Disclosures

Speaker's bureau:	**Servier, Bayer, Roche Boehringer Ingelheim**
Research grant:	**Servier, Boehringer Ingelheim, Novartis, Roche**
Advisory Board:	**Servier, Bayer, Roche Boehringer Ingelheim**

Update on Heart Failure

Pharmacological Treatment

Roberto Ferrari

ESC 2012 HF Guidelines (GL)

- Achievements
- Challenges
- Limitations
- Barriers
- Unmet needs

ESC 2012 HF GL: *Achievements*

- **Well structured and clear**
- **Recommendations - *and non* - motivated**
- **Uncertainties highlighted**
- **Neutral / balanced position**

Confirmation

- **Diuretics**
- **A β-blocker and an ACE inhibitor *as soon as possible* for:**
  - **Better action on remodelling**
  - **More sudden death reduction**

Main changes from 2008 GL

Drugs

- An expanded indication for **mineralocorticoid receptor antagonists** (MRAs).
- A new indication for the sinus node inhibitor **ivabradine**.

MRAs Journey

RALES: Spironolactone in severe HF (NYHA III – IV)

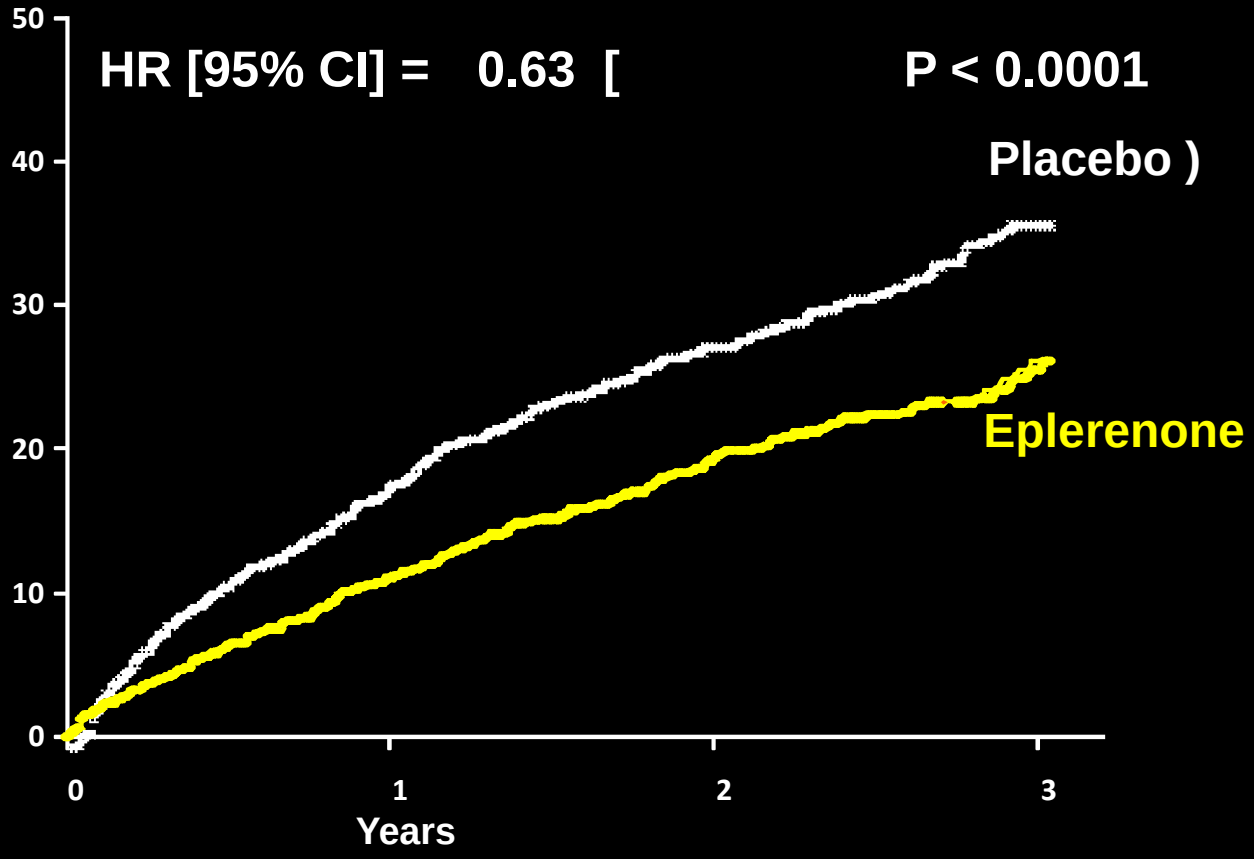
↓

EPHESUS: Eplerenone in post MI and LVD or HT

↓

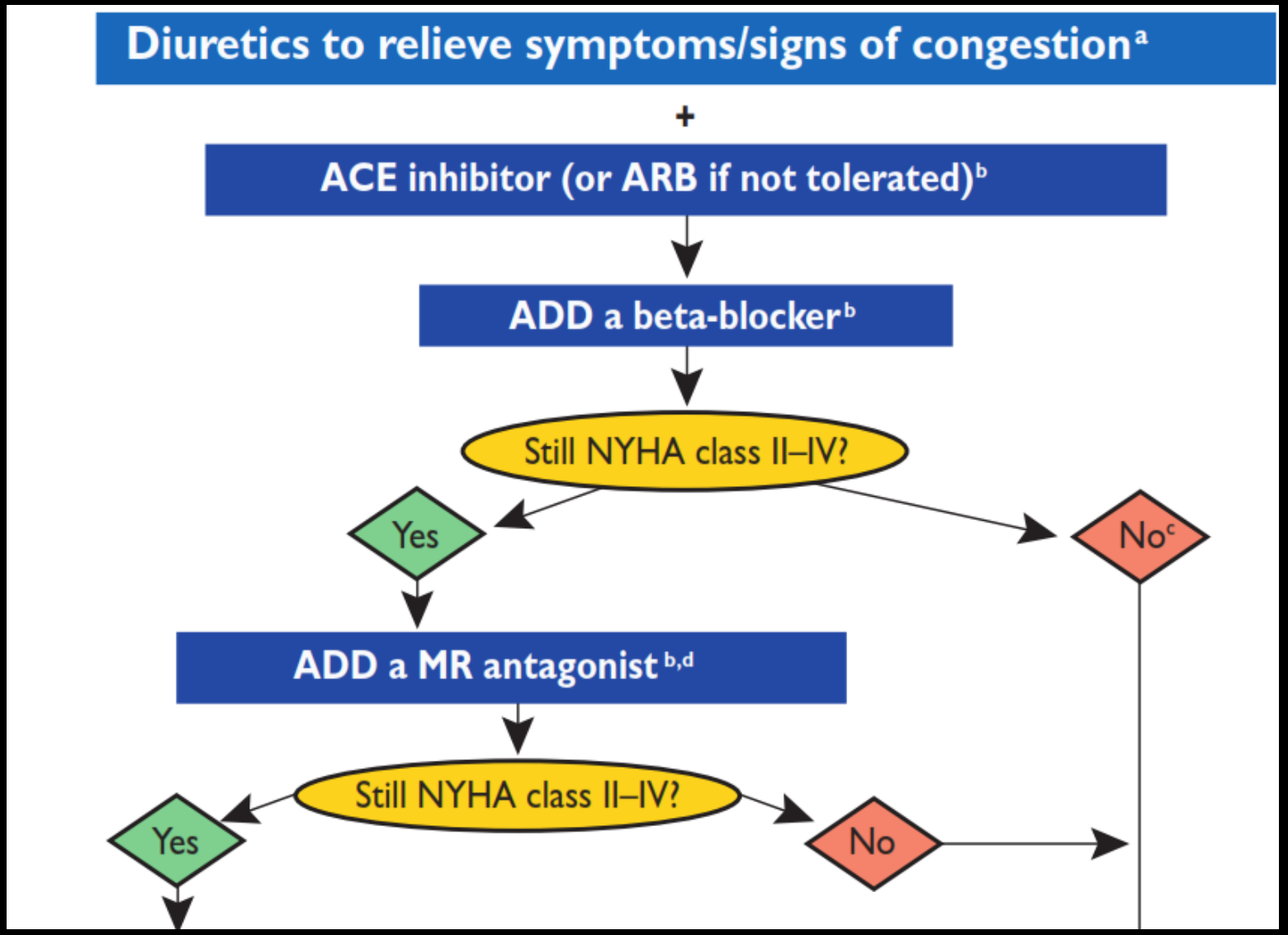
EMPHASIS: Eplerenone in mild HF (NYHA II – III) on top of contemporary treatment

EMPHASIS
CV Death /HF hospitalsations

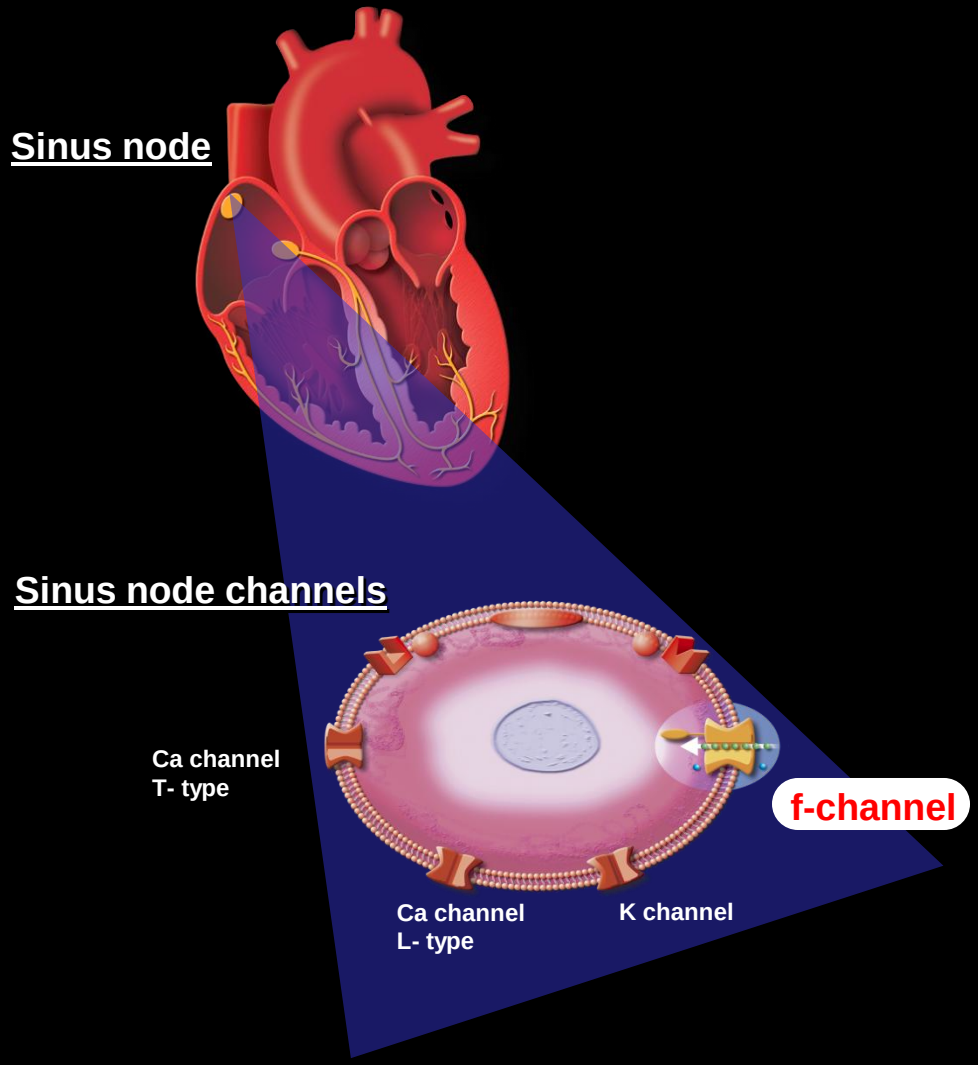


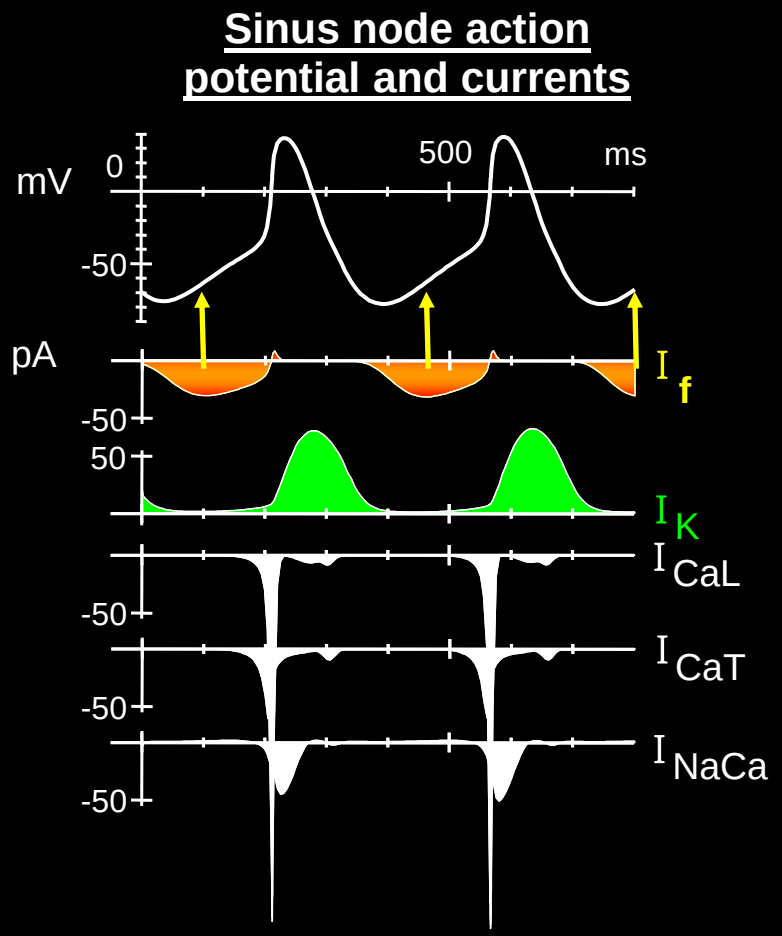
N Eng J Med 364;1 January 2011

Initial pharmacological therapy



If current in the sinus node: the determinant of HR





Robinson RB, DiFrancesco D. Fundamental and Clinical Cardiology; NY; Marcel Decker; 2001:151-170.

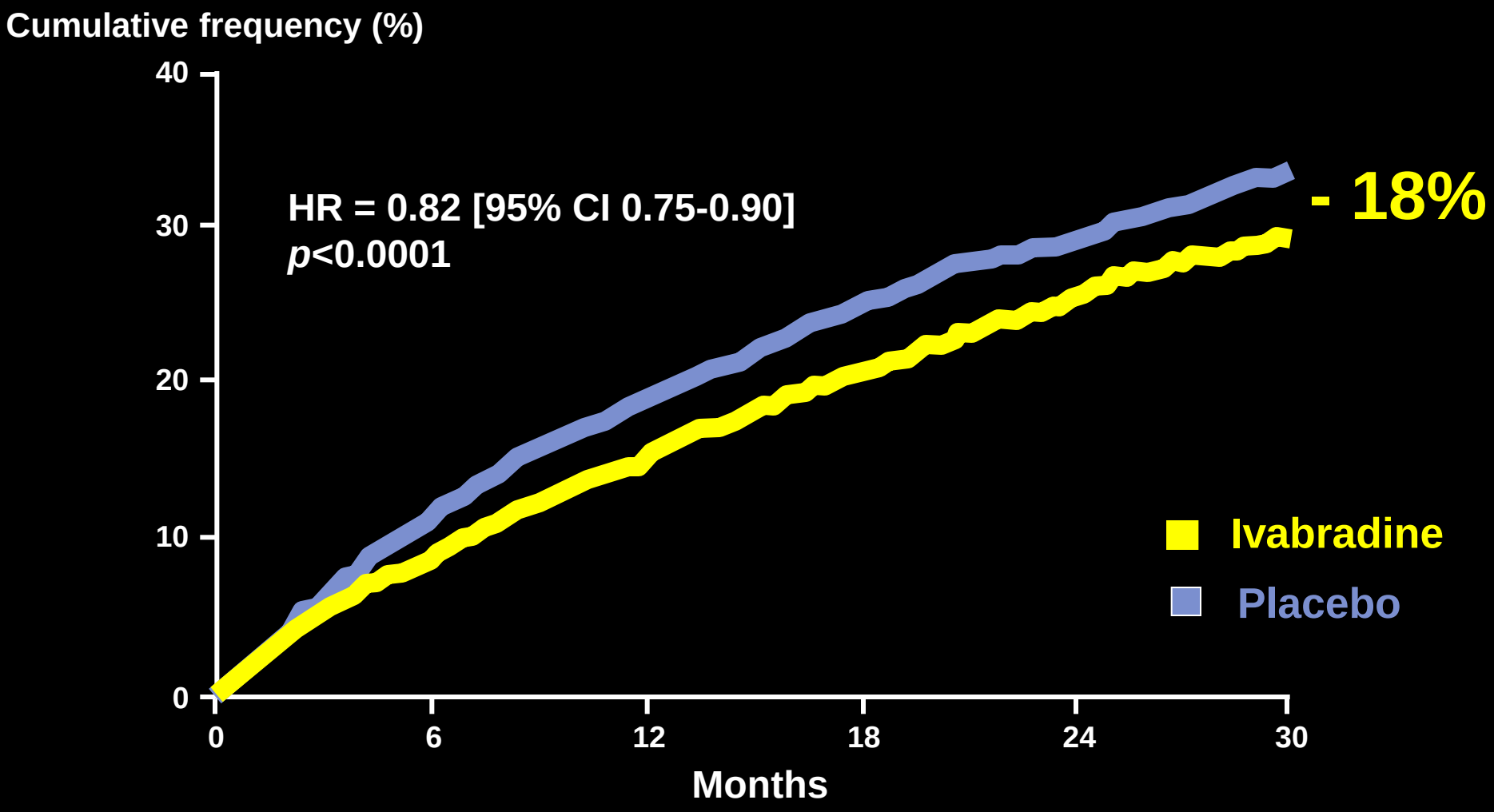
Objectives

To evaluate whether ivabradine improves outcomes in patients with:

1. Moderate to severe chronic HF
2. LV ejection fraction ≤ 35%
3. Sinus rhythm, HR ≥ 70 bpm and
4. Recommended therapy

Primary composite endpoint

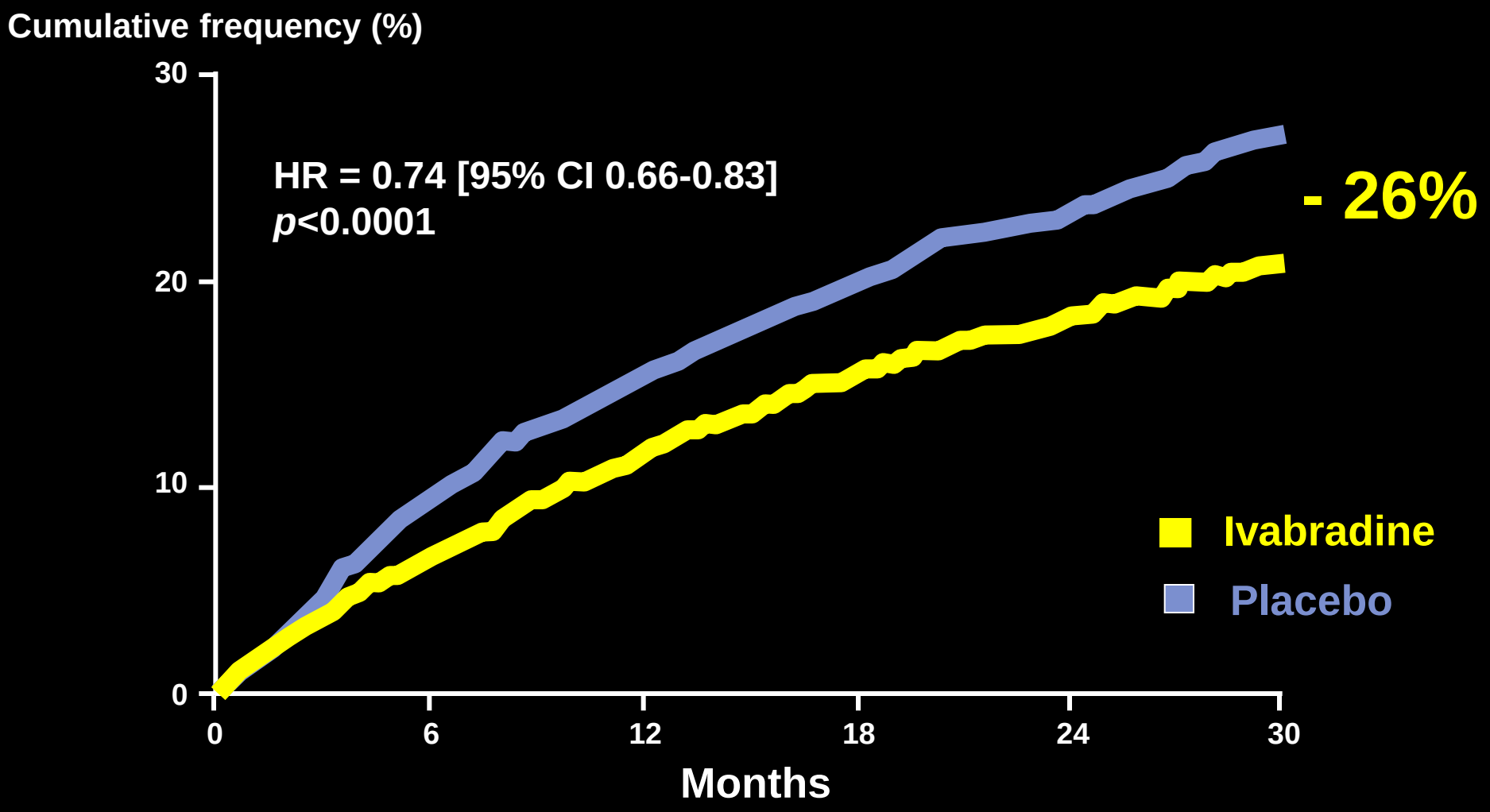
Ivabradine n=793 (14.5%PY) **Placebo n=937 (17.7%PY)**



Hospitalisation for heart failure

Ivabradine n=514 (9.4%PY)

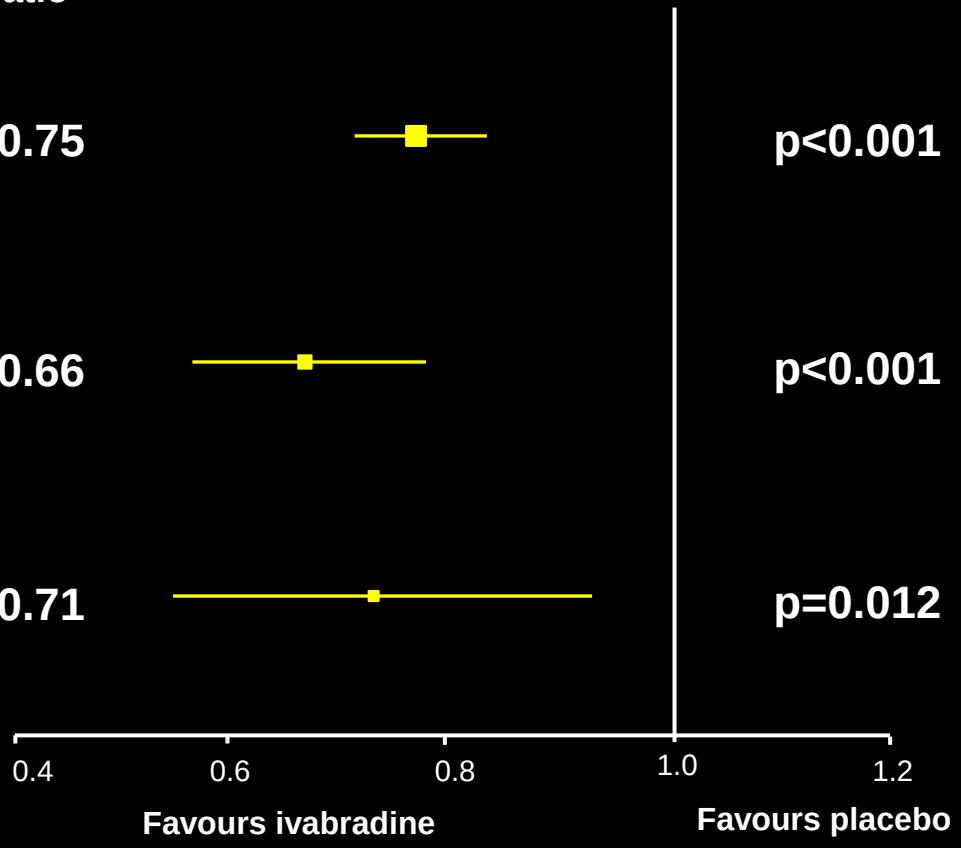
Placebo n=672 (12.7%PY)



Effect of ivabradine on recurrence of hospitalizations for HF

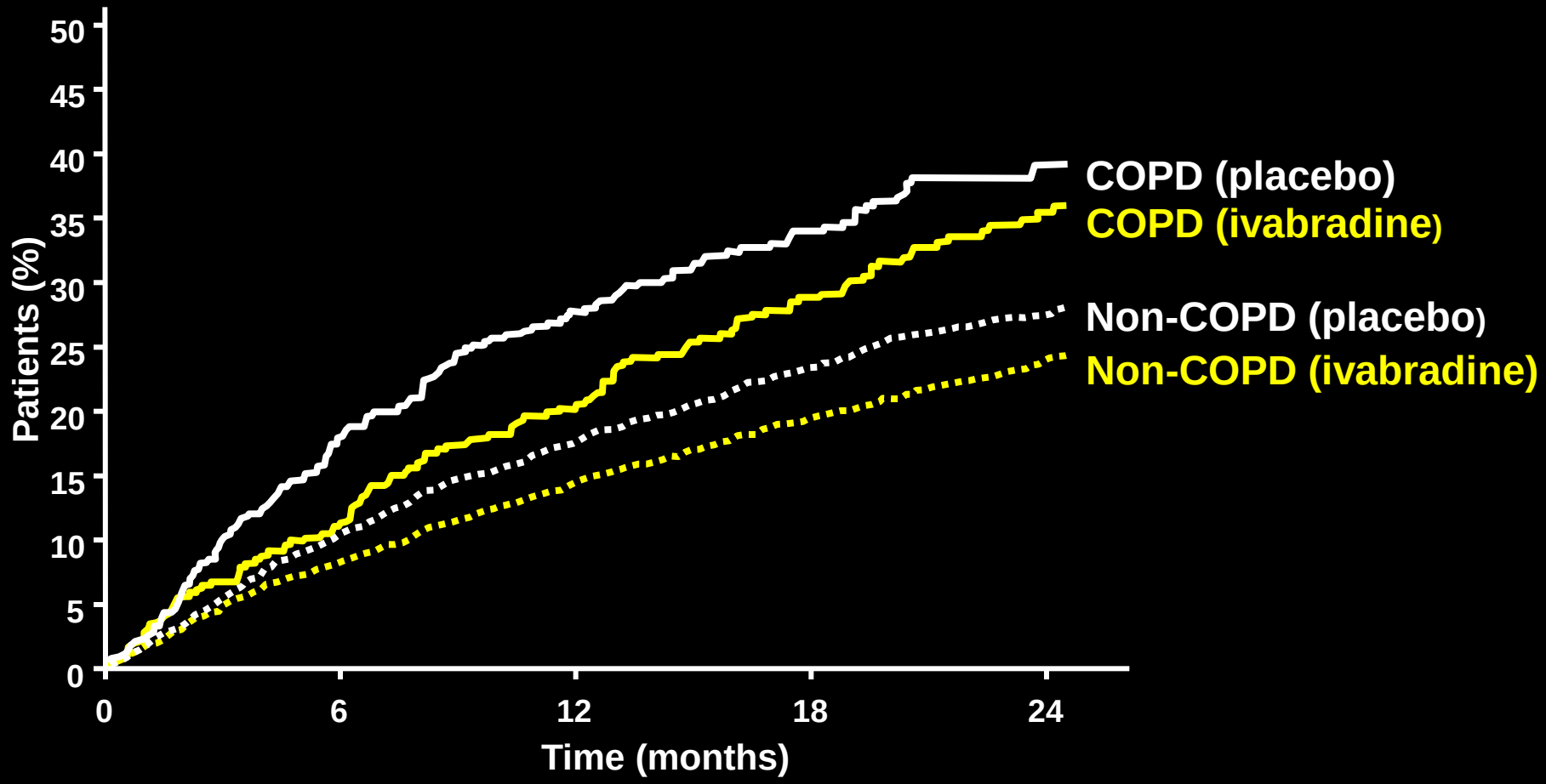
Total-time approach

	Ivabradine (n=3241)	Placebo (n=3264)	Hazard ratio	*p*-value
First hospitalization	514 (16%)	672 (21%)	0.75	p<0.001
Second hospitalization	189 (6%)	283 (9%)	0.66	p<0.001
Third hospitalization	90 (3%)	128 (4%)	0.71	p=0.012



Borer JS et al. *Eur Heart J* 2012;33(22):2813-20

Effect of ivabradine on composite of CV death or HF hospitalization



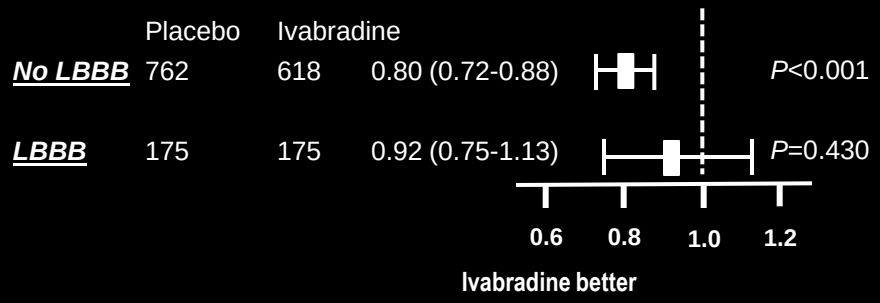
Ivabradine is safe and effective in lowering the relative risk of the primary composite end point in both COPD and non-COPD patients

Tavazzi L et al. *Eur Heart J.* 2013; 34, 652

Ivabradine can be used safely in patients with HF and LBBB

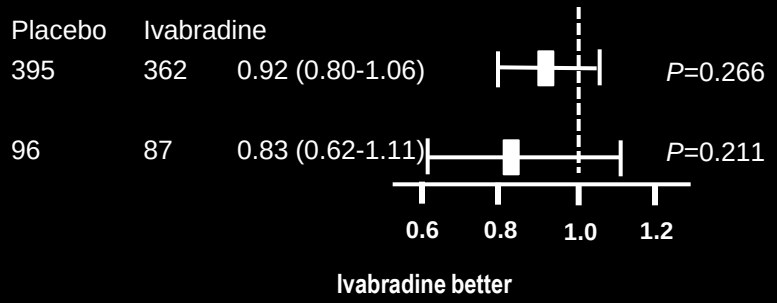
Primary Endpoint HR (95% CI)

P = 0.223 for interaction of treatment effect*



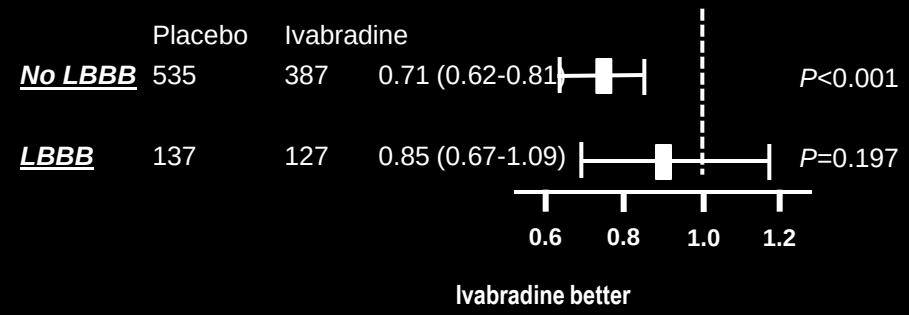
CV Mortality HR (95% CI)

P = 0.549 for interaction of treatment effect*



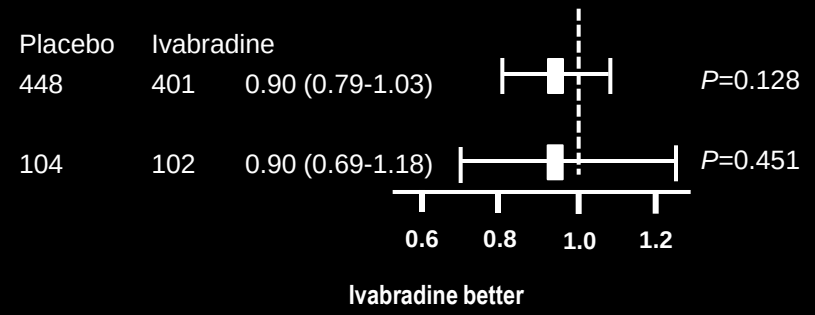
HF Hospitalization (95% CI)

P = 0.185 for interaction of treatment effect*



All Cause Mortality (95% CI)

P = 0.986 for interaction of treatment effect*

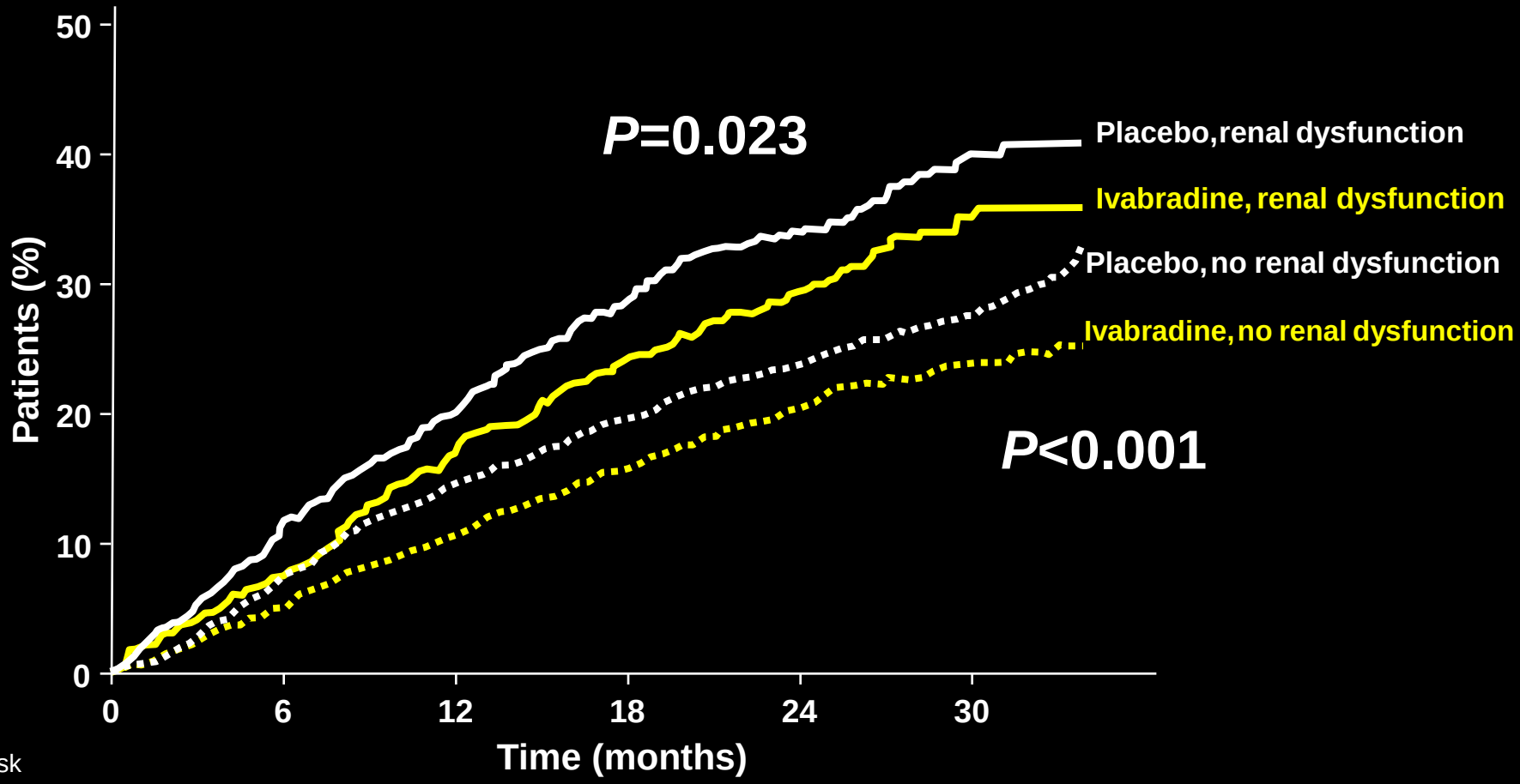


Ivabradine did not increase major adverse effects in LBBB compared with placebo.

The beneficial effect of treatment was directionally similar to that in patients without LBBB.

Reil JC et al. *Eur J Heart Fail*. 2013;15(9):1044-1052

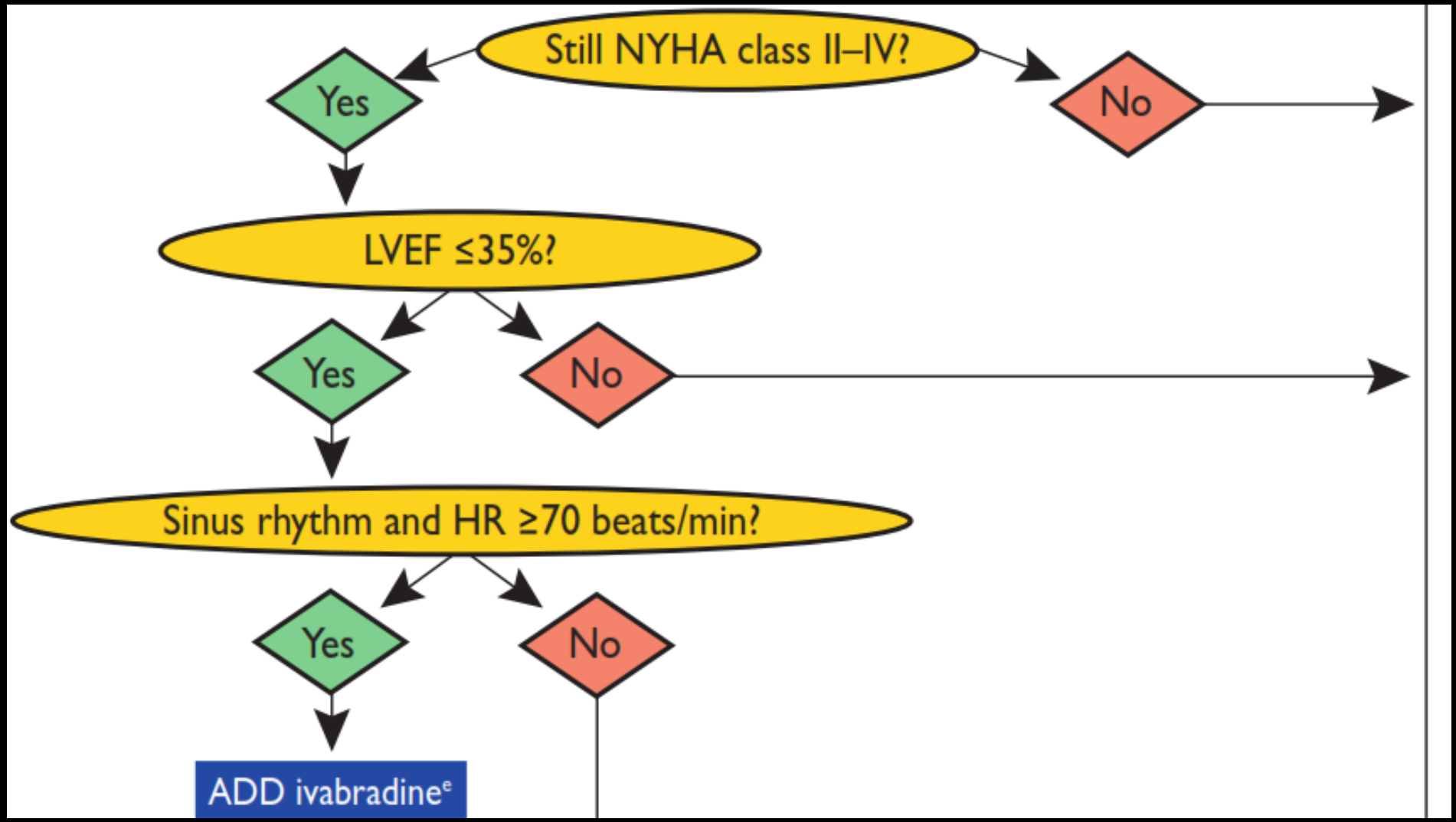
Effect of ivabradine on composite of CV death or HF hospitalization



N at risk

RD (pl)	799	706	612	488	261	95
RD (iva)	780	720	612	489	273	104
NRD (pl)	2293	2119	1847	1551	820	343
NRD (iva)	2288	2166	1963	1662	906	339

Pharmacological therapy – next step



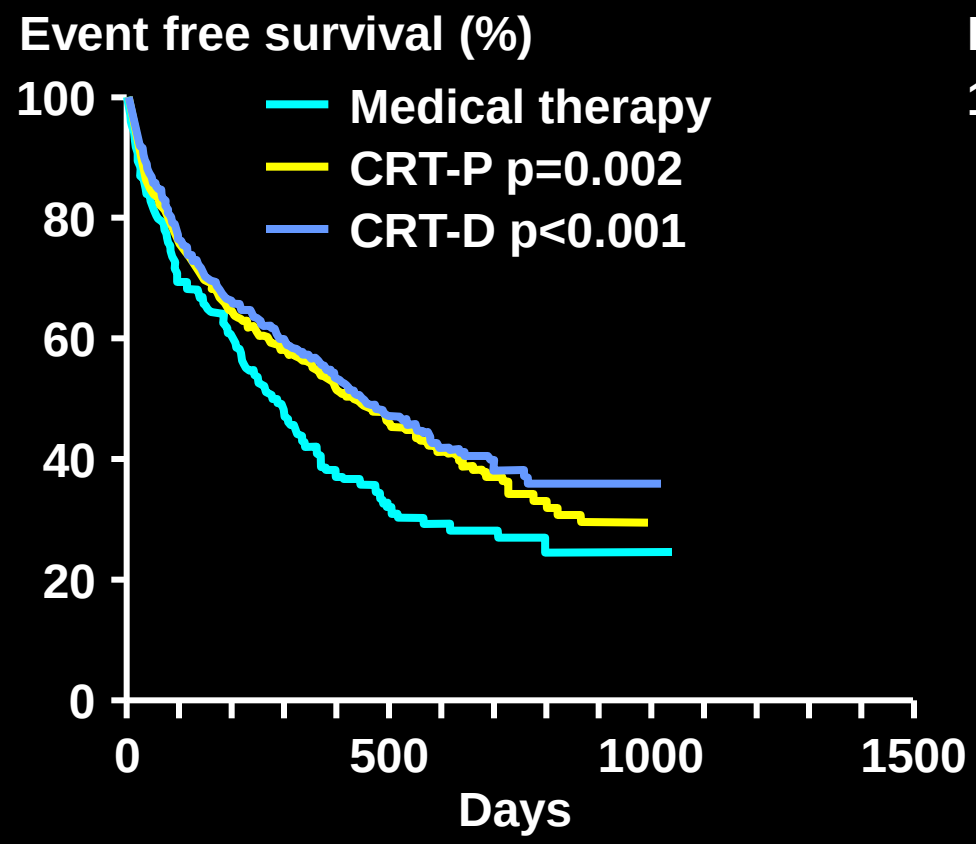
Main changes from 2008 GL

Devices and procedures

- **Expanded indication for resynchronisation (CRT)**
- **New role of coronary revascularisation**
- **Recognition of the growing use of assist devices (VADs).**

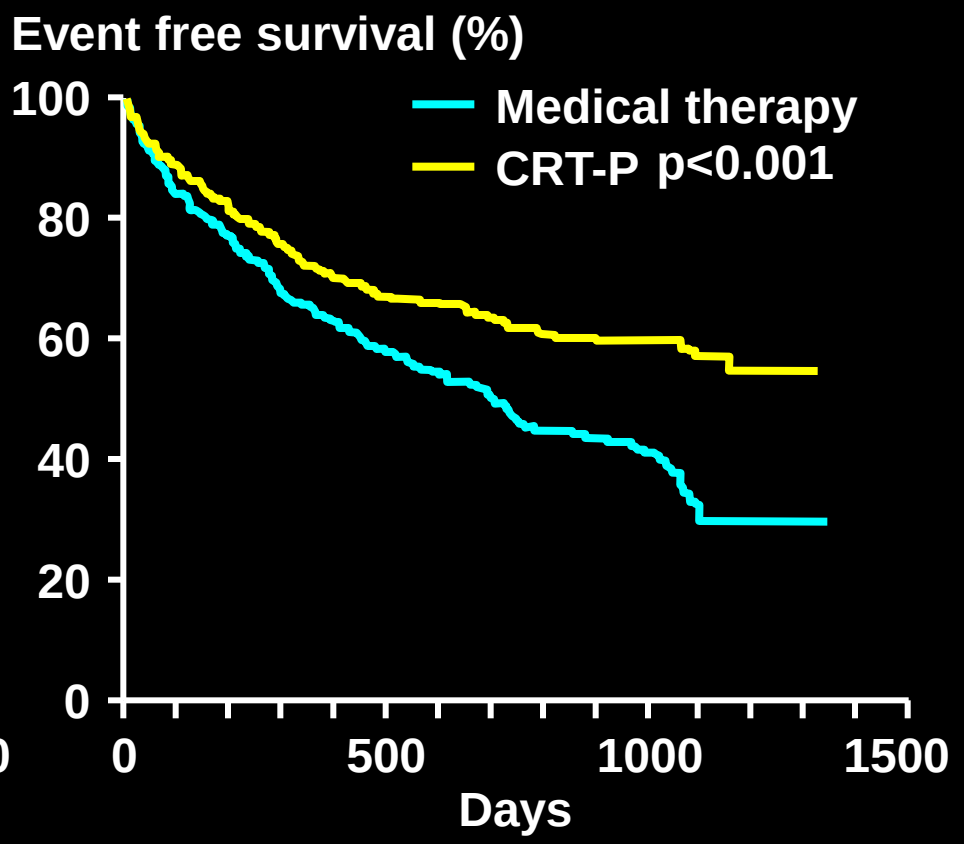
CRT journey

COMPANION
CV death or CV hospitalization



Bristow et al. Engl J Med 2004;350:2140-50

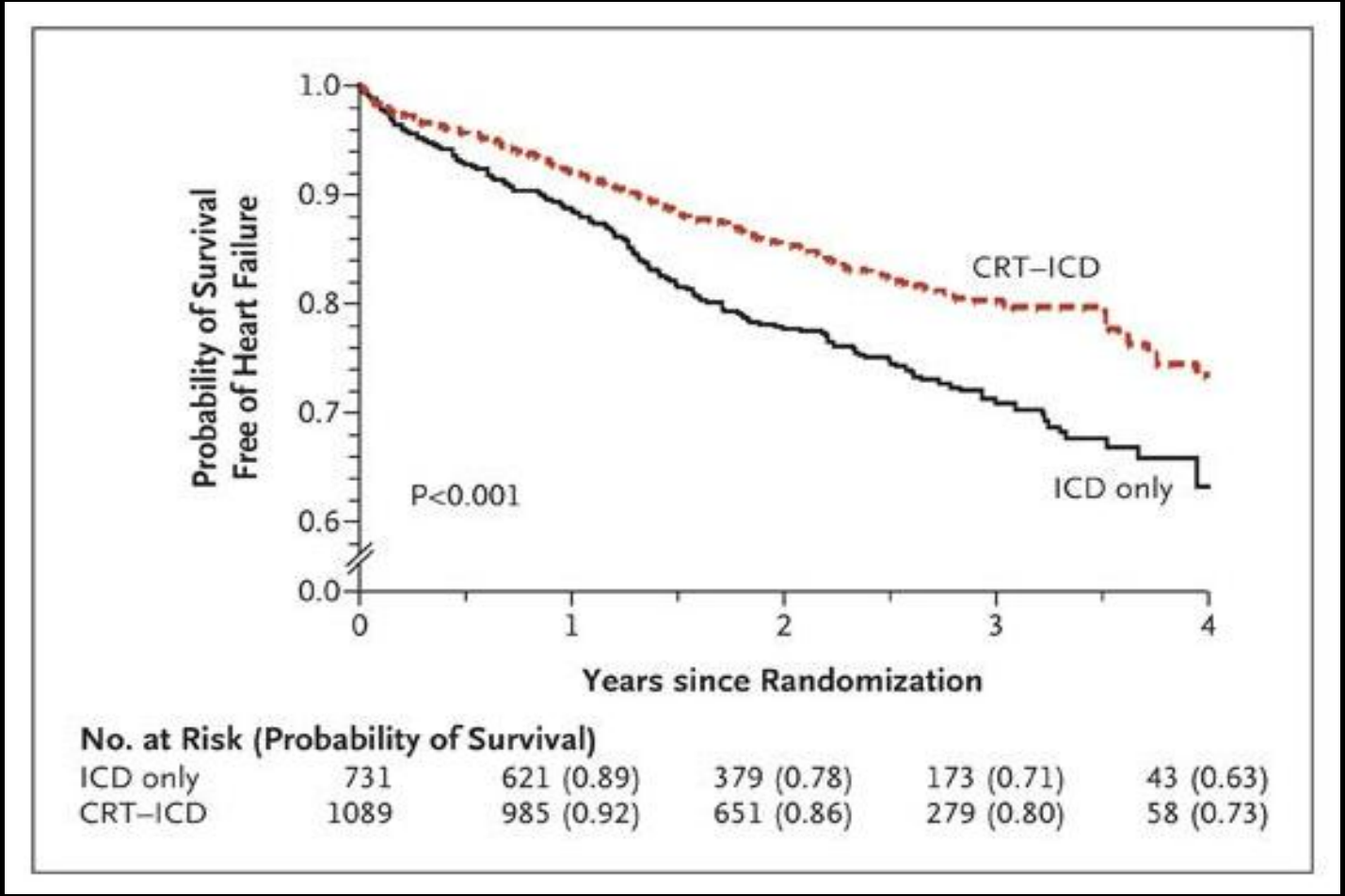
CARE-HF
Death or CV hospitalization



Cleland et al. NEJM 2005

MADIT – CRT Study (2009)

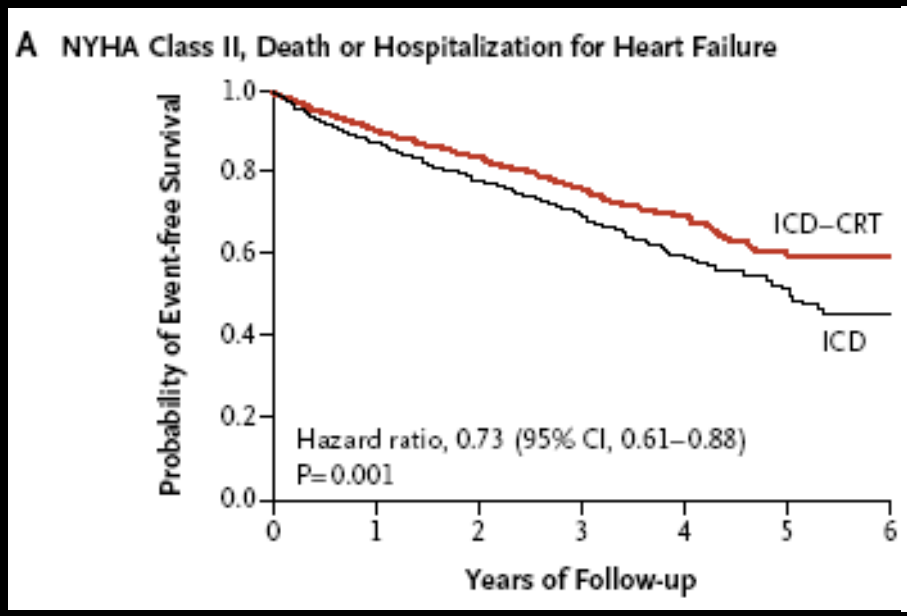
Multicenter Automatic Defibrillator Implantation Trial

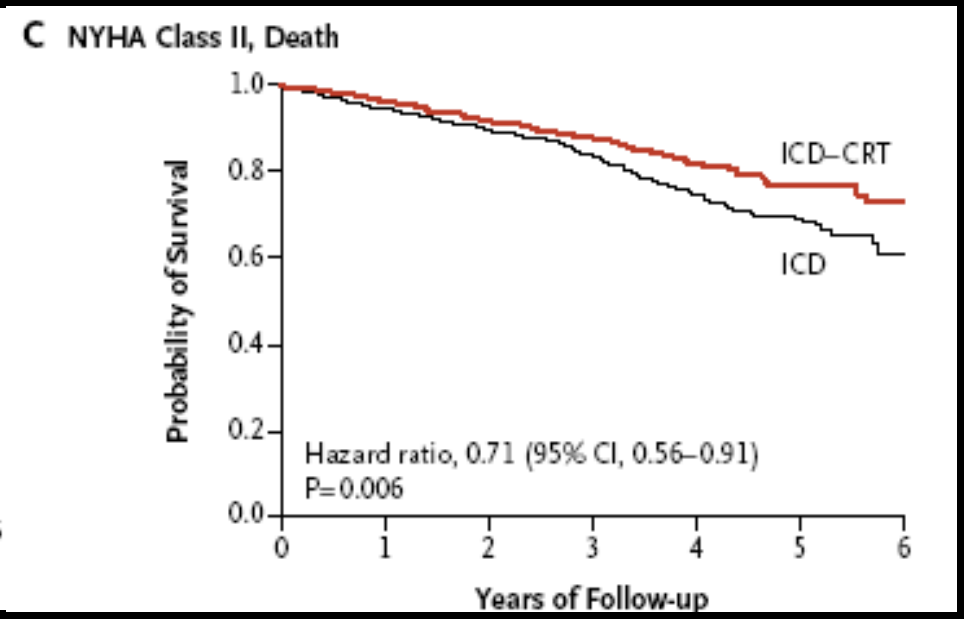


N Engl J Med. 2009 Oct 1;361(14):1329-38

RAFT

Resynchronised / Defibrillation for Ambulatory Heart Failure Trial





N Engl J Med 2010; 363:2385-2395

CRT indications in 2012

- ***NYHA class III, ambulatory IV***:

  LBBB QRS ≥120ms, LVEF ≤35% (rec IA)

  non-LBBB QRS ≥150ms, LVEF ≤35% (rec IIa A)

- ***NYHA class II***

  LBBB QRS ≥ 130ms, LVEF ≤30% (rec IA)

  non-LBBB ≥ 150ms, LVEF ≤30% (rec IIa A)

ESC 2012 GL – *CABG - PCI*

- **CABG is recommended in patients with systolic HF, angina, left main stenosis or 2/3 vessel coronary disease but not in those with angina and without viable myocardium**
- **PCI may be considered as an alternative when patients are unsuitable for CABG**

ESC 2012 GL: *challenges inconsistencies with the real world*

- **non reproducibility of the trials' context: (*Ex: issues in disease definitions and patient clinical profiles*)**
- **drug target dose (*optimal dose*) vs target effect (*optimal therapy*)**
- **>60% stent (*FDA*) and >50% ICD/CRT devices are implanted of label**

Acute HF Surveys and Registries
In-hospital outcome

Source	Patients n.	Age ys	Hospital stay (days)	In-hospital mortality %
OPTIMIZE HF	5751	72	4	1.6
IMPACT-HF	567	71	8	2.8
ADHERE	65000	72	4	4
Goldberg	2604	79	4	5.1
European HFS 2	3580	70	9	6.7
Italian AHFS	2807	73	9	7.3
FINN-AKVA	620	75	7	8
Rudiger	312	73	11.5	8
European HFS 1	11327	71	11	8.4
EFFECT	4031	76	-	8.9
Argentina Reg	2974	65-70	7-9	4-12
EFICA	599	73	15	27/43 (4weeks)

Target *dose* vs target *effect*

***Target dose*:**

- **defined in (*dated*) trials**
- **different background treatment**
- **by selected investigators**
- **other doses not tested**

***Target effect*:**

- **evaluated by a marker of *individual* efficacy and safety**

ESC 2012 GL: *Limitations*

- **Trials, and consequently the Guidelines, are single disease-oriented**
- **Over the age of 65 comorbidity is normal**
- **Lack of prognostic profiles**
- **Full text is a "*guide*"**
- **Pocket format, posters are "*prescriptive*"**

2012 GL - *Comorbidities: gaps in evidence*

- ***Anaemia***: erythropoiesis-stimulating agents, iron**?**
- ***Depression***: selective serotonin reuptake inhibitors, cognitive therapy**?**
- ***Diabetes***: metformin, GLP-1 agonists/analogues, DPP IV inhibitors, SGLT-2 inhibitors**?**
- ***Sleep-disordered breathing***: positive airways pressure therapies**?**
- ***COPD/Asthma***: Beta-blockers/Beta 2-agonists**?**

ESC 2012 GL: *Barriers from physicians*

- Uniformed
- Unconvinced
- Forgotten
- Influenced by marketing
- Unwilling to accept “compulsory recommendations”

ESC 2012 GL: *Barriers from patients*

- **Unconvinced of benefit**
- **Inadequately informed**
- **Fear of adverse reactions**
- **Costs**
- **Other treatment priorities**

ESC 2012 GL: *Barriers from patients*

- **40-80% of information is immediately forgotten. Half of the information recalled is incorrect!**
- **Both phisicians and patients elaborate *personal mindlines***

ESC 2012 GL: *Barriers from industry*

- **High prices of new drugs**
- **Consumer advertising**
- **Effective marketing of inferior drugs**
- **Direct and indirect funding of physicians,**

  organisations, patient groups etc.

It follows that…..there are still several unmet needs

- Prevention of HF
- Comorbiditeis
- Correct use of drugs and devices
- Value of remote monitoring

Conclusion:

HF patient and healthcare journey

- **Very complex**
- **Long lasting**
- **With several relapses**
- **A battle to win together**

END