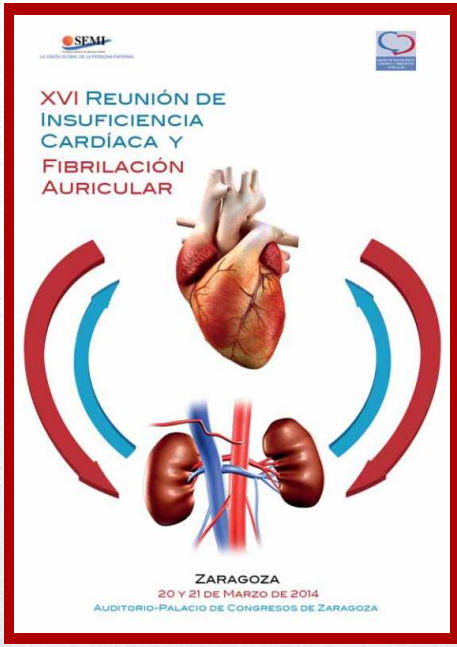


SERVICIO DE CARDIOLOGÍA
Hospital Universitario y Politécnico La Fe

FRECUENCIA CARDÍACA

Dr. Luis Almenar Bonet

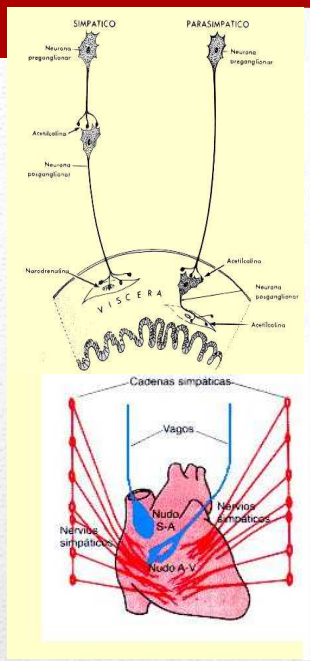
Unidad de Insuficiencia Cardíaca y Trasplante

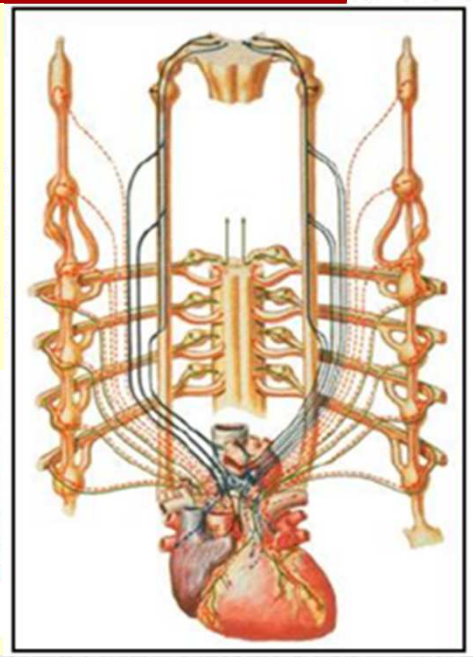
Hospital Universitario y Politécnico La Fe. Valencia

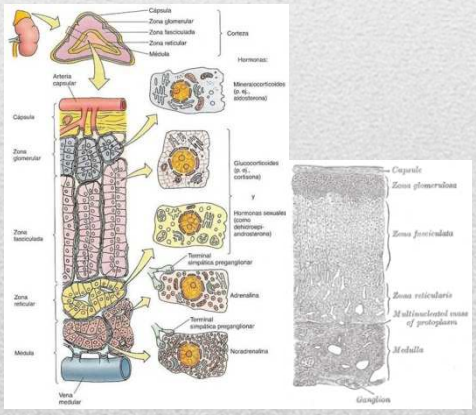
Mortalidad en IC

- Actualmente, existen grandes avances (médicos y dispositivos) que han demostrado mejorar la supervivencia en los pacientes con IC crónica. Sin embargo, la tasa de mortalidad sigue siendo muy elevada (75% a los 7 años)
- Por ello, existe necesidad imperiosa de identificar nuevas dianas terapéuticas. Las más útiles y prácticas son las que se pueden medir fácilmente y si son a la vez una marcador de riesgo y una diana terapéutica (p.ej. Factores de riesgo…. Fc)

- Sistema nervioso autónomo parasimpático
- Sistema nervioso autónomo simpático
- Niveles plasmáticos de catecolaminas







Determinantes de la Fc

- Sujetos sanos (o presuntamente sanos)
- Pacientes con HTA
- Cardiopatía isquémica
- IC con FE reducida
- Postrasplante cardíaco
- Otras (EPOC, Sdr. Metabólico, etc)

Fc y Pronóstico (morbilidad y mortalidad)

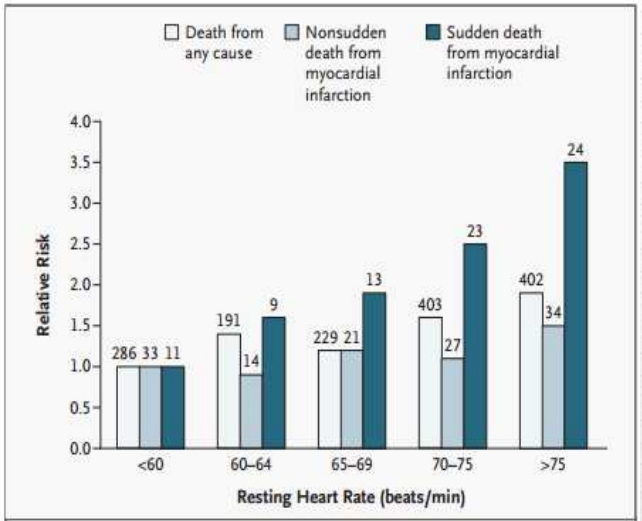


Figure 1. Relative Risks of Death from Any Cause and of Nonsudden and Sudden Death from Myocardial Infarction, According to the Quintile of Resting Heart Rate.

The reference group was subjects with a resting heart rate of less than 60 beats per minute (lowest quintile). The numbers over the bars indicate the numbers of subjects. Comparisons were performed with the Mantel–Haenszel chi-square test for trend. The test for trend showed a significant difference among quintiles with respect to the risk of death from any cause (P<0.001), nonsudden death from cardiac causes (P=0.02), and sudden death from cardiac causes (P<0.001). Adjustments were made for age, use or nonuse of tobacco, level of physical activity, presence or absence of diabetes, body-mass index, basal systolic blood pressure, cholesterol level, presence or absence of a parental history of sudden death or myocardial infarction, and exercise duration. Data are missing for five subjects who died of any cause, including one who died suddenly from myocardial infarction.

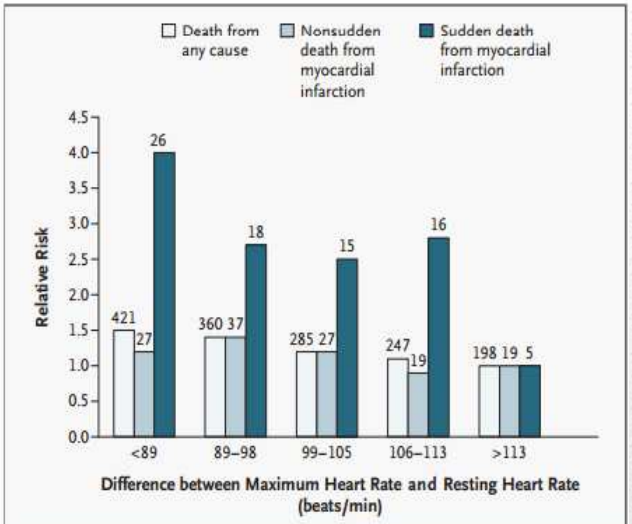


Figure 2. Adjusted Relative Risks of Death from Any Cause and from Nonsudden and Sudden Death from Myocardial Infarction, According to the Difference between the Resting and Maximum Heart Rate.

The reference group was subjects with a difference of more than 113 beats per minute between the resting and maximum heart rates (highest quintile). The numbers over the bars indicate the numbers of subjects. Comparisons were performed with the Mantel–Haenszel chi-square test for trend. The test for trend showed a significant difference among quintiles with respect to the risk of death from any cause (P<0.001), nonsudden death from cardiac causes (P=0.01), and sudden death from cardiac causes (P<0.001). Adjustments were made for age, use or nonuse of tobacco, level of physical activity, presence or absence of diabetes, body-mass index, basal systolic blood pressure, cholesterol level, presence or absence of a parental history of sudden death or myocardial infarction, and exercise duration. Data are missing for five subjects who died of any cause, including one who died suddenly from myocardial infarction.

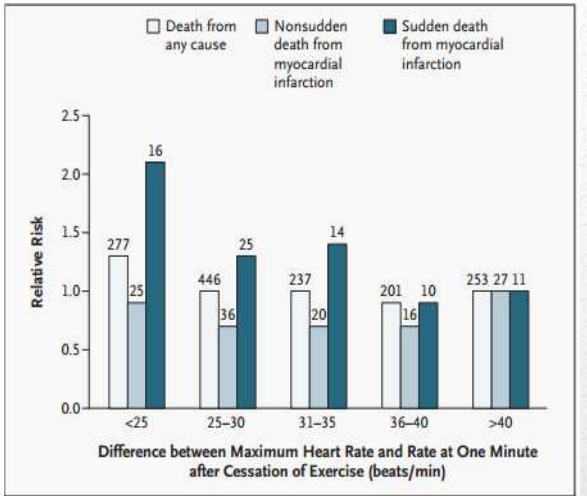


Figure 3. Adjusted Relative Risks of Death from Any Cause and from Nonsudden and Sudden Death from Myocardial Infarction, According to the Difference between Maximum Heart Rate and Heart Rate at One Minute after Cessation of Exercise.

The reference group was subjects with a difference of more than 40 beats per minute between the maximum heart rate and the heart rate at one minute after cessation of exercise (highest quintile). The numbers over the bars indicate the numbers of subjects. Comparisons were performed with the Mantel–Haenszel chi-square test for trend. The test for trend showed a significant difference among quintiles with respect to the risk of death from any cause (P<0.001) and sudden death from cardiac causes (P=0.03) but was not significant for nonsudden death (P=0.20). Adjustments were made for age, use or nonuse of tobacco, level of physical activity, presence or absence of diabetes, body-mass index, basal systolic blood pressure, cholesterol level, presence or absence of a parental history of sudden death or myocardial infarction, and exercise duration. Data on heart-rate recovery at one minute are missing for 102 subjects who died of any cause, including 5 who died suddenly from myocardial infarction and 5 who died, but not suddenly, from myocardial infarction.

Fc y personas “aparentemente” sanas

Jouven X et al. NEJM 2005

Table 3 Multivariable Cox regression survival analysis for total mortality

	Total mortality	
	HR (99% CI)	Overall *P*-value
Resting heart rate (bpm)		
≤62	Reference	<0.0001

Adjusted survival curves for overall mortality by RHR quintiles

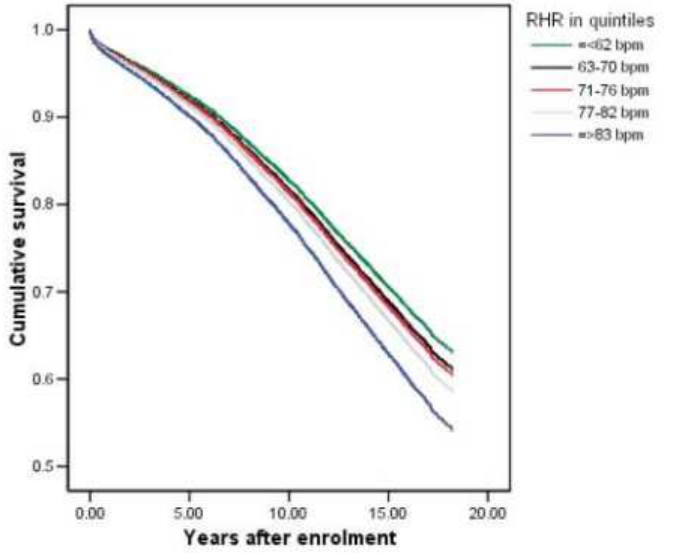


Figure 1 Adjusted for age, gender, hypertension, diabetes mellitus, cigarette smoking, clinically significant coronary vessel disease, EF, recreational activity, treatment with antiplatelets, diuretics, beta-blockers, and lipid-lowering drugs. RHR, resting heart rate.

Table 4 Multivariable Cox regression survival analysis for cardiovascular mortality

	CV mortality	
	HR (99% CI)	Overall *P*-value
Resting heart rate (bpm)		
≤62	Reference	<0.0001
63–70	1.05 (0.94–1.18)	
71–76	1.07 (0.94–1.21)	
77–82	1.14 (1.00–1.29)	

Adjusted* survival curves for CV mortality by RHR

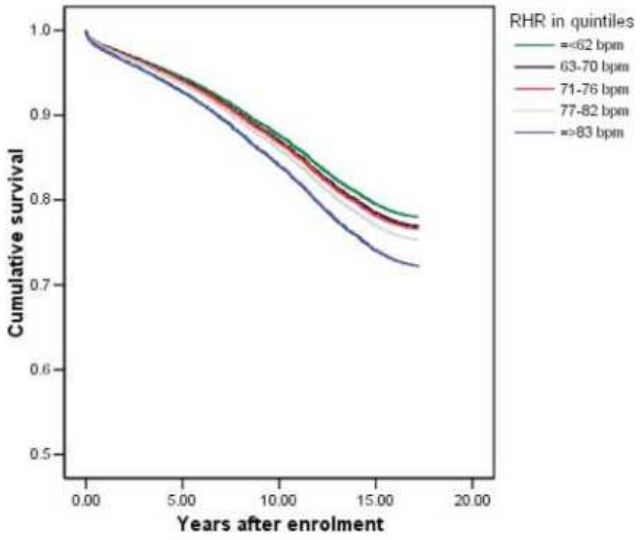


Figure 2 Asterisk indicates adjusted as *Figure 1* plus BMI. CV, cardiovascular; RHR, resting heart rate.

Fc y cardiopatía isquémica

Diaz A et al. Eur Heart J 2005

	Events, n (%)	Heart rate ≥70 versus <70 bpm		Heart rate higher by 5 bpm	
		HR (95% CI)	p value	HR (95% CI)	p value
Mortality					
Cardiovascular death	435 (8·0%)	1·34 (1·10–1·63)	0·0041	1·08 (1·03–1·12)	0·0005
Heart failure outcome					
Admission to hospital for heart failure (fatal and non-fatal)	427 (7·9%)	1·53 (1·25–1·88)	<0·0001	1·16 (1·11–1·21)	<0·0001
Coronary outcomes					
Admission to hospital for myocardial infarction (fatal and non-fatal)	226 (4·2%)	1·46 (1·11–1·91)	0·0066	1·07 (1·00–1·14)	0·052
Coronary revascularisation	186 (3·4%)	1·38 (1·02–1·86)	0·037	1·08 (1·01–1·16)	0·034

Table 2: **Adjusted hazard ratios (HR), 95% CIs, and p values for elevated resting heart rate at baseline and as a continuous variable for cardiovascular mortality and morbidity**

Fc e Insuficiencia Cardíaca (CI)

Fox K et al. Lancet 2008

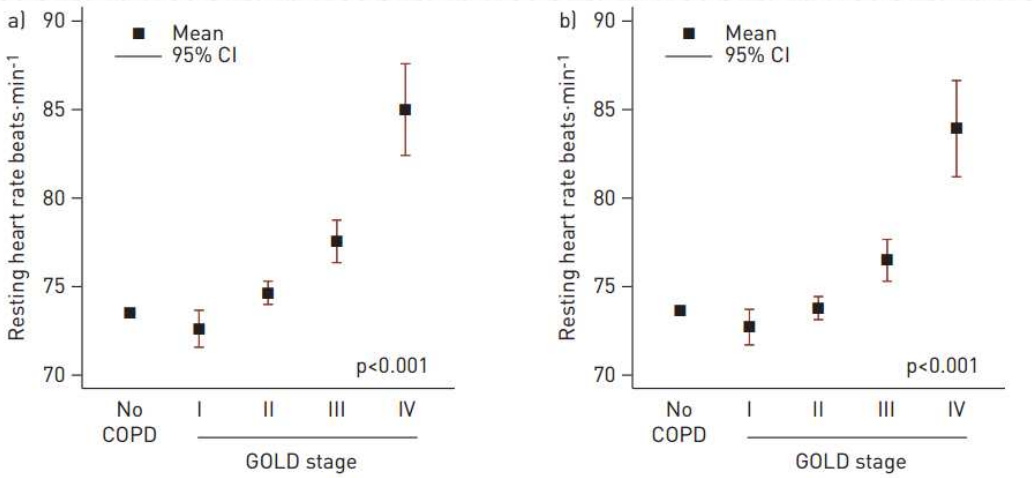


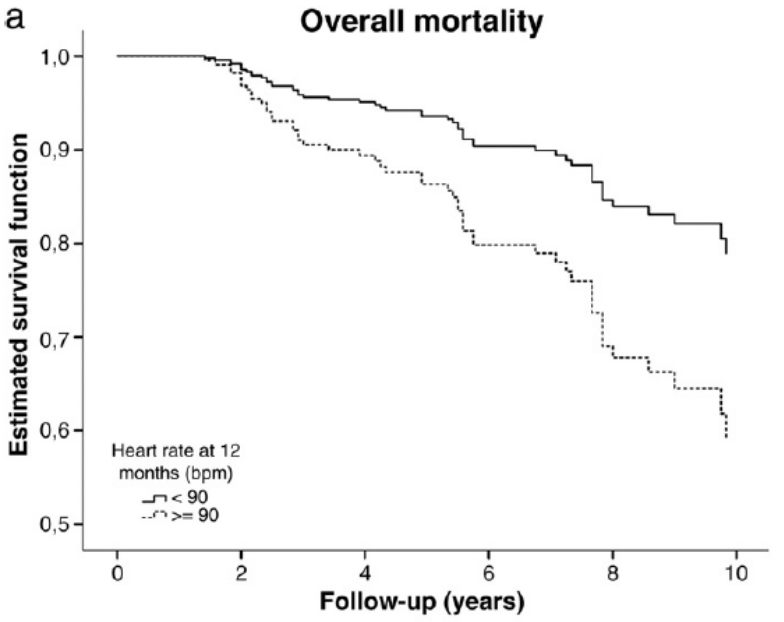
FIGURE 1 Resting heart rate and severity of chronic obstructive lung disease (COPD). Resting heart rate increase significantly with severity of COPD ($p<0.001$). a) Unadjusted analysis. b) Multivariate analysis adjusted for age, sex, smoking, systolic blood pressure, cholesterol, body mass index, physical activity, alcohol drinking habits, use of heart medication, use of antihypertensives, use of nitrates, previous ischaemic heart disease, electrocardiographic evidence of ischaemic heart disease, previous stroke, previous diagnosis of any cancer, self-reported diabetes or fasting glucose >11.1 mmol·L^{-1}. Data are presented as mean with error bars representing 95% CI. No COPD n=14 051, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I n=516, GOLD stage II n=1564, GOLD stage III n=457, GOLD stage IV n=108.

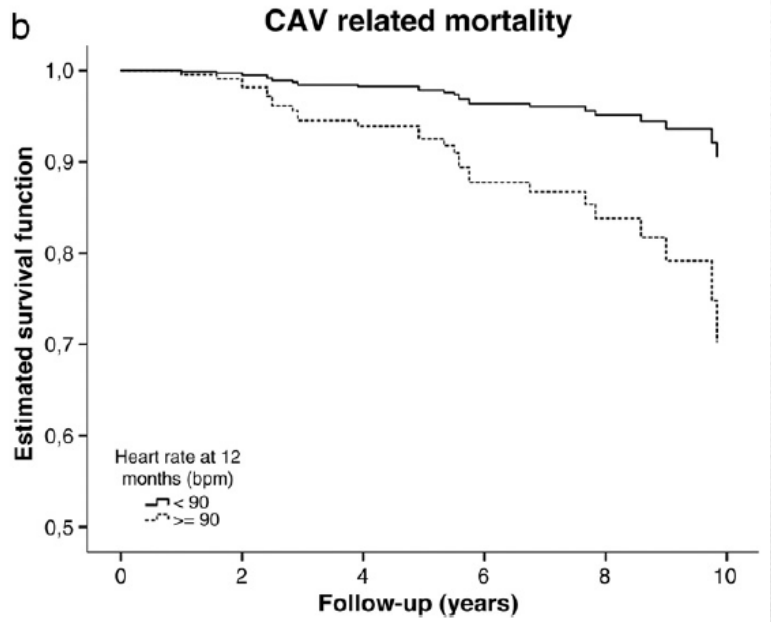
	Resting heart rate beats·min^{-1}			
	<64	65–74	75–84	⩾85
All-cause mortality				
Univariate	1¶	1.11 (1.05–1.17)	1.30 (1.23–1.37)	1.51 (1.42–1.60)
Multivariate#	1¶	1.16 (1.10–1.22)	1.31 (1.24–1.38)	1.51 (1.43–1.60)
Cardiovascular mortality				
Univariate	1¶	1.08 (1.00–1.17)	1.34 (1.24–1.45)	1.57 (1.45–1.70)
Multivariate#	1¶	1.16 (1.07–1.25)	1.36 (1.26–1.48)	1.57 (1.45–1.71)

Data are presented as hazard ratio (95% CI). #: multivariate analysis adjusted for age, sex, smoking, systolic blood pressure, cholesterol, body mass index, physical activity, alcohol consumption habits, use of heart medication, use of antihypertensives, use of nitrates, previous ischaemic heart disease, electrocardiographic evidence of ischaemic heart disease, previous stroke, previous diagnosis of any cancer, self-reported diabetes or fasting glucose >11.1 mmol·L^{-1}; ¶: reference.

Fc y EPOC

Jensen M et al. Eur Respir J 2013



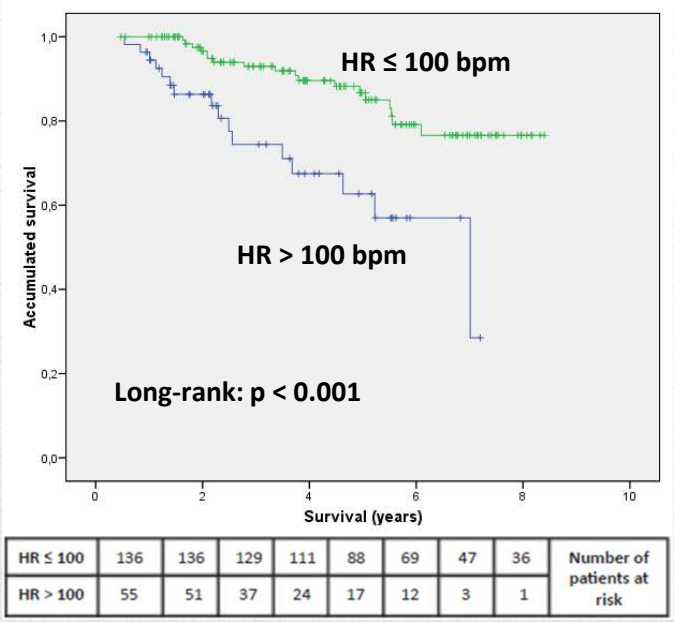


Multivariate Cox regression analysis for overall mortality.

	HR 95% CI	p
Median heart rate at 12 months ≥90 bpm	3.2 (1.4; 7.1)	0.004
CAV at 12 months	2.6 (0.7; 9.7)	0.16
Recipient on dialysis	1.9 (0.4; 8.7)	0.42
Male recipient/female donor	2.6 (0.7; 9.9)	0.16
Donor age (years)	1 (1; 1)	0.35

Fc y trasplante

Castel MA et al. Int. J. Cardiol. 2013



HR ≤ 100	136	136	129	111	88	69	47	36	Number of patients at risk
HR > 100	55	51	37	24	17	12	3	1	

Table 3. Multivariate analysis: heart rate determinants.

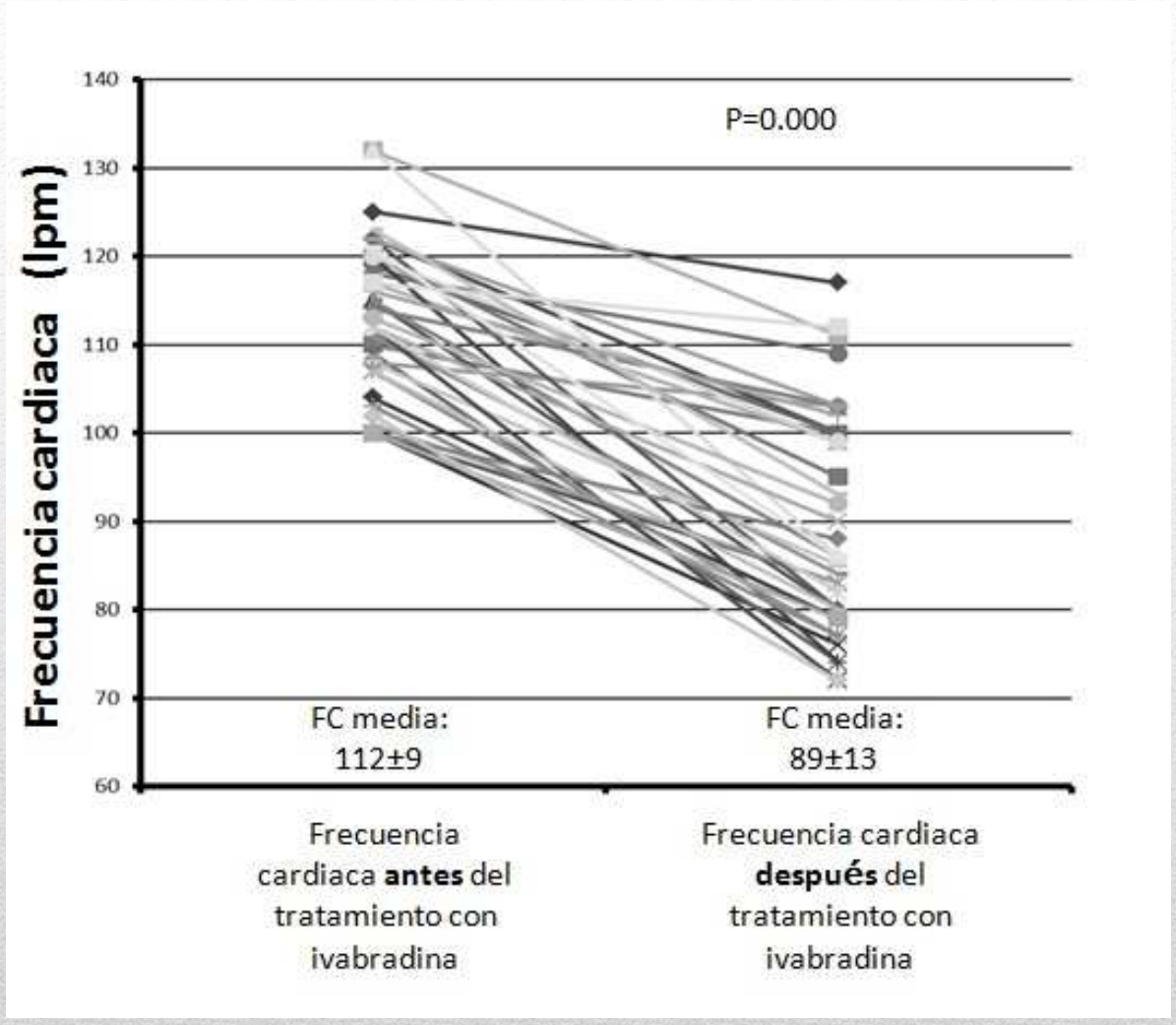
Dependent variable	Basal heart rate at 1 year		
Covariables	*P*	HR	95% CI
Cardiac allograft vasculopathy	0.75	0.32	−3.83–5.33
Donor age	0.68	−1.84	−0.37–0.01
Ischemia time	0.13	1.32	−0.01–0.07
Primary graft failure	0.38	−0.88	−7.50–2.86
No. of admissions because of infection in first year	0.31	1.01	−1.39–4.33
No. of rejections in first year	0.38	−0.89	−3.20–1.21

Table 2. Multivariate analysis: long-term survival.

Covariables	*P*	HR	95% CI
Not including cardiac allograft vasculopathy			
Basal heart rate	0.007	2.12	1.04–4.23
Donor age	0.003	1.06	1.02–1.10
No. of rejections in first year	0.03	1.55	1.05–2.28
Ischemia time	0.56	1.01	0.99–1.02
Primary graft failure	0.21	1.68	0.74–3.82
No. of admissions because of infection in first year	0.13	0.73	0.48–1.10
Creatinine at 1 year post-HTx	0.67	0.92	0.65–1.32
Including cardiac allograft vasculopathy			
Basal heart rate	0.044	1.69	1.03–6.33
Cardiac allograft vasculopathy	0.039	2.85	1.05–7.72
Donor age	0.026	1.07	1.01–1.12
No. of rejections in first year	0.74	1.10	0.62–1.92
Ischemia time	0.36	1.01	0.99–1.02
Primary graft failure	0.34	1.72	0.56–5.30
No. of admissions because of infection in first year	0.60	1.18	0.63–2.18
Creatinine at 1 year post-HTx	0.36	0.80	0.50–1.28

Fc y trasplante

Melero J et al, Transp Int. 2013



Seguridad y eficacia de la Ivabradina en Tc

Melero J et al, Comunicación ESC-HF 2014

Pharmacological treatments indicated in potentially all patients with symptomatic (NYHA functional class II–IV) systolic heart failure

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

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; EF = ejection fraction; HF = heart failure; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

Fármaco	Dosis Inicial (mg)	Dosis máxima Objetivo (mg)	Dosis media alcanzada (mg)
Captopril	6,25 x 3	50 x 3	12,5 x 3
Enalapril	2,5 x 2	20 x 2	10 x 2
Carvedilol	3,125 x 2	50 x 2	25 x 2
Bisoprolol	1,25 x 1	10 x 1	10 x 1
Metoprolol	12,5 x 2	75 x 2	50 x 2

- Sólo se alcanza el objetivo en el 50% de pacientes
- Mala tolerancia
- Están contraindicados

Tratamiento Beta-bloqueante en IC

¿Qué podemos hacer?

¿Qué podemos hacer ante ese escenario para disminuir el mal pronóstico asociado a una Fc elevada:

- **Reductores puros de la Fc**
  - Ivabradina
- **Otras drogas reductoras (con otros efectos añadidos)**
  - Digoxina
  - Amiodarona
  - Verapamil

Table 1 The mechanism of action and indications of drugs with heart rate-lowering effects in chronic heart failure

Drug	Mechanism of action	HF indication
Beta-blockers	Blocks adrenergic activity; slows sinus rate and prolongs AV conduction.	HF-rEF with sinus rhythm or AF; HF-pEF with AF
Ivabradine	Selective inhibition of the pacemaker modulating 'f' current (I_f) in the sinoatrial node; slows sinus rate. No effect on AV node.	HF-rEF with sinus rhythm
Digoxin	Increases vagal tone; inhibits sympathetic nervous system activity; slows sinus rate and prolongs AV conduction.	HF-rEF with sinus rhythm or AF; HF-pEF with AF
Verapamil	Blocks high voltage calcium channels; slows sinus rate and prolongs AV conduction.	HF-pEF with sinus rhythm or AF
Amiodarone	Blocks potassium channels; antiadrenergic effects; slows sinus rate and prolongs AV conduction.	HF-rEF with AF

AV, atrioventricular; HF-pEF, heart failure with preserved ejection fraction; HF-rEF, heart failure with reduced ejection fraction.

Mecanismo de acción de los fármacos reductores de la Fc en IC

Efectos en IC y FA

Fármaco	Indicaciones IC	Indicaciones RS	Indicaciones FA	Efectos 2ios
Beta-bloqueante	SI (reduce las hospitalizaciones CV y el riesgo de muerte prematura	SI, (Control de Fc en reposo y ejercicio)	SI (Control de Fc en reposo y ejercicio	Bradicardia sintomática, fatiga, empeoramiento IC, crisis asmáticas
Ivabradina	SI (asociada a BB para control de Fc)	SI (asociada a BB para control de Fc)	NO	Bradicardia Síntomas visuales
Digoxina	SI (asociada a BB para control de Fc	SI	SI	No descritos en ensayos
Amiodarona	SI (único antiarritmico recomendado en HFrEF)	SI	SI (junto con BB en caso de no tolerancia o no respuesta a BB+Digoxina)	Síntomas GI, disfunción tiroidea
Verapamil	NO (Efecto Inotropo negativo. Indicado sólo en HFpEF)	SI	SI	Síntomas GI y edemas

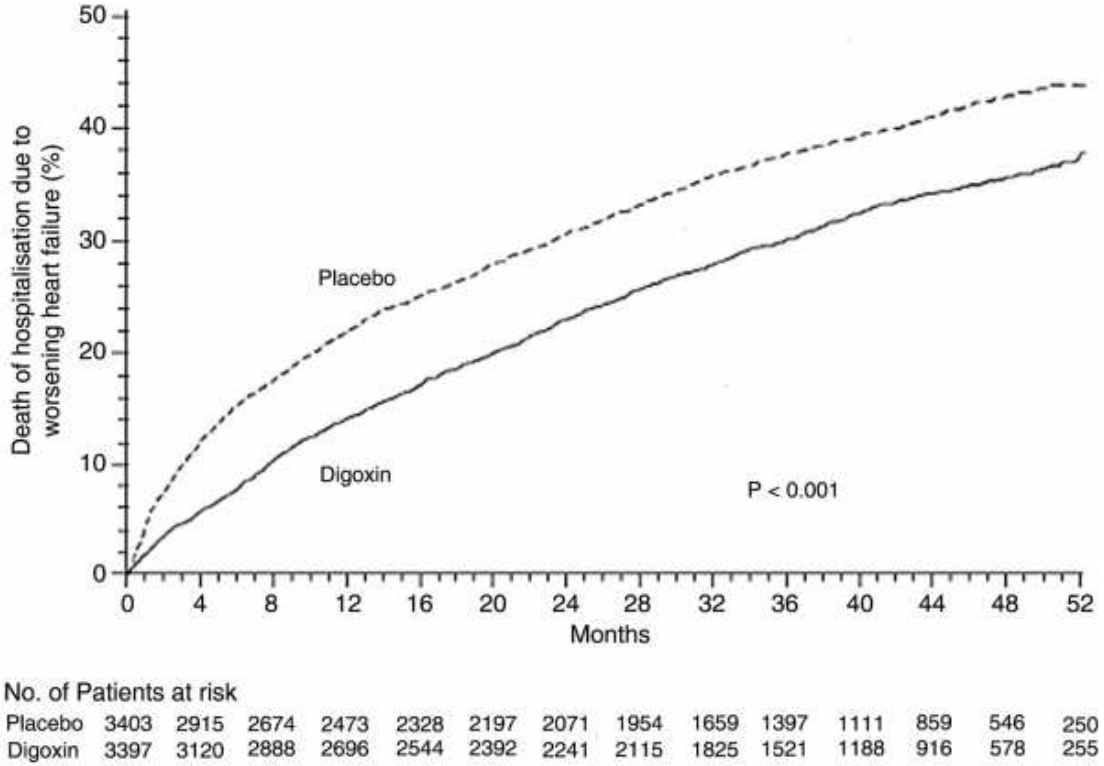
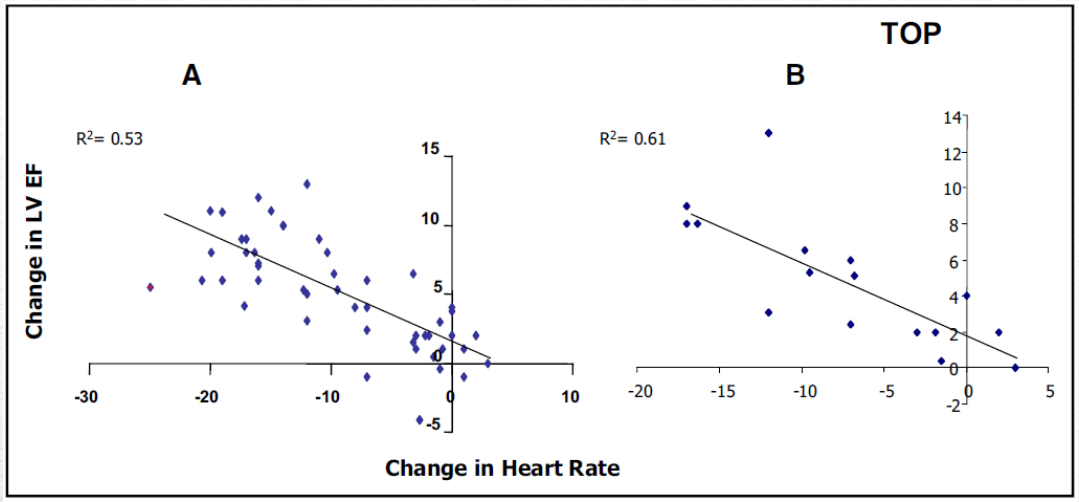
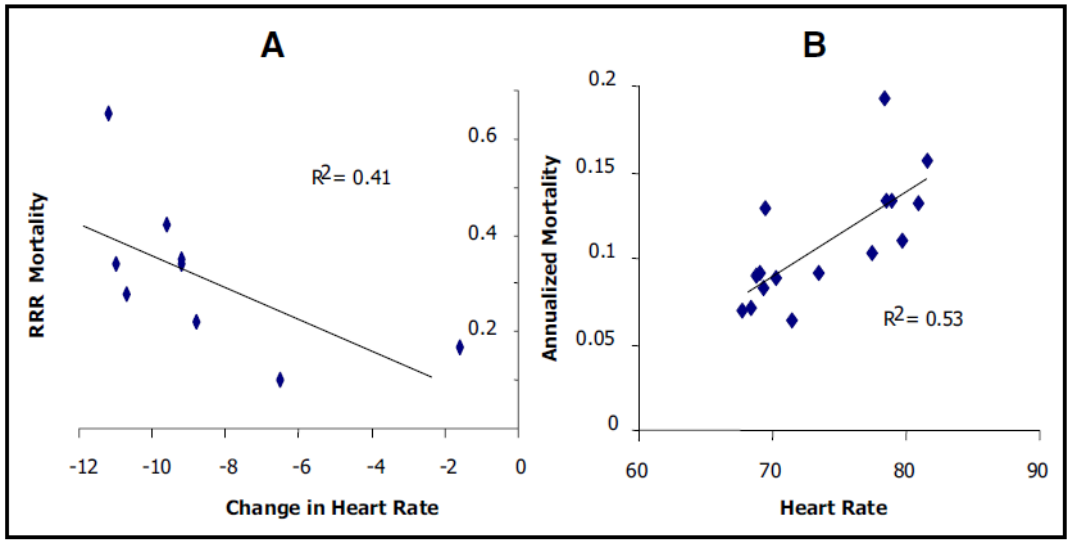


Figure 4 Incidence of death or hospitalization due to worsening heart failure in digoxin vs. placebo groups (DIG trial).[29]

Ensayo DIG

The Digitalis Investigation Group. N Engl J Med 1997





Los beneficios dependen sobre todo de la Fc

Flannery et al. Am J Cardiol 2008

Disbalance autonómico

Hipoactividad

Parasimpática

Hiperactividad

Simpática

↑ Fc ➔ Consumo O2 miocárdico ➔ Acortamiento de la diástole.

Estrés de pared ➔ Activar la respuesta celular endotelial inflamatoria.

¿qué ocurre en la IC?

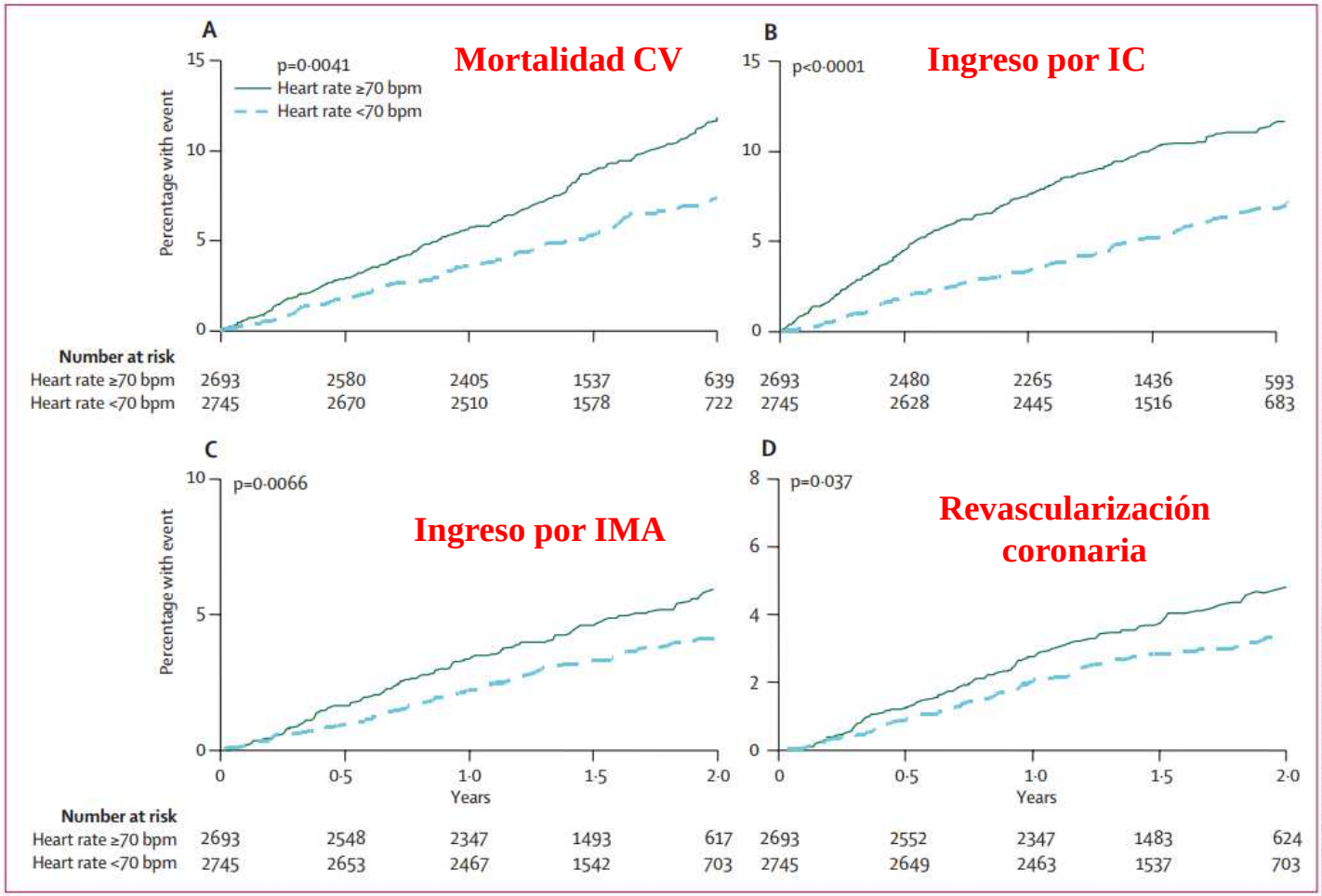


Figure 1: **Kaplan-Meier time-to-event plots split by heart rate for (A) cardiovascular death, (B) admission to hospital for heart failure, (C) admission to hospital for myocardial infarction, and (D) coronary revascularisation**

BEAUT*iful*. Relación Fc - Riesgo

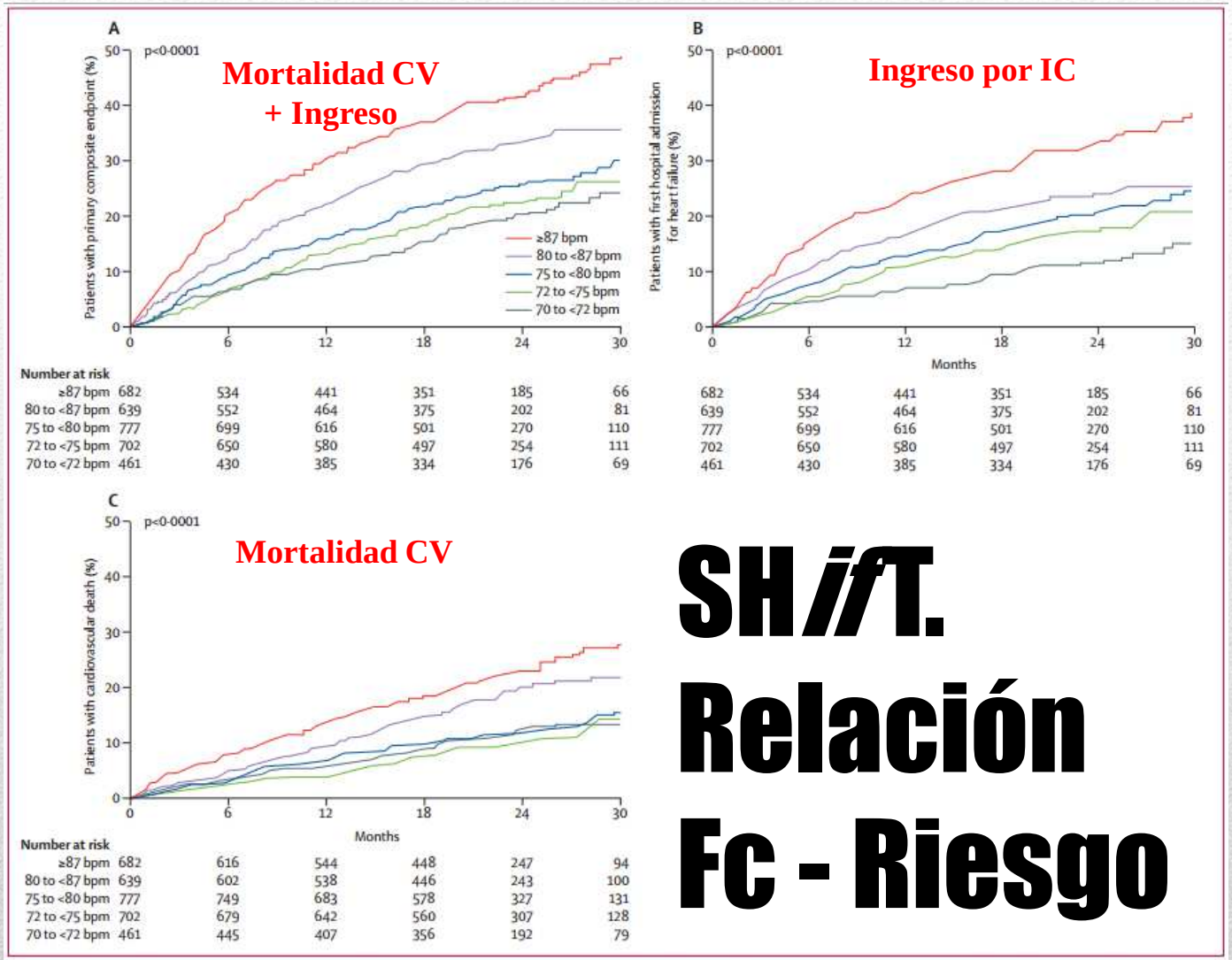


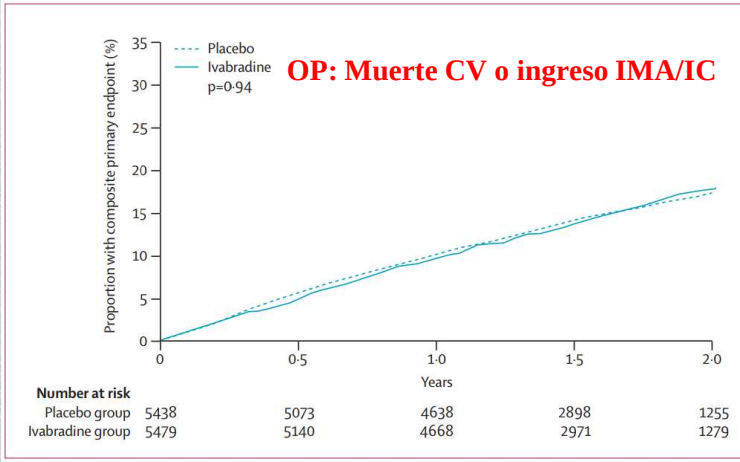
Figure 1: **Kaplan-Meier cumulative event curves for (A) the primary composite endpoint, (B) first hospital admissions for worsening heart failure, and (C) cardiovascular deaths in the placebo group,* according to groups defined by quintiles of heart rate at baseline**

Primary composite endpoint includes cardiovascular deaths and hospital admissions for worsening heart failure. The log-rank p value is shown for the difference between the Kaplan-Meier curves.
*n=3264.

	Total study population (N=10 917)				Prespecified subgroup with heart rate of 70 bpm or greater (N=5392)			
	Ivabradine group (N=5479)	Placebo group (N=5438)	HR (95% CI)	p value	Ivabradine group (N=2699)	Placebo group (N=2693)	HR (95% CI)	p value
Primary composite endpoint								
Cardiovascular death* or admission to hospital for myocardial infarction or new-onset or worsening heart failure†	844 (15·4%)	832 (15·3%)	1·00 (0·91–1·10)	0·94	463 (17·2)	498 (18·5)	0·91 (0·81–1·04)	0·17
Mortality endpoints								
All-cause death	572 (10·4%)	547 (10·1%)	1·04 (0·92–1·16)	0·55	331 (12·3)	324 (12·0)	1·02 (0·87–1·19)	0·82
Cardiovascular death*	469 (8·6%)	435 (8·0%)	1·07 (0·94–1·22)	0·32	269 (10·0)	263 (9·8)	1·02 (0·86–1·21)	0·82
Cardiac death‡	136 (2·5%)	151 (2·8%)	0·89 (0·71–1·12)	0·33	82 (3·0)	97 (3·6)	0·84 (0·62–1·12)	0·24
Heart failure endpoints								
Admission to hospital for heart failure†	426 (7·8%)	427 (7·9%)	0·99 (0·86–1·13)	0·85	268 (9·9)	271 (10·1)	0·97 (0·82–1·15)	0·76
Cardiovascular death* or admission to hospital for new-onset or worsening heart failure†	757 (13·8%)	723 (13·3%)	1·04 (0·94–1·15)	0·48	436 (16·2)	442 (16·4)	0·97 (0·85–1·11)	0·71
Coronary endpoints								
Admission to hospital for myocardial infarction*†	199 (3·6%)	226 (4·2%)	0·87 (0·72–1·06)	0·16	85 (3·1)	131 (4·9)	0·64 (0·49–0·84)	0·001
Admission to hospital for myocardial infarction† or unstable angina	303 (5·5%)	317 (5·8%)	0·95 (0·81–1·11)	0·50	143 (5·3)	182 (6·8)	0·78 (0·62–0·97)	0·023
Coronary revascularisation	155 (2·8%)	186 (3·4%)	0·83 (0·67–1·02)	0·078	76 (2·8)	108 (4·0)	0·70 (0·52–0·93)	0·016

Data are numbers of events (%), hazard ratios (HR) and 95% CIs, and p values. *Cardiac death, vascular procedure death, presumed arrhythmic death, stroke death, other vascular death, or sudden death of unknown cause. †Admission to hospital for myocardial infarction or heart failure includes fatal and non-fatal events. ‡Death from myocardial infarction, heart failure, or cardiac procedures.

***Table 4*: Primary and secondary endpoints**



OP: Muerte CV o ingreso IMA/IC

***Figure 3*: Kaplan–Meier time-to-event plot, by treatment group for composite primary endpoint in the total study population**

BEAUTIFUL. CI estable + DVI

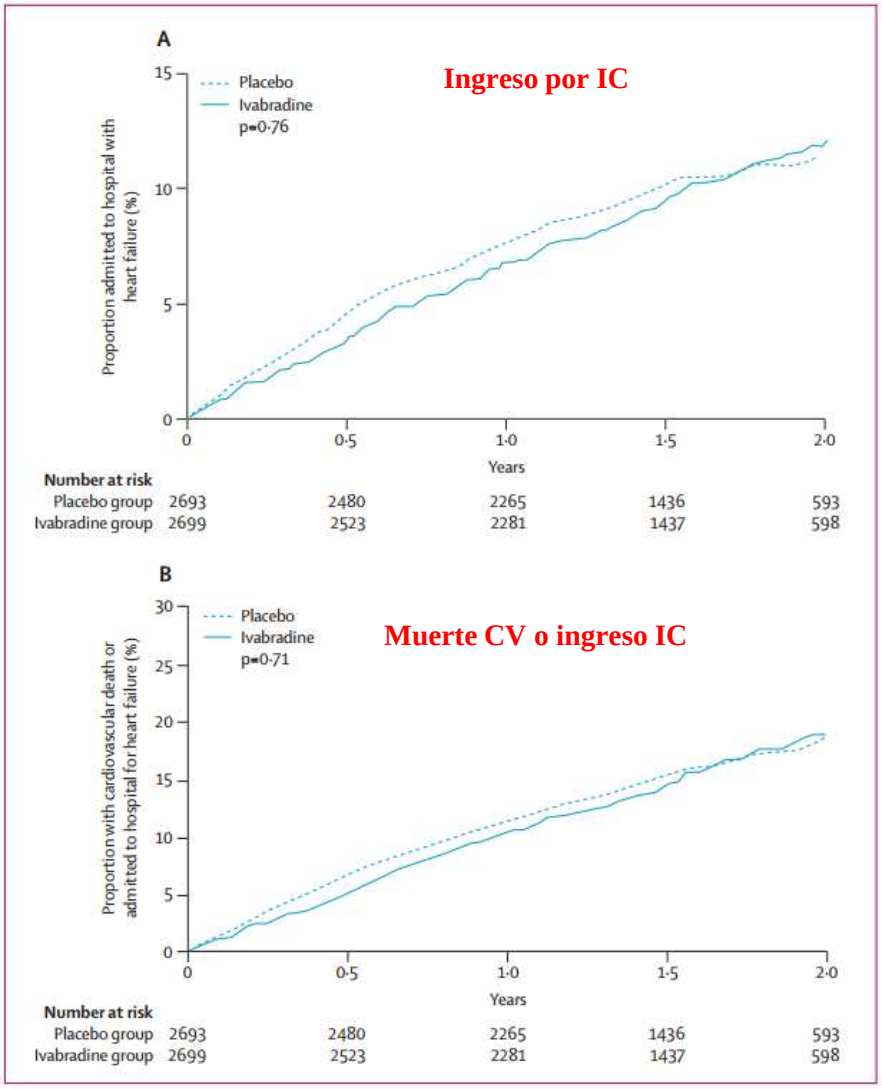


Figure 6: Kaplan–Meier time-to-event plots, by treatment group in the prespecified subgroup with heart rate of 70 bpm or greater, for the secondary endpoints of (A) admission to hospital for new-onset or worsening heart failure and (B) cardiovascular death or admission to hospital for new-onset or worsening heart failure

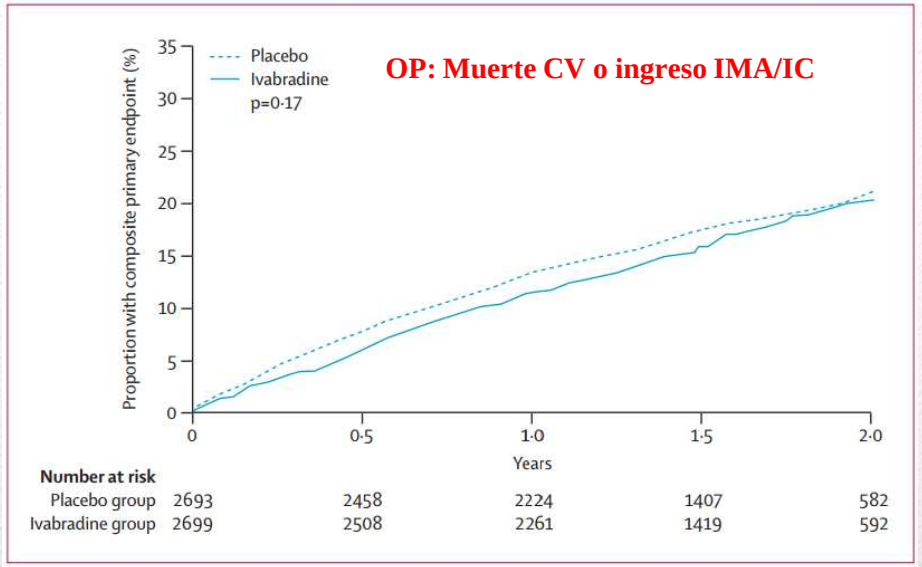


Figure 5: Kaplan–Meier time-to-event plot, by treatment group in the prespecified subgroup with heart rate of 70 bpm or greater for composite primary endpoint

BEAUT*if*UL. CI estable + DVI, Fc≥70

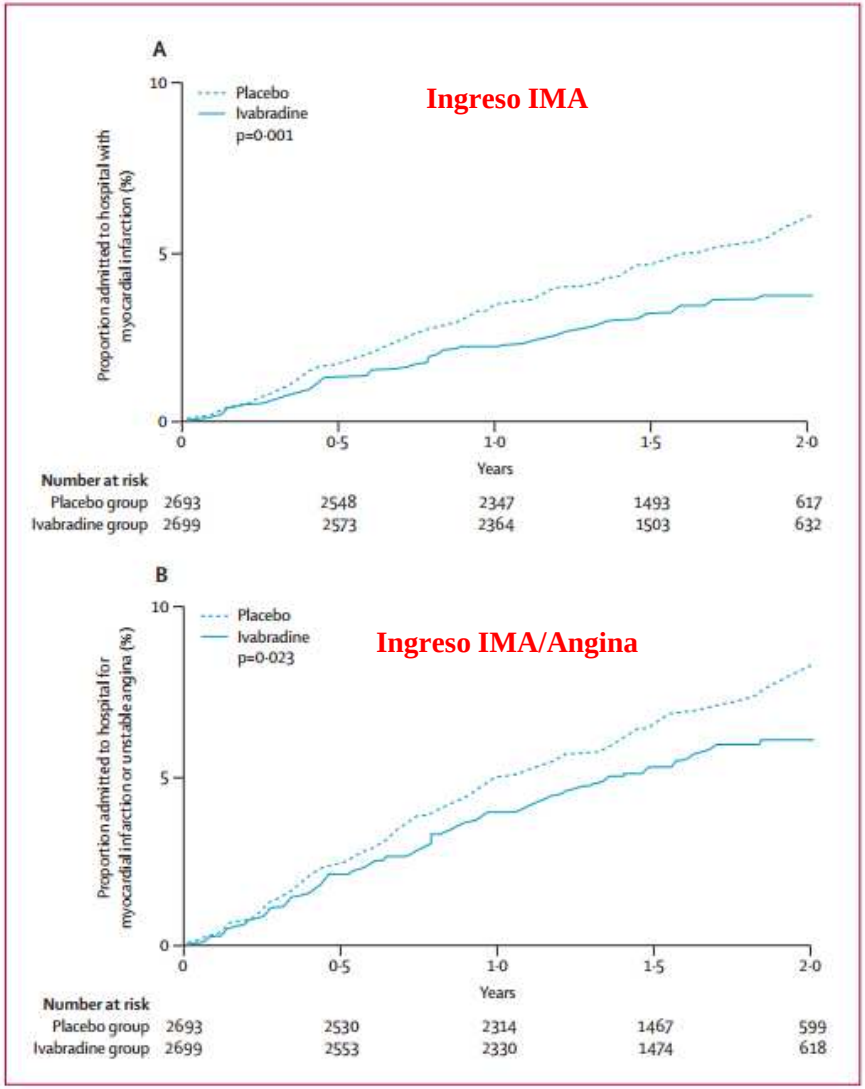


Figure 7: Kaplan–Meier time-to-event plots, by treatment group in the prespecified subgroup with heart rate of 70 bpm or greater for the secondary endpoints of (A) admission to hospital for acute myocardial infarction endpoint and (B) admission to hospital for acute myocardial infarction or unstable angina

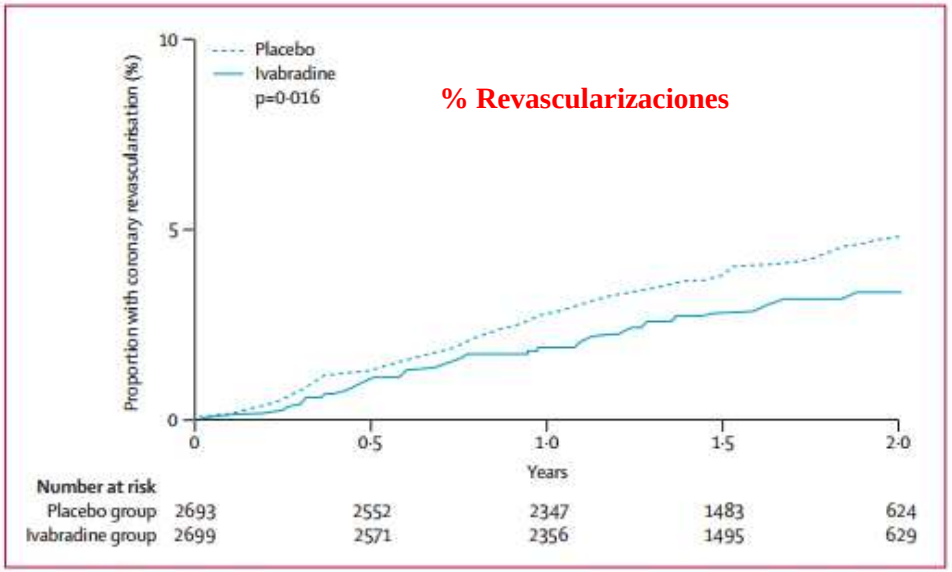


Figure 8: Kaplan–Meier time-to-event plot, by treatment group in the prespecified subgroup with heart rate of 70 bpm or greater for secondary endpoint of coronary revascularisation

BEAUT*if*UL. CI estable + DVI, Fc≥70

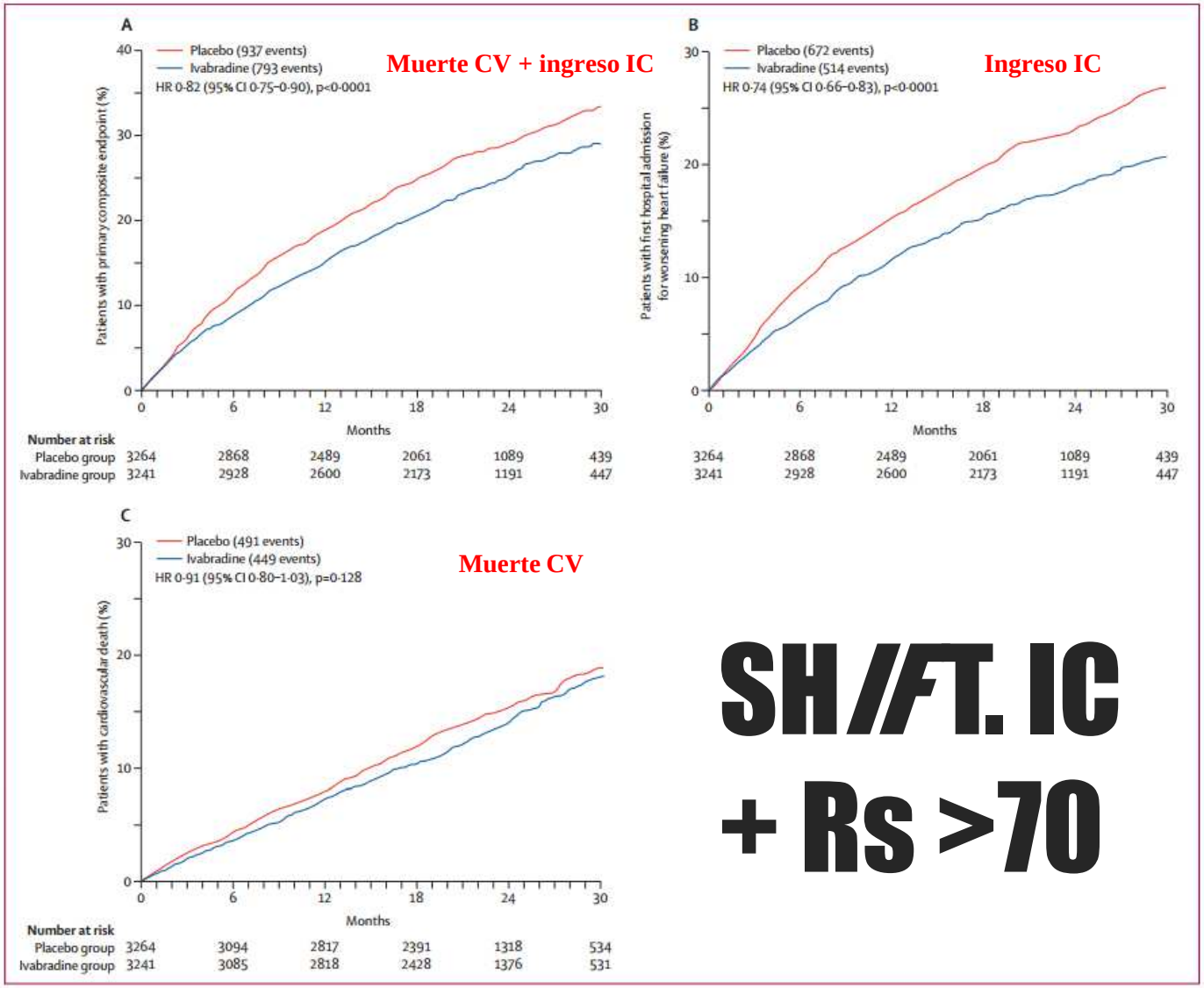


Figure 3: Kaplan-Meier cumulative event curves for (A) the primary composite endpoint of cardiovascular death or hospital admission for worsening heart failure, (B) hospital admission for worsening heart failure, and (C) cardiovascular death

SH//FT. IC + Rs >70

	Ivabradine group (n=3241)	Placebo group (n=3264)	HR (95% CI)	p value
Primary endpoint				
Cardiovascular death or hospital admission for worsening heart failure	793 (24%)	937 (29%)	0·82 (0·75–0·90)	<0·0001
Mortality endpoints				
All-cause mortality	503 (16%)	552 (17%)	0·90 (0·80–1·02)	0·092
Cardiovascular mortality	449 (14%)	491 (15%)	0·91 (0·80–1·03)	0·128
Death from heart failure	113 (3%)	151 (5%)	0·74 (0·58–0·94)	0·014
Other endpoints				
All-cause hospital admission	1231 (38%)	1356 (42%)	0·89 (0·82–0·96)	0·003
Hospital admission for worsening heart failure	514 (16%)	672 (21%)	0·74 (0·66–0·83)	<0·0001
Any cardiovascular hospital admission	977 (30%)	1122 (34%)	0·85 (0·78–0·92)	0·0002
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction	825 (25%)	979 (30%)	0·82 (0·74–0·89)	<0·0001

Data are number of first events (%), hazard ratio (HR; 95% CI), and p values.

Table 3: **Effects on primary and major secondary endpoints**

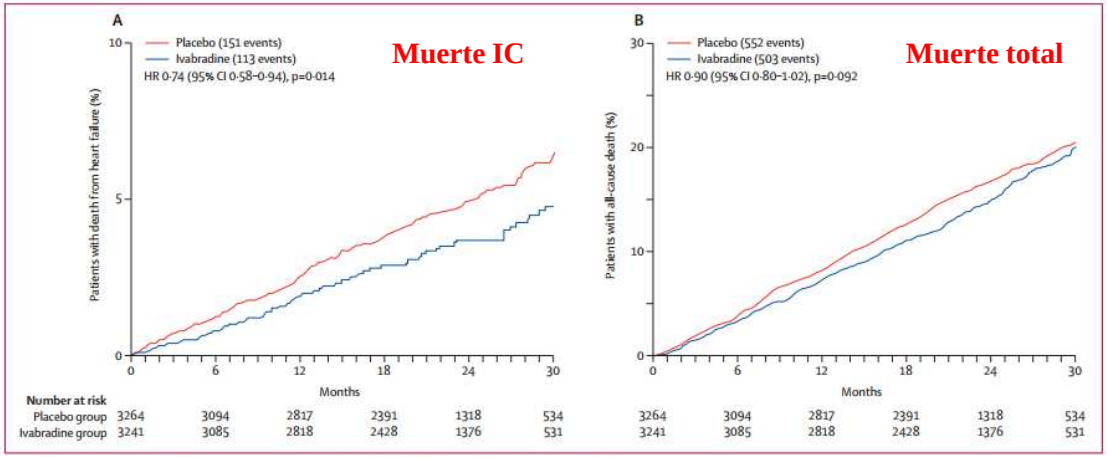
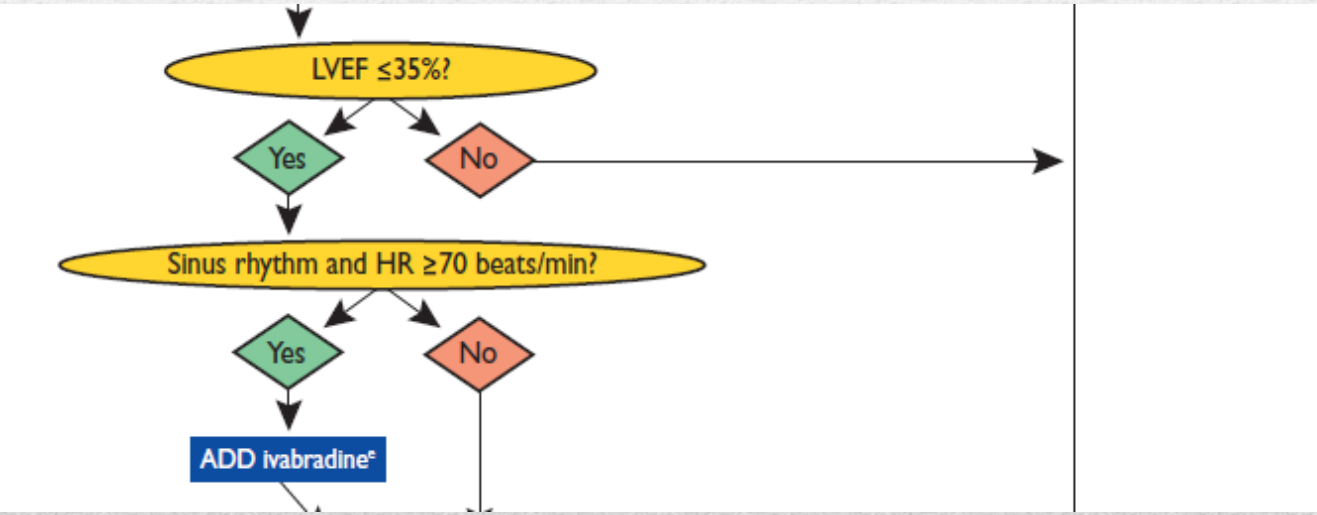


Figure 4: **Kaplan-Meier cumulative event curves for (A) death from heart failure and (B) all-cause death**

SH/FT. IC + Rs ≥ 70

Ivabradina		
Se debe considerar para reducir el riesgo de hospitalización por IC en pacientes en ritmo sinusal con FE ≤35%, frecuencia cardiaca ≥70 lpm de forma mantenida y síntomas persistentes (clases II-IV de la NYHA) a pesar del tratamiento con una dosis basada en la evidencia de un beta-bloqueante (o la dosis máxima tolerada por debajo de dicha dosis), un inhibidor de la ECA (o un ARA) y un ARM (o un ARA).	**IIa**	**B**
Se puede considerar para reducir el riesgo de hospitalización en pacientes en ritmo sinusal con FE ≤35% y frecuencia cardiaca ≥70 lpm que no toleran un betabloqueante. Los pacientes también deben recibir un inhibidor de la ECA (o un ARA) y un ARM (o un ARA).	**IIb**	**C**



Indicaciones Ivabradina

ESC - Heart Failure Guidelines. Eur Heart J 2012

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

Ivabradina en CI

ESC - Heart Failure Guidelines. Eur Heart J 2012

Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

Swedberg K et al. Lancet 2010

Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial

Böhm M et al. Lancet 2010

Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study

Ekman I et al. Eur Heart J 2011

Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy

Tardif JC et al. Eur Heart J 2011

Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: the SHIFT Study

Borer JS et al. Eur Heart J 2012

Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study

Böhm et al. Clin Res Cardio 2012

Nuevas evidencias. IVABRADINA

Relevancia	Limitaciones
1-Reduce la morbi-mortalidad (SHIFT) 2-Reduce la necesidad de revascularización (BEAUTIFUL) 3-Reduce los ingresos por IMA (BEAUTIFUL)	-El BEAUTIFUL y el SHIFT se comentan como complementarios pero son ensayos muy distintos no comparables -La reducción del objetivo primario es sólo del 18% en términos relativos y del 5% en términos absolutos (SHIFT) -La reducción es sólo de los ingresos por IC (SHIFT)
4-Reduce los volúmenes ventriculares y aumenta la FEVI (SHIFT)	-La reducción de los volúmenes ventriculares fue sólo del 7 ml/m2 y el incremento de la FEVI de 2,4 puntos. En más del 50% del grupo ivabradina no hubo ningún cambio (SHIFT)
5-Mejora la CVRS (SHIFT)	-El incremento de la puntuación de la calidad de vida fue 5 puntos KCCQ sobre un total de 100 (SHIFT)
-Se demuestra la importancia de la Fc en la fisiopatología de la IC y el concepto de que su reducción (por ella misma) contribuye significativamente a mejorar el pronóstico. -Excelente tolerabilidad (bradicardias que obliguen a suspender el fármaco el 1%)	

Relevancia / Limitaciones de la IVABRADINA

Características de los pacientes
Fracción de eyección deprimida (idealmente <35%)
Clase funcional II ó III
Ritmo sinusal
Frecuencia cardíaca basal en reposo ≥ 70 lpm
Tratamiento óptimo previo (IECA/ARA II, diuréticos, beta-bloqueantes y antialdosterónicos)

Sólo a los que se benefician

Conclusiones

- La frecuencia cardíaca elevada es un marcador de riesgo de mortalidad en sujetos «presuntamente sanos» y en pacientes con muchas tipos de afectación cardíaca y primariamente no cardíaca
- Podemos reducir la Fc con diversos agentes bradicardizantes específicos (Ivabradina) o con otros efectos añadidos (beta-bloqueantes, digoxina, amiodarona)
- La reducción de esa frecuencia cardiaca redundará en una menor muerte súbita, hospitalizaciones CV y mortalidad global
- ¿Más ensayos?

¡ Gracias !

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Hospital Universitario y Politécnico La Fe

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Heart-Rate Profile during Exercise as a Predictor of Sudden Death

Xavier Jouven, M.D., Ph.D., Jean-Philippe Empana, M.D., Peter J. Schwartz, M.D., Michel Desnos, M.D., Dominique Courbon, M.S.C., and Pierre Ducimetière, Ph.D.

BACKGROUND

Changes in heart rate during exercise and recovery from exercise are mediated by the balance between sympathetic and vagal activity. Since alterations in the neural control of cardiac function contribute to the risk of sudden death, we tested the hypothesis that among apparently healthy persons, sudden death is more likely to occur in the presence of abnormal heart-rate profiles during exercise and recovery.

METHODS

A total of 5713 asymptomatic working men (between the ages of 42 and 53 years), none of whom had clinically detectable cardiovascular disease, underwent standardized graded exercise testing between 1967 and 1972. We examined data on the subjects' resting heart rates, the increase in rate from the resting level to the peak exercise level, and the decrease in rate from the peak exercise level to the level one minute after the termination of exercise.

RESULTS

During a 23-year follow-up period, 81 subjects died suddenly. The risk of sudden death from myocardial infarction was increased in subjects with a resting heart rate that was more than 75 beats per minute (relative risk, 3.92; 95 percent confidence interval, 1.91 to 8.00); in subjects with an increase in heart rate during exercise that was less than 89 beats per minute (relative risk, 6.18; 95 percent confidence interval, 2.37 to 16.11); and in subjects with a decrease in heart rate of less than 25 beats per minute after the termination of exercise (relative risk, 2.20; 95 percent confidence interval, 1.02 to 4.74). After adjustment for potential confounding variables, these three factors remained strongly associated with an increased risk of sudden death, with a moderate but significantly increased risk of death from any cause but not of nonsudden death from myocardial infarction.

CONCLUSIONS

The heart-rate profile during exercise and recovery is a predictor of sudden death.

Table 1. Baseline Characteristics and Their Association with Selective Outcomes during Follow-up.*

Characteristic	Controls (N=5503)†	Sudden Death from Myocardial Infarction (N=81)		Nonsudden Death from Myocardial Infarction (N=129)	
		Baseline Level	Univariate Relative Risk (95% CI)‡	Baseline Level	Univariate Relative Risk (95% CI)‡
Age — yr	47.6±1.9	48±1.8	1.23 (0.98–1.54)	47.8±1.8	1.03 (0.86–1.24)
Body-mass index	25.7±3.1	26.7±3.3	1.34 (1.09–1.66)	26.1±3.1	1.15 (0.97–1.37)
Tobacco use — g/day§	11.4 (10.5)	15.5 (10.0)	1.41 (1.18–1.70)	13.7±10.9	1.29 (1.10–1.51)
Resting heart rate — beats/min	68.1±9.5	71.4±9.8	1.39 (1.15–1.68)	69.6±10.7	1.23 (1.04–1.44)
Systolic blood pressure — mm Hg	137.8±17.4	142.7±22.0	1.31 (1.08–1.60)	143.1±17.9	1.30 (1.11–1.53)
Total cholesterol — mg/dl	221.0±41.6	246.8±43	1.67 (1.40–2.00)	239.6±52.9	1.49 (1.27–1.75)
Triglycerides — mg/dl¶	132.4±106.5	152.2±99.2	1.26 (1.04–1.53)	155.8±132.4	1.31 (1.13–1.54)
Duration of exercise test — min	7.3±2.5	6.0±2.3	0.59 (0.47–0.73)	6.7±2.6	0.76 (0.63–0.90)
Diabetes — no./total no. (%)	268/5255 (5.1)	5/78 (6.4)	2.39 (0.87–6.53)	6/118 (5.1)	1.08 (0.34–3.38)
Current physical activity — no./total no. (%)‖	823/5446 (15.1)	11/80 (13.8)	0.87 (0.46–1.65)	19/129 (14.7)	0.96 (0.59–1.56)
Parental history — no./total no. (%)					
Myocardial infarction	366/5442 (6.7)	5/79 (6.3)	0.92 (0.37–2.28)	18/128 (14.1)	2.32 (1.41–3.81)
Sudden death	570/5443 (10.5)	15/79 (19.0)	2.02 (1.15–3.53)	14/128 (10.9)	1.10 (0.63–1.92)

* Plus–minus values are means ±SD. Body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.
† Subjects in this group either were alive or died from causes other than myocardial infarction during follow-up. This group is also the reference group for the estimation of relative risk.
‡ For continuous variables, the relative risk is for an increase of 1 SD.
§ Tobacco use is the average use (in grams per day) in the five years preceding the study.
¶ The relative risk for triglycerides is for an increase of 1 SD in the triglyceride level (0.51) after log transformation.
‖ Physical activity applies to subjects who performed more than one hour of regular activity per week. The subjects retained in the sample are those who performed the exercise test.

Table 2. Relative Risk of Sudden Death and Nonsudden Death from Myocardial Infarction and Death from Any Cause According to Heart-Rate Variables.*

Variable	Death from Any Cause (N=1516)		Sudden Death from Myocardial Infarction (N=81)		Nonsudden Death from Myocardial Infarction (N=129)	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Resting heart rate >75 beats/minute†						
Univariate analysis	1.31 (1.20–1.74)	<0.001	3.92 (1.91–8.00)	<0.001	1.90 (1.17–3.07)	0.009
Multivariate analysis	1.89 (1.60–2.24)	<0.001	3.46 (1.60–7.44)	0.001	1.55 (0.90–2.66)	0.11
Increase during exercise <89 beats/minute‡						
Univariate analysis	2.13 (1.79–2.52)	<0.001	6.18 (2.37–16.11)	<0.001	1.58 (0.87–2.85)	0.12
Multivariate analysis	1.51 (1.26–1.81)	<0.001	3.98 (1.49–10.61)	0.006	1.17 (0.62–2.18)	0.68
Decrease at 1 min after cessation of exercise <25 beats/minute§						
Univariate analysis	1.54 (1.30–1.84)	<0.001	2.20 (1.02–4.74)	0.04	1.36 (0.79–2.35)	0.34
Multivariate analysis	1.27 (1.06–1.53)	<0.001	2.06 (0.92–4.59)	0.08	0.93 (0.51–1.72)	0.85

The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis

Meta-analysis Global Group in Chronic Heart Failure (MAGGIC)

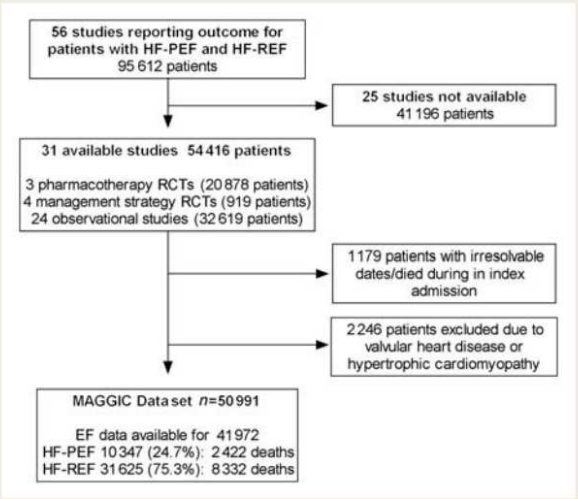

Figure 1 Flow chart of studies for meta-analysis.

Table 2 Cox's proportional adjusted hazards ratios for all-cause death and cardiovascular death

Variable	Death from any cause Hazard ratio (95% CI)	Cardiovascular death Hazard ratio (95% CI)
HF-PEF	0.68 (0.64, 0.71)	0.55 (0.49, 0.61)
Male gender	1.23 (1.18, 1.28)	1.23 (1.14, 1.33)
Age (years)	1.04 (1.04, 1.04)	1.03 (1.03, 1.04)
Ischaemic aetiology	1.07 (1.02, 1.12)	1.11 (1.03, 1.19)
Hypertension	0.93 (0.89, 0.97)	0.94 (0.88, 1.00)
Diabetes	1.41 (1.35, 1.47)	1.51 (1.41, 1.62)
Atrial fibrillation	1.10 (1.05, 1.16)	1.28 (1.16, 1.41)

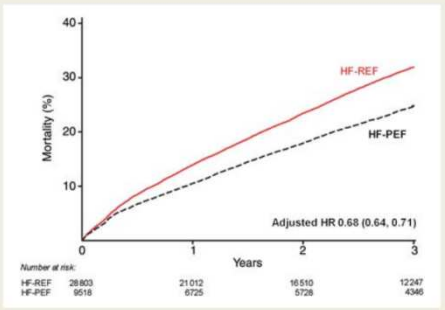

Figure 2 Mortality for patients with HF-PEF (heart failure with preserved left ventricular ejection fraction) and HF-REF (heart failure with low left ventricular ejection fraction), adjusted for age, gender, aetiology of heart failure, hypertension, diabetes, atrial fibrillation.

Table 1 Baseline characteristics of the groups

	Whole group	HF-PEF	HF-REF	Missing LVEF	P-value (HF-PEF vs. HF-REF)
n (31 studies)	50 991	10 347	31 625	9019	—
Age [years (SD)]	68 (12)	71 (12)	66 (12)	71 (13)	<0.001
Women (%)	35%	50%	28%	44%	<0.001
Medical history					
Hypertension	43%	51%	41%	40%	<0.001
Myocardial infarction	43%	27%	51%	31%	<0.001
Atrial fibrillation	21%	27%	18%	23%	<0.001
Diabetes	23%	23%	24%	21%	0.005
Ischaemic aetiology	54%	43%	59%	49%	<0.001
Medication					
ACE-inhibitor or ARB	67%	44%	75%	64%	<0.001
β-Blocker	34%	33%	39%	23%	<0.001
Diuretic	82%	78%	83%	83%	<0.001
Spironolactone	21%	16%	24%	17%	<0.001
Digoxin	43%	32%	47%	44%	<0.001
Clinical status					
NYHA class (I/II/III/IV) (%)	11/47/34/8	14/48/29/9	10/46/37/7	19/48/25/8	All <0.004
Heart rate (b.p.m.)	79 (18)	78 (21)	79 (18)	79 (17)	0.019
SBP (mmHg)	131 (23)	141 (25)	128 (22)	135 (24)	<0.001
DBP (mmHg)	77 (13)	79 (14)	76 (12)	80 (13)	<0.001
LVEF % (median, IQR)	36 (27, 48)	60 (55, 61)	31 (24, 39)	—	—

Values represent mean (standard deviation) unless stated. ARB, angiotensin receptor blocker; IQR, inter-quartile range; NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction.

Mortalidad por IC

European Heart Journal (2012) **33**, 1750–1757
doi:10.1093/eurheartj/ehr254

CLINICAL RESEARCH
Heart failure/cardiomyopathy

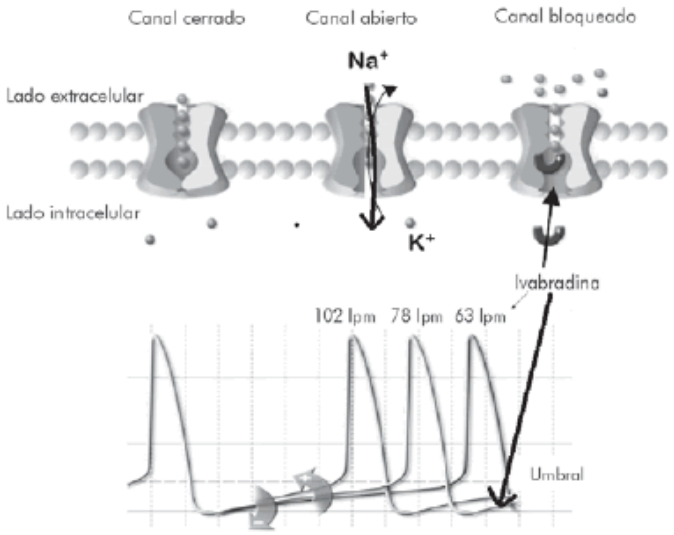

Figura 5. La ivabradina bloquea los canales f entrando en el poro del canal desde el lado intracelular y uniéndose a un sitio localizado en la zona de flujo iónico. De esta forma disminuye la pendiente de despolarización diastólica espontánea y así mismo la frecuencia cardiaca.

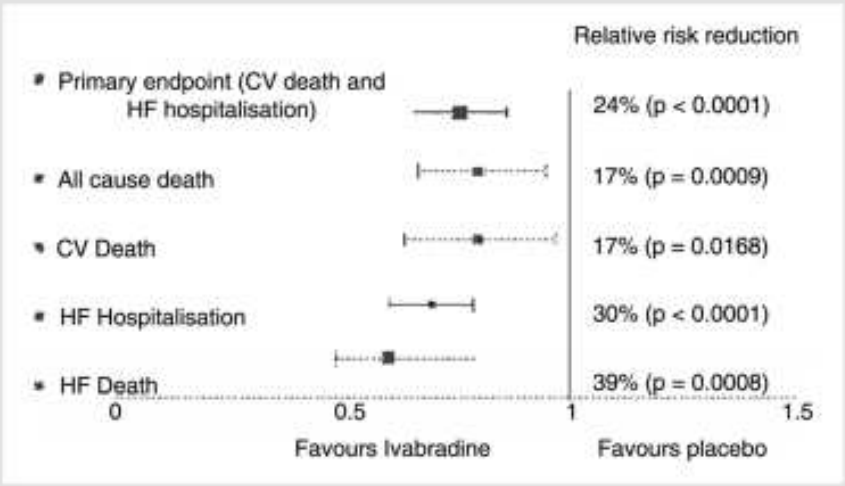

Figure 3 Subgroup analysis of the patients in the SHIFT trial with baseline heart rate ≥75 b.p.m. ($n = 4150$).[23] CV, cardiovascular; HF, heart failure.