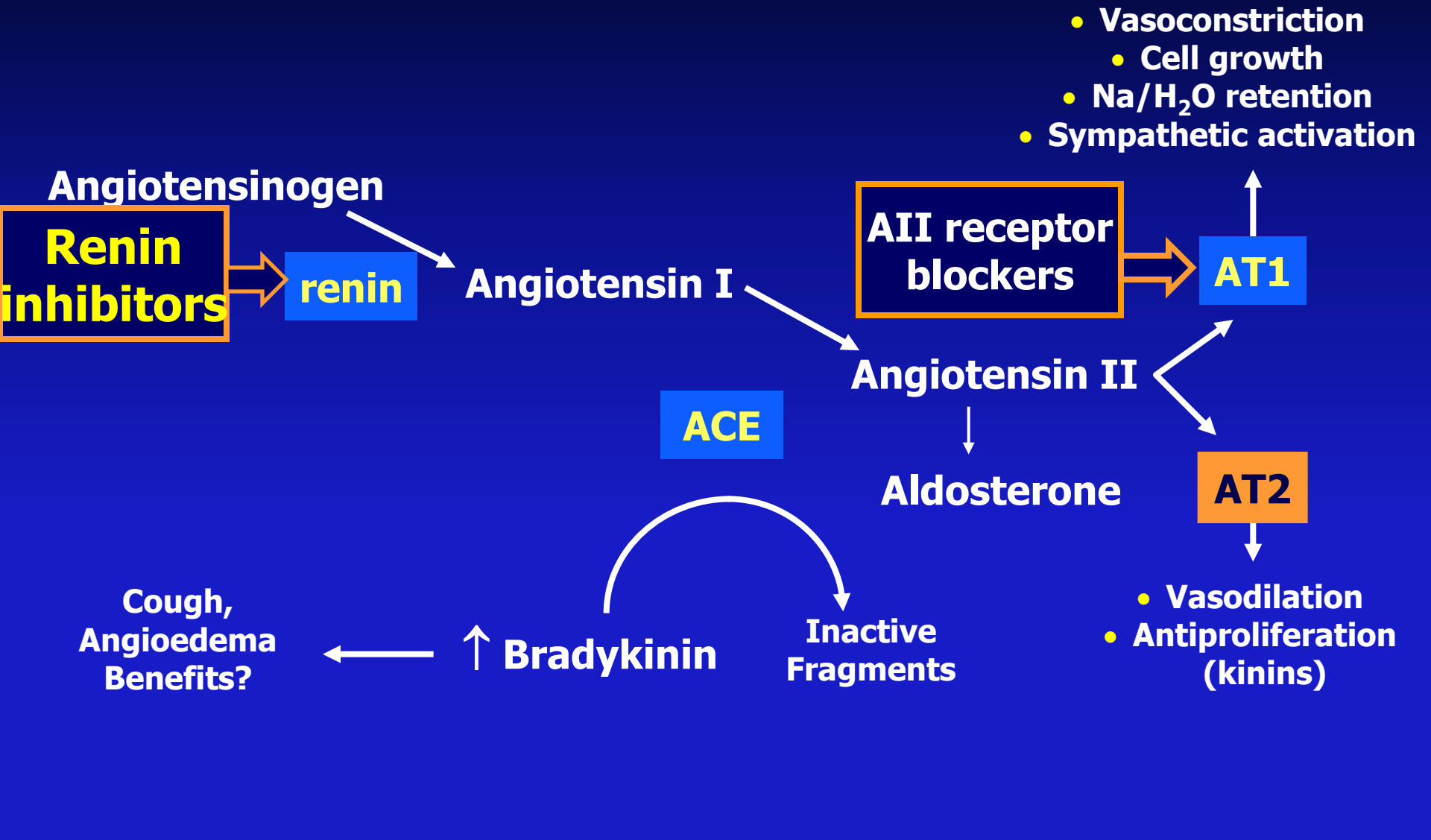
- Casistica
  - 6800 pz con FE ≤ 45%
  - 988 pz con FE > 45%
- Risultati (digossina vs. placebo)
  - Follow up, 37 mesi (28-58)
  - Mortalità, n.s.
  - ⇩12% morti per CHF, p=0.06
  - ⇩6% ospedalizzazioni totali
  - ⇩28% ospedalizzazioni per CHF, p < 0.001
  - Nessuna differenza tra pazienti con FE ≤ o > 45%



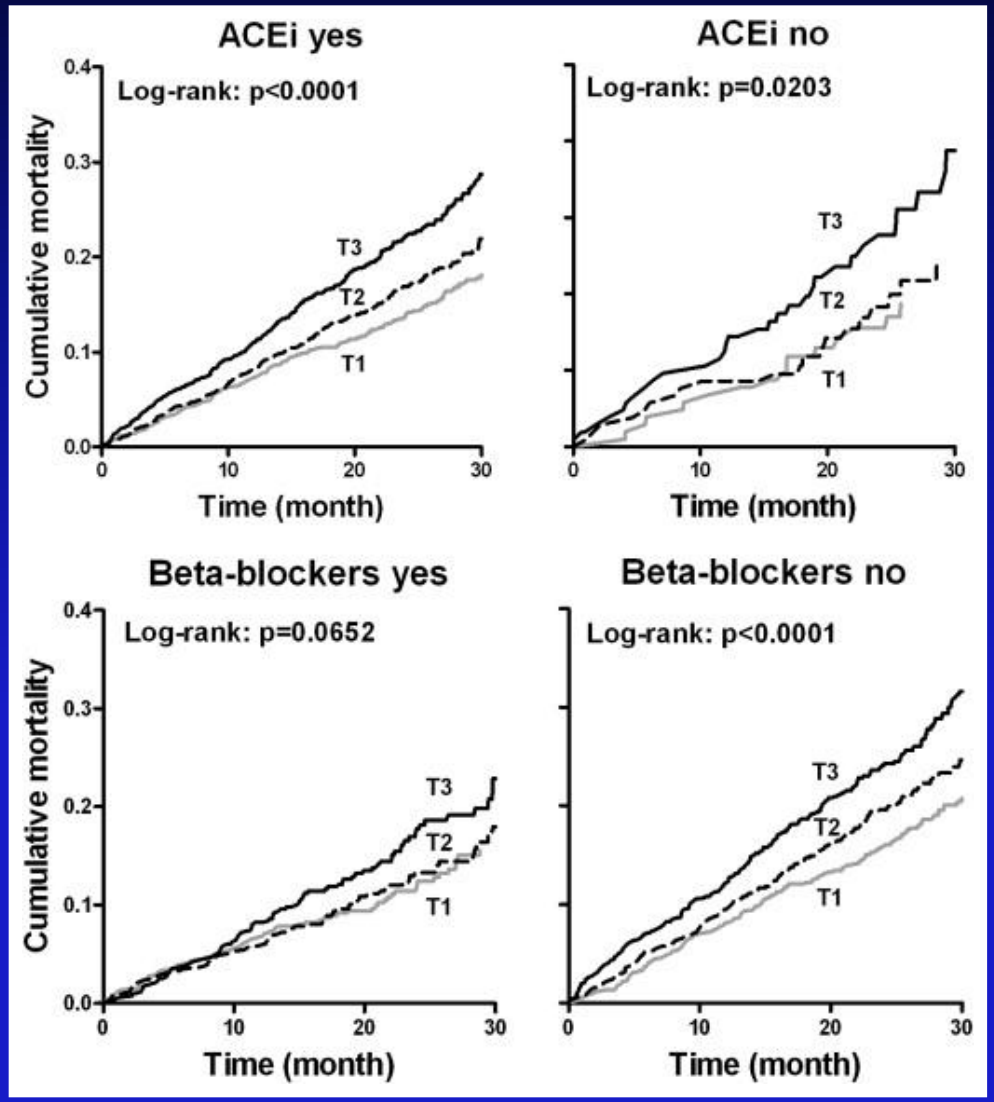


DIG Investigators, NEJM 1997;336:525

Pharmacologic modulation of the Renin-Angiotensin System

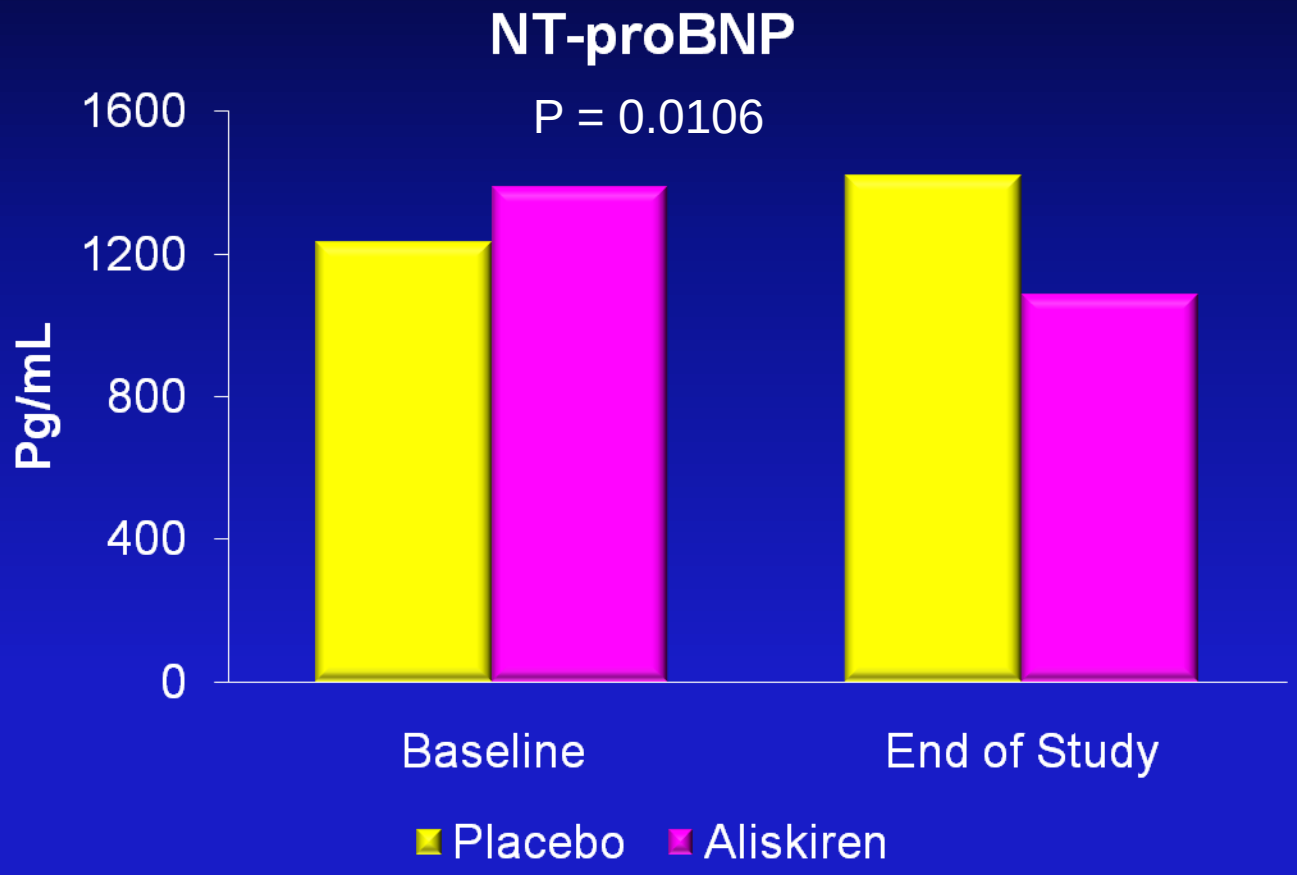


Elevated plasma renin activity predicts adverse outcome in HF, independently of pharmacologic therapy: data from Val-HeFT



Masson et al., J Card Fail 2010;16:964-70

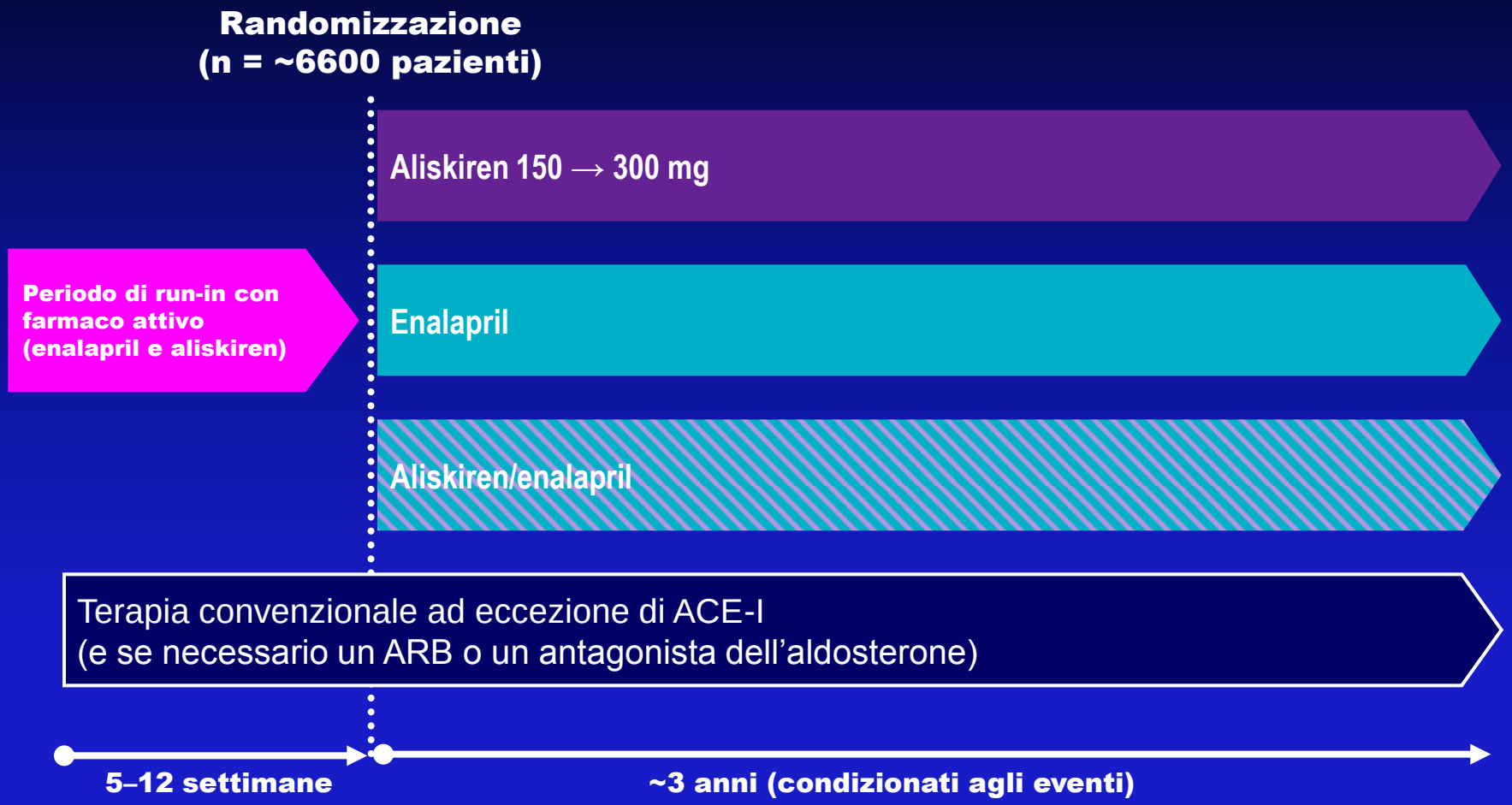
Effects of the Oral Direct Renin Inhibitor Aliskiren in 202 Patients With Symptomatic Heart Failure (ALOFT)



McMurray et al. Circ Heart Fail 2008; 1:74

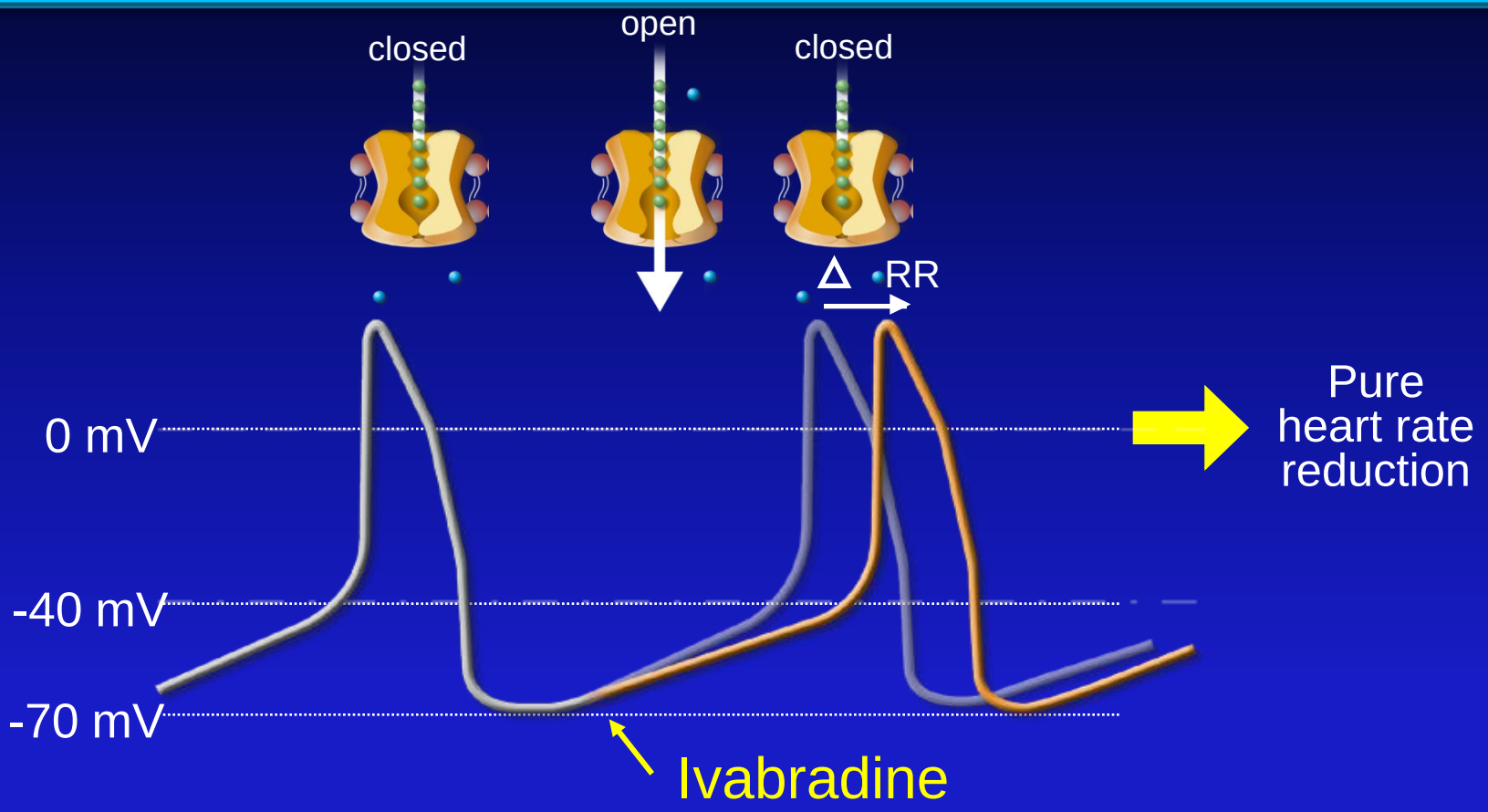
Disegno dello studio

ATMOSPHERE
Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE



ATMOSPHERE iniziato nel 1º trimestre del 2009

Ivabradine: pure heart rate reduction

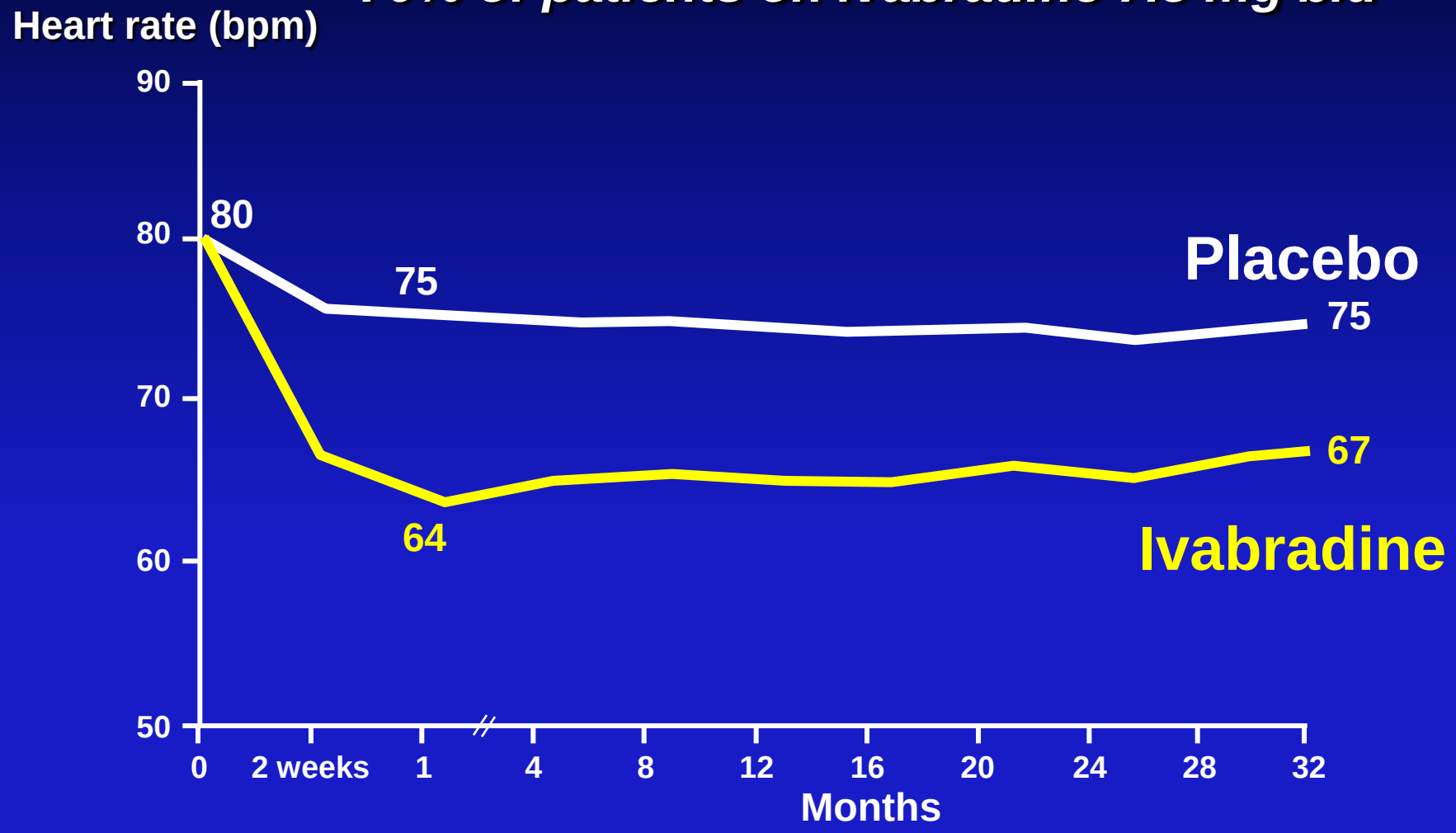


I_f inhibition reduces the diastolic depolarization slope, thereby lowering heart rate

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

Mean heart rate reduction

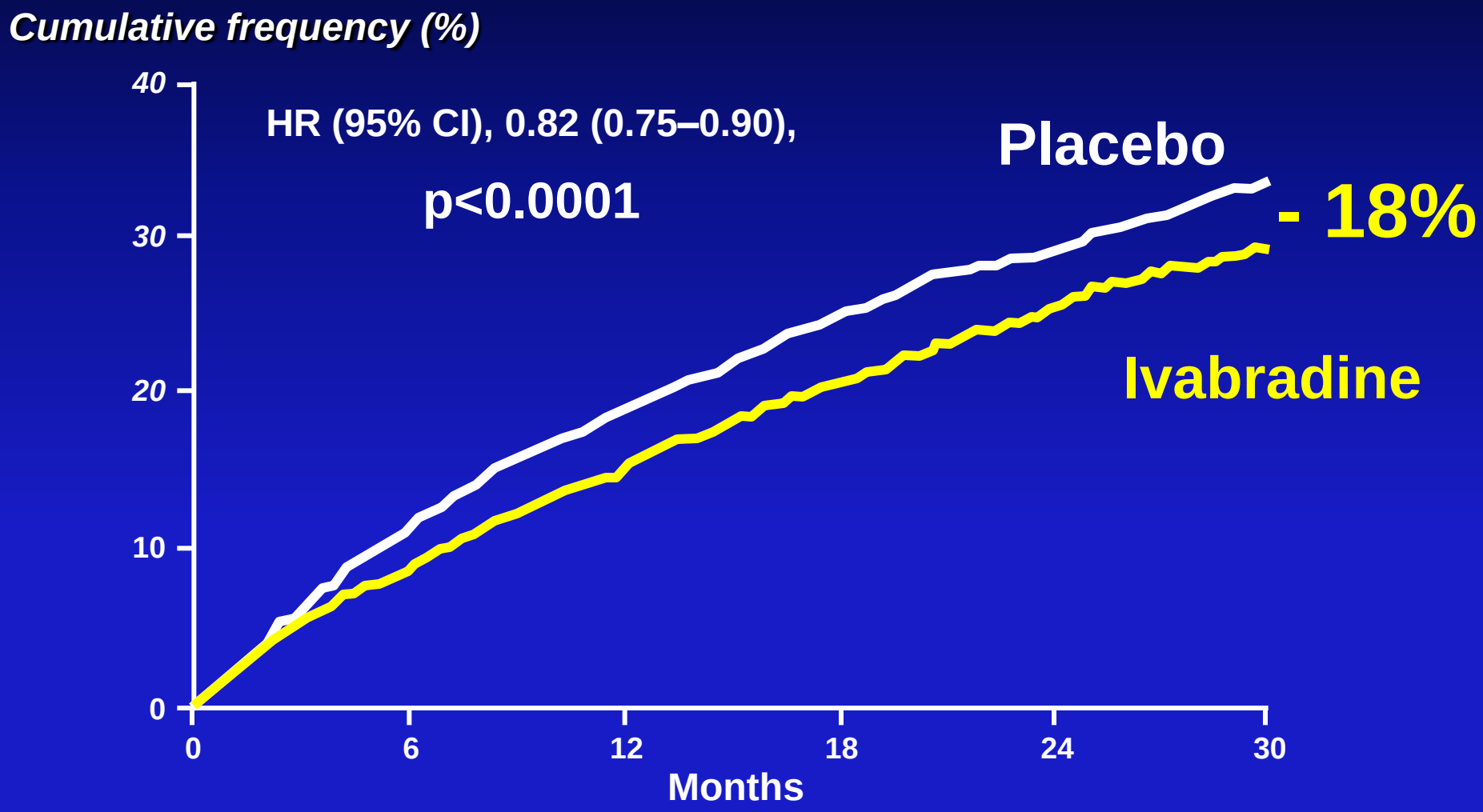
70% of patients on ivabradine 7.5 mg bid



Swedberg K, et al. Lancet. 2010;online August 29.

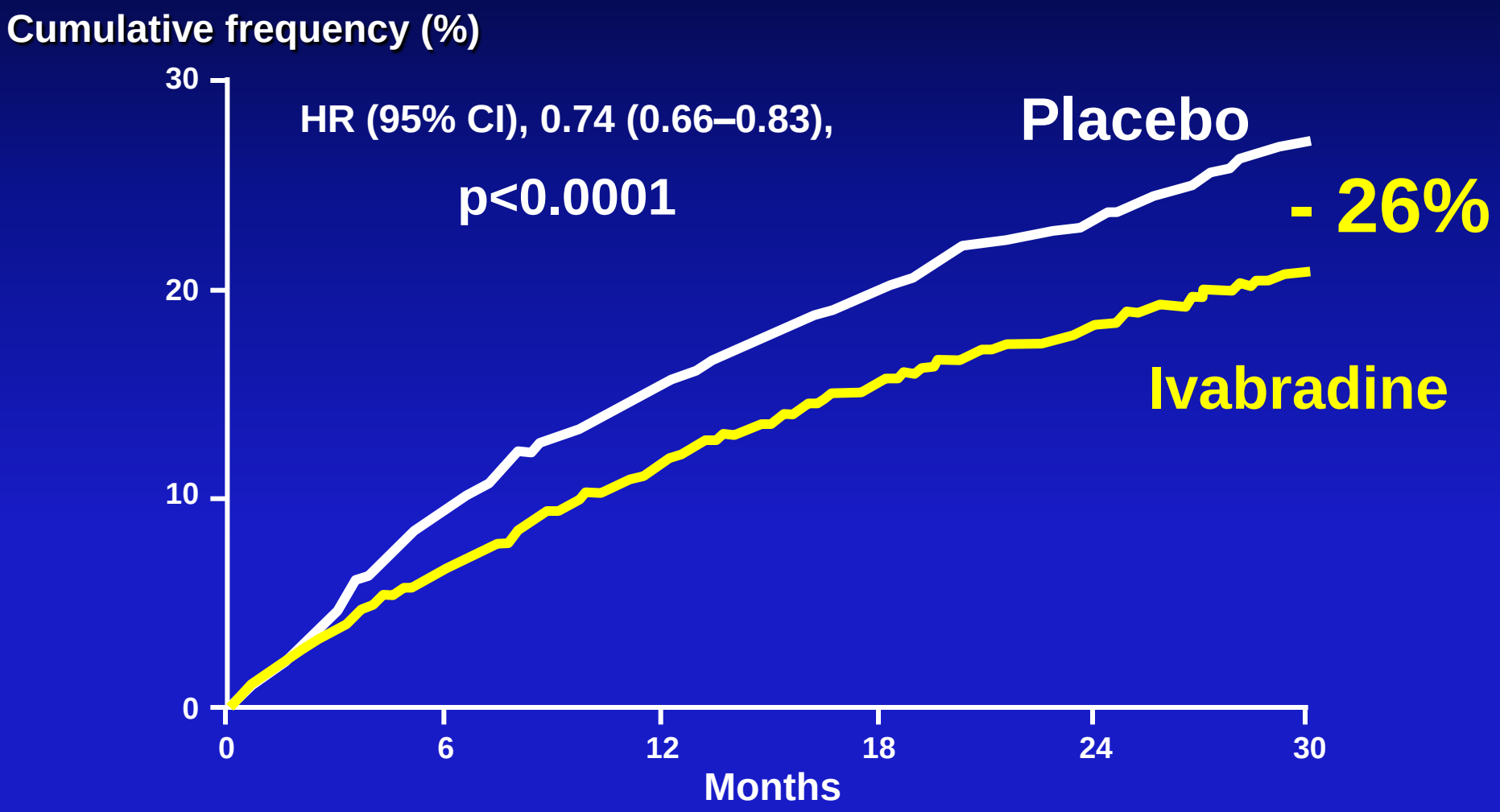
Primary composite endpoint

(CV death or hospital admission for worsening HF)



Swedberg K, et al. Lancet. 2010;online August 29.

Hospitalization for HF



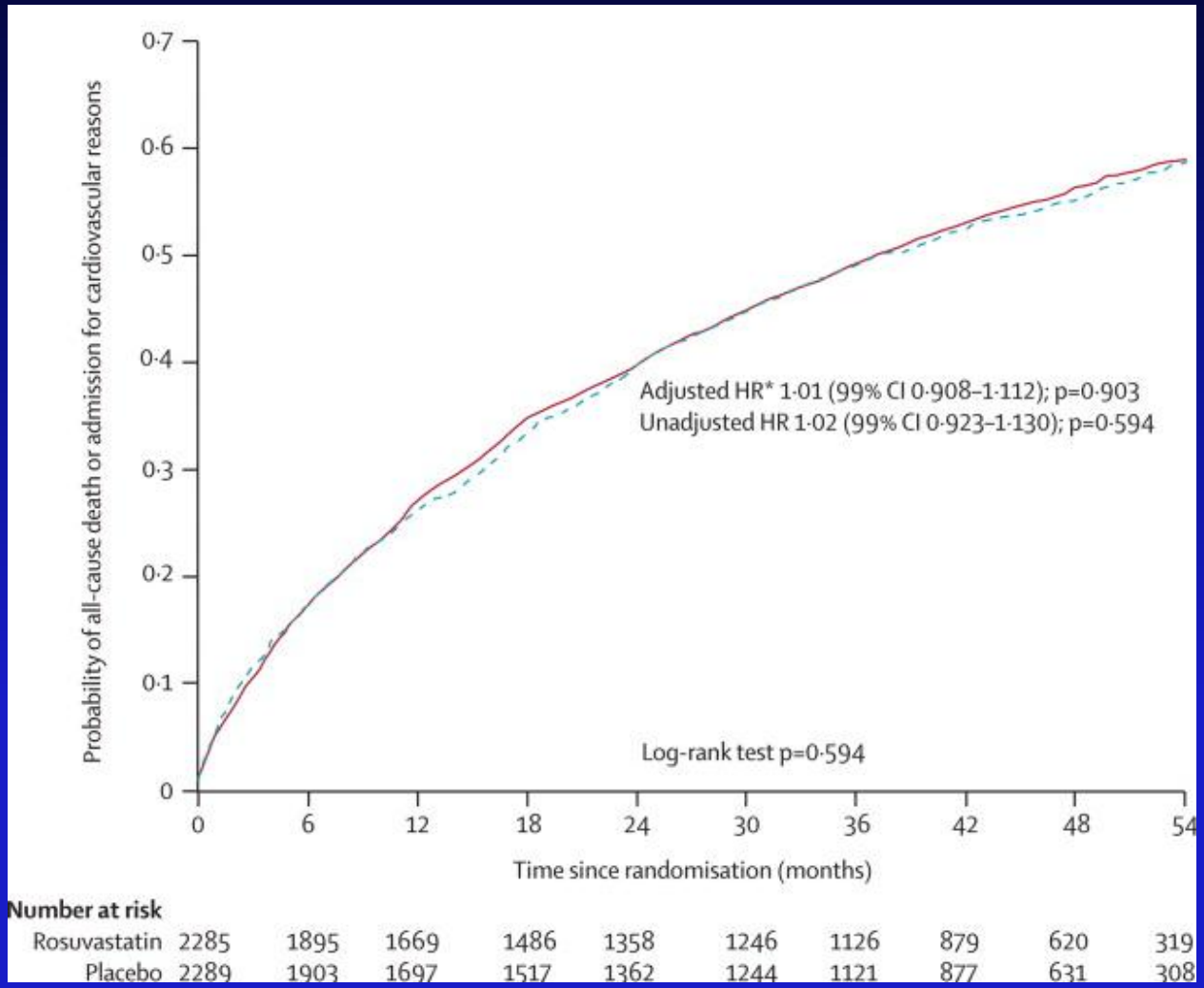
Swedberg K, et al. Lancet. 2010;online August 29.

Anti-thrombotic agents

- **Anti-coagulation**
  - Indicated in CHF with permanent, persistent, or paroxysmal atrial fibrillation without contraindications to anticoagulation
  - Evidence of systemic embolism
  - Intracardiac thrombus
- **Antiplatelet agents**
  - Associated with greater risk of hospitalisations
  - No evidence of reduction in atherosclerotic risk in patients with HF

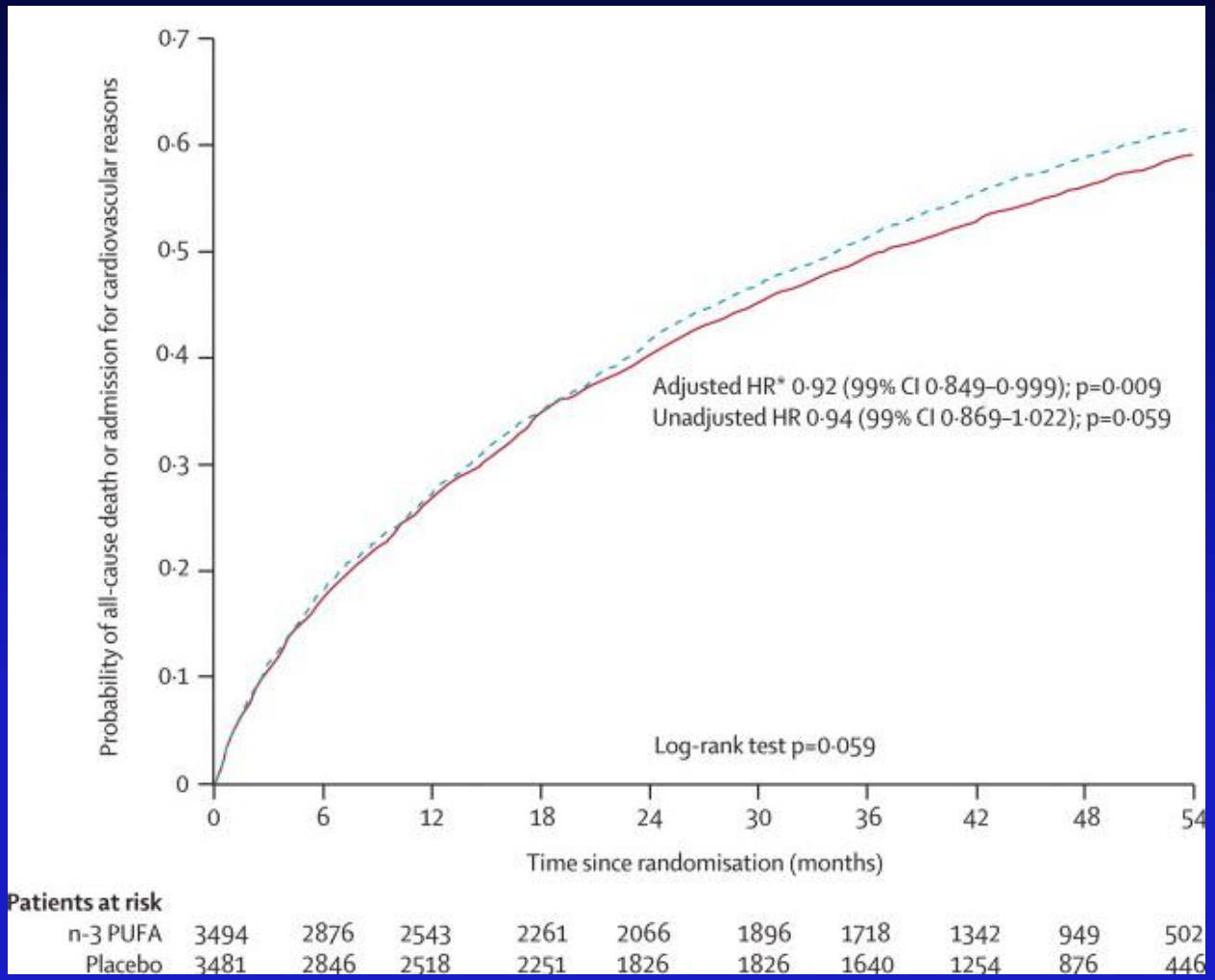
ESC Guidelines on the diagnosis and treatment of CHF EHJ 2008

Effect of rosuvastatin in patients with chronic HF (the GISSI-HF trial)



The Lancet DOI:10.1016/S0140-6736(08)61239-8

Effect of n-3 polyunsaturated fatty acids in patients with chronic HF (the GISSI-HF trial)



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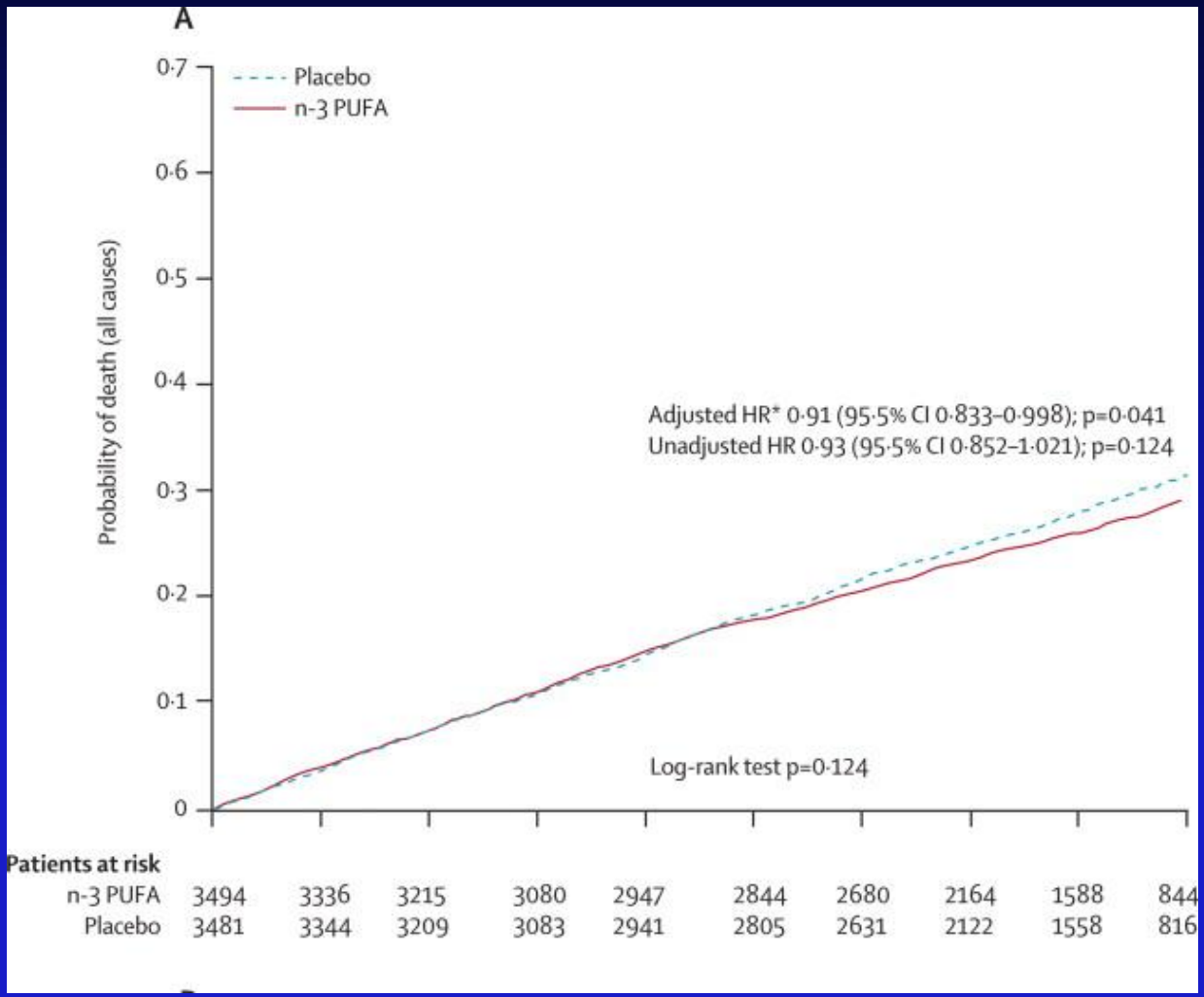
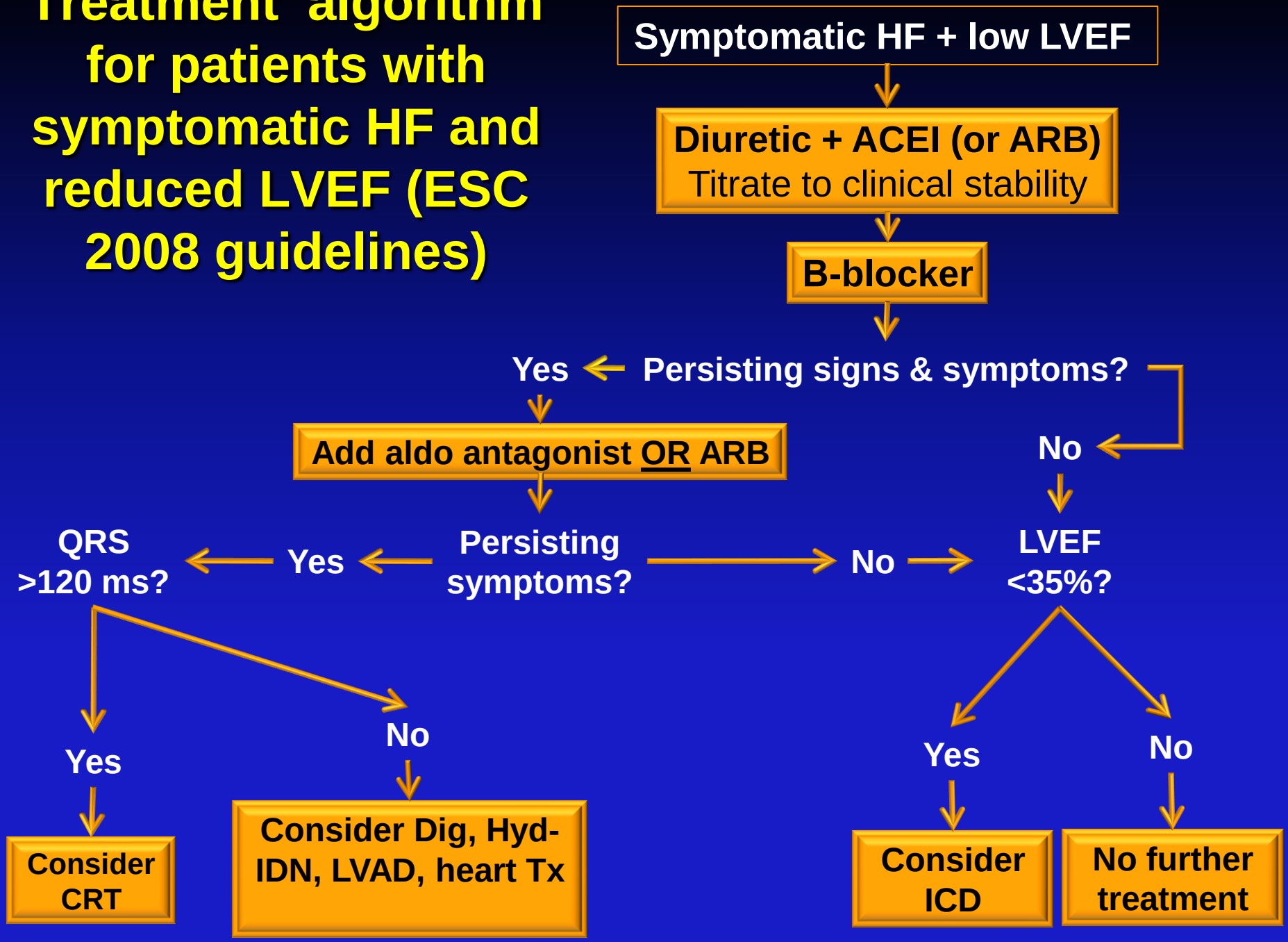
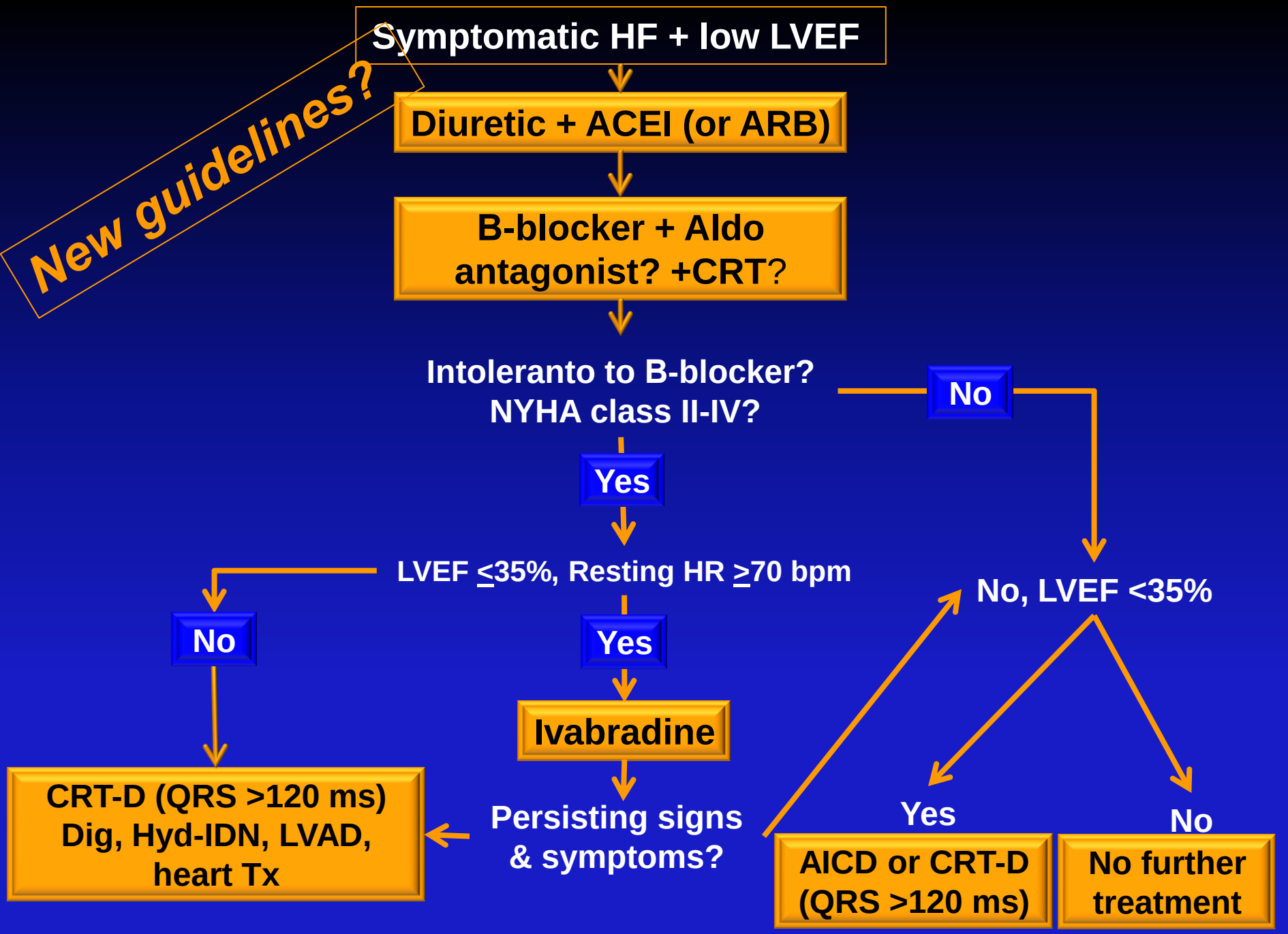


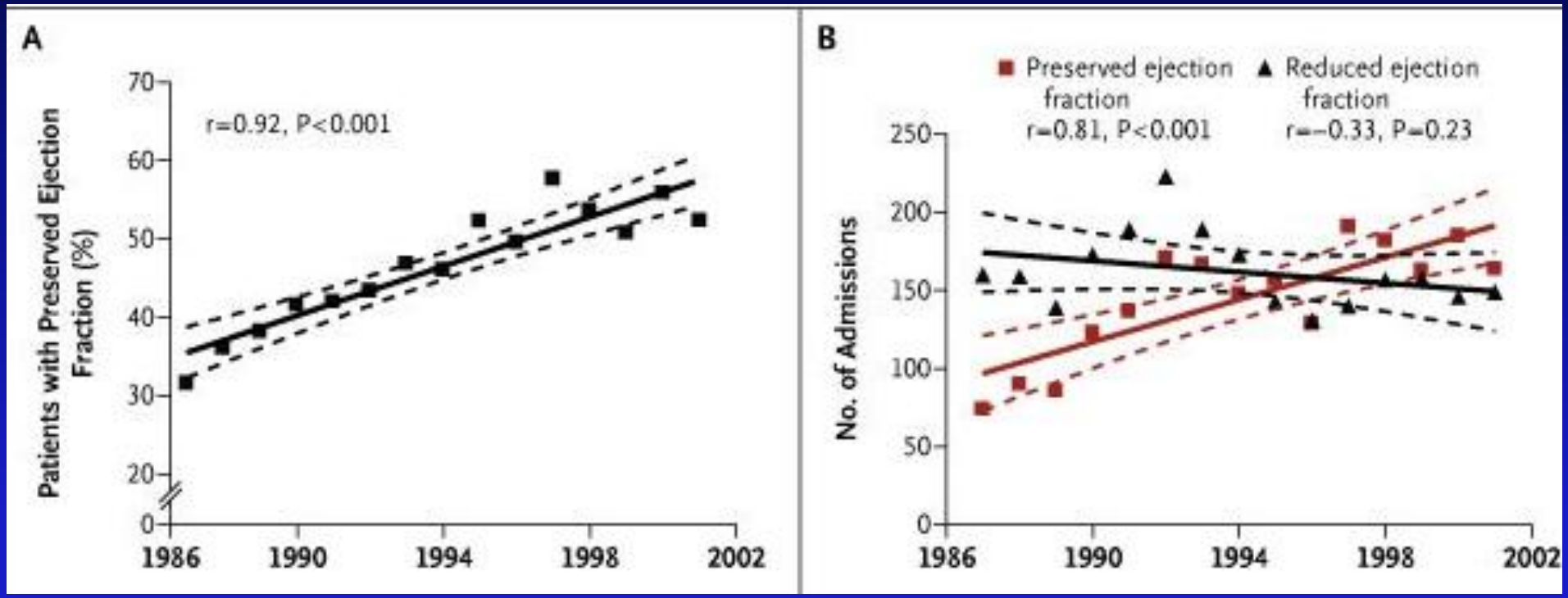
The Lancet DOI:10.1016/S0140-6736(08)61239-8

Treatment algorithm for patients with symptomatic HF and reduced LVEF (ESC 2008 guidelines)




New guidelines?
Symptomatic HF + low LVEF
Diuretic + ACEI (or ARB)
B-blocker + Aldo antagonist? +CRT?
Intoleranto to B-blocker?
NYHA class II-IV?
No
Yes
LVEF ≤35%, Resting HR ≥70 bpm
No
Yes
Ivabradine
Persisting signs & symptoms?
CRT-D (QRS >120 ms) Dig, Hyd-IDN, LVAD, heart Tx
No, LVEF <35%
Yes
No
AICD or CRT-D (QRS >120 ms)
No further treatment

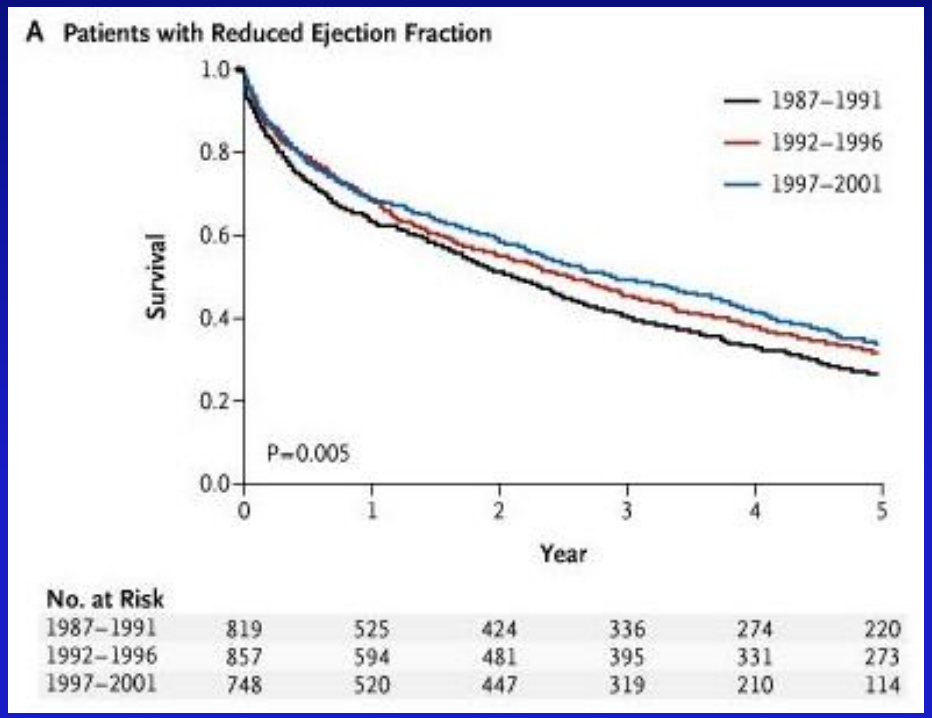
Secular Trends in the Prevalence of Heart Failure with Preserved Ejection Fraction

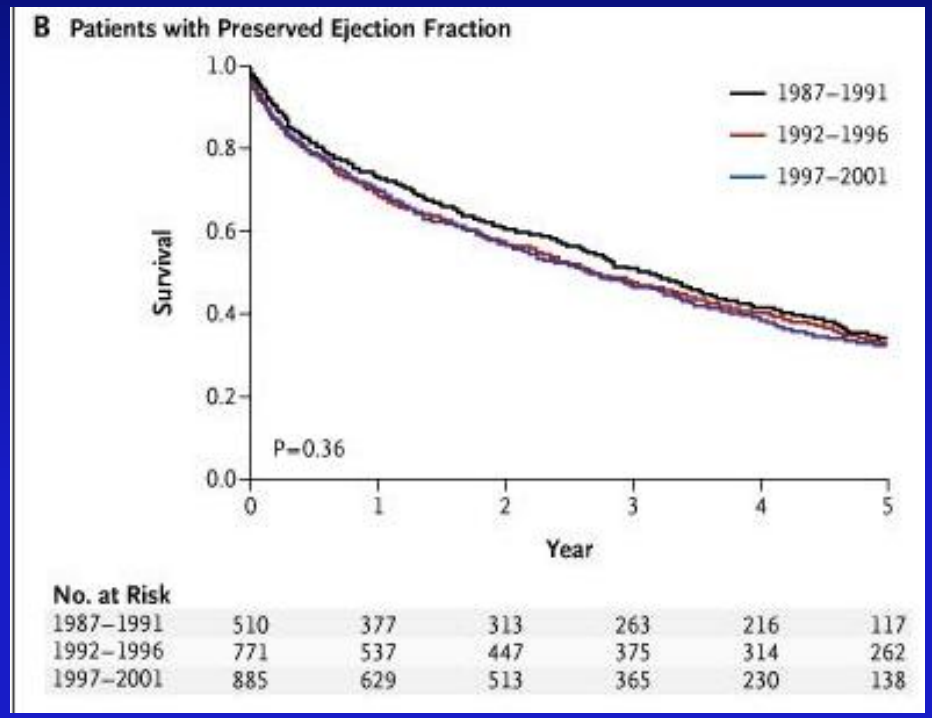


Owan T et al. N Engl J Med 2006;355:251-259

Increased Survival among Patients with Heart Failure Reduced EF but not in those with Preserved EF

All consecutive patients hospitalized with decompensated heart failure at Mayo Clinic Hospitals, Minnesota (n=4596)

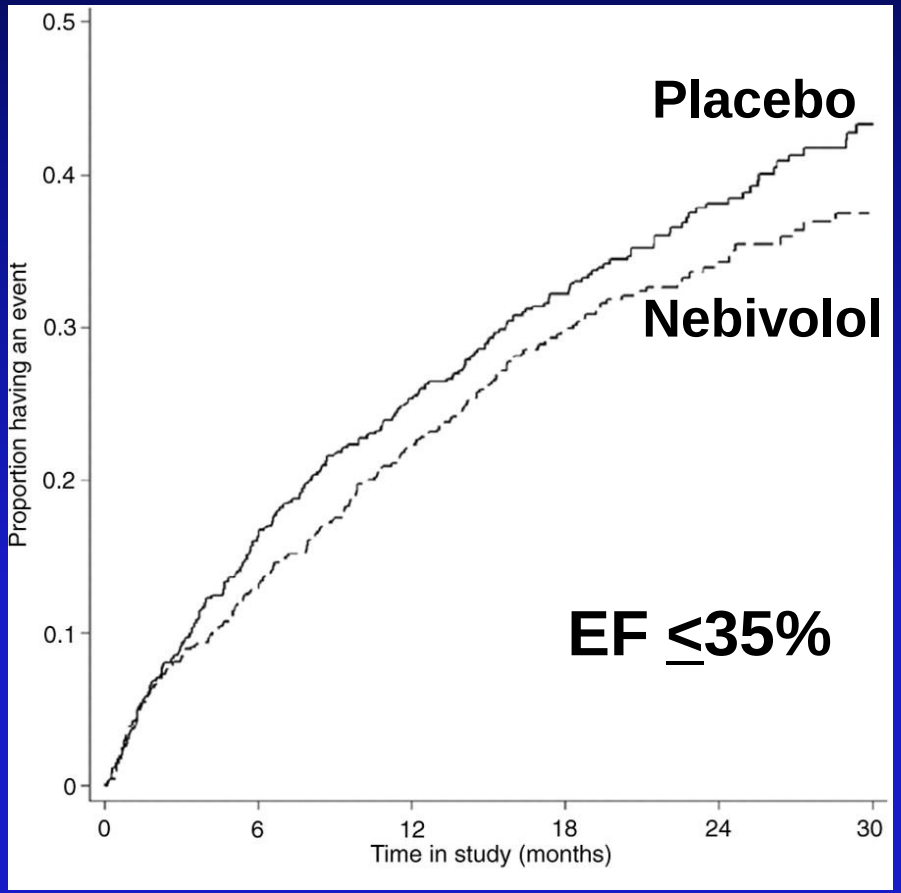


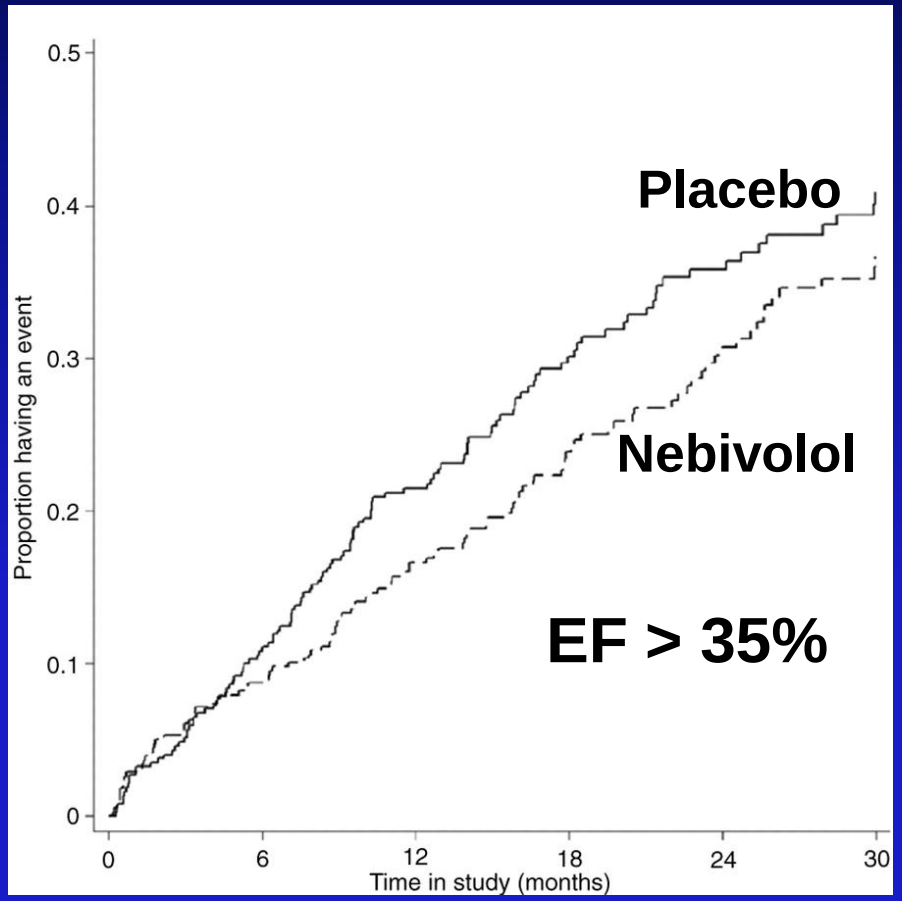


Owan T et al. N Engl J Med 2006;355:251-259

Beta-Blockade With Nebivolol in Elderly Heart Failure Patients With Impaired and Preserved Left Ventricular Ejection Fraction

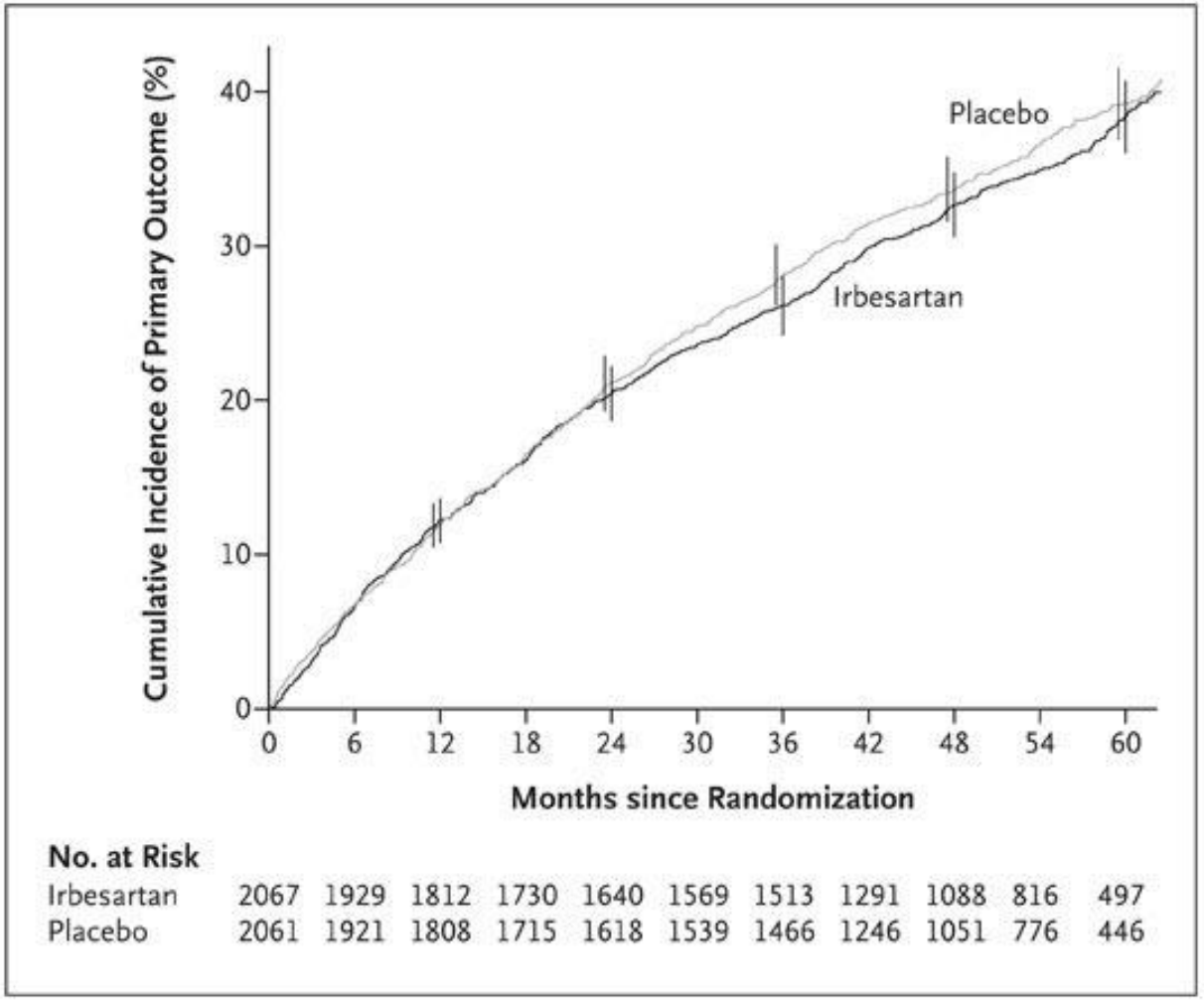
Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure)





van Veldhuisen, D. J. et al. J Am Coll Cardiol 2009;53:2150-2158

I-PRESERVE. Kaplan-Meier Curves for the Primary Outcome (all-cause death or CV hospitalization)



Massie BM et al. N Engl J Med 2008;359:2456-2467

Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function: TOPCAT

- Sponsor
  - National Heart, Lung, and Blood Institute (NHLBI)
- Primary Outcome Measures:
  - Aborted cardiac arrest
  - Composite of hospitalization for the management of heart failure
- Secondary Outcome Measures:
  - All cause mortality
  - Cardiovascular death or hospitalization
  - Hospitalization for heart failure
  - Sudden death or aborted cardiac arrest
- Randomization: placebo or spironolactone 1:1
- Estimated enrollment: 3515 patients
- Estimated completion date: December 2012

Efficacia della terapia medica

- 14-34% dei pazienti vengono reospedalizzati entro 6 mesi dal precedente ricovero (1)
- Più del 60 % delle reospedalizzazioni sono causate da una inadeguata compliance alla terapia farmacologica e alla dieta (2,3)
- Solo circa il 50 % dei pazienti ha una adeguata compliance alla terapia prescritta (4)

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[3] M Monane et al. Noncompliance with congestive heart failure therapy in the elderly; Arch Intern Med 1994; 154:433-437
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2010 Focused Update of ESC Guidelines on Device Therapy in Heart Failure

An Update of the 2008 ESC guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure and the 2007 ESC guidelines for Cardiac and Resynchronization Therapy, developed in collaboration with the HFA and EHRA

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Grazie
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