Novedades Terapéuticas en IC. Ivabradina

Las recomendaciones de las Guías de Práctica Clínica

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Área Cardiovascular. Hospital Clínico Universitario de Santiago de Compostela

Ivabradina en la IC-2012

¿Cuál es la Evidencia?

¿Qué dicen las Guías de Práctica Clínica?

Implicaciones Clínicas

Cuestiones Pendientes

The role of heart rate in cardiovascular disease

Elevated heart rate

+

Atherosclerosis

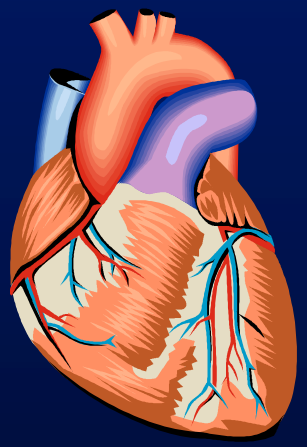
Endothelial dysfunction↑

Oxidative stress↑

Plaque stability↓

Arterial stiffness↑

+



+

Chronic heart failure

Oxygen demand↑

Ventricular efficiency ↓

Ventricular relaxation↑

+

Ischemia

Oxygen consumption↑

Duration of diastole↓

Coronary perfusion↓

Remodeling

Cardiac hypertrophy↑

Reil JC and Böhm M. *Lancet* 2008: 779-780

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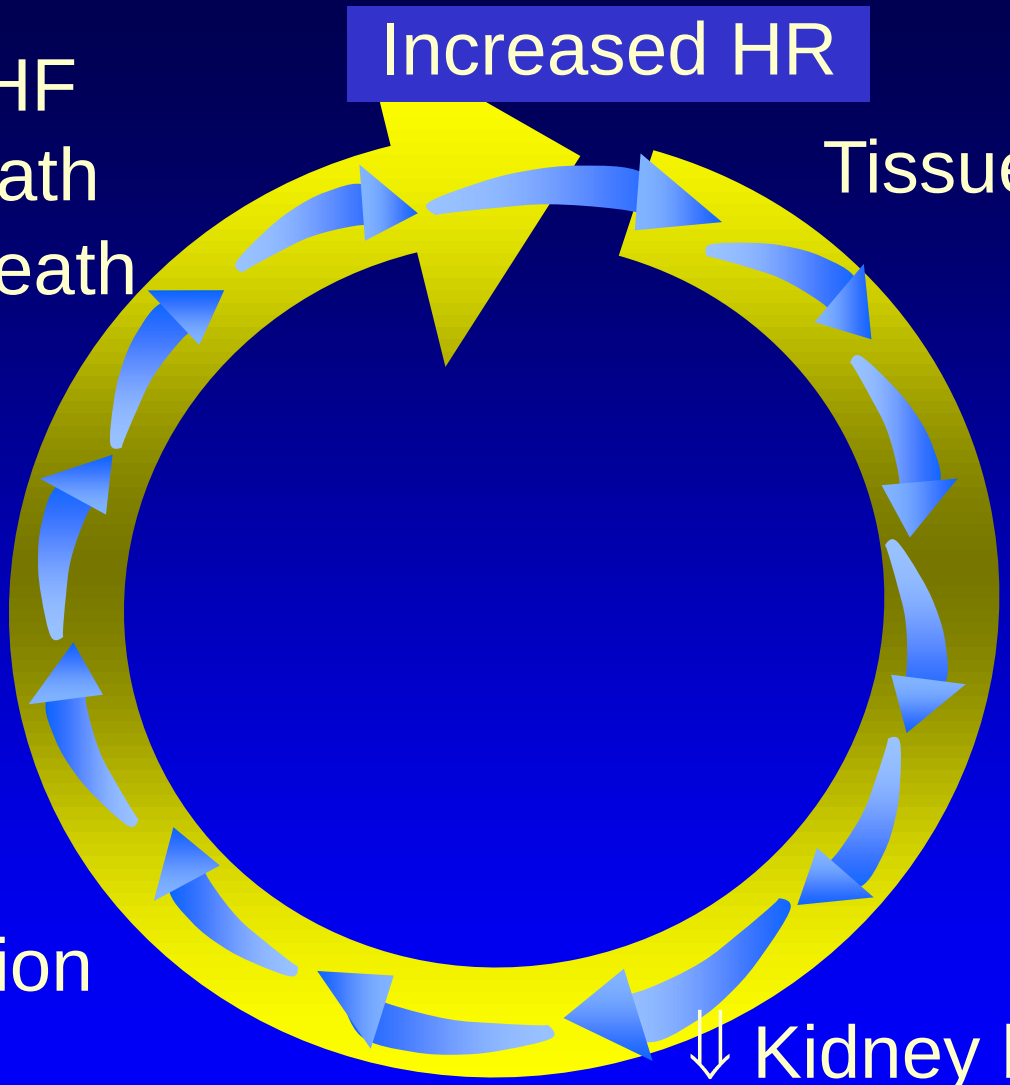
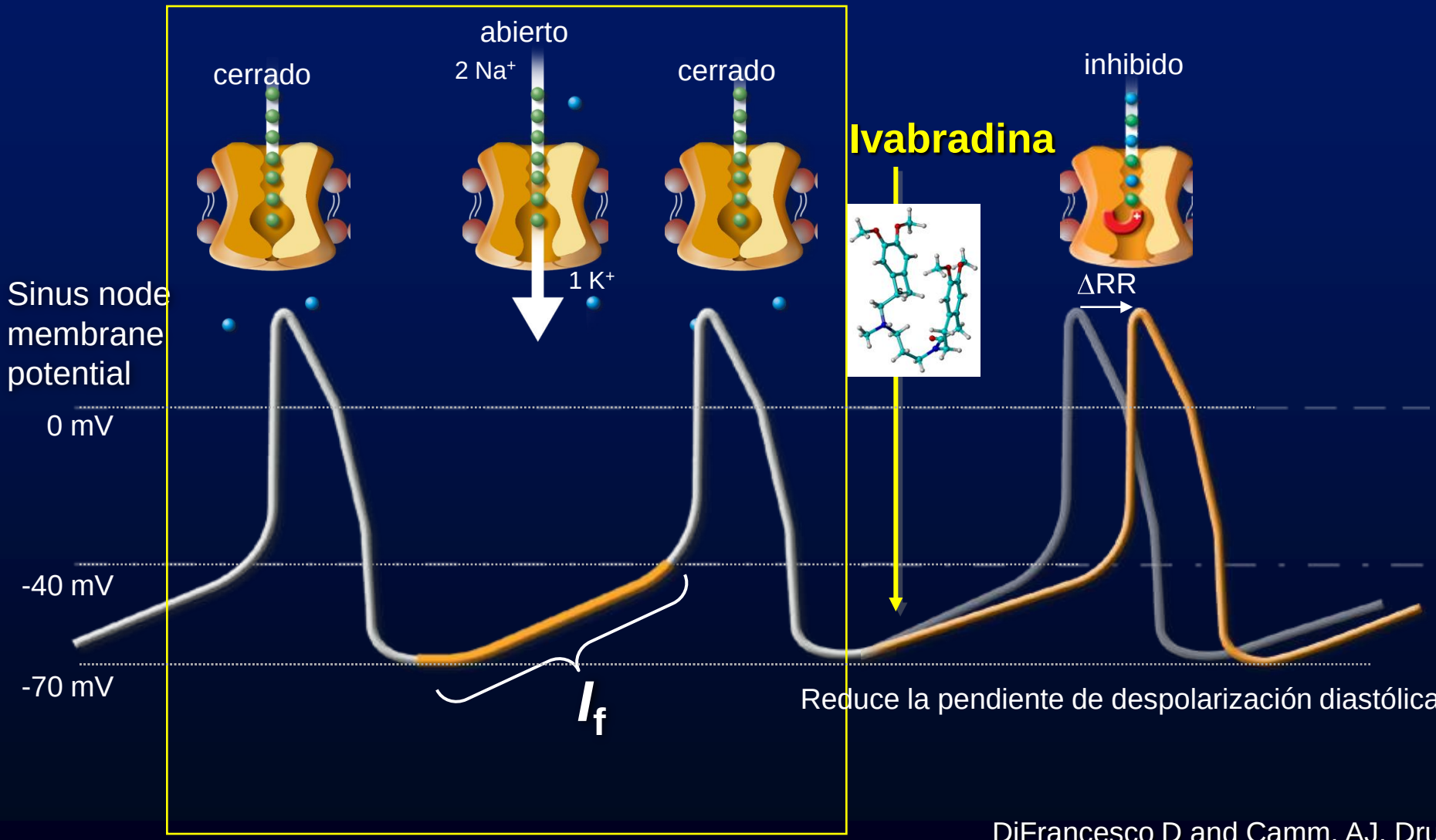
HR in Heart Failure



Ivabradina reduce exclusivamente la FC sin producir otros efectos CV



Reduce la pendiente de despolarización diastólica

DiFrancesco D and Camm. AJ. Drugs. 2004

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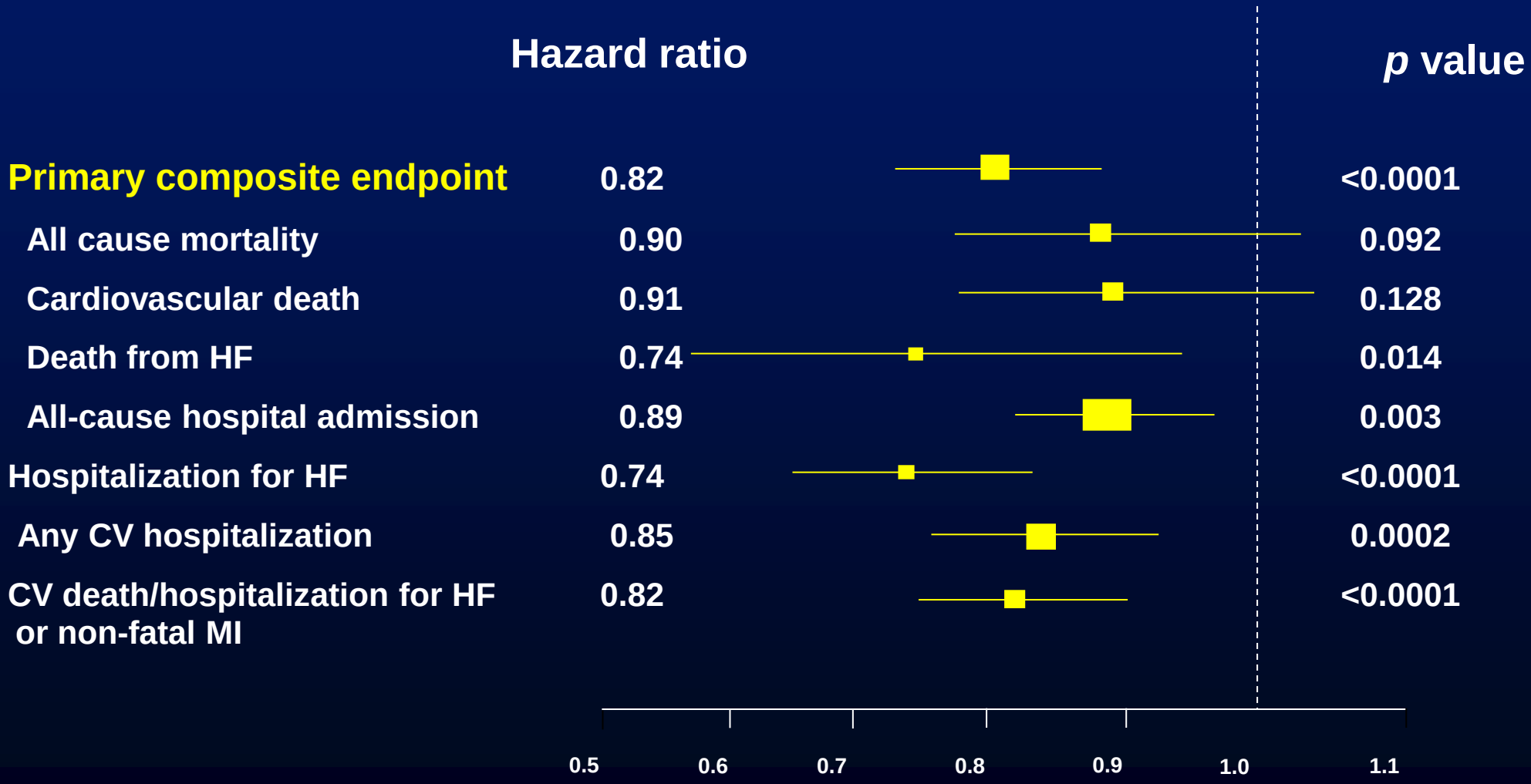
Main study results: effect of ivabradine on major outcomes



Swedberg K, et al. *Lancet* 2010;376: 875-885.

Abandonos del estudio por acontecimientos adversos

	Ivabradina N=3232, % (n)	Placebo N=3260, % (n)	*p*
Todos los acont.adversos	14% (467)	13% (416)	0.051
Insuficiencia cardiaca	2% (70)	3% (82)	0.367
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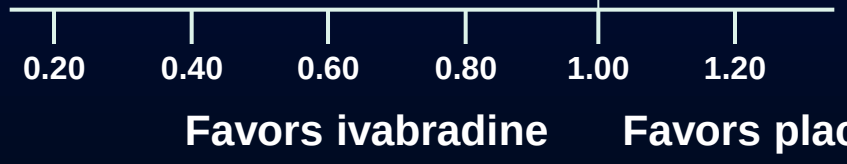
Visión borrosa	<1% (1)	<1% (1)	1.000

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

Effect of ivabradine on major outcomes in patients with HR ≥75 bpm

	Hazard ratio	95% CI	*P*
Primary composite end point	**0.76**	**0.68-0.85**	**<0.0001**
Cardiovascular mortality	**0.83**	**0.71-0.97**	**0.0166**
Hospitalization for worsening HF	**0.70**	**0.61-0.80**	**<0.0001**
Death from HF	**0.61**	**0.46-0.81**	**0.0006**
All-cause mortality	**0.83**	**0.72-0.96**	**0.0109**
All-cause hospitalization	**0.82**	**0.75-0.90**	**<0.0001**
Any cardiovascular hospitalization	**0.79**	**0.71-0.88**	**<0.0001**



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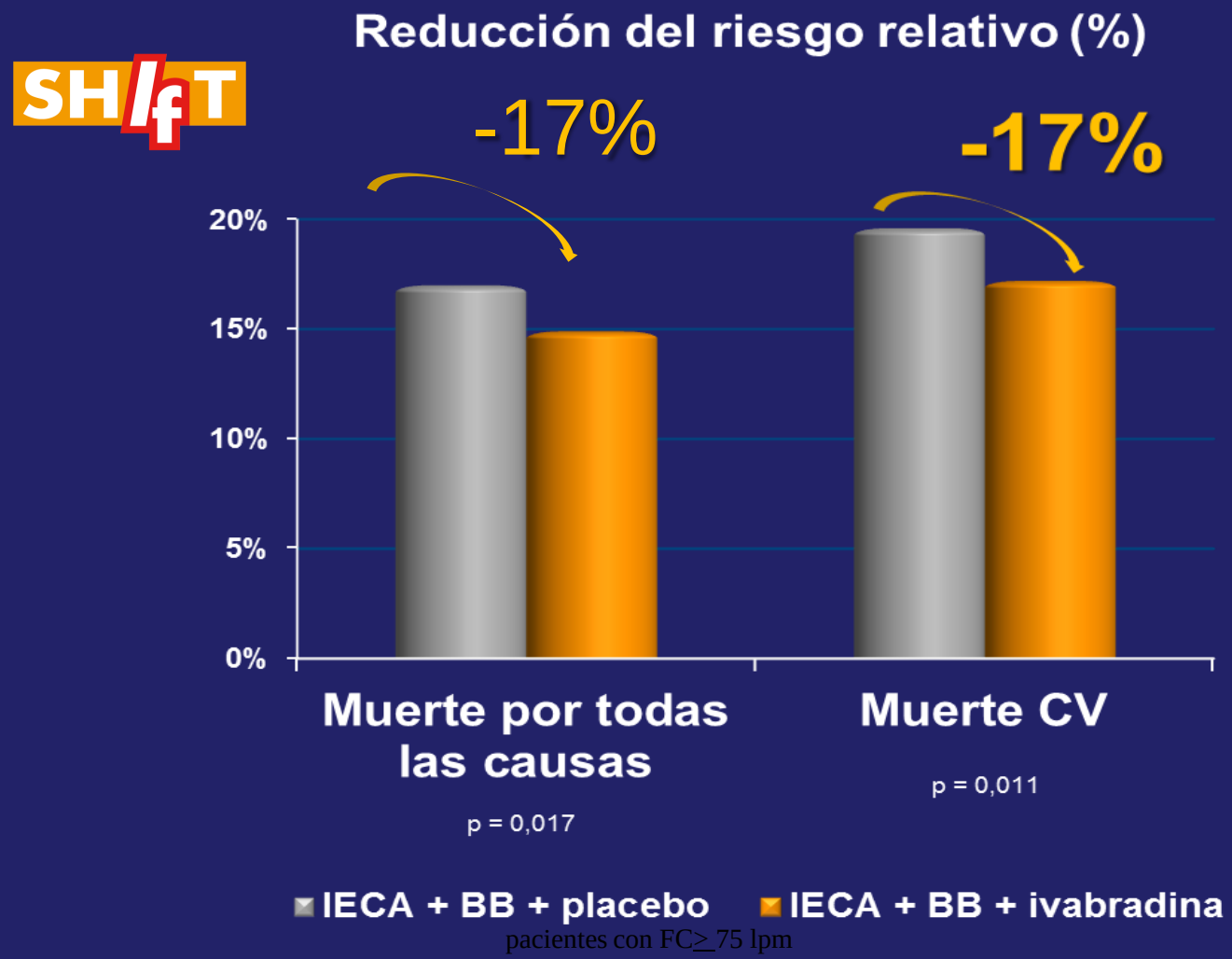
Böhm M, et al. Clin Res Cardiol. Online 11 May 2012.

Ivabradina reduce la mortalidad por todas las causas y la muerte CV en pacientes con IC sistólica y FC ≥75 lpm[1]

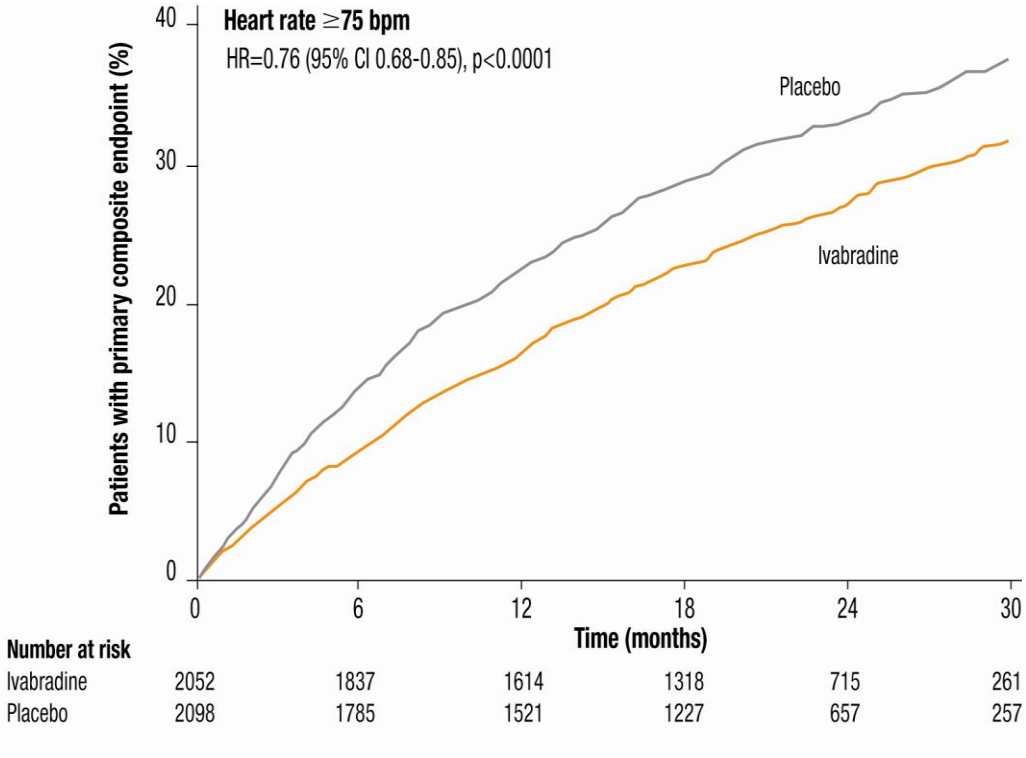
En el subgrupo de pacientes con frecuencia cardíaca ≥ 75 lpm (n = 4150), se observó una mayor reducción en la variable de valoración principal combinada del 24% (hazard ratio: 0,76, IC 95% [0,68 ; 0,85] - p <0,0001) y en las otras variables de valoración secundarias, incluyendo muerte por todas las causas (hazard ratio: 0,83, IC 95% [0,72; 0,96] - p = 0,0109) y muerte CV (hazard ratio: 0,83, IC 95% [0,71; 0,97] - p = 0,0166)

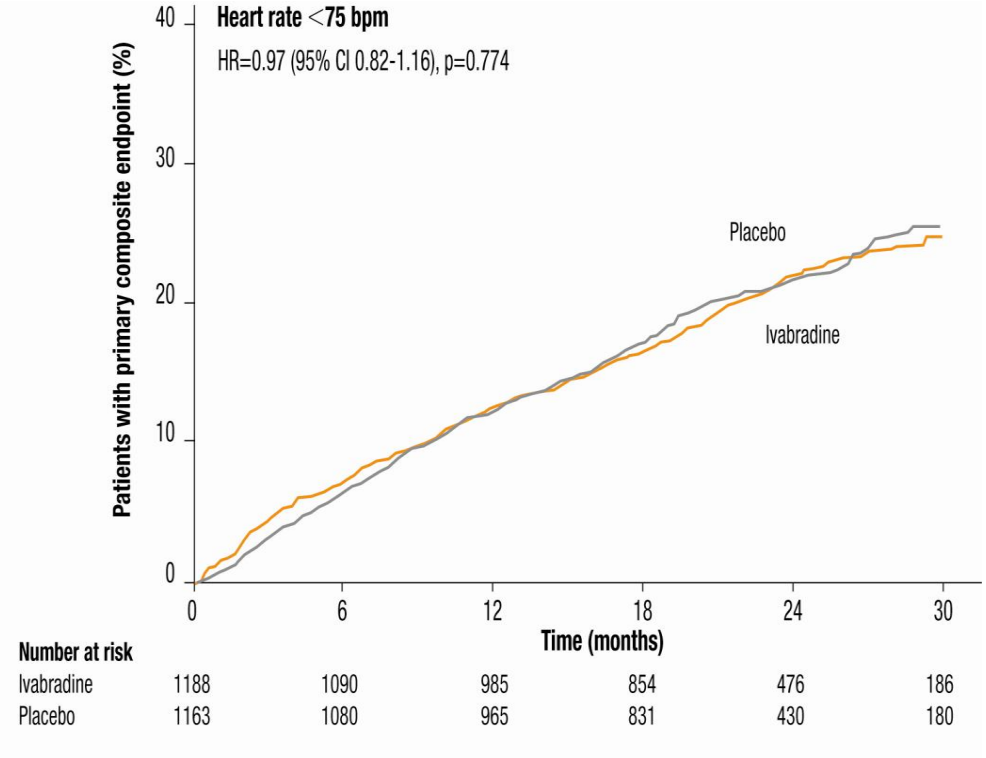


pacientes con FC≥ 75 lpm

SHIFT Study. Cumulative event curves on ivabradine or placebo for the primary endpoint events in patients with a heart rate ≤ 75 bpm or a heart rate > 75 bpm

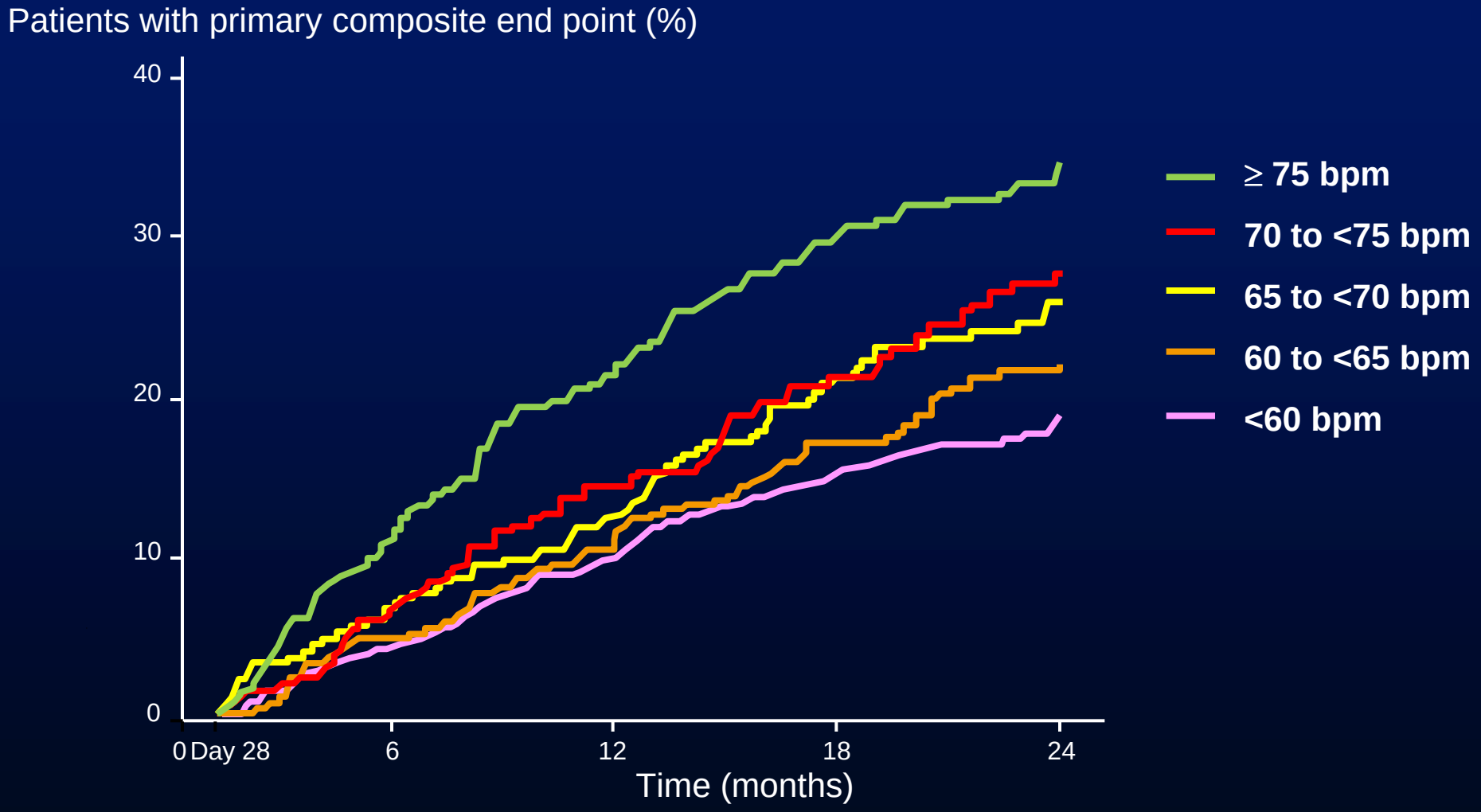
Primary composite endpoint





Böhm M, et al. Clin Res Cardiol. Online 11 May 2012.

Effect of ivabradine on outcomes according to HR achieved at 28 days



Böhm M, et al. Clin Res Cardiol. Online 11 May 2012.

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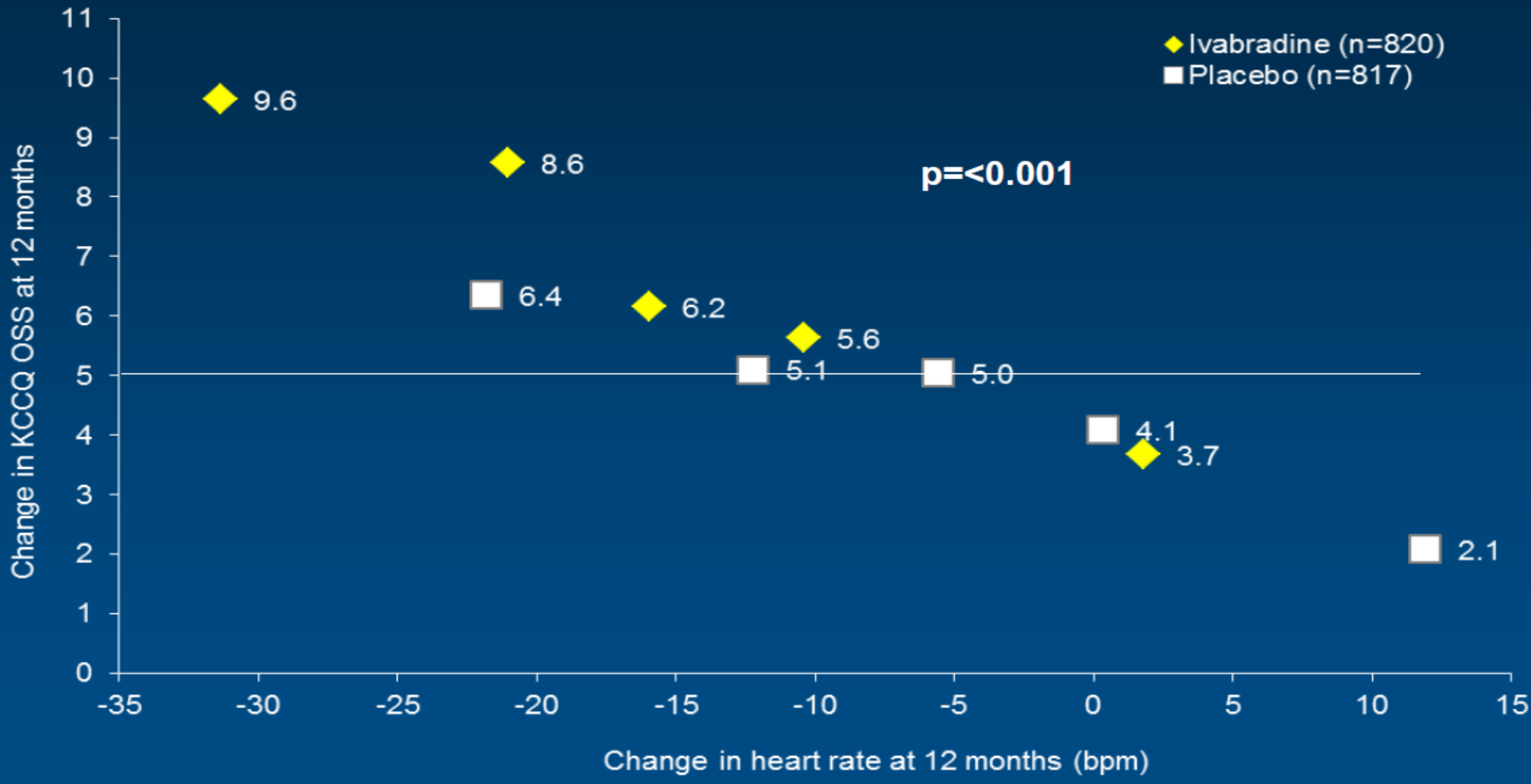
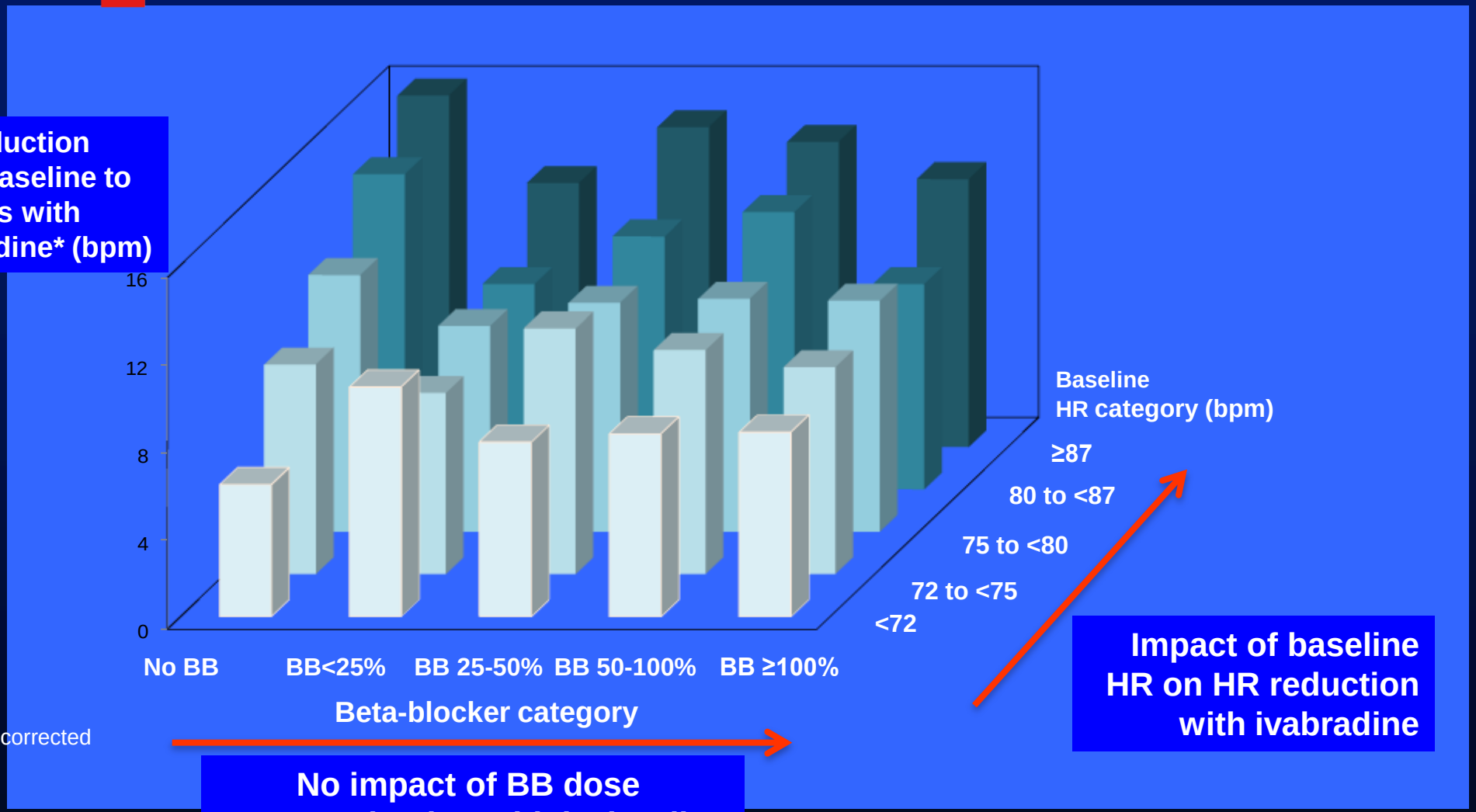
Mean of change KCCQ overall score at 12 months by quintiles of HR change



HR REDUCTION ACCORDING TO ON BETA-BLOCKER AND HR CATEGORY



*Placebo corrected

Swedberg K, et al. J Am Coll Cardiol 2012; 59:1938-1945

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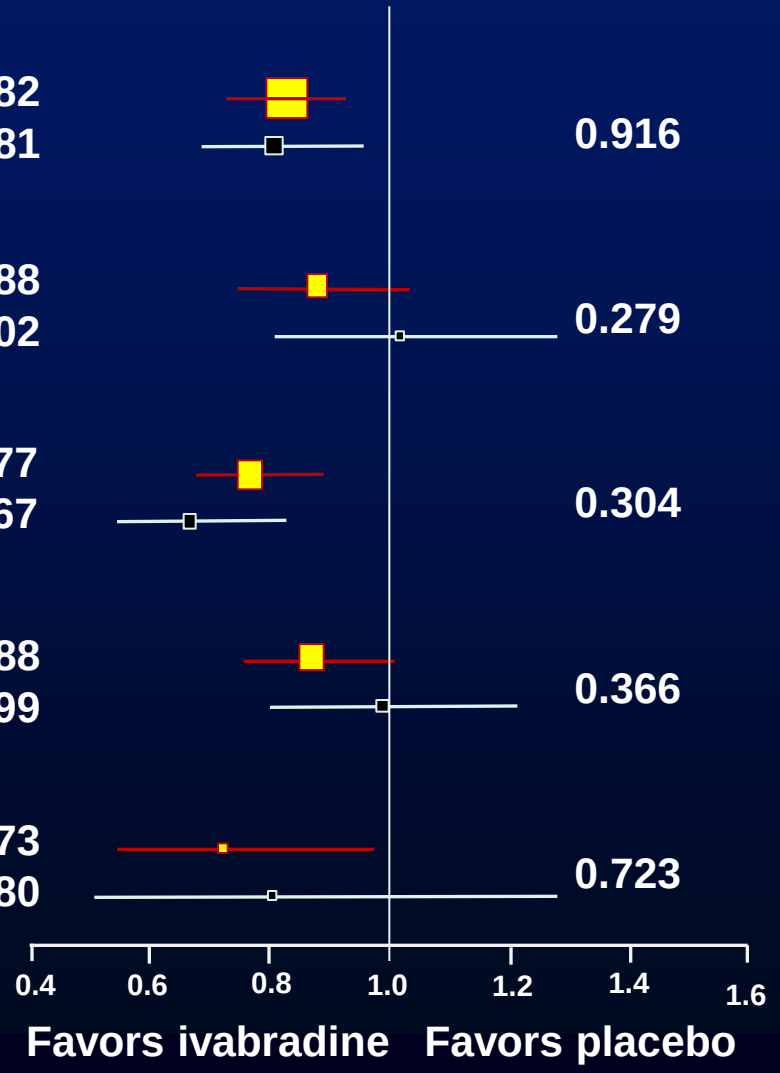
IVABRADINE IMPROVES OUTCOMES IN PATIENTS WITH CHF TAKING BACKGROUND TREATMENT WITH ALDOSTERONE ANTAGONISTS

	Ivabradine	Placebo	Hazard ratio*	*P* interaction
Primary endpoint (%)				
With AA, n=3922	28	33	0.82	0.916
Without AA, n=2583	19	23	0.81	
Cardiovascular death (%)				
With AA	16	18	0.88	0.279
Without AA	11	11	1.02	
Hospitalization for HF (%)				
With AA	19	23	0.77	0.304
Without AA	11	17	0.67	
Death from any cause (%)				
With AA	17	19	0.88	0.366
Without AA	13	13	0.99	
Death from HF (%)				
With AA	4	6	0.73	0.723
Without AA	3	3	0.80	



Heart Failure 2012 BELGRADE 19-22 MAY

Komajda et al. Late breaking trial. Heart Failure 2012

Major findings of SHIFT echo substudy

Heart rate lowering with Ivabradine associated with substantial reverse remodeling after 8 months:

LVESVI	- 5.8 mL/m^2	P < 0.001 – 0.002 vs. Placebo
LVEDVI	- 5.5 mL/m^2	
EF	+ 2.7 %	

Pronounced LV reverse remodeling (reduction in LVESVI ≥15%) in significantly more patients with Ivabradine (38%) vs. Placebo (25%; p=0.005)

Ivabradina en la IC-2012

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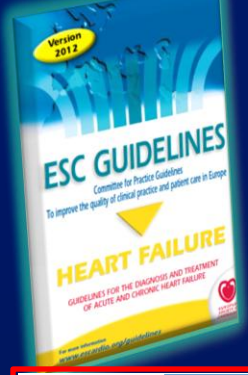
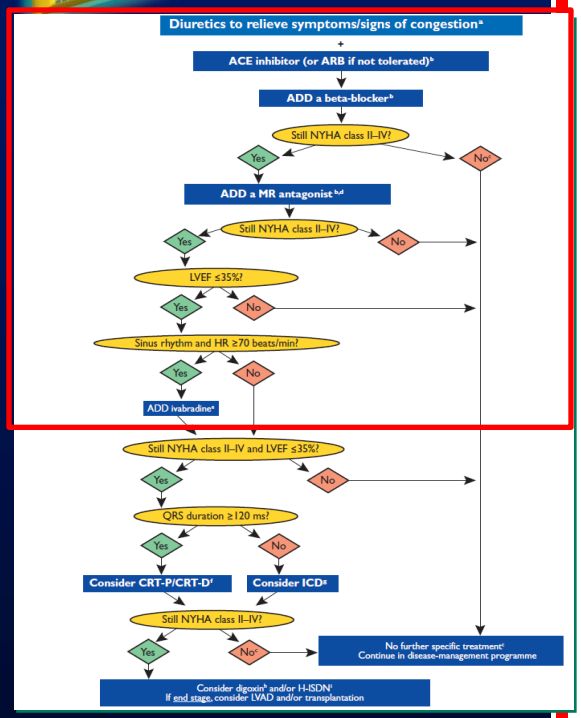
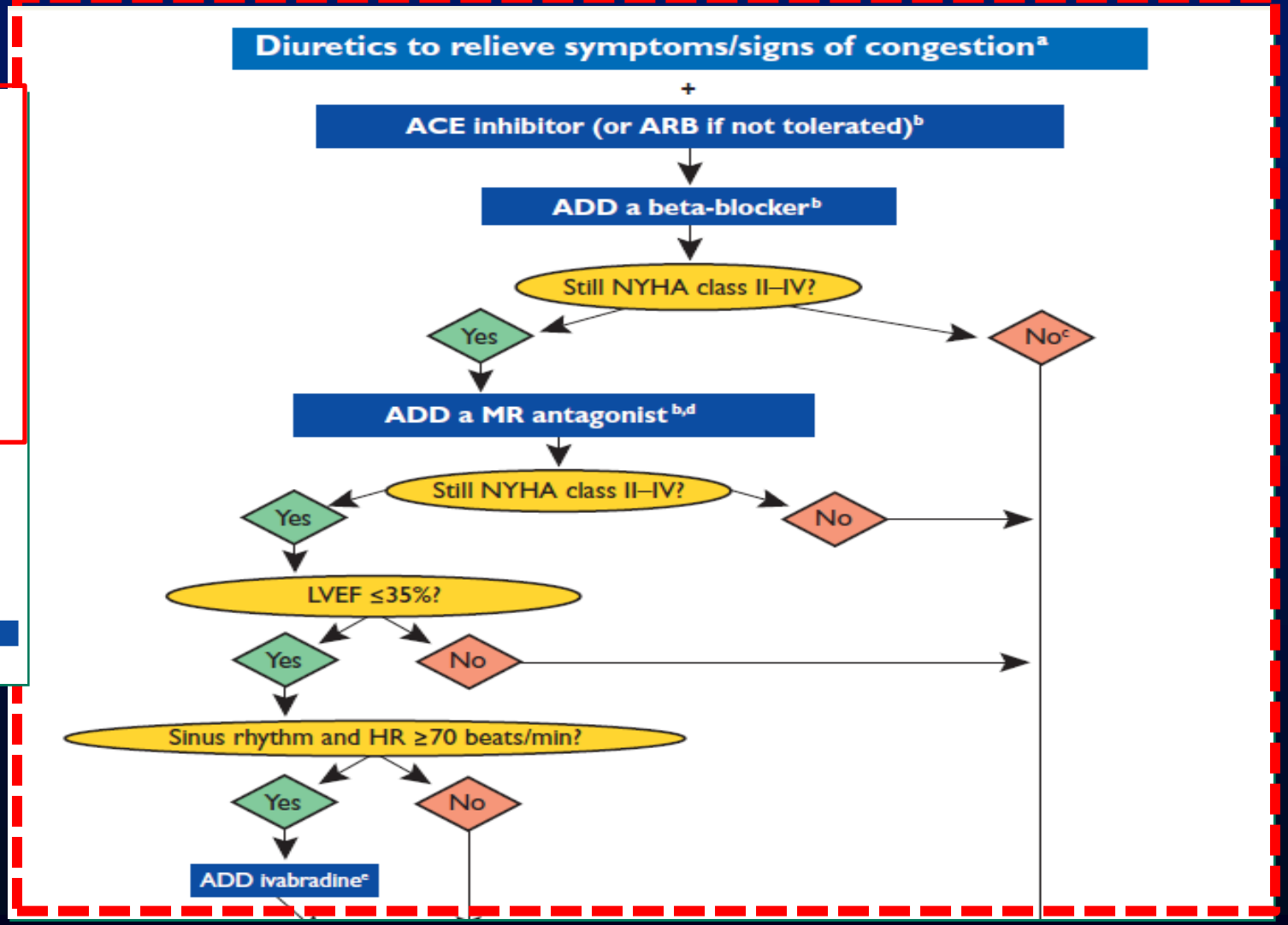
Cuestiones Pendientes

MANAGEMENT OF SYSTOLIC CHF: NEW ESC GUIDELINE







ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur Heart J .2012

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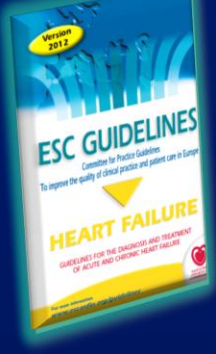
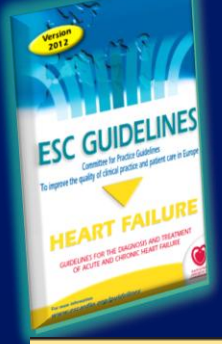


ACTUALIZACIÓN DE LA TERAPIA FARMACOLÓGICA DE LA IC: RECOMENDACIONES FÁRMACOS CLASE I A

Recommendations	Class[a]	Level[b]	Ref[c]
An ACE inhibitor is recommended, in addition to a beta-blocker, for all patients with an EF ≤40% to reduce the risk of HF hospitalization and the risk of premature death.	I	A	87–91
A beta-blocker is recommended, in addition to an ACE inhibitor (or ARB if ACE inhibitor not tolerated), for all patients with an EF ≤40% to reduce the risk of HF hospitalization and the risk of premature death.	I	A	92–98
An MRA is recommended for all patients with persisting symptoms (NYHA class II–IV) and an EF ≤35%, despite treatment with an ACE inhibitor (or an ARB if an ACE inhibitor is not tolerated) and a beta-blocker, to reduce the risk of HF hospitalization and the risk of premature death.	I	A	99, 100



ACTUALIZACIÓN DE LA TERAPIA FARMACOLÓGICA DE LA IC: UNA NUEVA INDICACIÓN PARA IVABRADINA EN PACIENTES CON IC

Ivabradine			
Should be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤35%, a heart rate remaining ≥70 b.p.m., and persisting symptoms (NYHA class II–IV) despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB).[c]	IIa	B	112
May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤35% and a heart rate ≥70 b.p.m. who are unable to tolerate a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB).[c]	IIb	C	–

Recommendations for the pharmacological treatment of stable angina pectoris in patients with symptomatic HF (NYHA functional class II–IV) and LV systolic dysfunction

Alternatives to a beta-blocker:			
(i) Ivabradine should be considered in patients in sinus rhythm who cannot tolerate a beta-blocker, to relieve angina (effective antianginal treatment and safe in HF).	IIa	A	112, 122
Step 2: Add a second anti-anginal drug			
The following may be added to a beta-blocker (or alternative)—taking account of the combinations not recommended below.			
The addition of ivabradine is recommended when angina persists despite treatment with a beta-blocker (or alternative), to relieve angina (effective antianginal treatment and safe in HF).	I	A	112, 122

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur Heart J .2012

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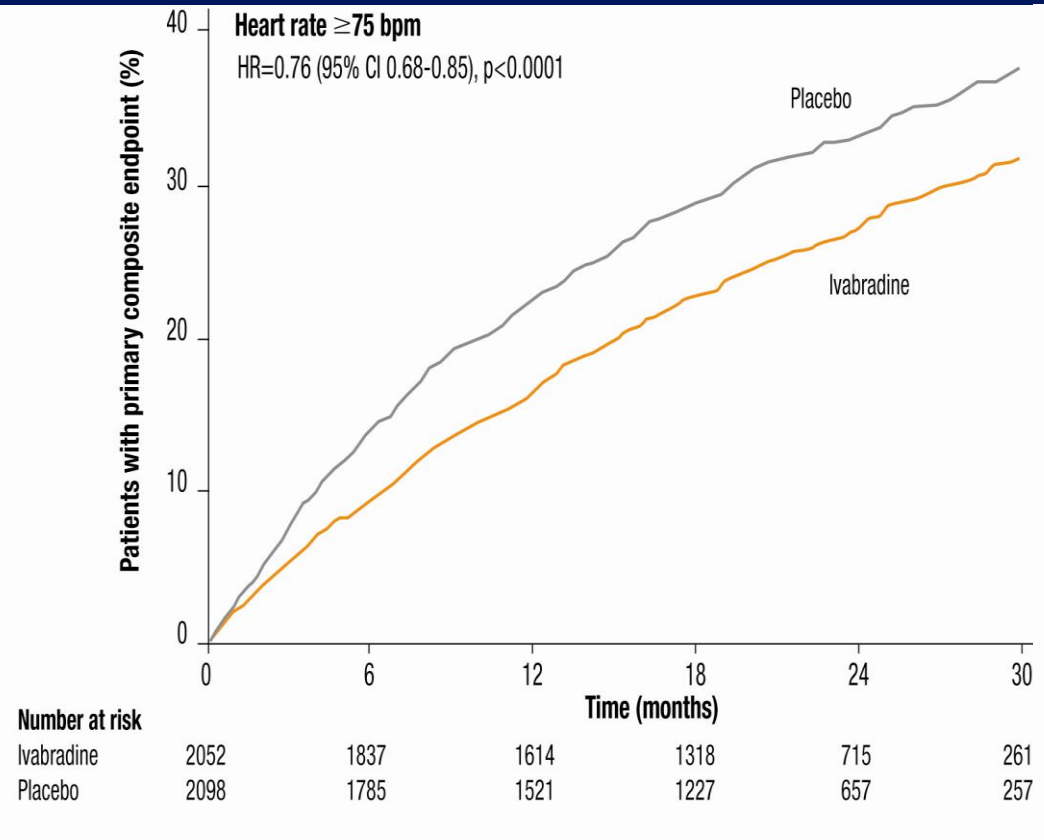
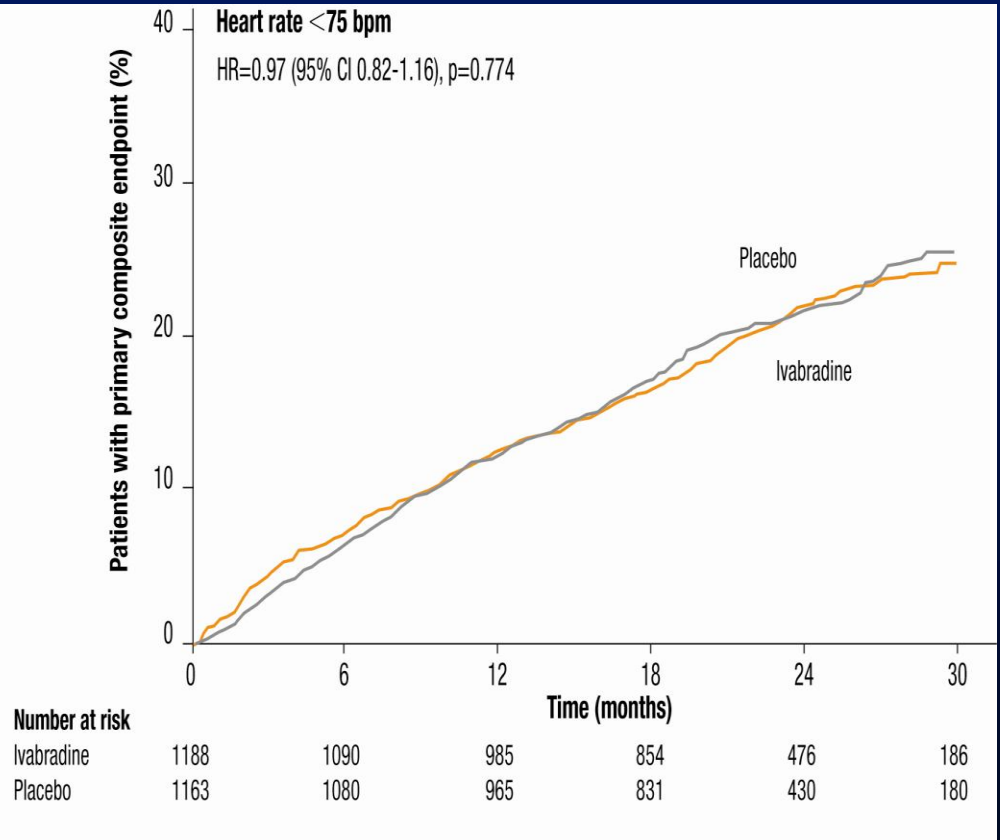
SHIFT Study. Cumulative event curves on ivabradine or placebo for the primary endpoint events in patients with a heart rate ≤ 75 bpm or a heart rate > 75 bpm

Primary composite endpoint





Böhm M, et al. Clin Res Cardiol. Online 11 May 2012.

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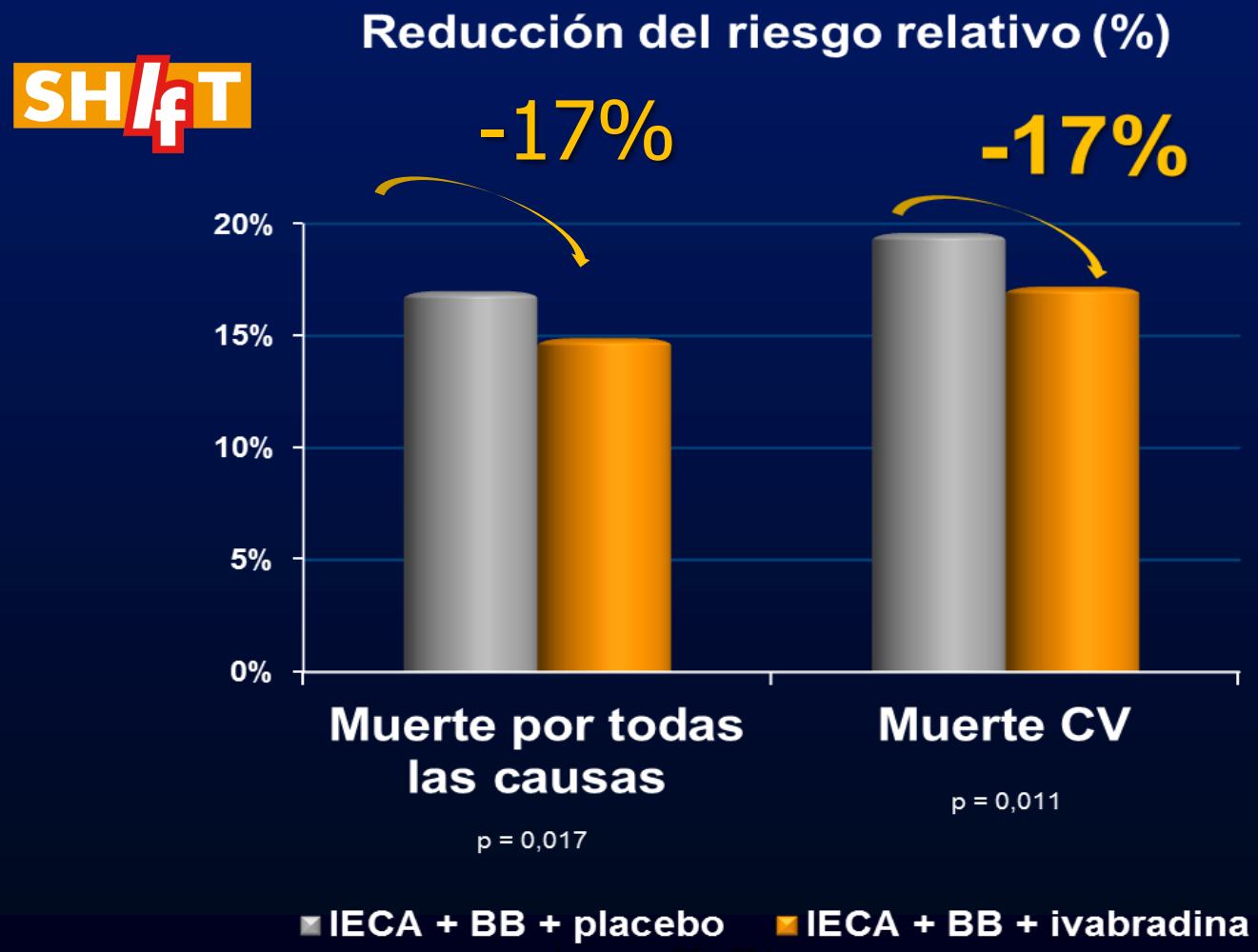

Ivabradina en la IC-2012

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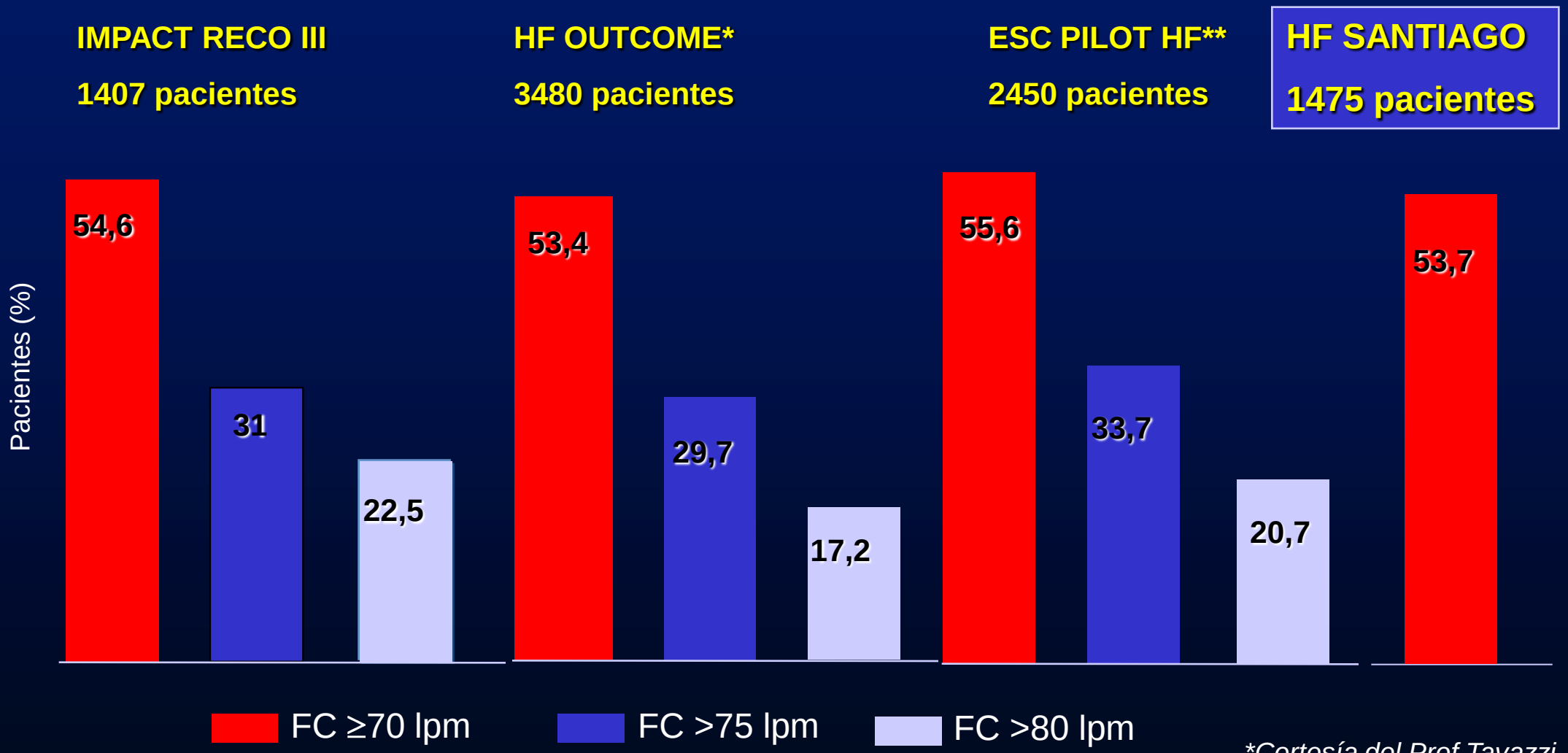
Registro de IC: más del 50 % de los pacientes tiene una FC ≥70 lpm

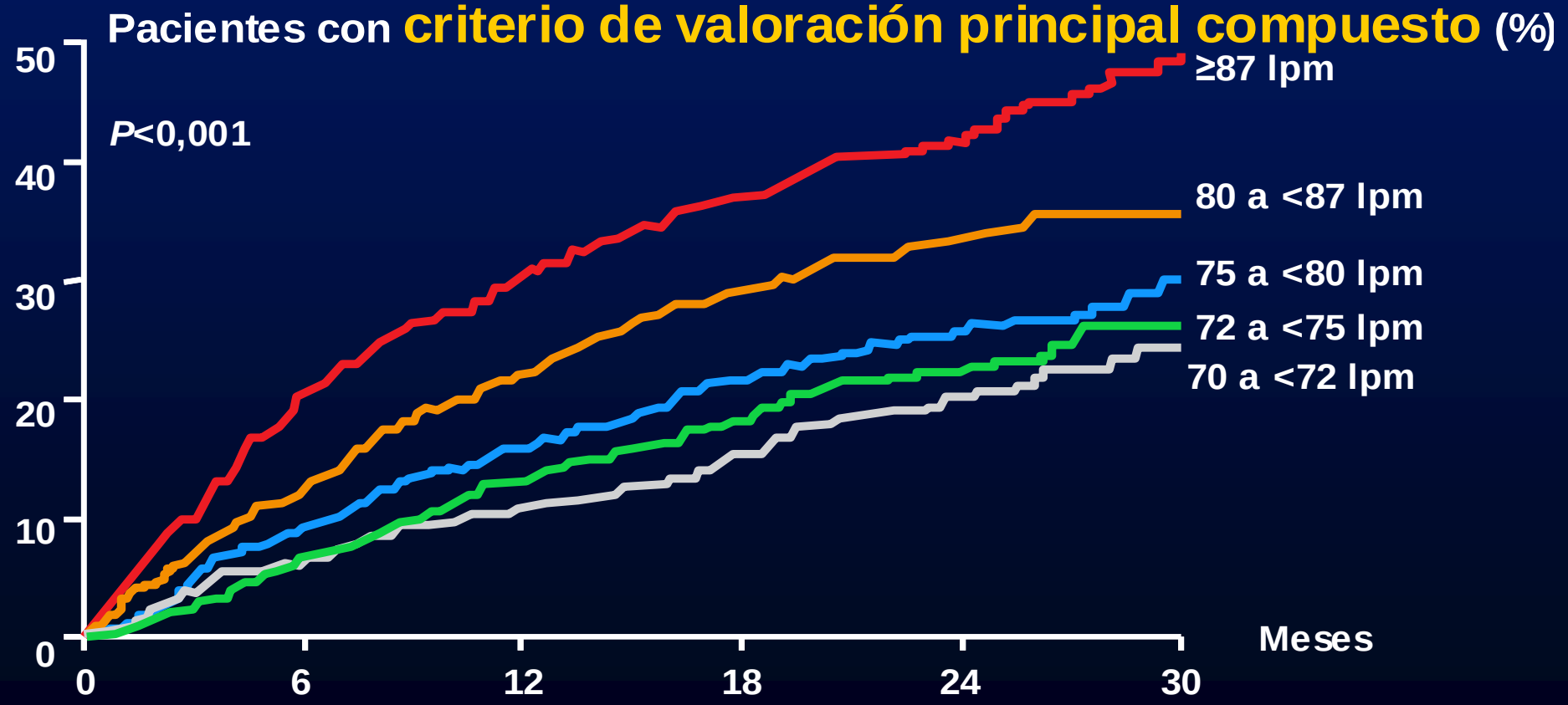


*Cortesía del Prof Tavazzi
**Cortesía del Prof Maggioni

La FC inicial es un predictor de eventos en el grupo placebo

Aumento del riesgo de un 2,9 % por incremento de 1 lpm

Aumento del riesgo de un 15,6 % por incremento de 5 lpm



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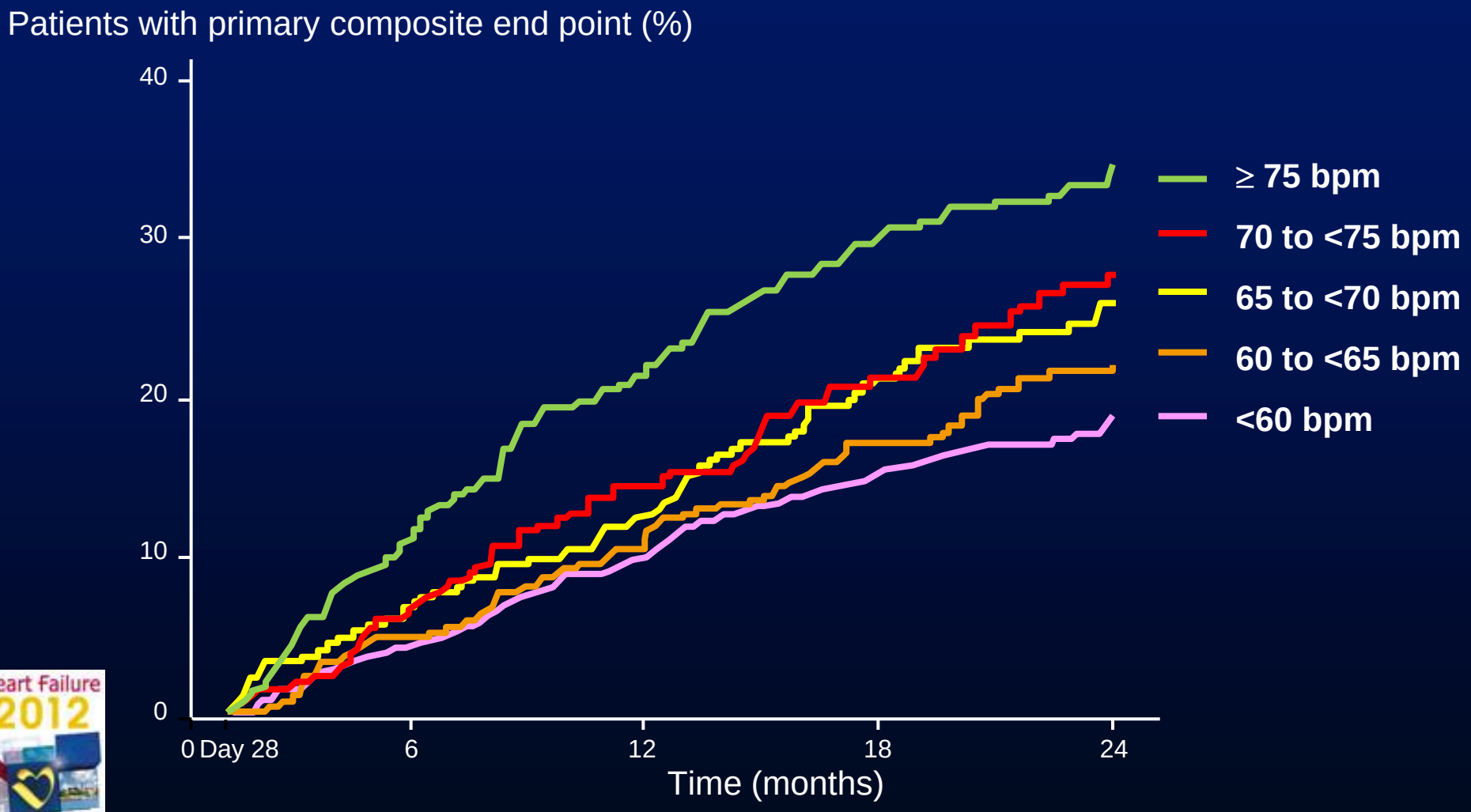
Lancet. Online 29-08-2010

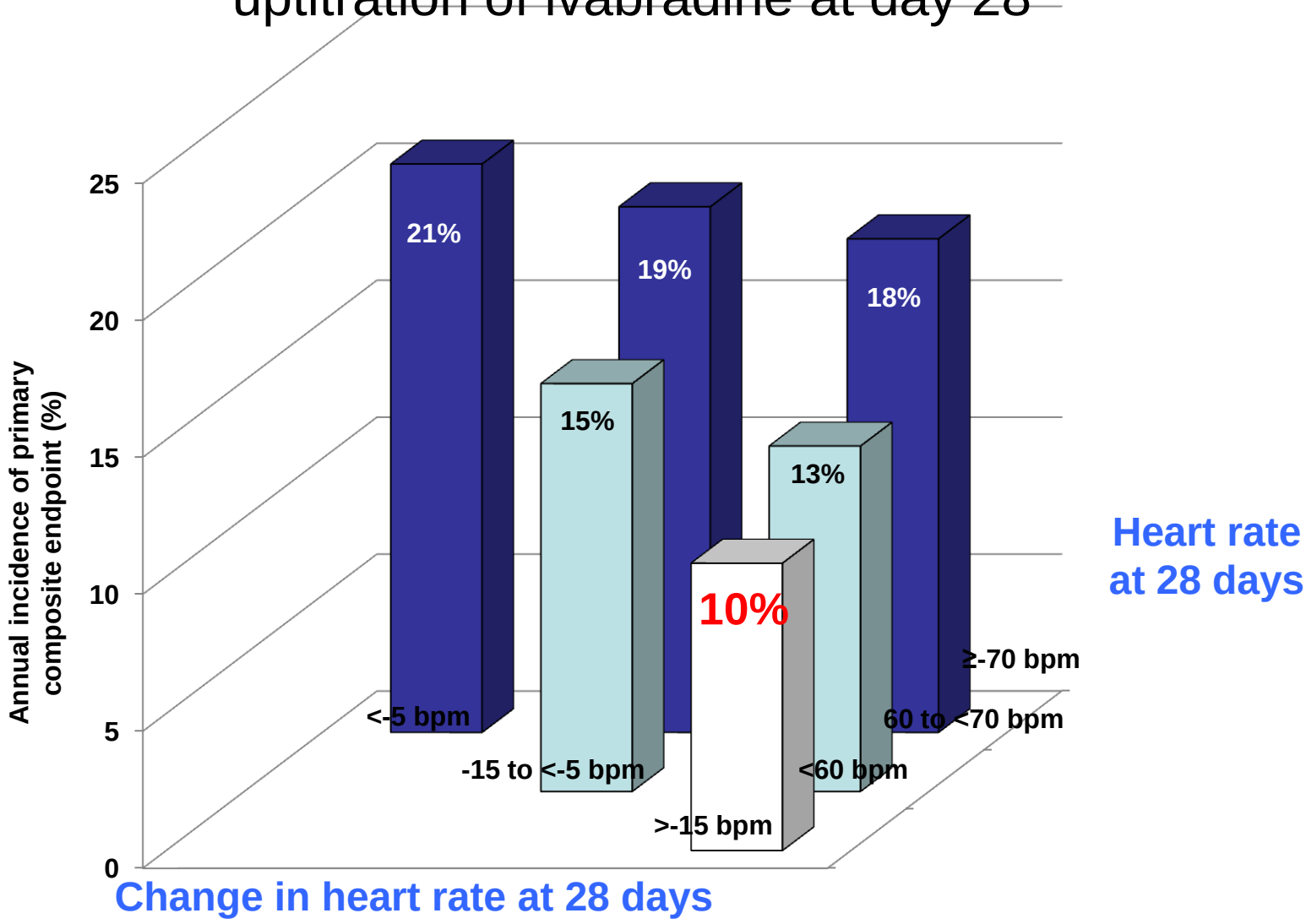
Effect of ivabradine on outcomes according to HR achieved at 28 days



Heart Failure 2012 BELGRADE 19-22 MAY

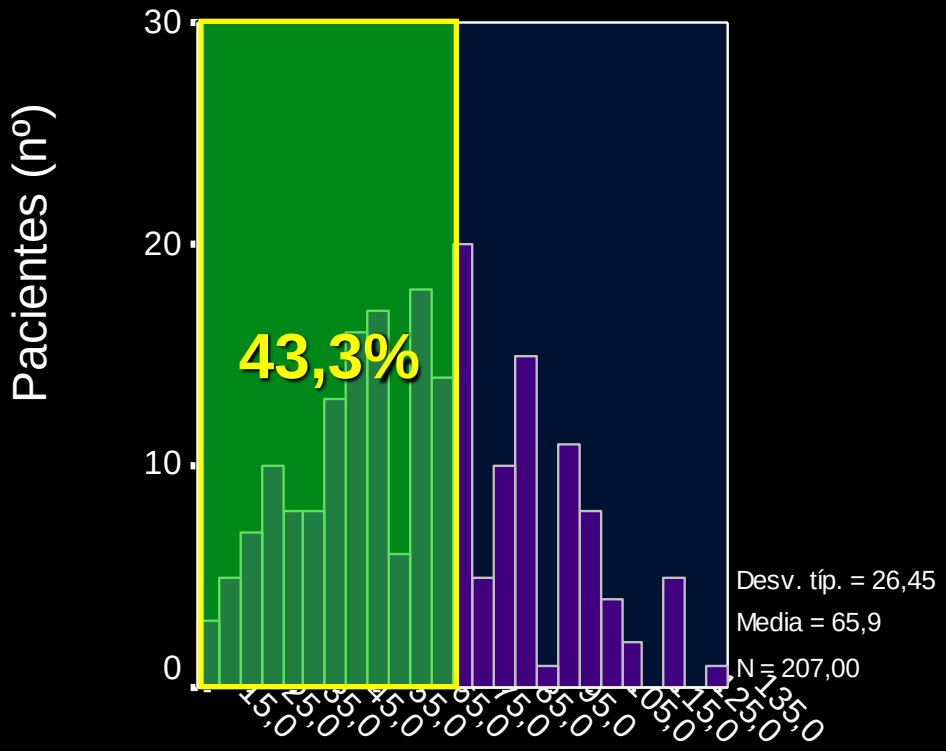
Böhm M, et al. Clin Res Cardiol. Online 11 May 2012.

SHIFT Study. Annual incidence of the primary endpoint in relation to categories of heart rate reduction or heart rate achieved after uptitration of ivabradine at day 28

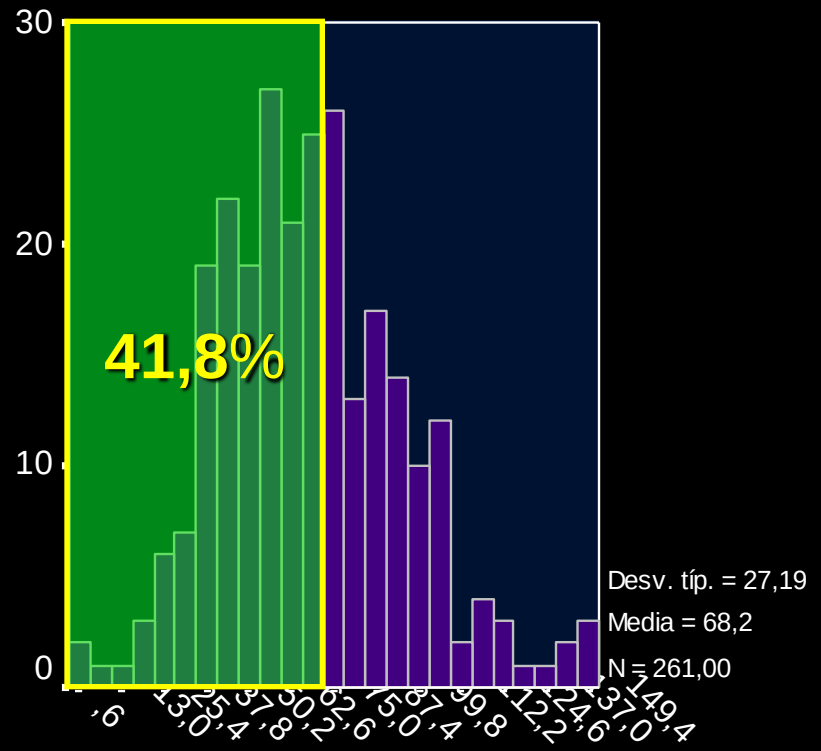


Distribución de la Población del Estudio en Relación a la Función Renal

FEVI ≥ 50%



FEVI < 50%



Insuficiencia Renal: TFG < 60 ml/min/1.73m2

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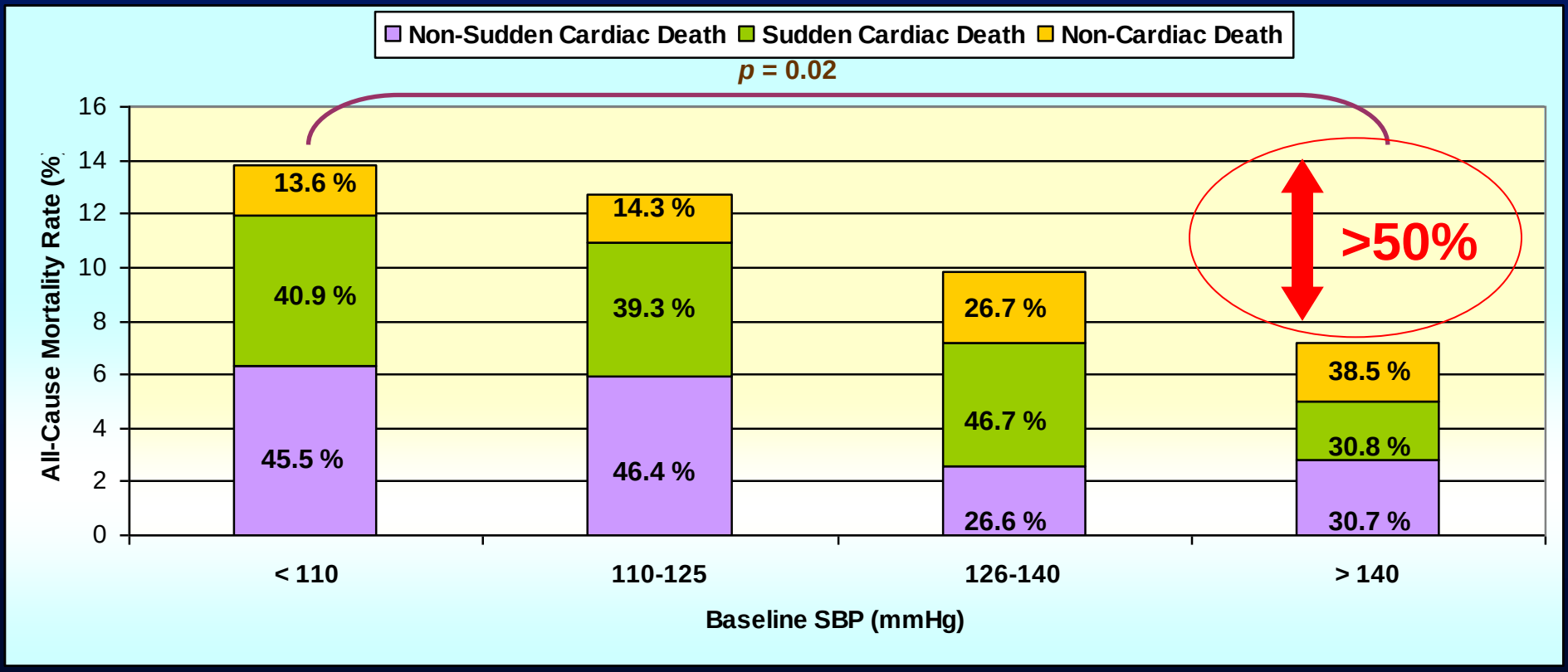
Grigorian L, et al . REC 2006:59:99

Association of BP and Its Evolving Changes with the Survival of Patients with Heart Failure



Cause-specific death rates in subgroups of patients with chronic HF defined by the quartiles of the distribution of baseline SBP in the whole study group. The P value refers to the differ-ences of cause-specific mortality in the SBP subgroups.

Grigorian-Shamagian L et al. Journal of Cardiac Failure, 2008

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Ivabradina: Sin efectos deletéreos sobre Función Renal y Presión Arterial

Beneficios adicionales al mejor tratamiento preventivo posible

Estudio	IECA/ARAII, o total, %	BB, %	Diuréticos %	Antag Aldost %
CONSENSUS 1987 (n=253)	ST	2	98	55
SOLVD 1991 (n=2569)	ST	7	85	NA
MERIT HF, 1999 (n=3991)	95	ST	91	NA
CIBIS II, 1999 (n=2647)	96	ST	99	NA
COPERNICUS, 2001 (n=2289)	96	ST	99	20
RALES 1987 (n=253)	94	10	100	ST
CHARM Added, 2003 (n=2548)	ACE+ ST	55	90	17
SENIORS, 2005 (n=2128)	82	ST	86	29
HEAAL, 2009 (n=3846)	ST	72	77	38
SHIFT, 2010 (n=6505)	**91**	**89**	**84**	**61**

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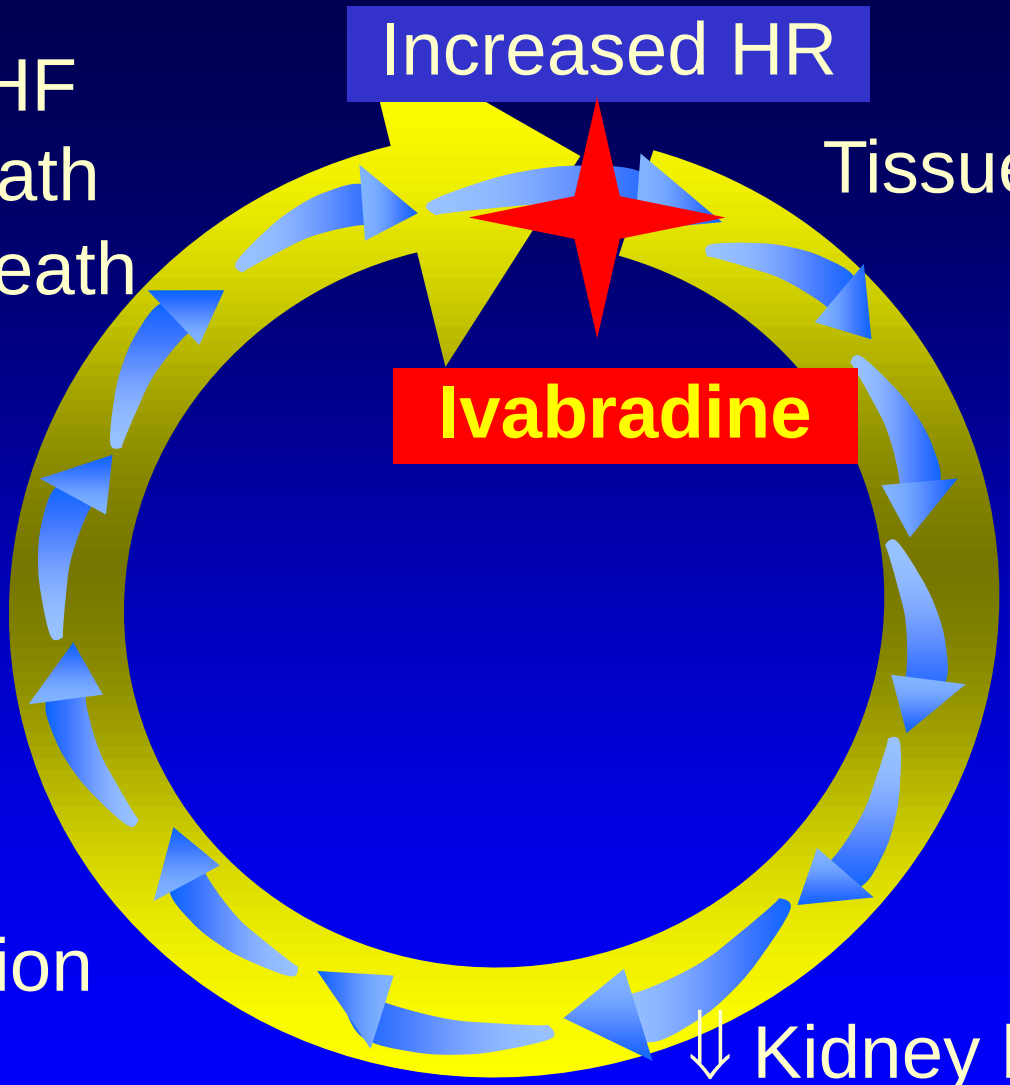
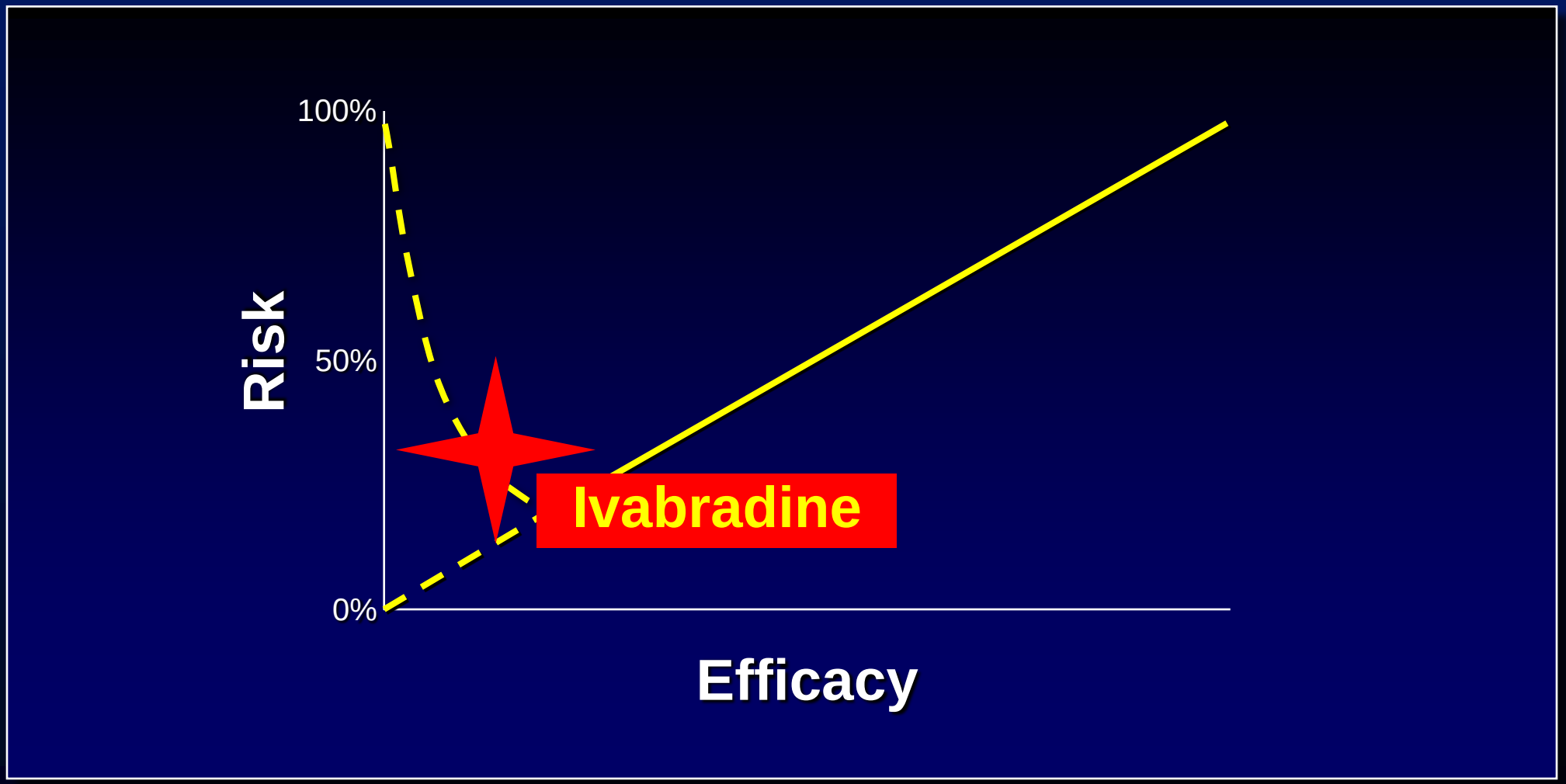


J-curve or Linear Relationship with Efficacy vs Adverse Events in HF



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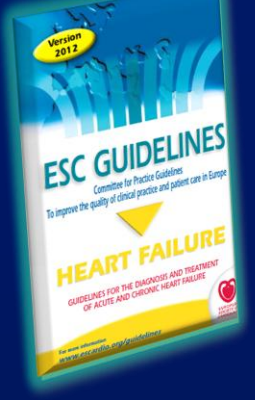
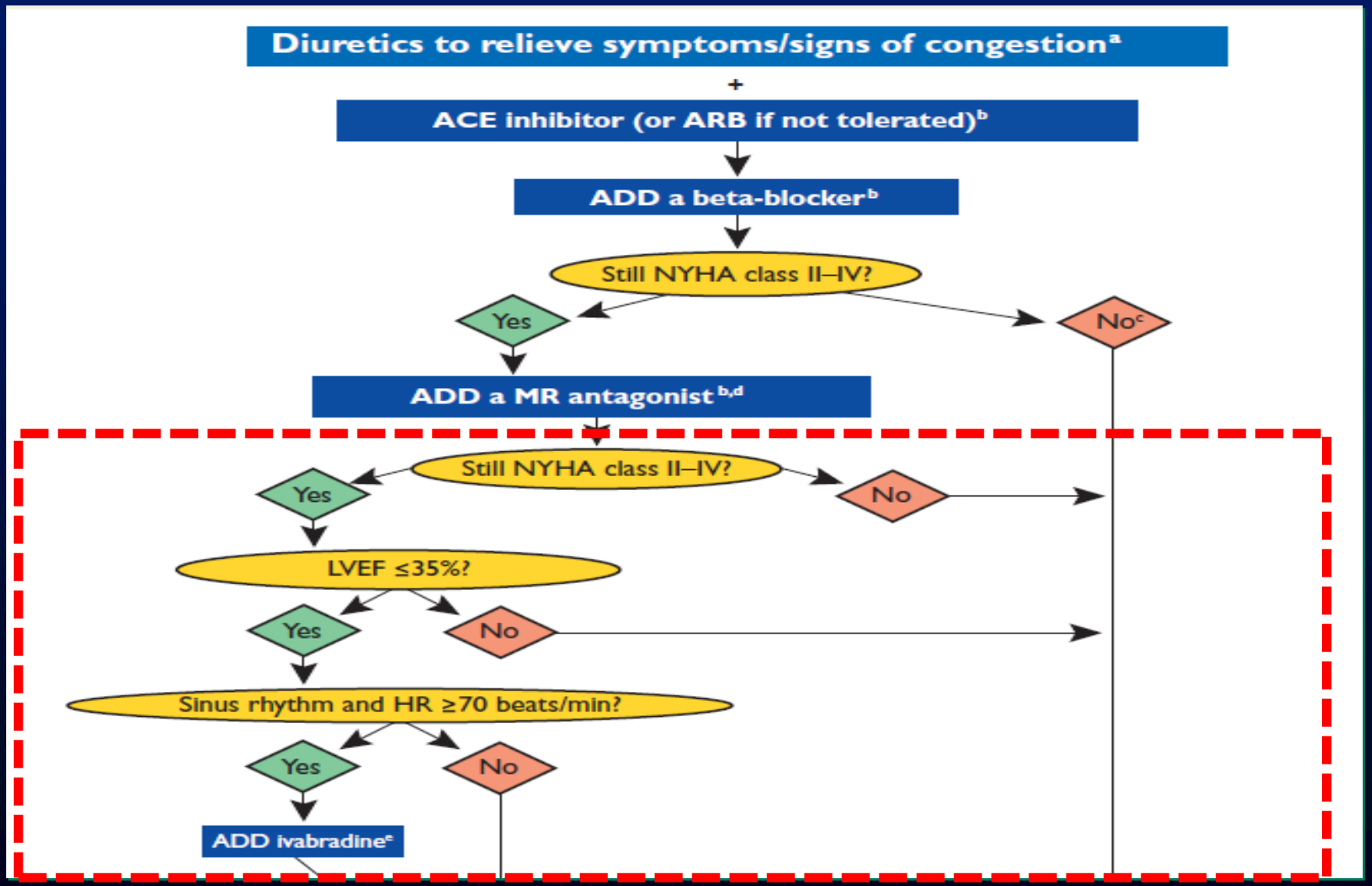


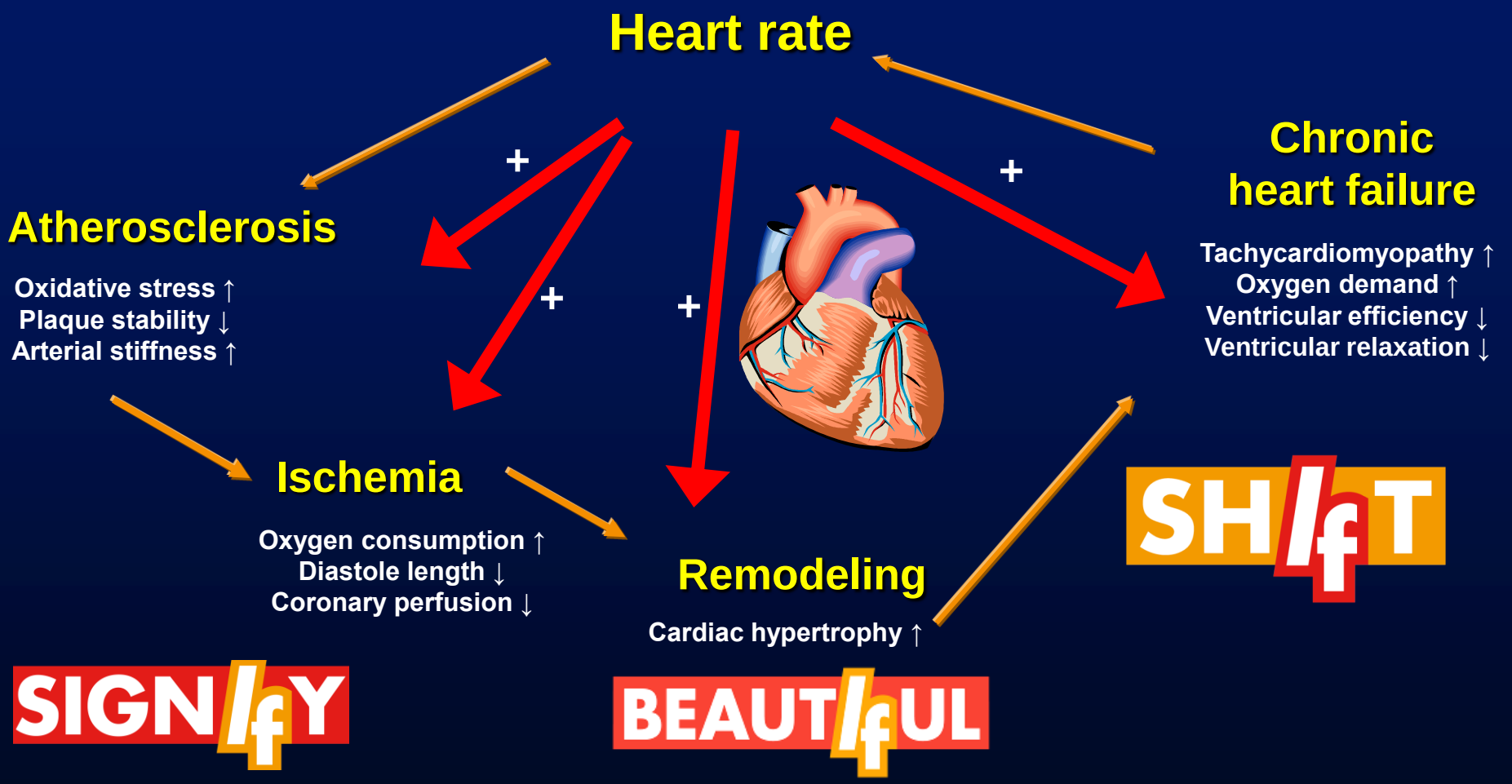
Ivabradine in the management of systolic CHF: new ESC Guideline



Cuestiones Pendientes. Ivabradina

- ¿Objetivo de FC o bradicardia sintomática?
- ¿Efecto en pacientes con hipotensión?
- ¿Ivabradina en IC con FSP?
- ¿Efecto cardíaco? ¿Efecto vascular? ¿Efecto renal?
- ¿Efecto en disfunción renal avanzada?

Cardioprotective effects of heart rate reduction with ivabradine



Adapted from Reil JC and Böhm M. *Lancet* 2008;372: 779-780.

Ivabradina en la IC-2012

¿Cuál es la Evidencia?

¿Qué dicen las Guías de Práctica Clínica?

Implicaciones Clínicas

Cuestiones Pendientes