And the Beat Goes On: Heart Rate and Its Modulation In Heart Failure

XXIV Giornate Cardiologiche Torinesi
Advances in Cardiac Arrhythmias and Great Innovations in Cardiology
Turin, 26 October 2012

Davide Castagno, MD
Division of Cardiology
Department of Medical Sciences
University of Turin

Presentation outline

- Epidemiology
- Underlying pathophysiology
- New data regarding specific subgroups (e.g. HF-PEF)
- Evidence regarding heart rate modulating treatments
- New approaches in the pipeline

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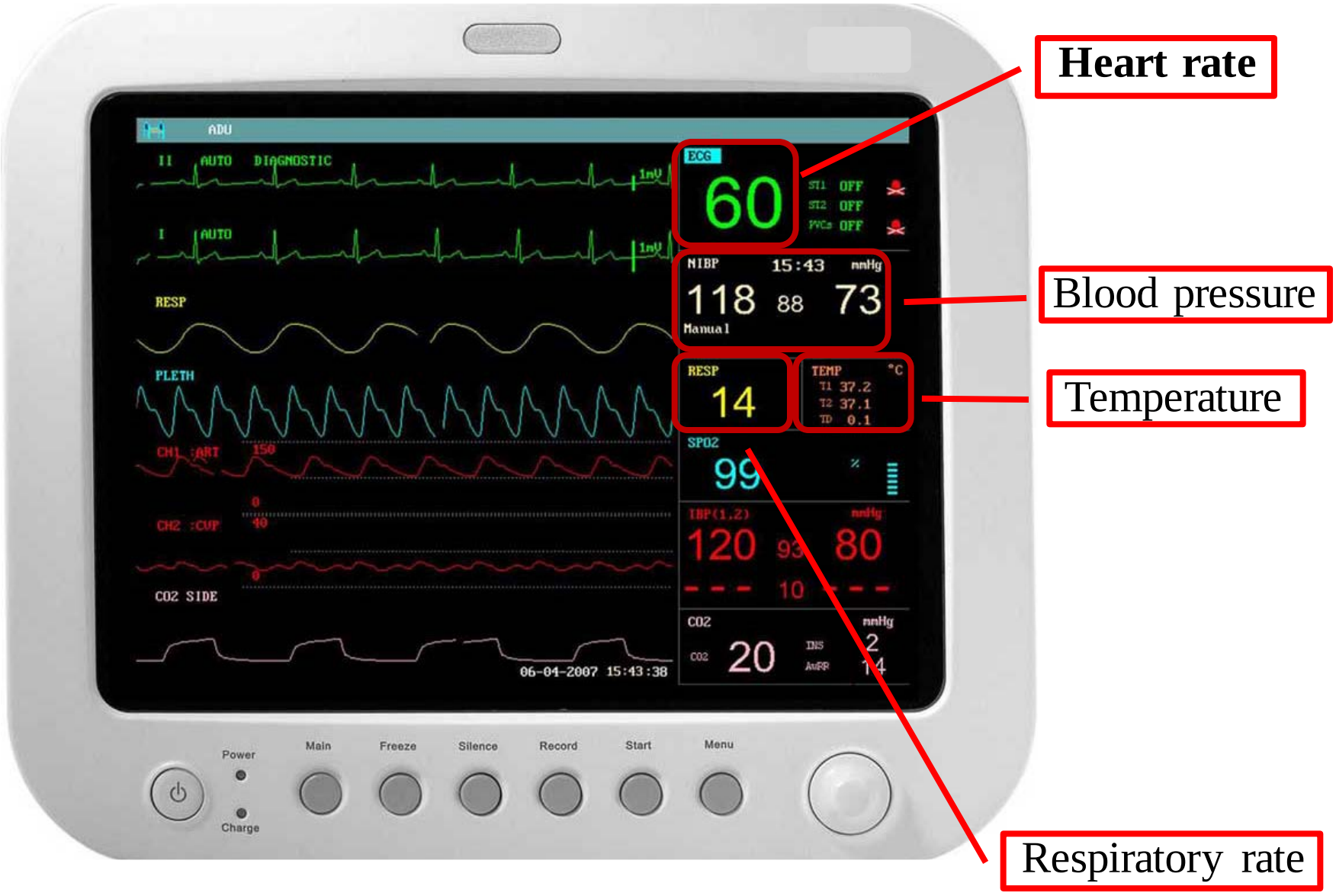
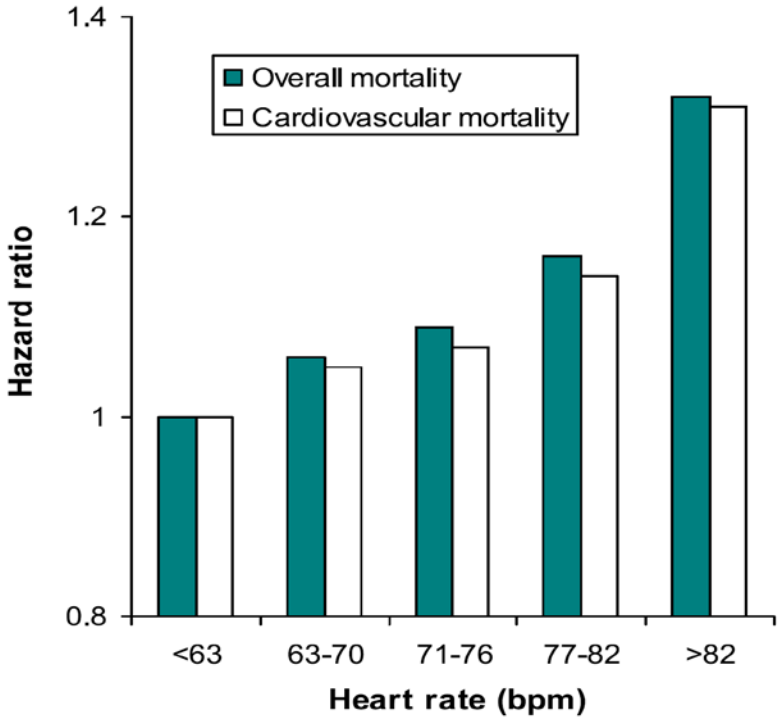

Heart rate
Blood pressure
Temperature
Respiratory rate
ADU
II AUTO DIAGNOSTIC
I AUTO
RESP
PLETH
CH1 :ART
CH2 :CVP
CO2 SIDE
06-04-2007 15:43:38
ECG
60
NIBP 15:43 mmHg
118 88 73
Manual
RESP
14
TEMP °C
T1 37.2
T2 37.1
TD 0.1
SPO2
99
%
IBP(1,2) mmHg
120 93 80
10
CO2 mmHg
20
Power
Charge
Main
Freeze
Silence
Record
Start
Menu

Epidemiology - Heart rate and CV diseases

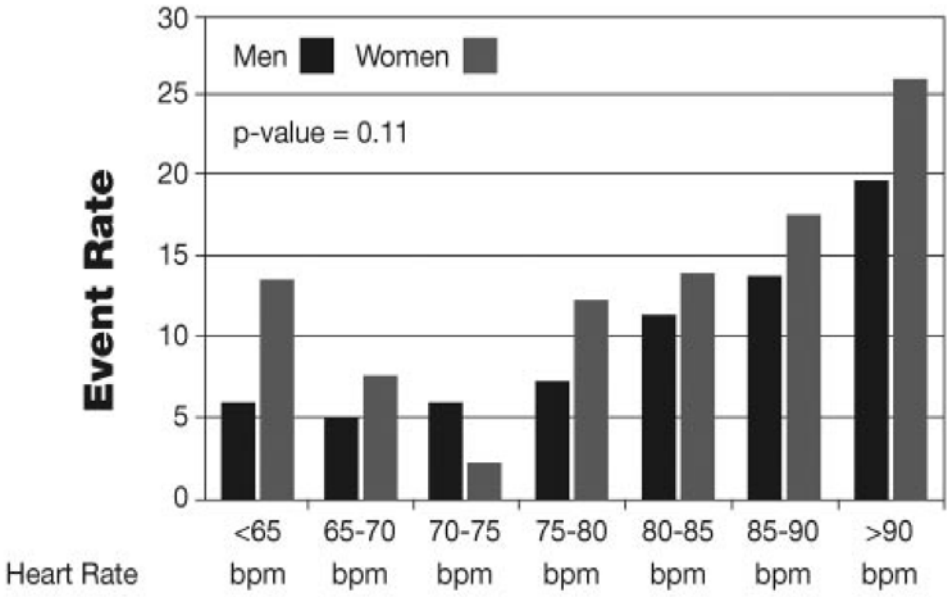
Elevated resting heart rate

CV mortality / morbidity

24913 patients with suspected or proven CAD



1539 patients undergoing ICD implantation



Diaz A et al. Eur Heart J 2005; 26:967-974

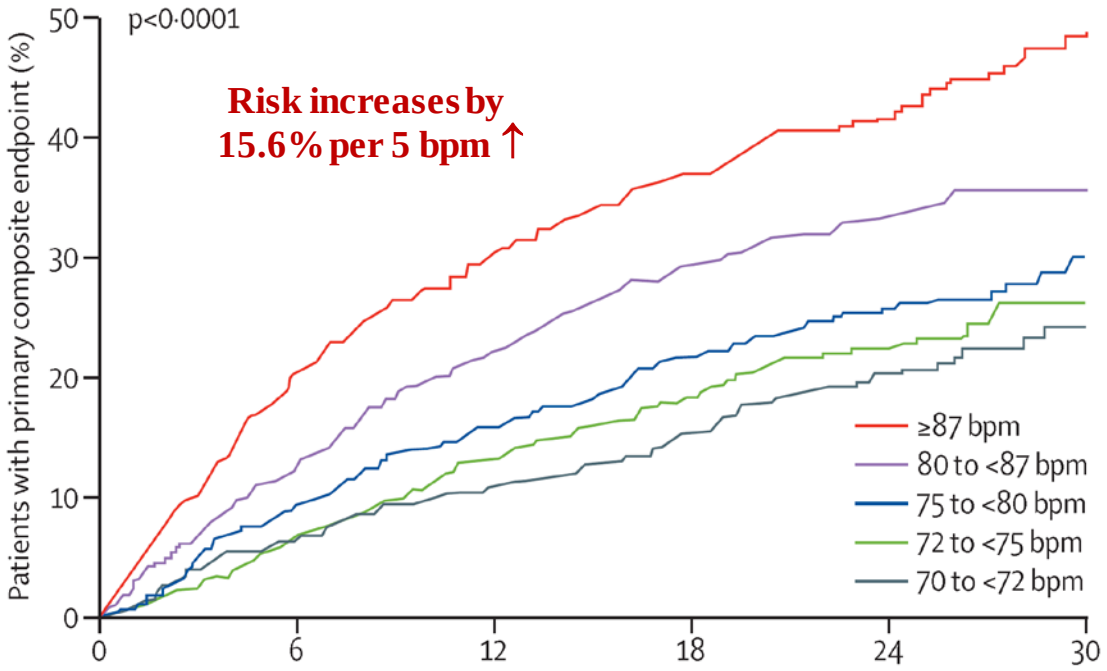
Ahmadi-Kashani M et al. Circulation 2009; 120:2040-2045

Epidemiology - Heart rate and systolic HF

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

Michael Böhm, Karl Swedberg, Michel Komajda, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators

Patients with CV death and hosp. for worsening HF (%)



Heart rate as *risk marker*

↓

Heart rate as *risk factor*

↓

Heart rate reduction

↓

Improvements in outcomes

Böhm M, et al. Lancet. 2010;376:886-894.

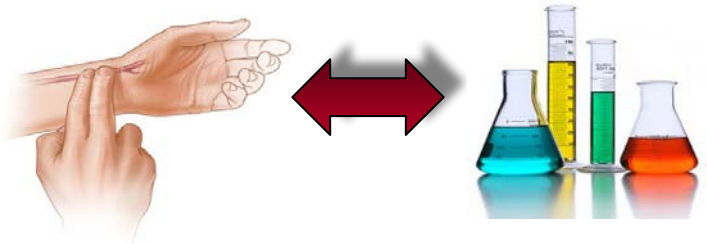
Low tech *vs.* High tech biomarkers

Minimal and Null Predictive Effects for the Most Popular Blood Biomarkers of Cardiovascular Disease

John P.A. Ioannidis, Ioanna Tzoulaki

Heart rate

- ✓ Inexpansive
- ✓ Easily assessable
- ✓ Modifiable
- ✓ Heart rate reducton improves clinical outcome



Homocysteine

- ✓ Expansive ($$$)
- ✓ Lab required
- ✓ Modifiable
- ✓ Homcystein levels rectification does not improve prognosis

Biomarkers should be used wisely together with clinical experience: "A fool with a tool is still a fool"

Ioannidis P, et al. Circ Res 20112; 110:658-662

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Heart rate in CV pathophysiology

SYMPATHETIC

PARASYMPATHETIC

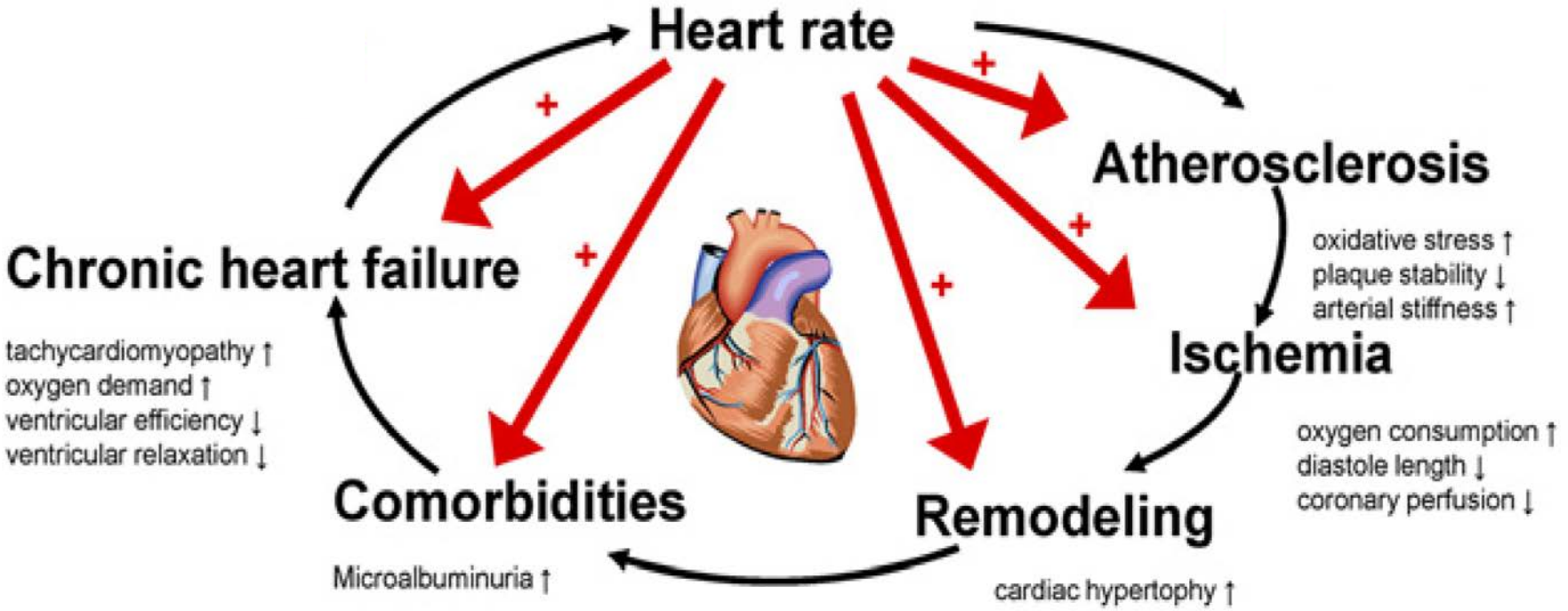
Cardiac Output (Q) **= SV × HR**

Myocardial O_2 demand

Coronary blood flow

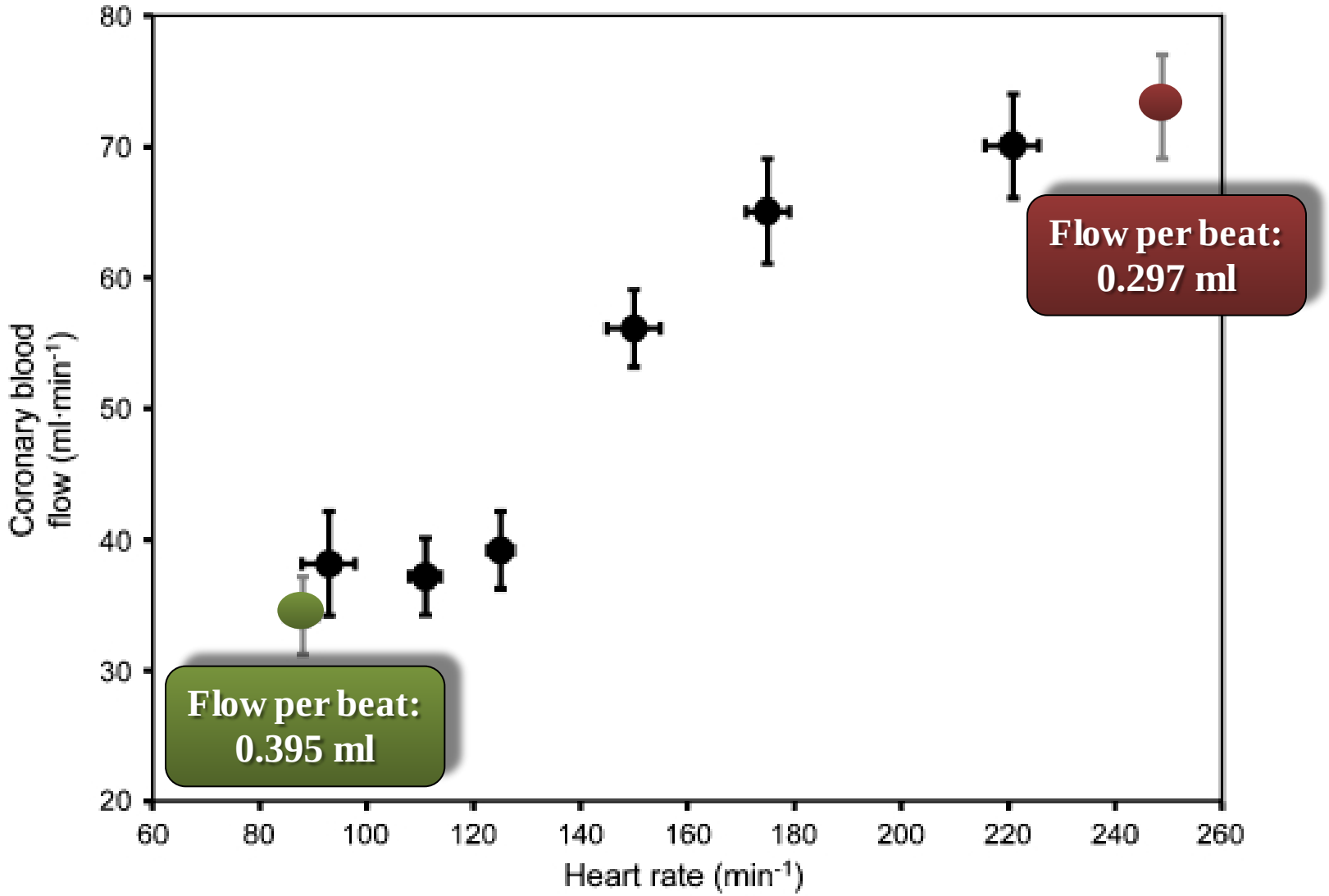
Myocardial performance

Heart rate in CV pathophysiology



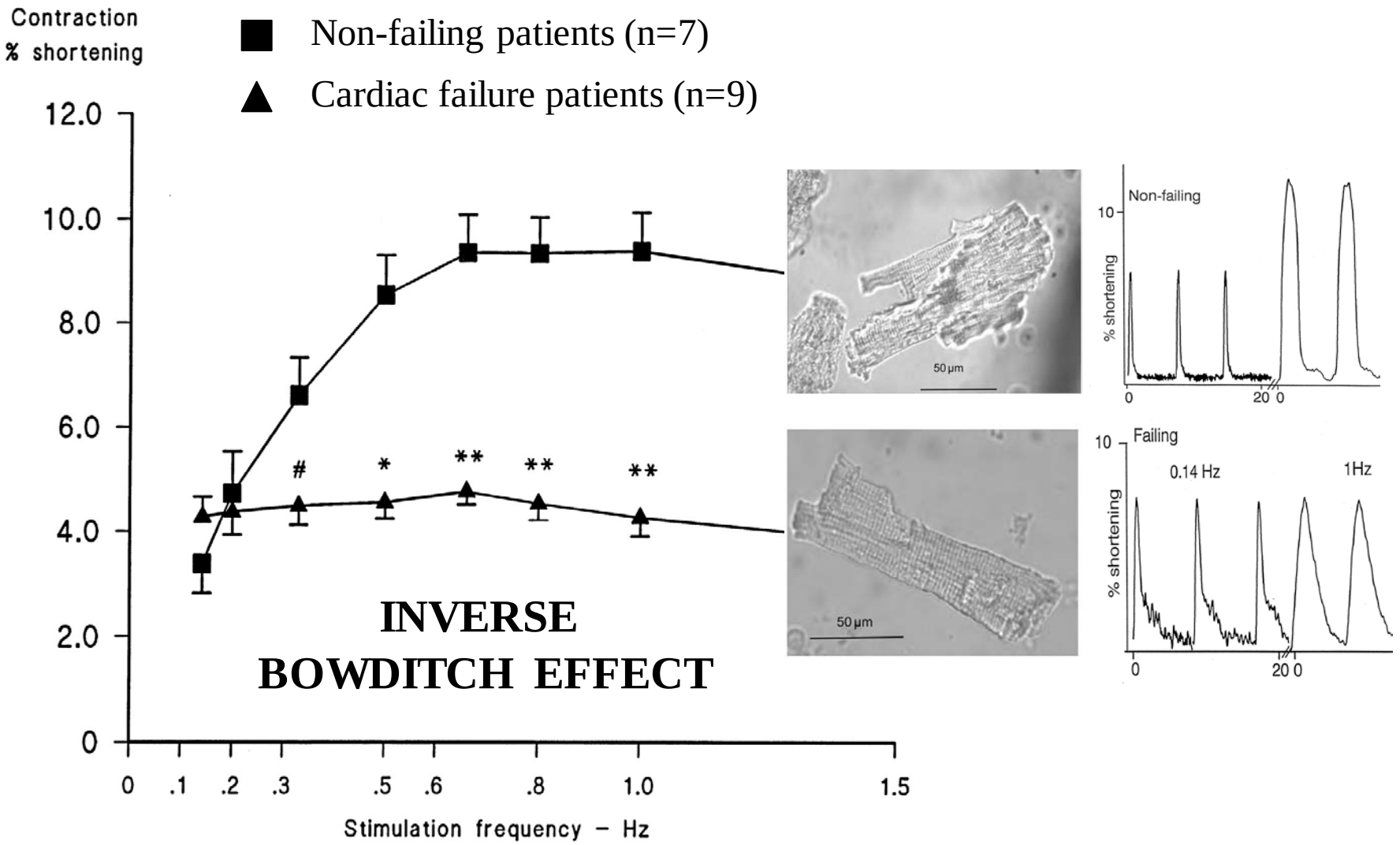
Adapted from Bohm M. et al. Heart 2012; 110:658-662

Heart rate and myocardial O_2 consumption



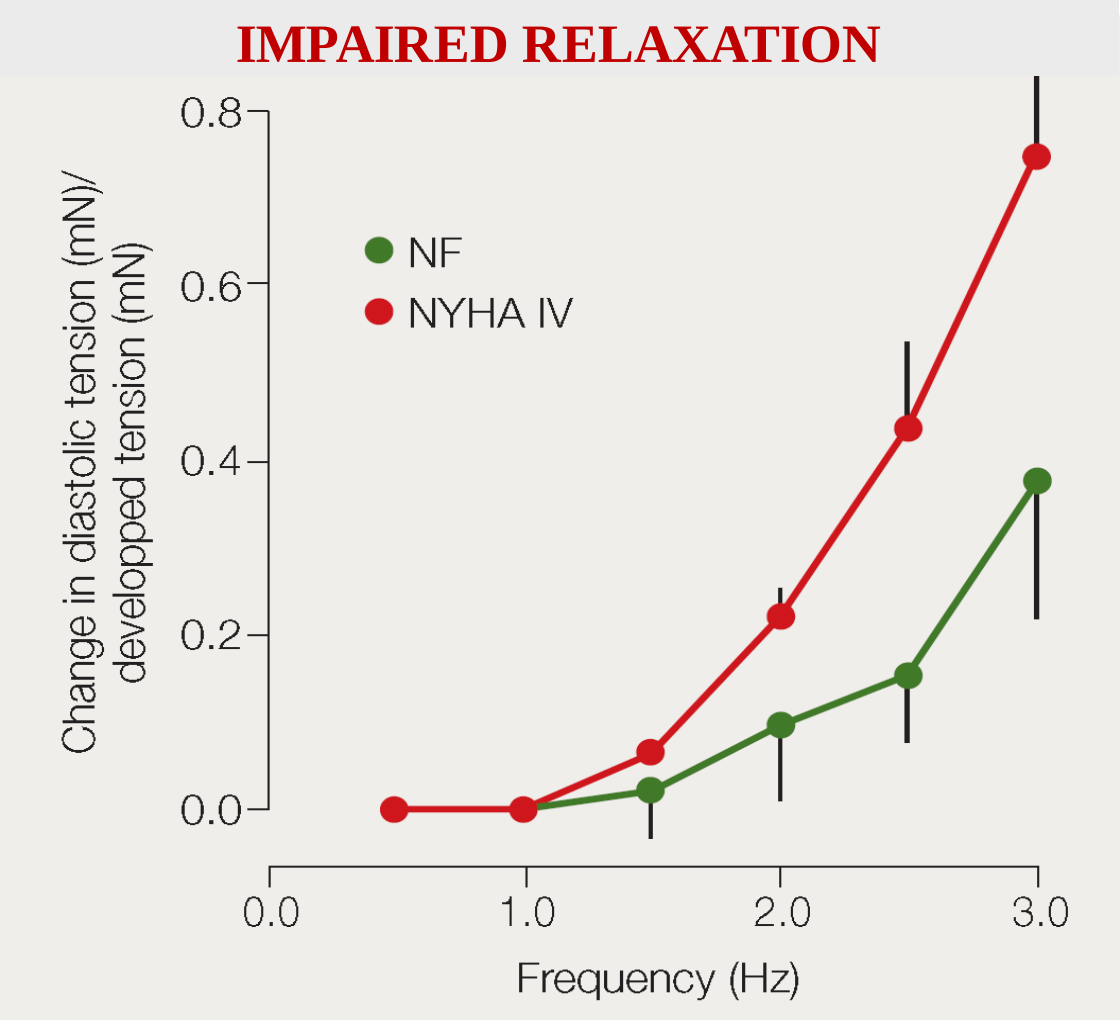
Adapted from Heusch G. et al. Br J Pharmacol. 2008 April; 153: 1589–1601

Heart rate in HF pathophysiology



Adapted from Davies CH et al. Circulation 1995; 92:2540-2549
Jacques AM et al. Cardiovasc Res 2008; 79:481-491

Heart rate in HF pathophysiology



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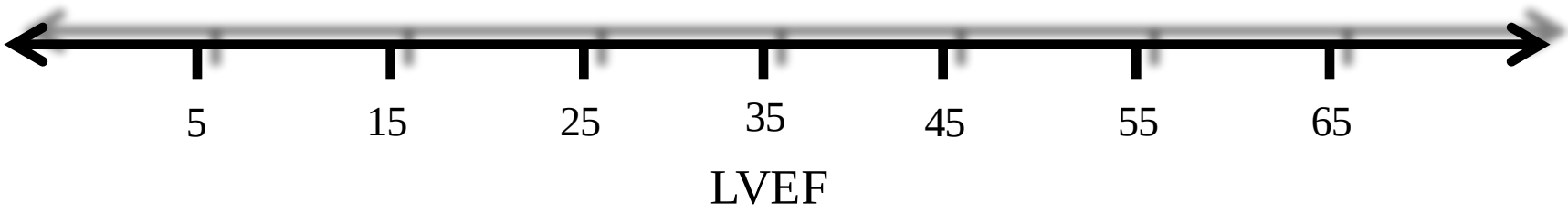
HF-REF vs. HF-PEF

HF With Reduced Ejection Fraction (HF-REF)

HF With Preserved Ejection Fraction (HF-PEF)



Adapted from Circulation 2011; 123: 1996-2005

Heart rate across the LVEF continuum

Heart Failure

Association of Heart Rate and Outcomes in a Broad Spectrum of Patients With Chronic Heart Failure

Results From the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) Program

Davide Castagno, MD,*† Hicham Skali, MD, MSc,* Madoka Takeuchi, MS,* Karl Swedberg, MD, PhD,‡ Salim Yusuf, MBBS, DPhil,§ Christopher B. Granger, MD,‖ Eric L. Michelson, MD,¶ Marc A. Pfeffer, MD, PhD,* John J. V. McMurray, MD,*# Scott D. Solomon, MD,* for the CHARM Investigators

Boston, Massachusetts; Turin, Italy; Gothenburg, Sweden; Hamilton, Ontario, Canada; Durham, North Carolina; Wilmington, Delaware; and Glasgow, United Kingdom

JACC 2012; 59: 1785-1795

CHARM

CHARM Program

3 components trials investigating the effect of candesartan on clinical outcomes

CHARM Alternative	CHARM Added	CHARM Preserved
n = 2028	n = 2548	n = 3025
LVEF ≤40% ACE inhibitor intolerant	LVEF ≤40% ACE inhibitor treated	LVEF >40% ACE inhibitor treated /not treated

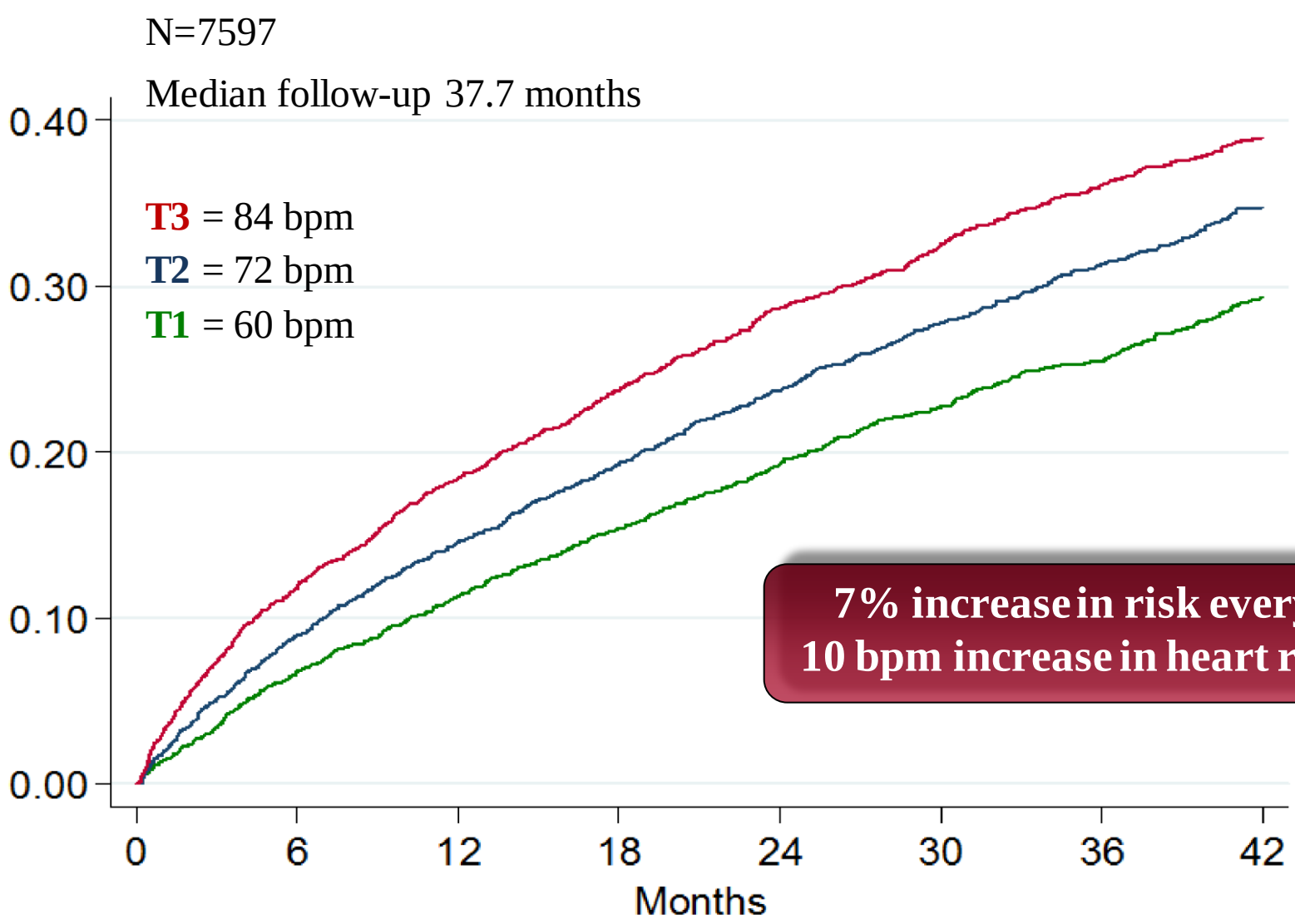
Primary outcome for each study: CV death or HF hospitalization

Primary endpoint for overall program: All-cause death

Pfeffer MA et al. Lancet 2003; 362:759-66

CHARM

Probability of CV-death or HF hospitalization

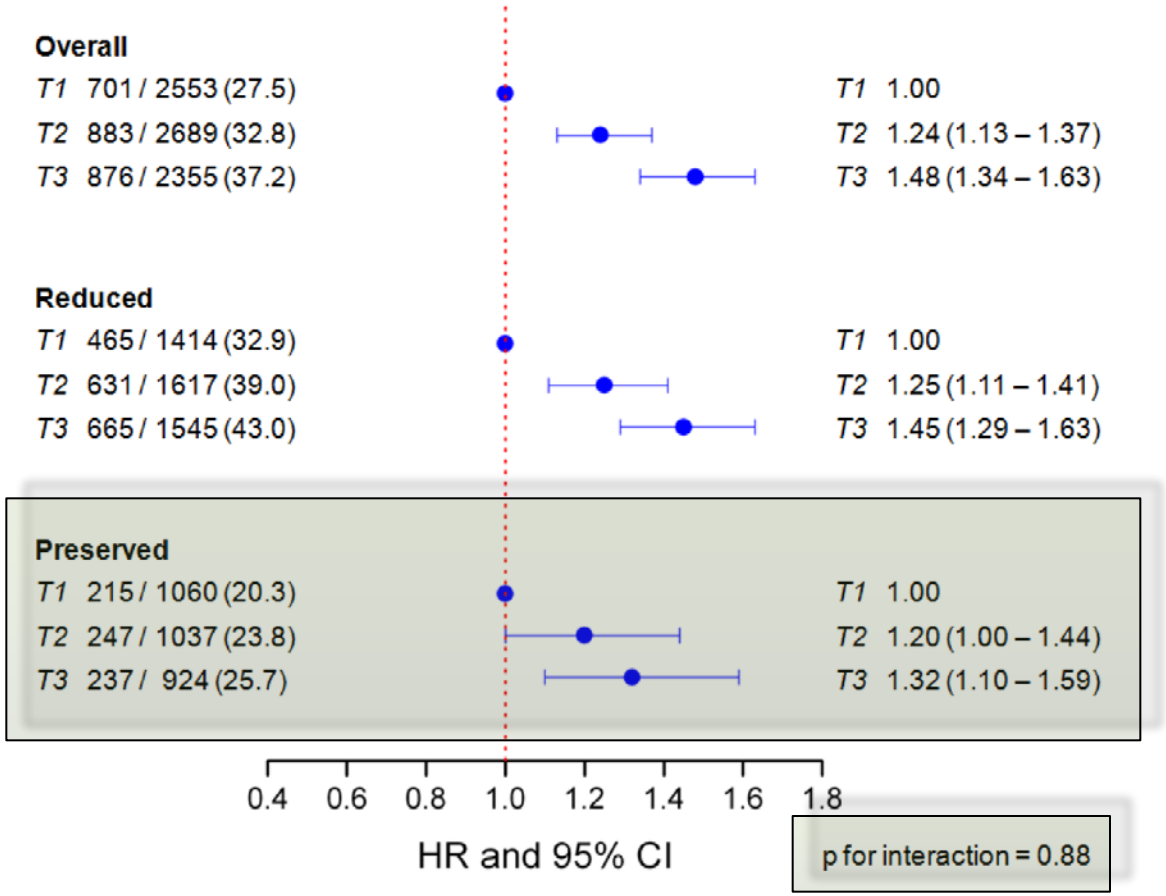


7% increase in risk every 10 bpm increase in heart rate

Castagno D et al. JACC 2012; 59: 1785-1795

CHARM

Reduced (≤40%) vs. Preserved (>40%) EF



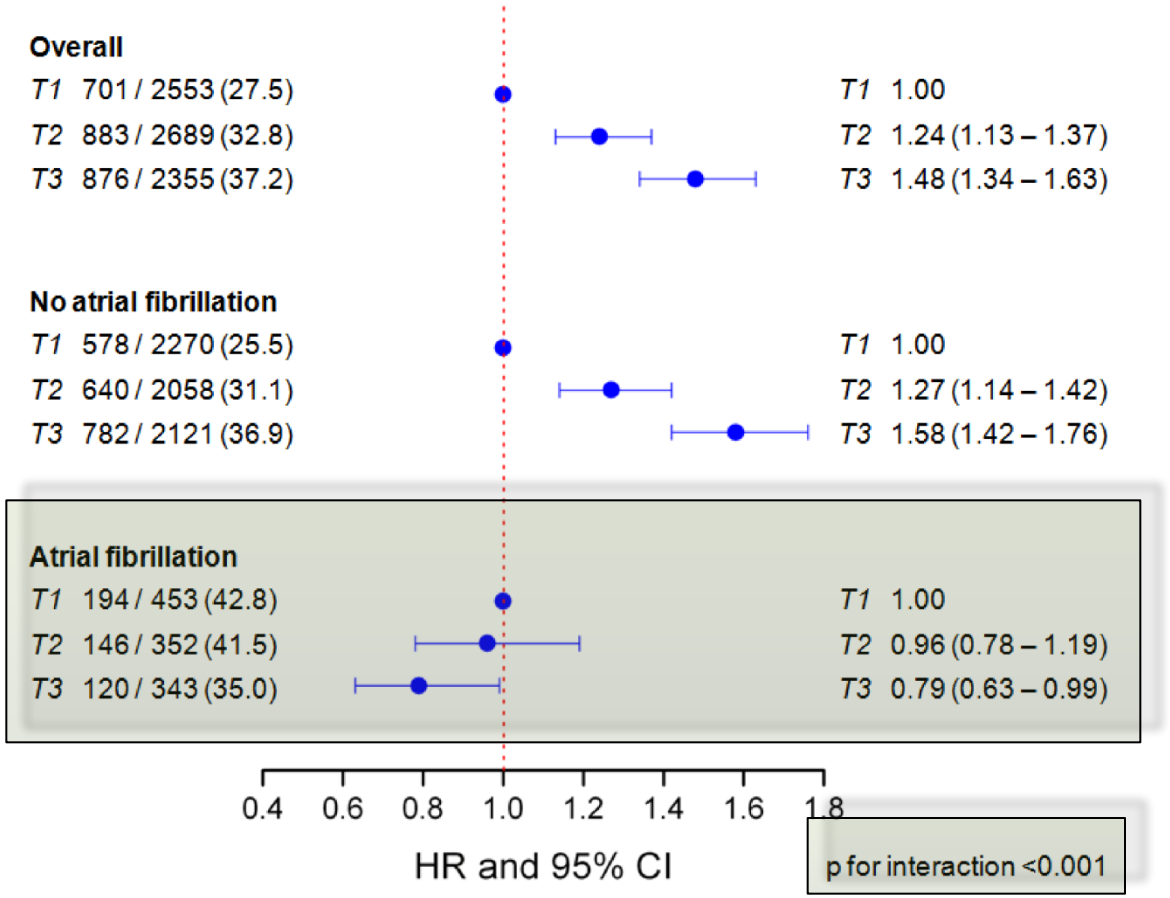
ADJUSTED HR (95% CI)*
1.00
1.11 (1.01–1.23)
1.23 (1.11–1.36)
—
1.00
1.15 (1.01–1.30)
1.25 (1.11–1.42)
—
1.00
1.14 (0.94–1.37)
1.14 (0.93–1.38)
—

Multivariable model adjusted for: age, LVEF, diabetes, BMI, Previous HF hospitalization, sex, NYHA class, radiologic cardiomegaly, DBP, randomized treatment and beta-blocker use at baseline

Castagno D et al. JACC 2012; 59: 1785-1795

CHARM

Baseline sinus rhythm vs. atrial fibrillation



ADJUSTED HR (95% CI)*
1.00
1.11 (1.01–1.23)
1.23 (1.11–1.36)
—
1.00
1.14 (1.02–1.28)
1.28 (1.14–1.44)
—
1.00
0.97 (0.78–1.21)
0.85 (0.67–1.07)
—

Multivariable model adjusted for: age, LVEF, diabetes, BMI, Previous HF hospitalization, sex, NYHA class, radiologic cardiomegaly, DBP, randomized treatment and beta-blocker use at baseline

Castagno D et al. JACC 2012; 59: 1785-1795

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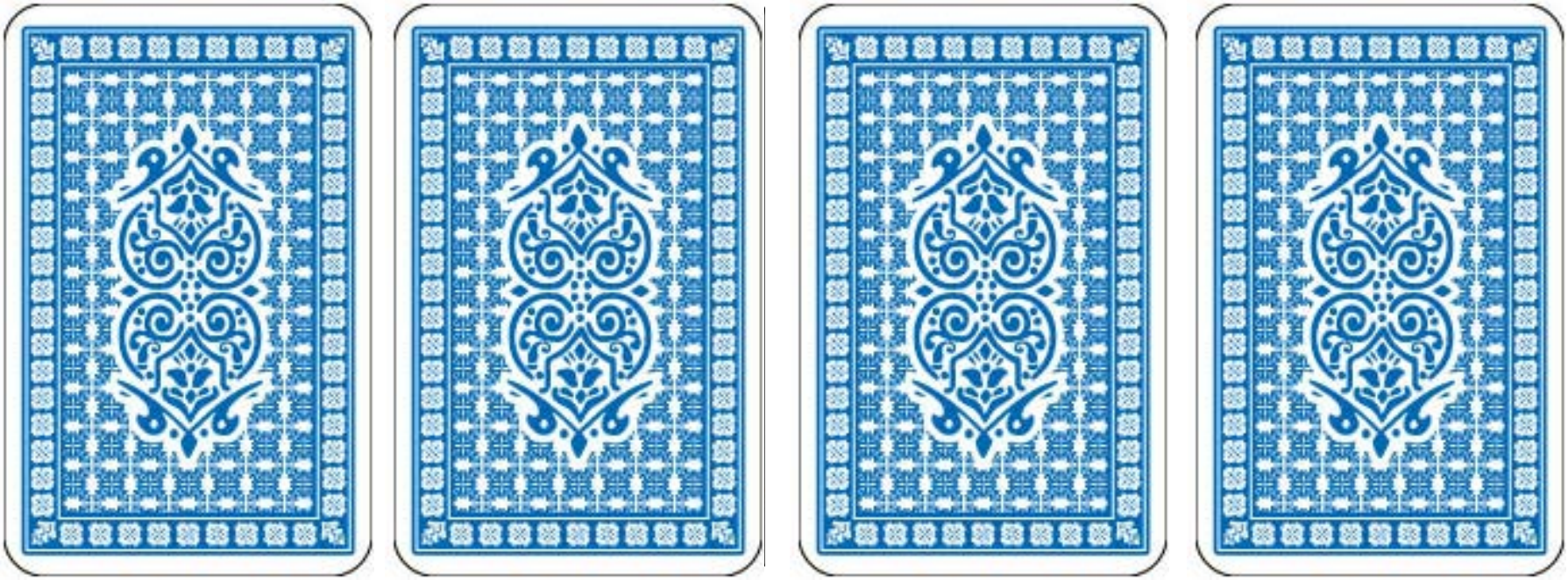
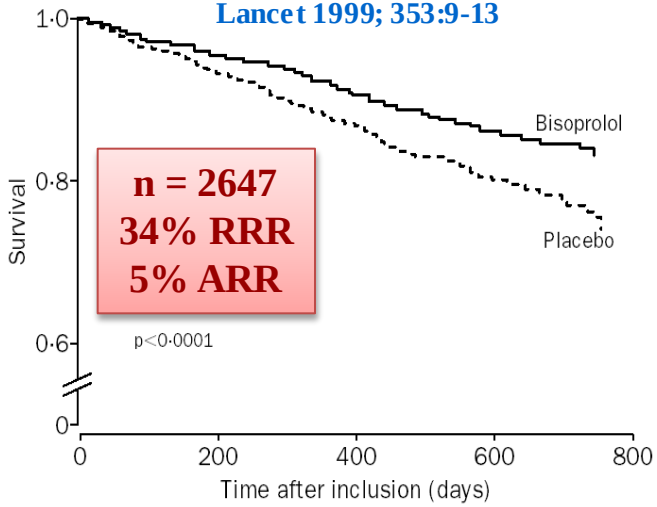
Heart rate modulators



Beta-blocker clinical trials in HF-REF

CIBIS-2 1999

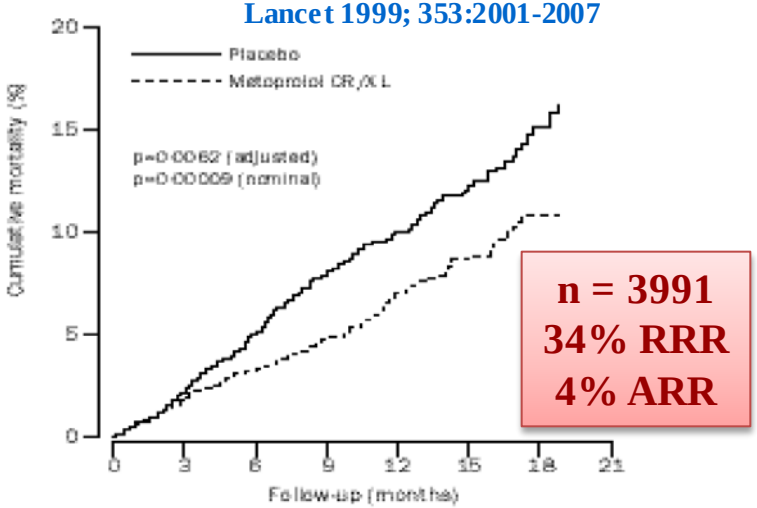
Lancet 1999; 353:9-13



n = 2647
34% RRR
5% ARR

MERIT-HF 1999

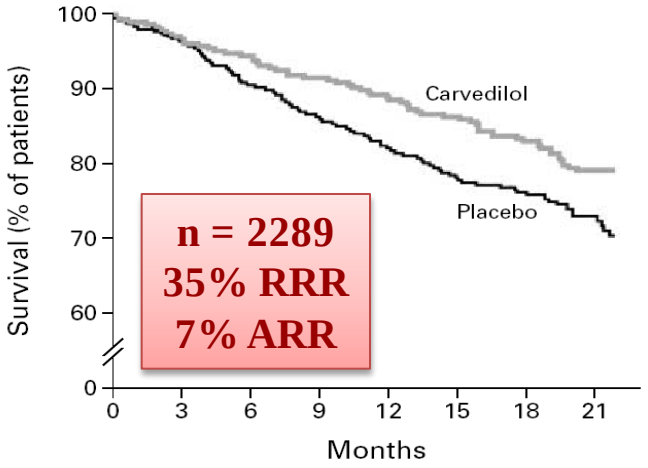
Lancet 1999; 353:2001-2007



n = 3991
34% RRR
4% ARR

COPERNICUS 2001

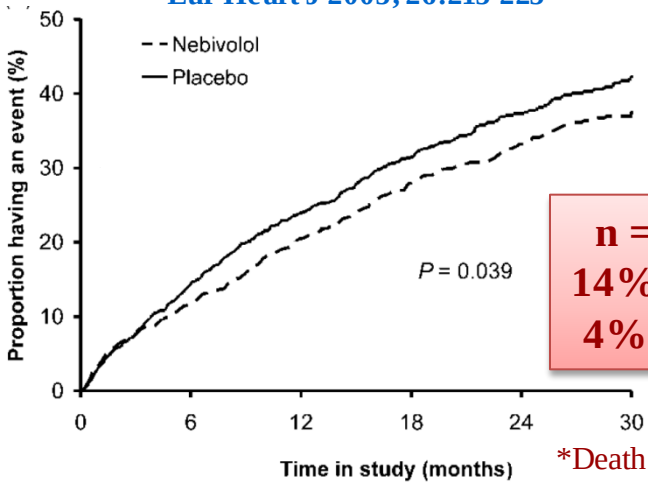
NEJM 2001; 344:1651-1658



n = 2289
35% RRR
7% ARR

SENIORS 2005

Eur Heart J 2005; 26:215-225



n = 2128
14% RRR*
4% ARR*

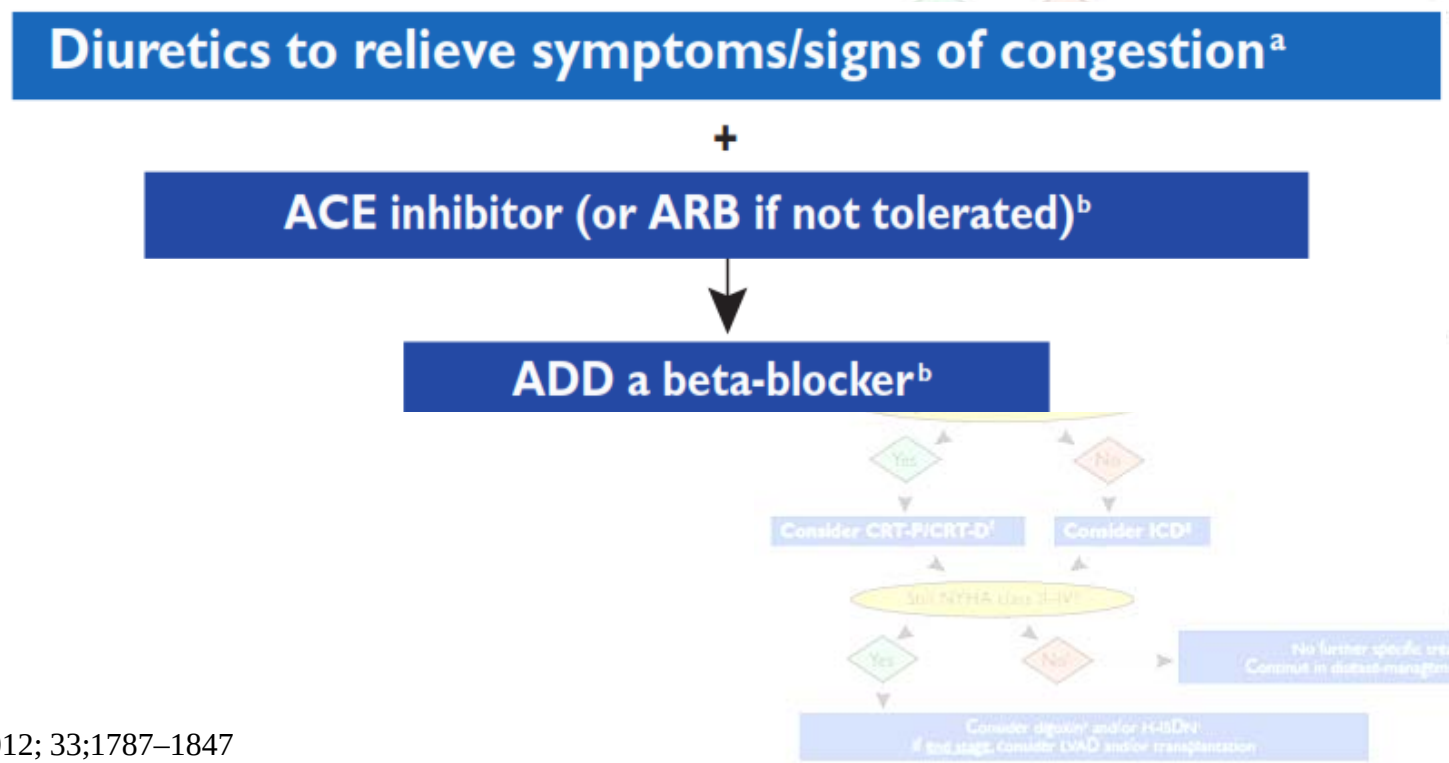
*Death or CV-Hosp

European Heart Journal
doi:10.1093/eurheartj/ehs104

ESC GUIDELINES

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

**The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiol
Developed in collaboration with the Heart Failure Association (H of the ESC**



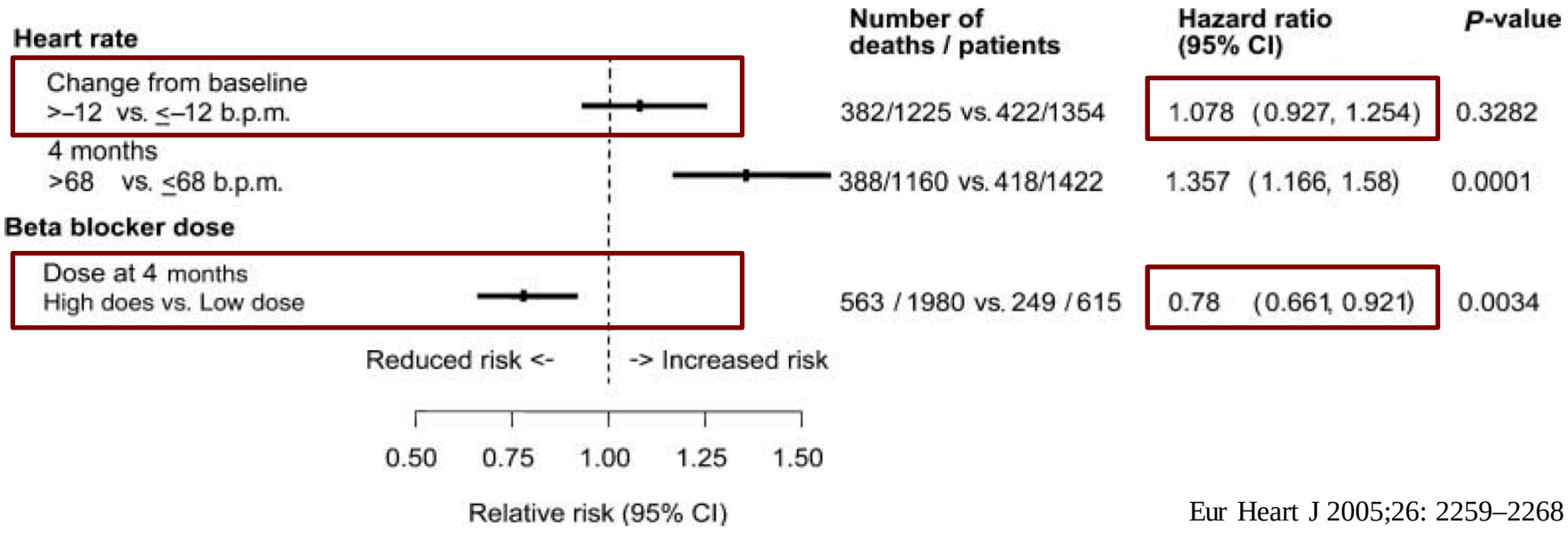
Eur Heart J 2012; 33;1787–1847

Target dose vs. target heart rate

Target β-blocker dose

Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial

Marco Metra[1*], Christian Torp-Pedersen[2], Karl Swedberg[3], John G.F. Cleland[4], Andrea Di Lenarda[5], Michel Komajda[6], Willem J. Remme[7], Beatrix Lutiger[8], Armin Scherhag[8,9], Mary Ann Lukas[10], Andrew Charlesworth[11], Philip A. Poole-Wilson[12], for the COMET investigators[†]

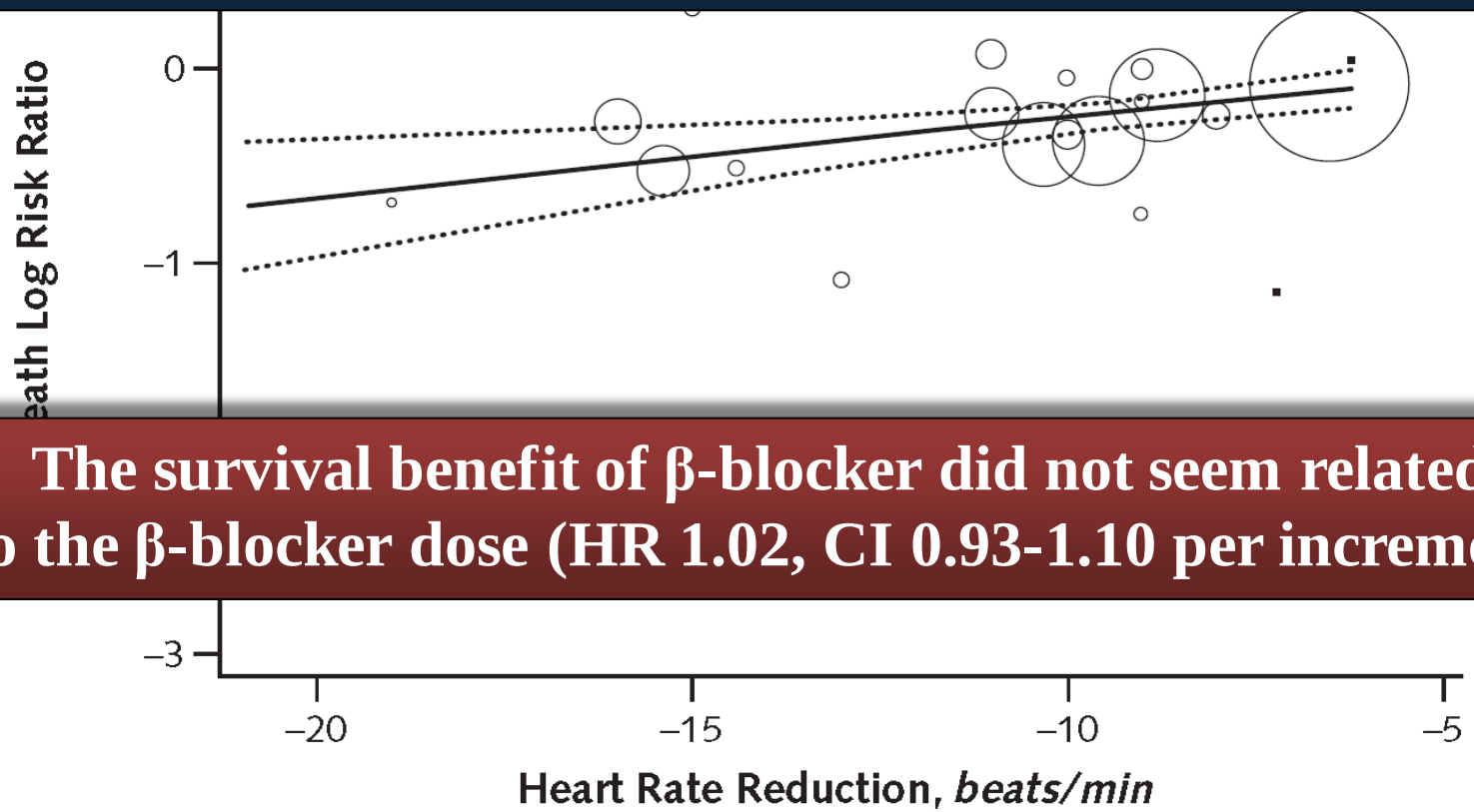


Eur Heart J 2005;26: 2259–2268

Target heart rate reduction

23 Randomized Controlled Trials

For every 5 bpm ↓ in heart rate with β-blocker treatment a 18% ↓ in the risk of death occurred (HR 0.82, CI 0.71-0.94)



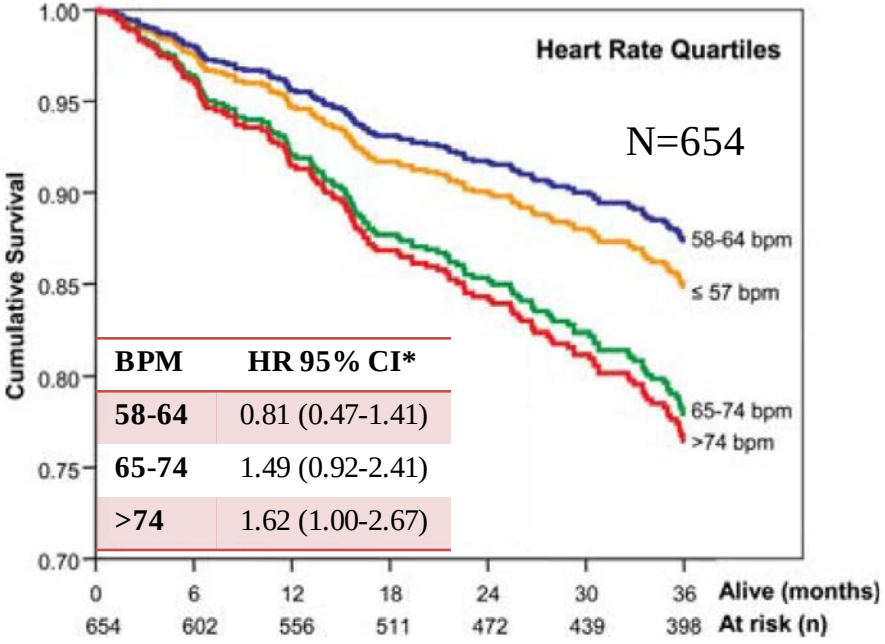
The survival benefit of β-blocker did not seem related to the β-blocker dose (HR 1.02, CI 0.93-1.10 per increment)

McAlister FA et al. Ann Intern Med 2009; 150:784-794

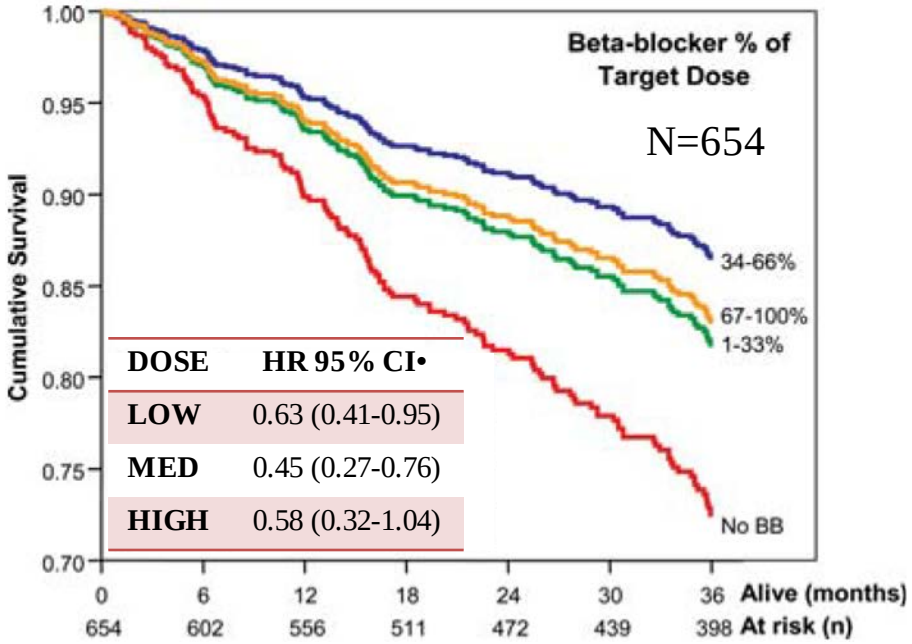
Target both!

Heart rate achieved or beta-blocker dose in patients with chronic heart failure: which is the better target?

Damien Cullington*, Kevin M. Goode, Andrew L. Clark, and John G.F. Cleland



BPM	HR 95% CI*
58-64	0.81 (0.47-1.41)
65-74	1.49 (0.92-2.41)
>74	1.62 (1.00-2.67)



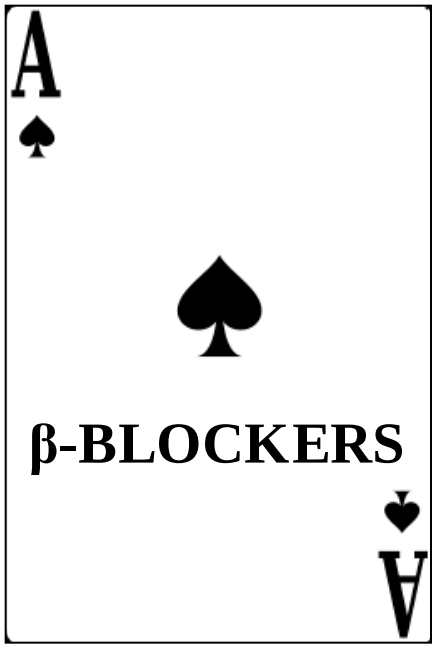
DOSE	HR 95% CI•
LOW	0.63 (0.41-0.95)
MED	0.45 (0.27-0.76)
HIGH	0.58 (0.32-1.04)

* ≤57 bpm as referent

• No beta-blocker as referent

EurJ Heart Fail 2012;14:737–747

Heart rate modulators



SHIFT Trial

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

*Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators**

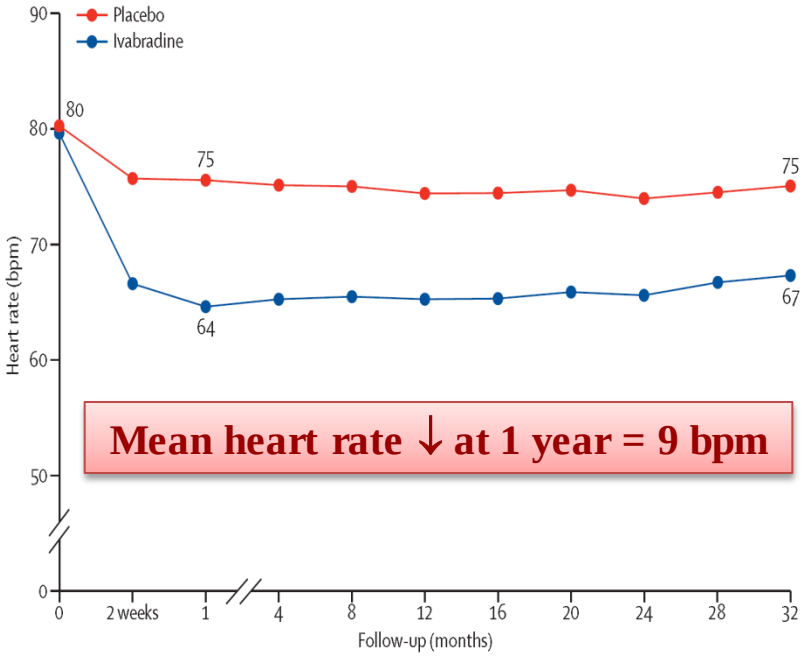
Evaluate whether ivabradine improves CV outcomes in:

1. Moderate to severe chronic heart failure (NYHA II-IV)
2. Left ventricular ejection fraction ≤ 35%
3. Heart rate ≥ 70 bpm in sinus rhythm
4. Recommended heart failure therapy

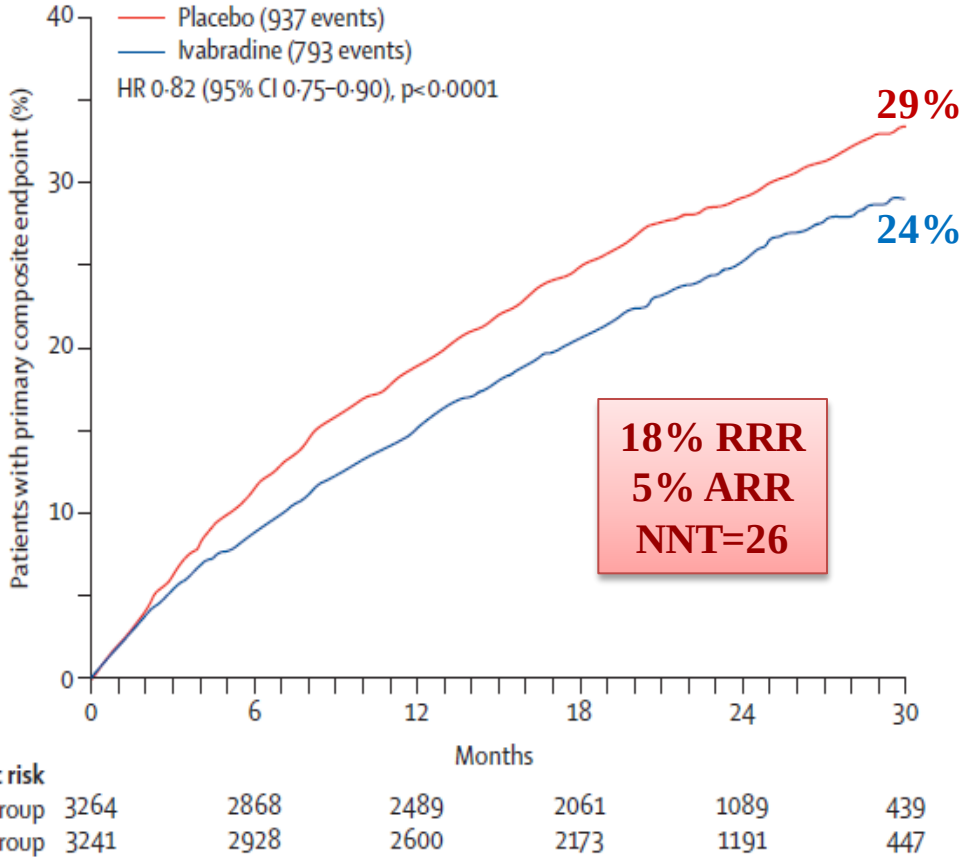
Lancet 2010; 376: 875-85

SHIFT Primary Endpoint
(CV-death or hospital admission for worsening HF)

6505 patients
Median follow-up 22.9 months



Mean heart rate ↓ at 1 year = 9 bpm

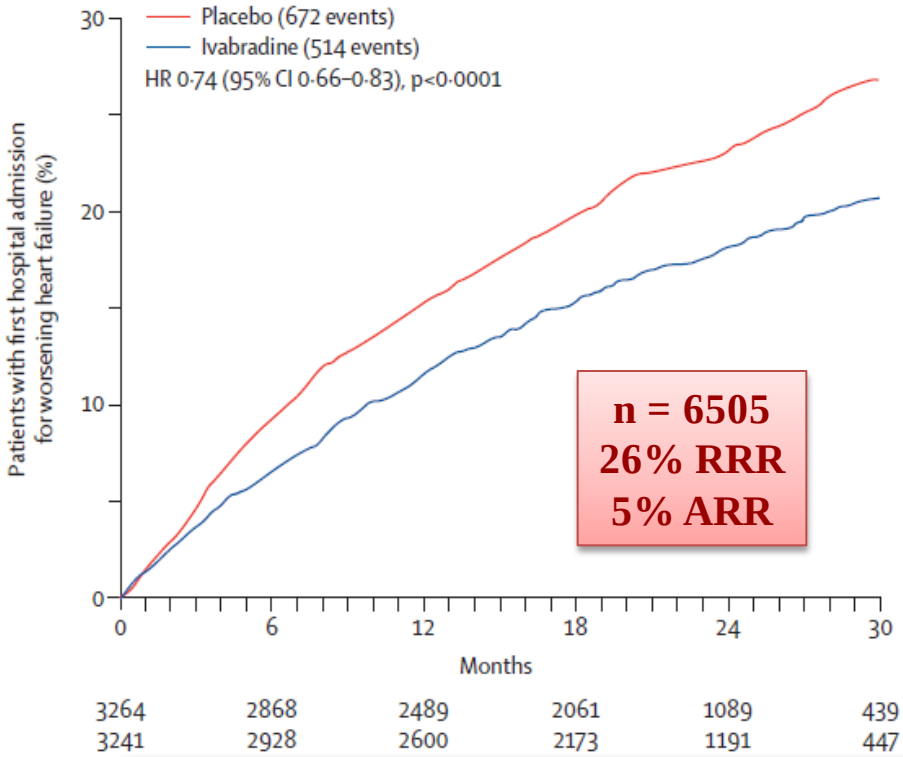


18% RRR
5% ARR
NNT=26

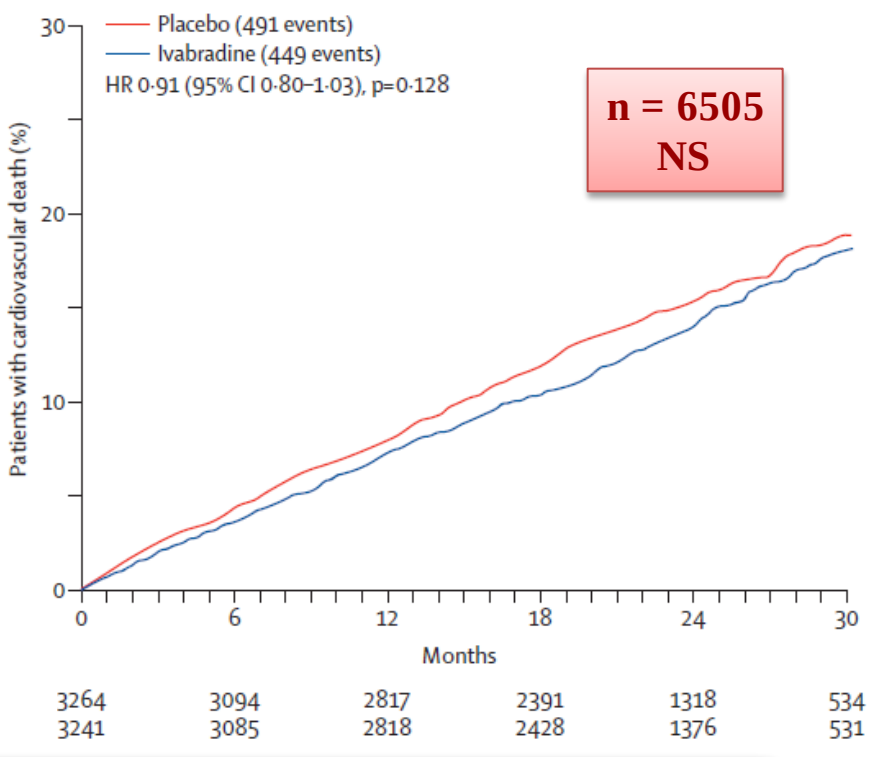
Swedberg K et al. Lancet 2010; 376: 875-85

Components of the Primary Endpoint

Hospital admission for HF



CV-death



Primary endpoint reduction driven by the effect of ivabradine on HF hospitalization

Swedberg K et al. Lancet 2010; 376: 875-85

β-blocker Dose and Response to Ivabradine

Effects on Outcomes of Heart Rate Reduction by Ivabradine in Patients With Congestive Heart Failure: Is There an Influence of Beta-Blocker Dose?

Findings From the SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial) Study

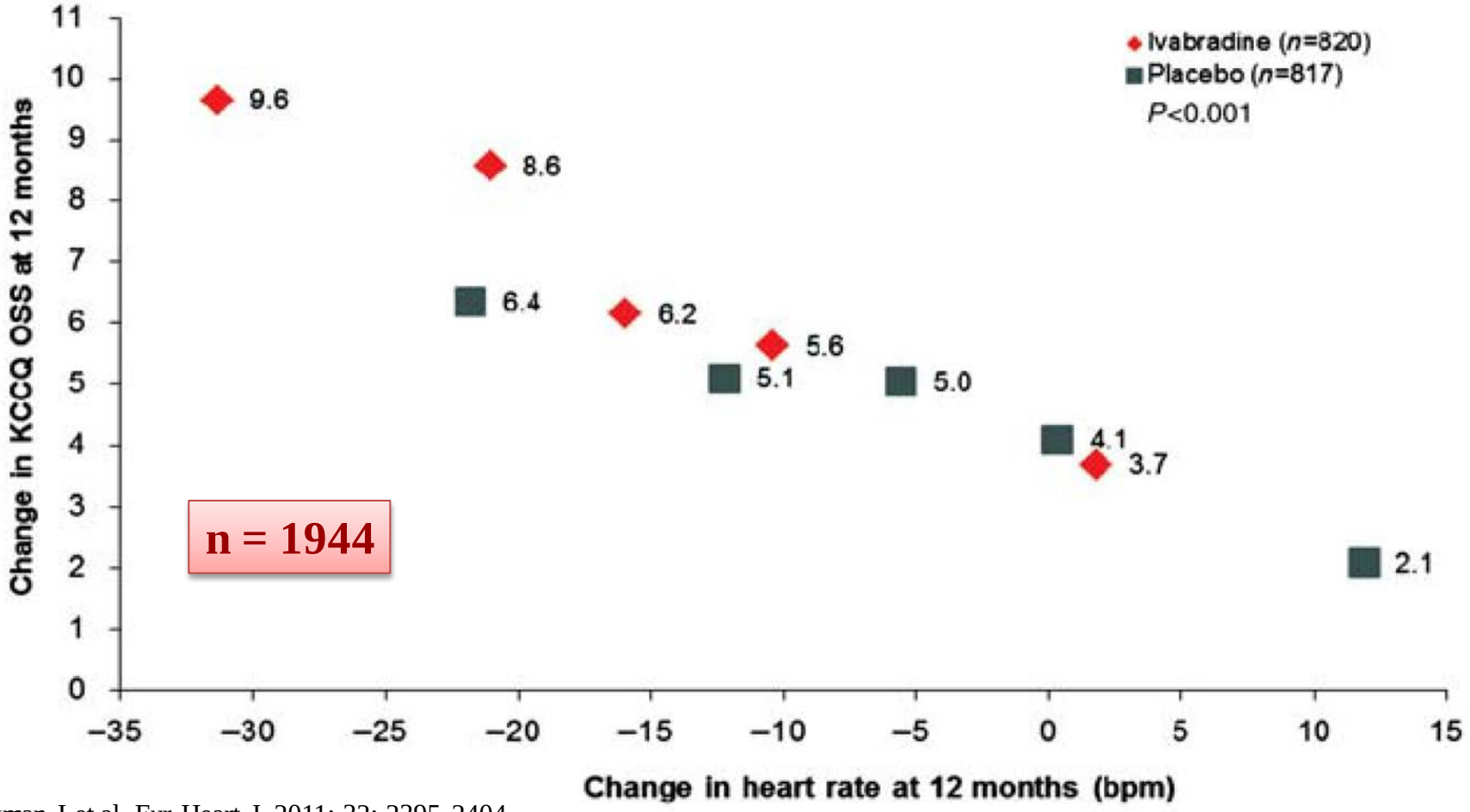
Karl Swedberg, MD,* Michel Komajda, MD,† Michael Böhm, MD,‡ Jeffrey Borer, MD,§ Michele Robertson, BSc,‖ Luigi Tavazzi, MD,¶ Ian Ford, PhD,‖ for the SHIFT Investigators

	Ivabradine	Placebo	(vs. Placebo) HR (95% CI), p Value	(Interaction) Heterogeneity
Primary endpoint				
No beta-blocker	101 (29.4%)	134 (39.3%)	0.71 (0.55–0.93), 0.012	0.35
Beta-blocker <25%	148 (30.8%)	171 (40.0%)	0.74 (0.59–0.92), 0.007	
Beta-blocker 25% to <50%	204 (26.2%)	260 (30.8%)	0.81 (0.68–0.98), 0.029	
Beta-blocker 50% to <100%	181 (21.6%)	212 (24.8%)	0.88 (0.72–1.07), 0.193	
Beta-blocker ≥100%	149 (20.1%)	150 (20.1%)	0.99 (0.79–1.24), 0.913	

J Am Coll Cardiol 2012; 59: 1938-45

Effect of ivabradine on Quality of Life

- **Qol assessed by means of the Kansas City Cardiomyopathy Questionnaire (the higher the score the better the QoL)**

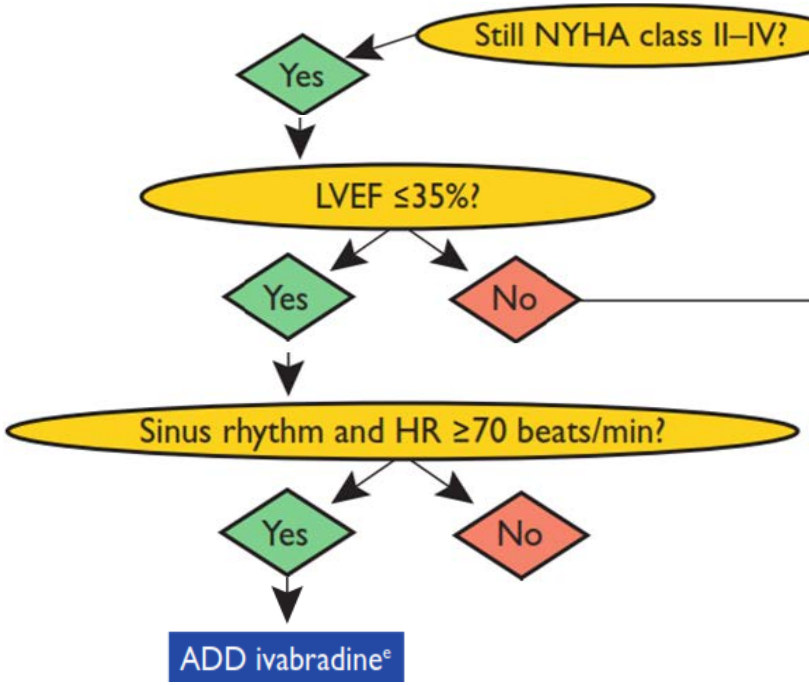


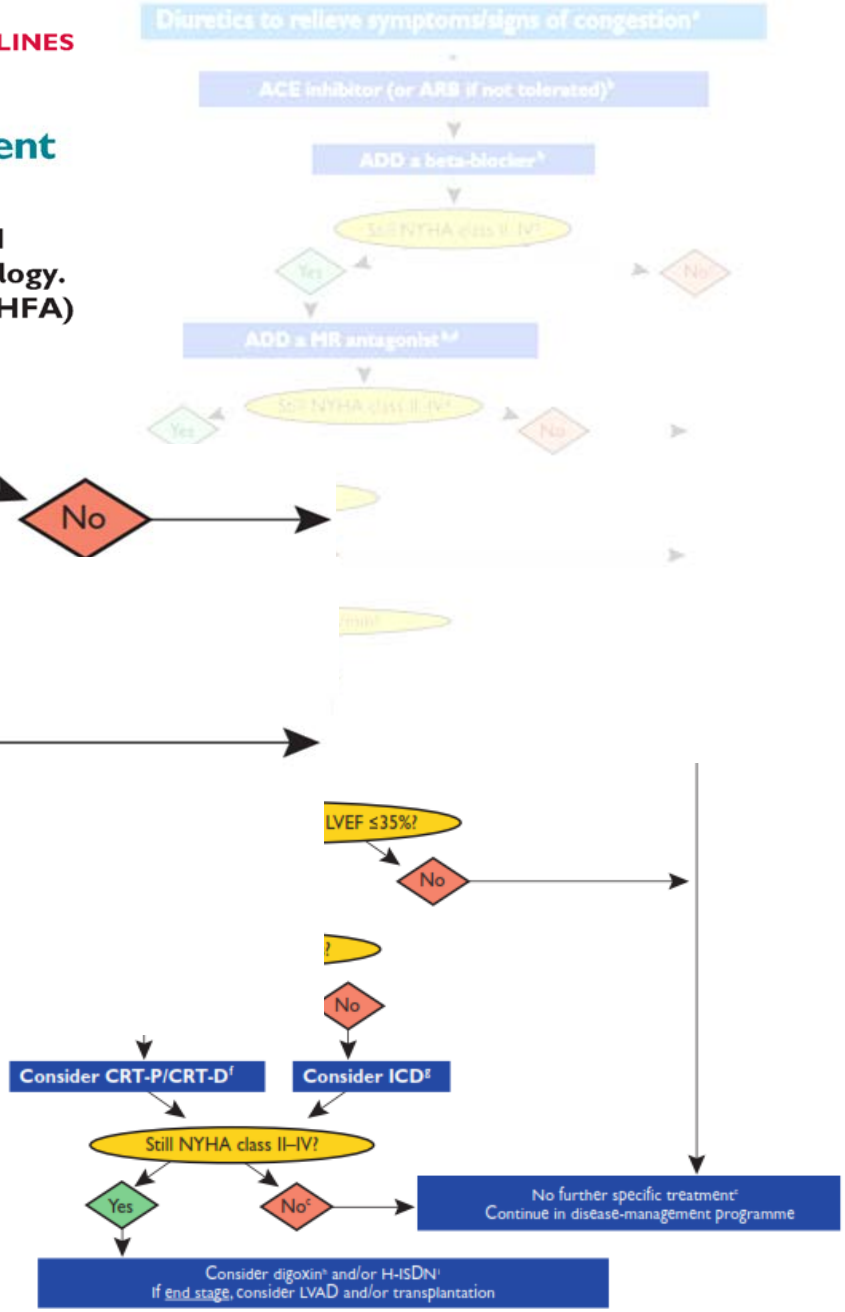
Ekman I et al. Eur Heart J 2011; 32: 2395-2404

European Heart Journal
doi:10.1093/eurheartj/ehs104

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

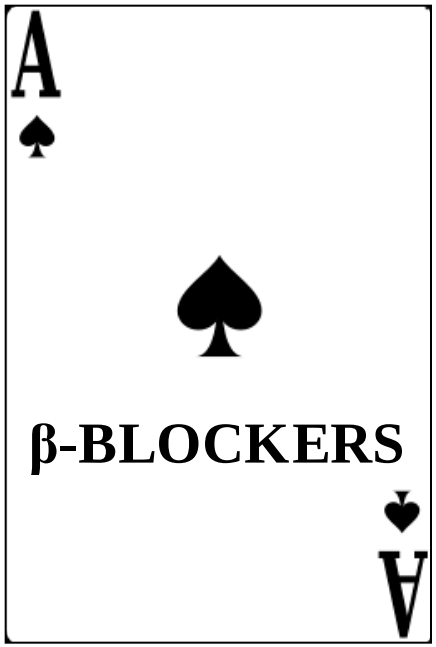
The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC





Eur Heart J 2012; 33;1787–1847

Heart rate modulators

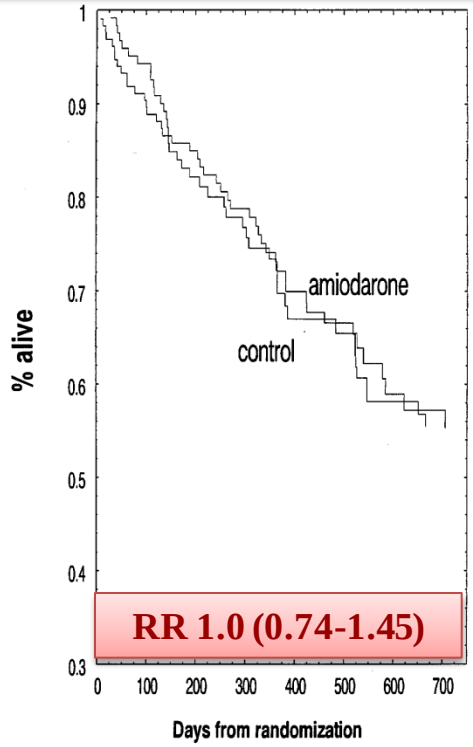


GESICA Trial

Heart Rate Is a Marker of Amiodarone Mortality Reduction in Severe Heart Failure

DANIEL R. NUL, MD, HERNÁN C. DOVAL, MD, HUGO O. GRANCELLI, MD,
SERGIO D. VARINI, MD, SAUL SOIFER, MD, SERGIO V. PERRONE, MD,
NOEMÍ PRIETO, MD, OMAR SCAPIN, MD, ON BEHALF OF THE GESICA-GEMA INVESTIGATORS*

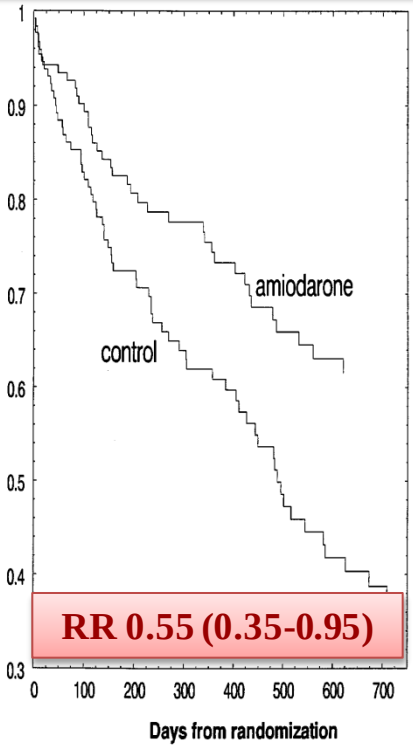
Baseline heart rate <90 bpm



RR 1.0 (0.74-1.45)

N = 516
Follow-up 2 yrs

Baseline heart rate ≥90 bpm



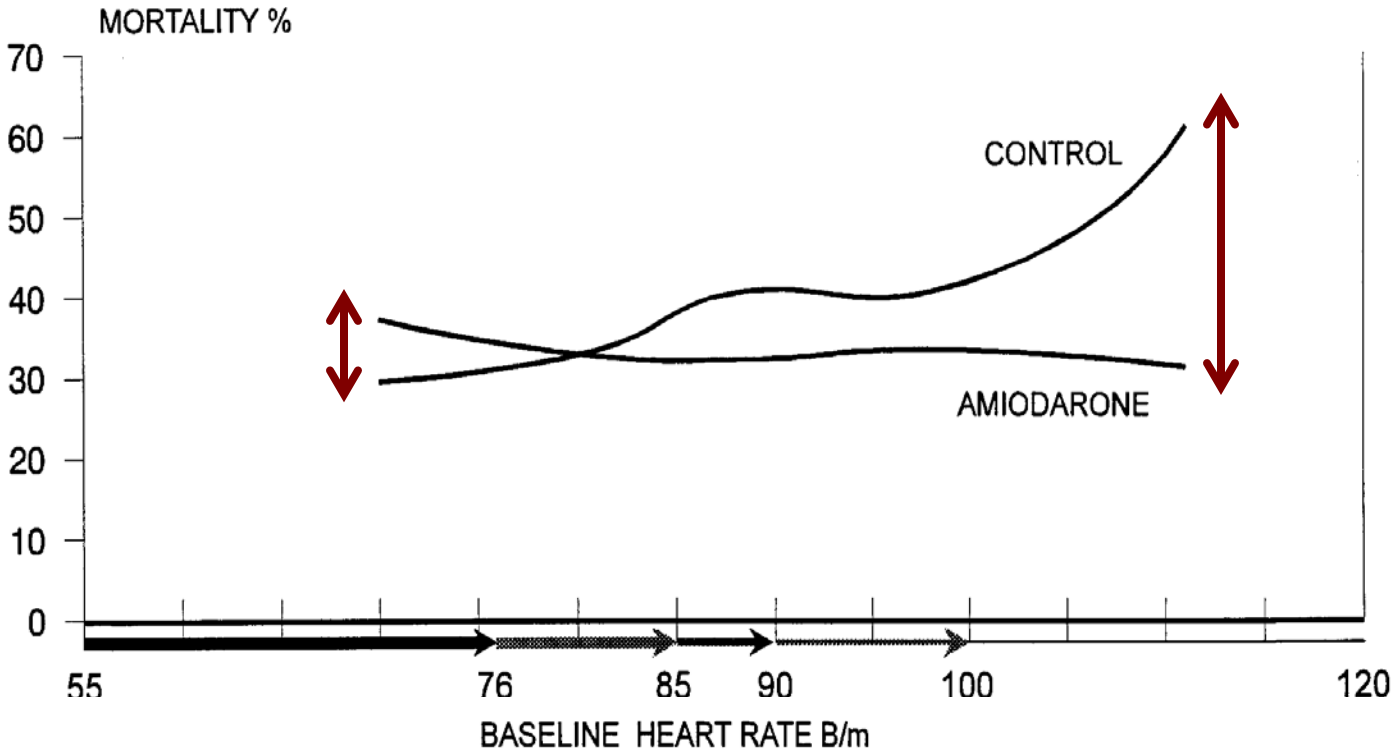
RR 0.55 (0.35-0.95)

Nul DR et al.
J Am Coll Cardiol 1997
29:1199-1205

GESICA Trial

Heart Rate Is a Marker of Amiodarone Mortality Reduction in Severe Heart Failure

DANIEL R. NUL, MD, HERNÁN C. DOVAL, MD, HUGO O. GRANCELLI, MD,
SERGIO D. VARINI, MD, SAUL SOIFER, MD, SERGIO V. PERRONE, MD,
NOEMÍ PRIETO, MD, OMAR SCAPIN, MD, ON BEHALF OF THE GESICA-GEMA INVESTIGATORS*



Nul DR et al. J Am Coll Cardiol 1997; 29:1199-1205

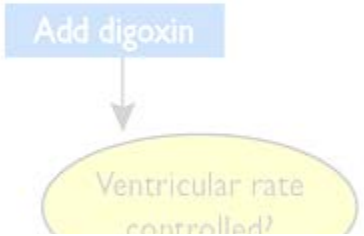
European Heart Journal
doi:10.1093/eurheartj/ehs104

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

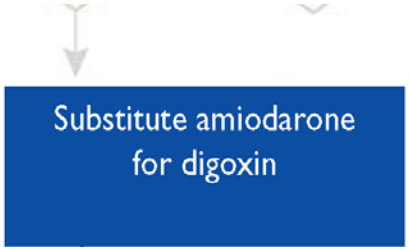
IIb | C

(ii) Amiodarone may be considered in patients unable to tolerate a beta-blocker or digoxin.



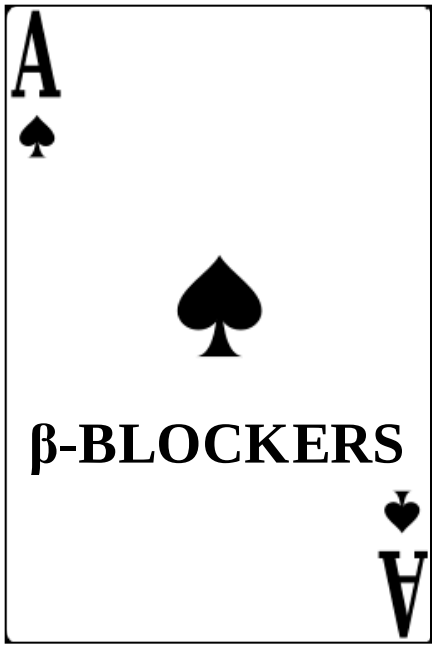
IIb | C

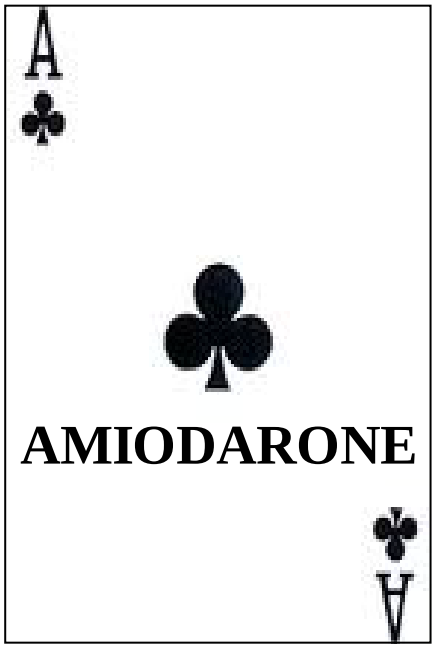
(i) Amiodarone may be considered in addition to either a beta-blocker or digoxin (but not both) to control the ventricular rate in patients with an inadequate response and unable to tolerate the combination of both a beta-blocker and digoxin.



Eur Heart J 2012; 33;1787–1847

Heart rate modulators





DIG Trial

The New England Journal of Medicine

VOLUME 336 FEBRUARY 20, 1997 NUMBER 8

THE EFFECT OF DIGOXIN ON MORTALITY AND MORBIDITY IN PATIENTS WITH HEART FAILURE

6800 patients with symptomatic HF

sinus rhythm

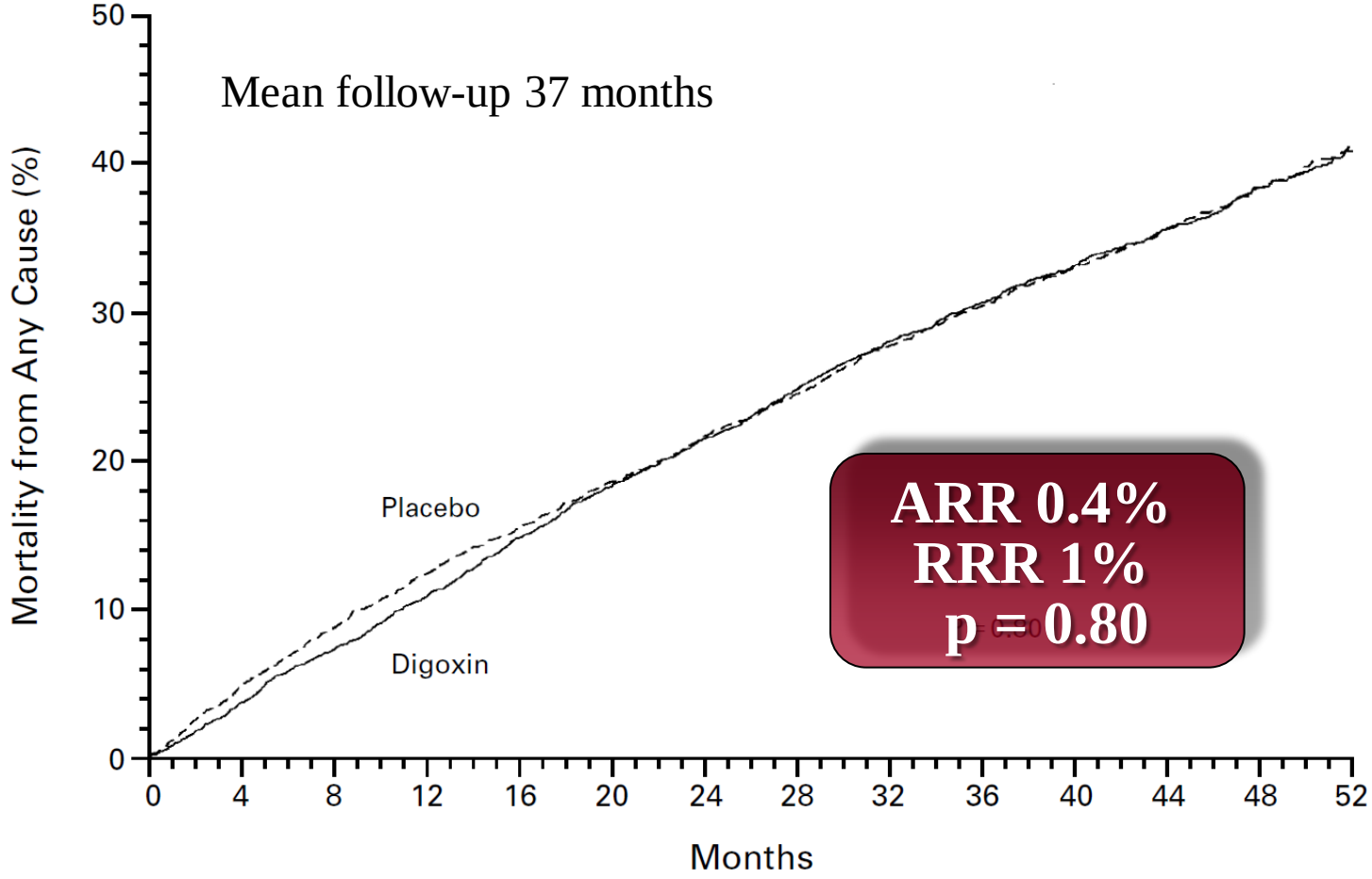
LVEF≤45%

THE DIGITALIS INVESTIGATION GROUP*

Rekha Garg, M.D., Richard Gorlin, M.D., Thomas Smith, M.D., and Salim Yusuf, M.D., assume responsibility for the contents of this article on behalf of the Digitalis Investigation Group.

N Engl J Med 1997; 336:525-33

DIG Primary Endpoint – All-cause mortality

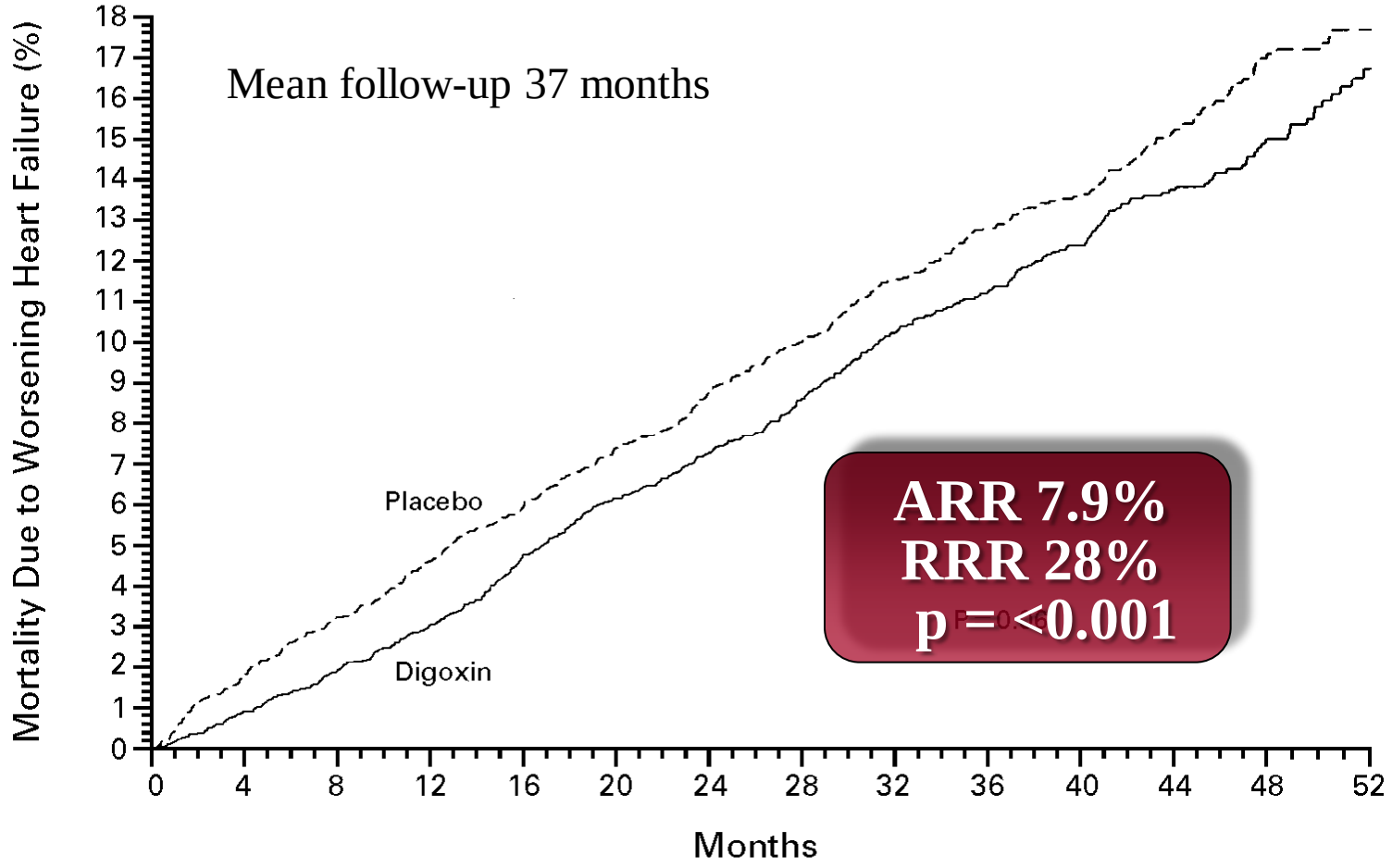


No. of Patients at Risk

Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

N Engl J Med 1997; 336:525-33

Secondary Endpoint – HF Hospitalization



ARR 7.9%
RRR 28%
p =<0.001

No. of Patients at Risk

Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

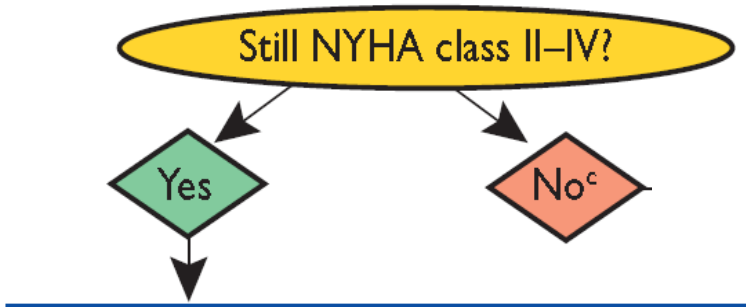
N Engl J Med 1997; 336:525-33

European Heart Journal
doi:10.1093/eurheartj/ehs104

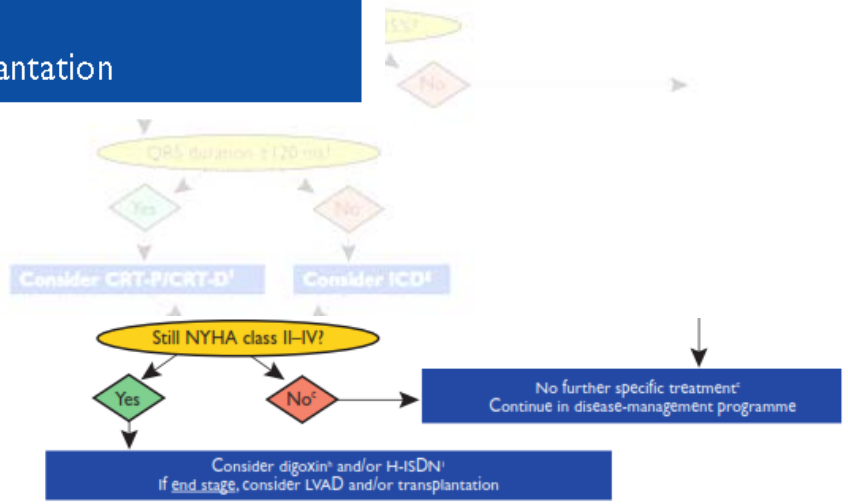
ESC GUID

ESC Guidelines for the diagnosis and treatm of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute ar Chronic Heart Failure 2012 of the European Society of Cardi Developed in collaboration with the Heart Failure Association of the ESC



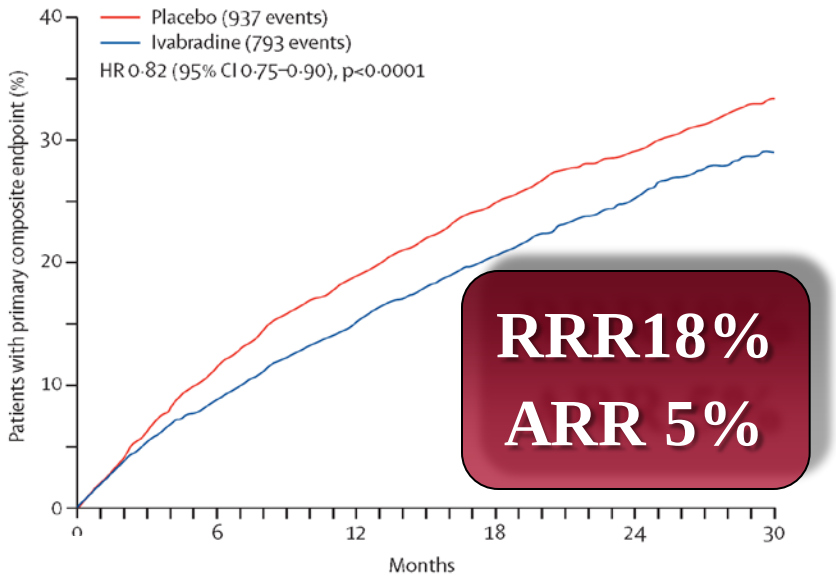
Consider digoxin[h] and/or H-ISDN[i]
If end stage, consider LVAD and/or transplantation



Eur Heart J 2012; 33;1787–1847

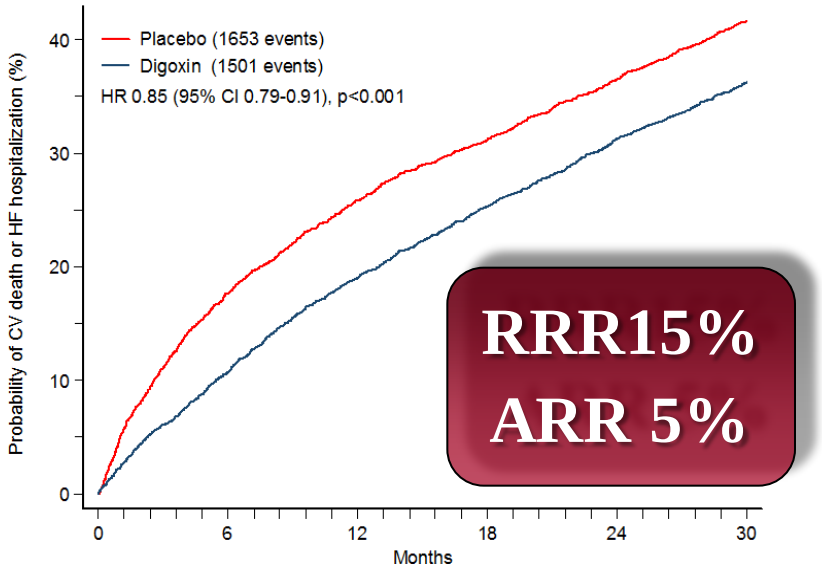
Should we SHIFT out thinking?

SHIFT



RRR18%
ARR 5%

DIG



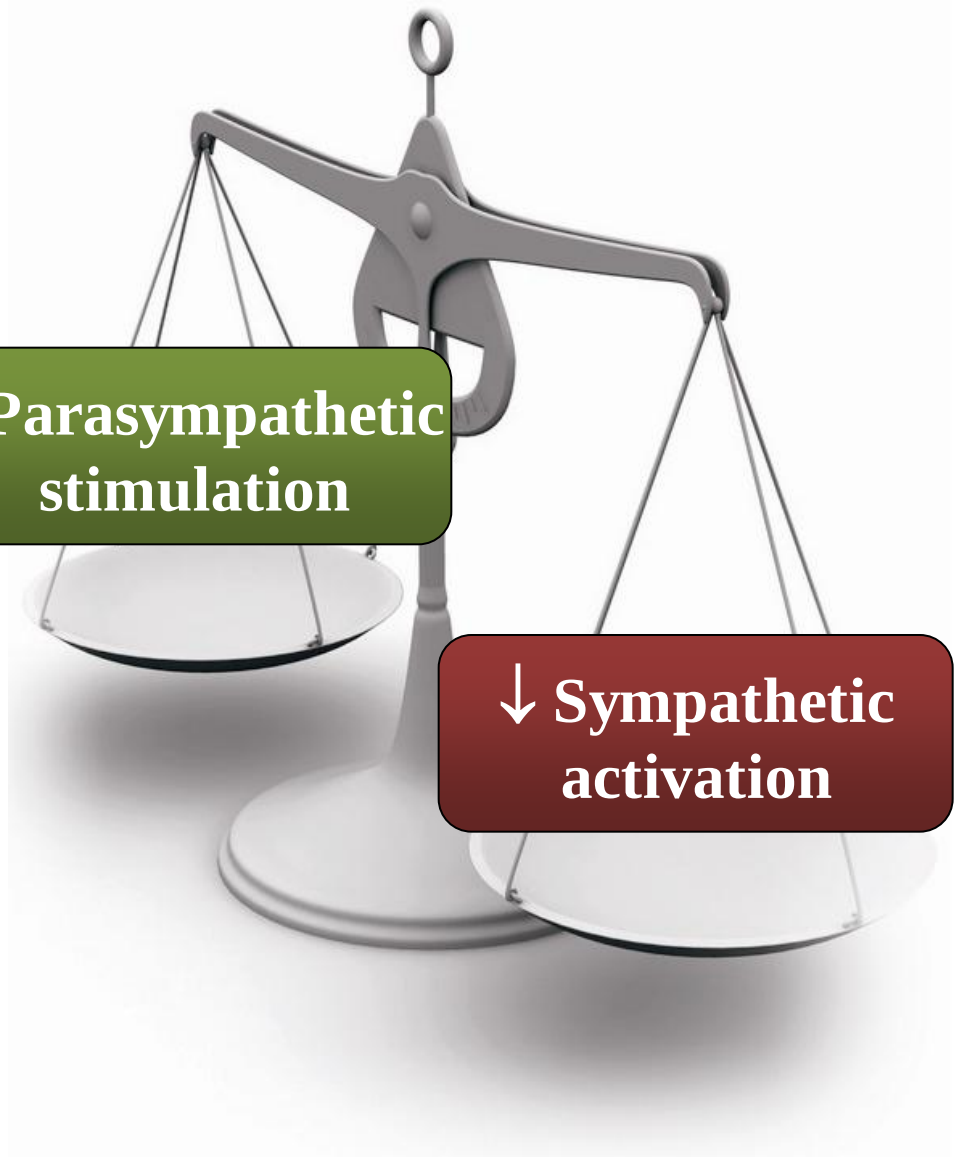
RRR15%
ARR 5%

	DIG		SHIFT	
	HR (95% CI)	P-value	HR (95% CI)	P-value
CV-Death or HF hospitalization	0.85 (0.79-0.91)	<0.001	0.82 (0.75-0.90)	<0.001
CV-Death	1.01 (0.93-1.10)	0.78	0.91 (0.80-1.03)	0.13
HF hospitalization	0.72 (0.66-0.79)	<0.001	0.74 (0.66-0.83)	<0.001

Castagno D et al. Eur Heart J 2012; 33:1137-41

New approaches

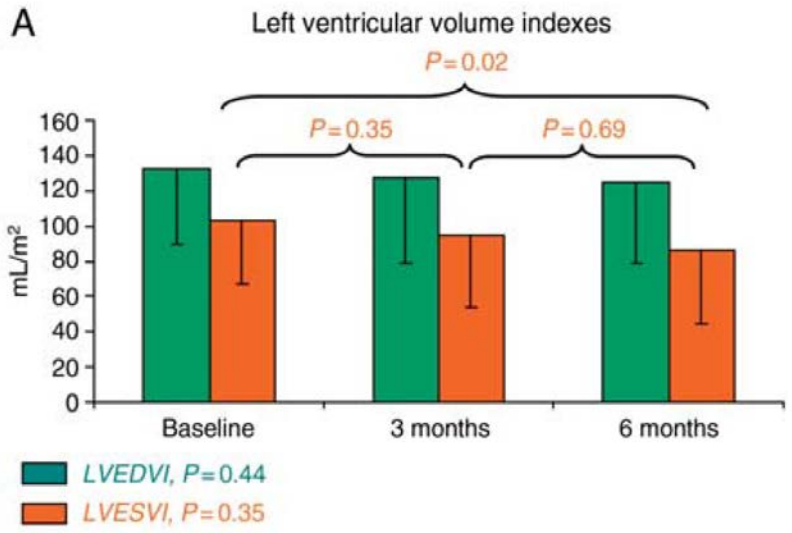
Autonomic modulation therapies

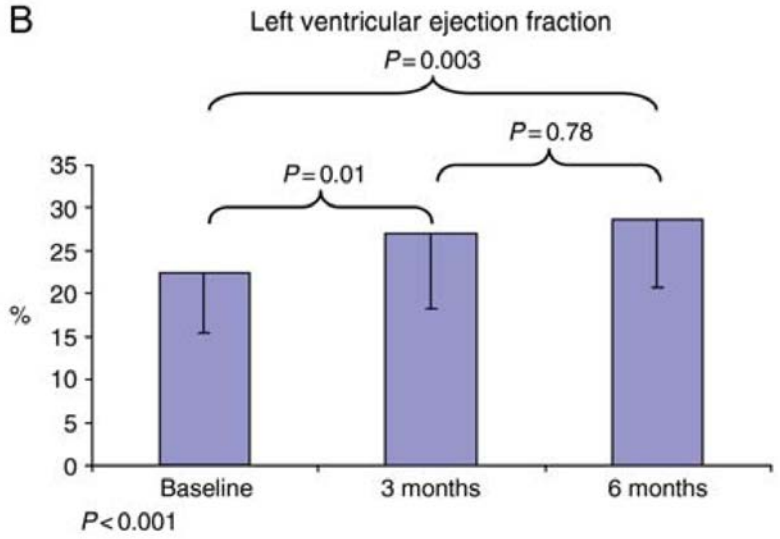


Vagal nerve stimulation

Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure

Gaetano M. De Ferrari[1]*, Harry J.G.M. Crijns[2], Martin Borggrefe[3], Goran Milasinovic[4], Jan Smid[5], Markus Zabel[6], Antonello Gavazzi[7], Antonio Sanzo[1], Robert Dennert[3], Juergen Kuschyk[4], Srdjan Raspopovic[5], Helmut Klein[6,8], Karl Swedberg[9], and Peter J. Schwartz[1,10,11,12,13], for the CardioFit Multicenter Trial Investigators





Eur Heart J 2011; 32:847-855

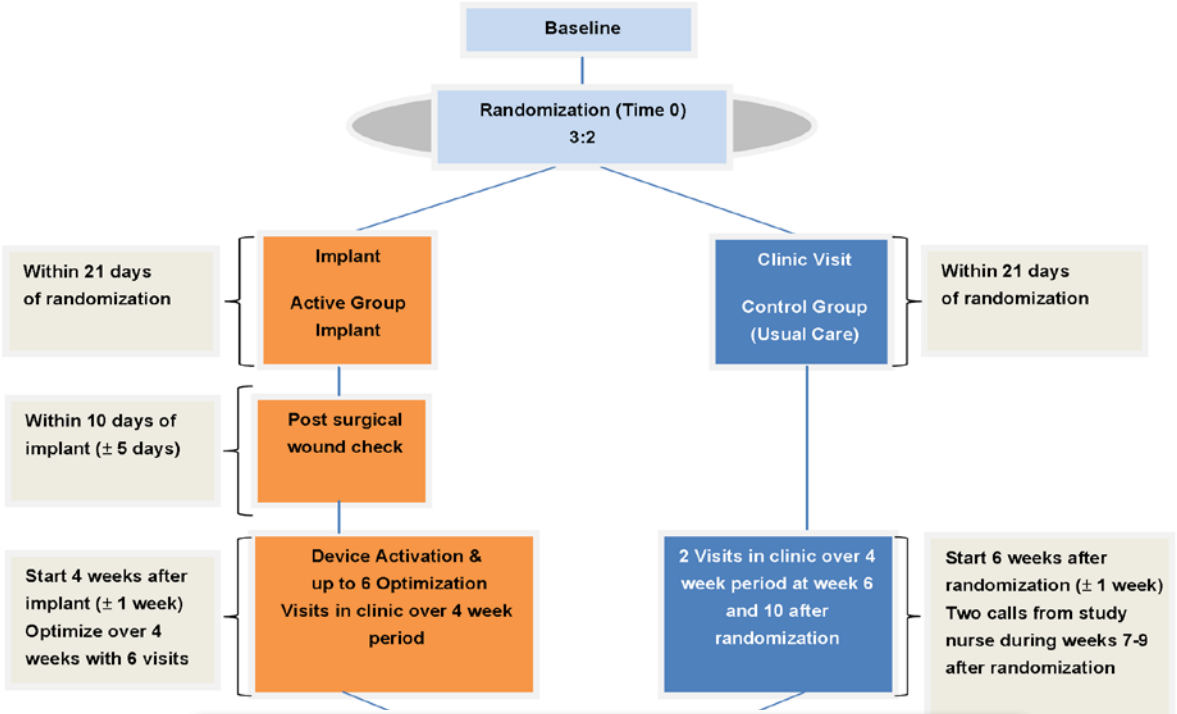
Vagal nerve stimulation

Rationale and study design of the *IN*crease *O*f *V*agal *T*on*E* in *H*eart *F*ailure study: INOVATE-HF

Paul J. Hauptman, MD,[a] Peter J. Schwartz, MD,[b,c] Michael R. Gold, MD, PhD,[d] Martin Borggrefe, MD, PhD,[e] Dirk J. Van Veldhuisen, MD, PhD,[f] Randall C. Starling, MD, MPH,[g] and Douglas L. Mann, MD[h] *Saint Louis, MO; Pavia, Italy; Charleston, SC; Mannheim, Germany; Groningen, The Netherlands; and Cleveland, OH*

Key Inclusion Criteria

- NYHA III
- Age>18 yrs
- Optimal medical therapy
- LVEF<40%
- 6MWT 150 to 425 m
- LVEDD 50 to 80 mm



Am Heart J 2012; 163: 954-962

Take home messages

- Experimental and clinical evidence support the concept that high heart rate with sinus rhythm leads to poor outcomes in heart failure
- Cardiovascular risk assessment by measuring resting heart rate becomes a new paradigm and provides a target for effective treatments
- Beta-blocker therapy at best tolerated dose achieving a target heart rate is the current mainstay of heart failure treatment

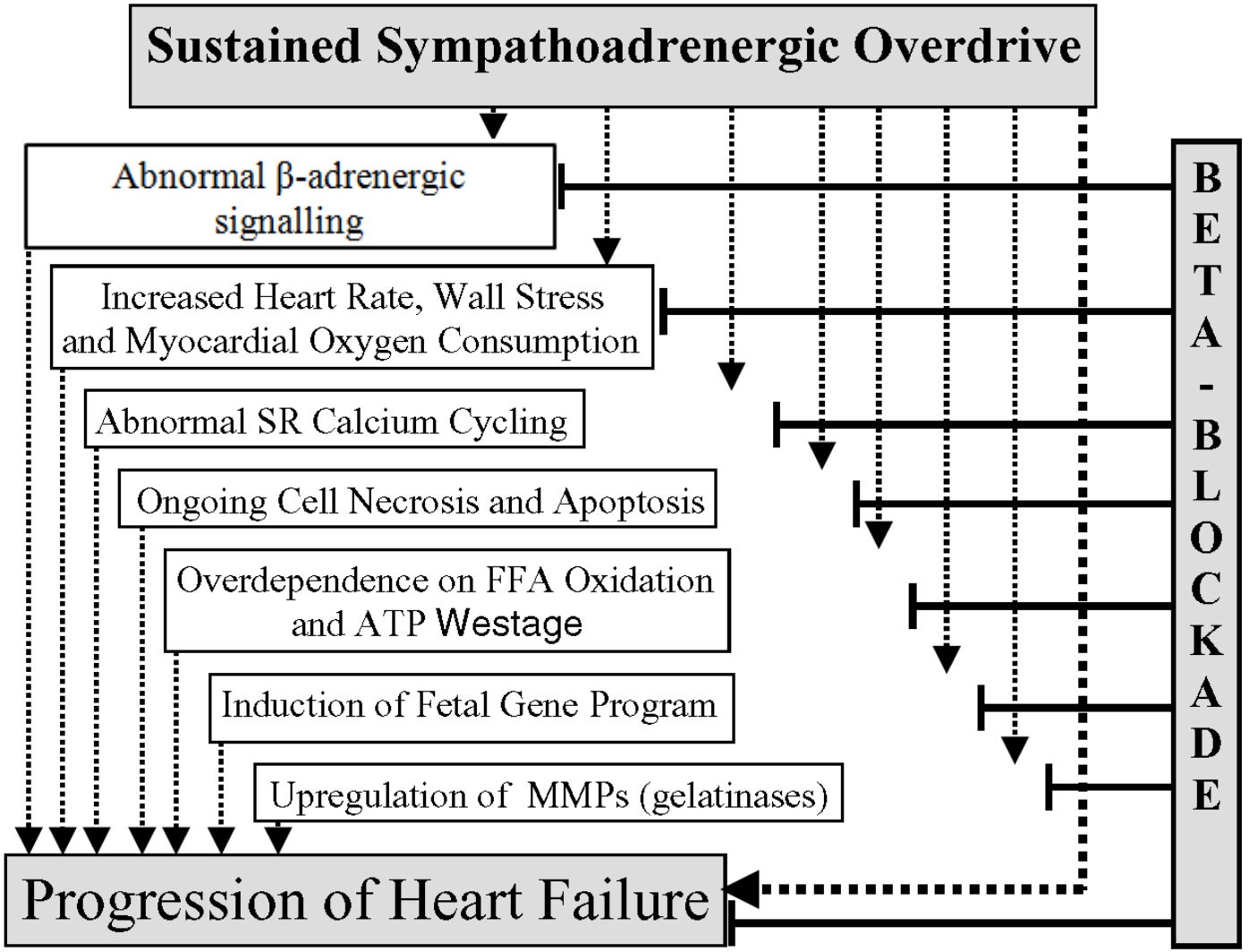
Take home messages

- Ivabradine added to beta-blocker has shown to improve long-term outcomes mostly acting on hospital admissions for worsening heart failure
- Cardiological community dismissed digoxin too readily and we should reappraise its potential role in the treatment of heart failure
- Autonomic modulation seems a promising treatment option and, if proved effective, it maybe synergic with existing medical therapy


Thank you

BACK-UP SLIDES

Beta-blockers mechanisms of action



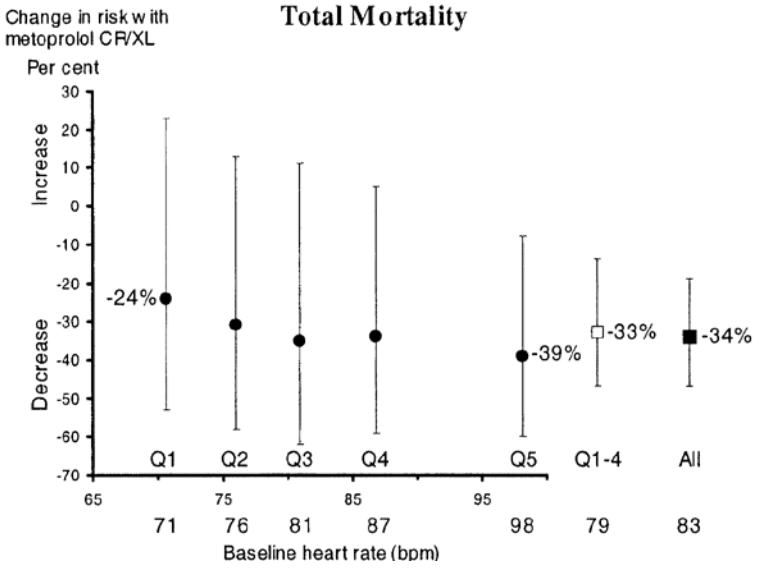
Adapted from Sabbah HN, Heart Fail Rev 2004; 9:91-97

Target β-blocker dose

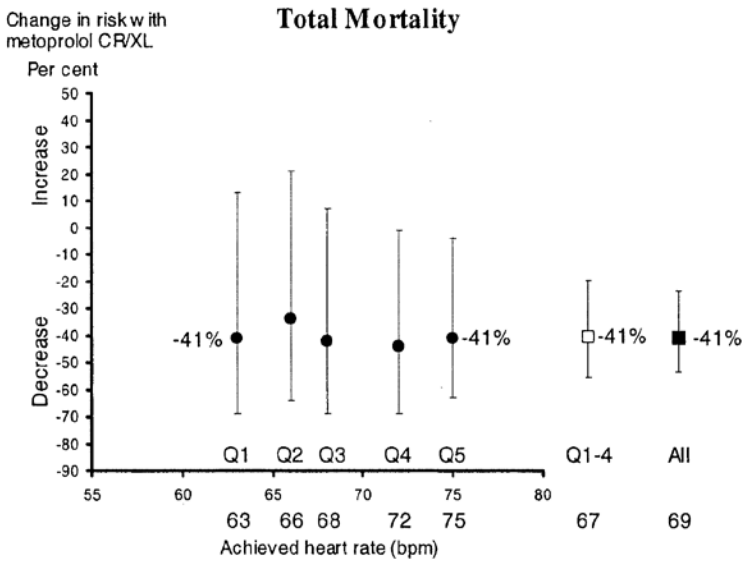
What Resting Heart Rate Should One Aim For When Treating Patients With Heart Failure With a Beta-Blocker?

Lars Gullestad, MD, PHD,* John Wikstrand, MD, PHD,†‡ Prakash Deedwania, MD, FACC,§ Åke Hjalmarson, MD, PHD,‖ Kenneth Egstrup, MD, DMSCI, FESC,¶ Uri Elkayam, MD, PHD,# Stephen Gottlieb, MD,** Andrew Rashkow, MD,†† Hans Wedel, PHD,‡‡ Georgina Bermann, PHD,‡ John Kjekshus, MD, PHD§§, for the MERIT-HF Study Group

BASELINE HEART RATE



ACHIEVED HEART RATE

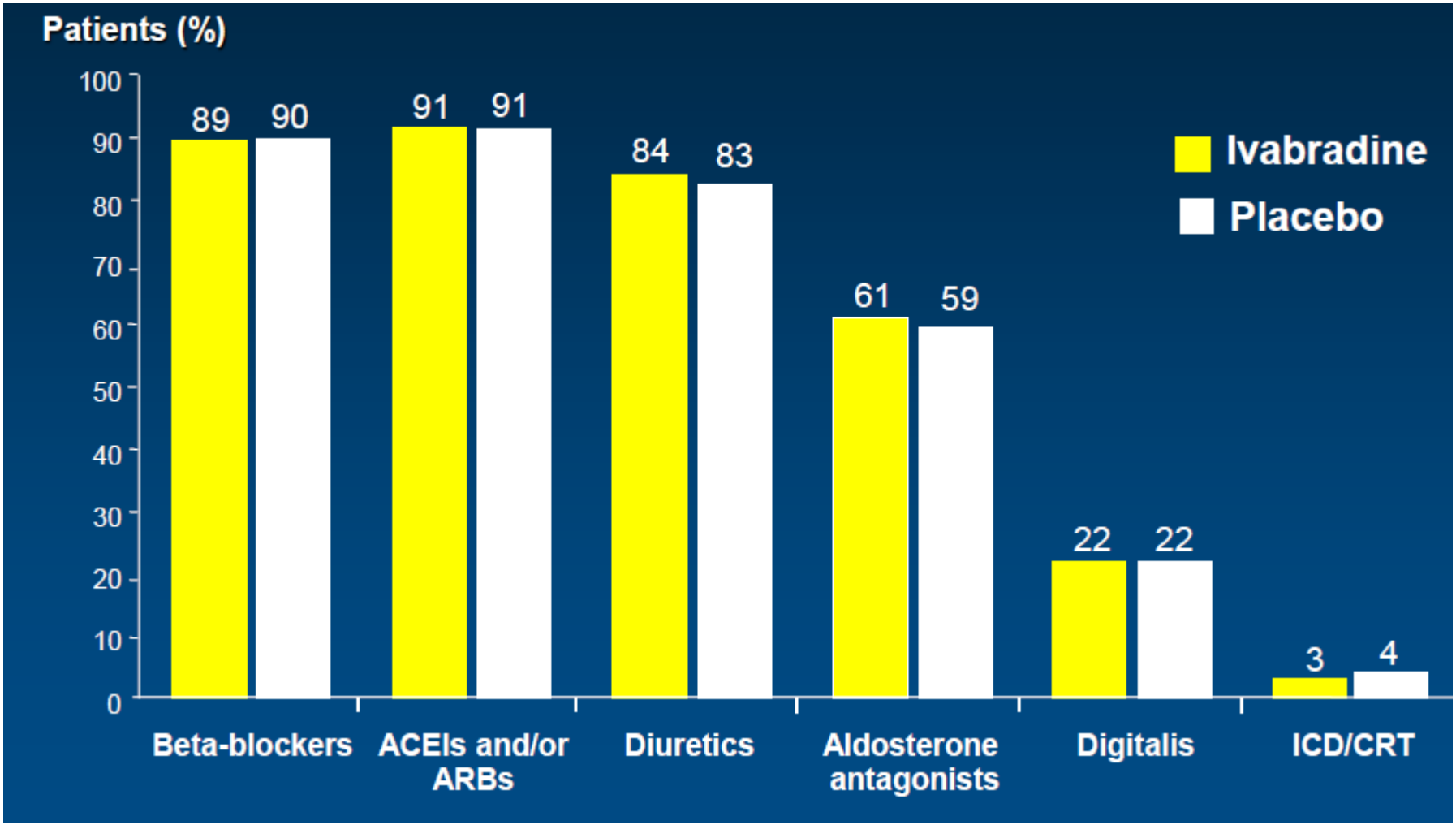


Eur Heart J 2005;26: 2259–2268

SHIFT Baseline Characteristics

	Ivabradine group (n=3241)	Placebo group (n=3264)
Demographic characteristics		
Age (years)	60·7 (11·2)	60·1 (11·5)
Sex (male)	2462 (76%)	2508 (77%)
Cardiac parameters		
Heart rate (bpm)	79·7 (9·5)	80·1 (9·8)
LVEF (%)	29·0% (5·1)	29·0% (5·2)
eGFR (mL/min per 1·73 m^2)	74·6 (22·9)	74·8 (23·1)
NYHA class		
Class II	1585 (49%)	1584 (49%)
Class III	1605 (50%)	1618 (50%)
Class IV	50 (2%)	61 (2%)
Medical history		
Primary cause of heart failure		
Ischaemic	2215 (68%)	2203 (67%)
Non-ischaemic	1026 (32%)	1061 (33%)
Myocardial infarction	1829 (56%)	1837 (56%)
Hypertension	2162 (67%)	2152 (66%)
Diabetes	973 (30%)	1006 (31%)
Previous stroke	228 (7%)	295 (9%)

SHIFT Baseline Medications



Lancet 2010; 376: 875-85

Secondary Endpoints

Endpoints	Hazard ratio	95% CI	*p* value
All-cause death	0.90	[0.80;1.02]	*p*=0.092
Death from HF	0.74	[0.58;0.94]	*p*=0.014
Hospitalisation for any cause	0.89	[0.82;0.96]	*p*=0.003
Hospitalisation for CV reason	0.85	[0.78;0.92]	*p*=0.0002

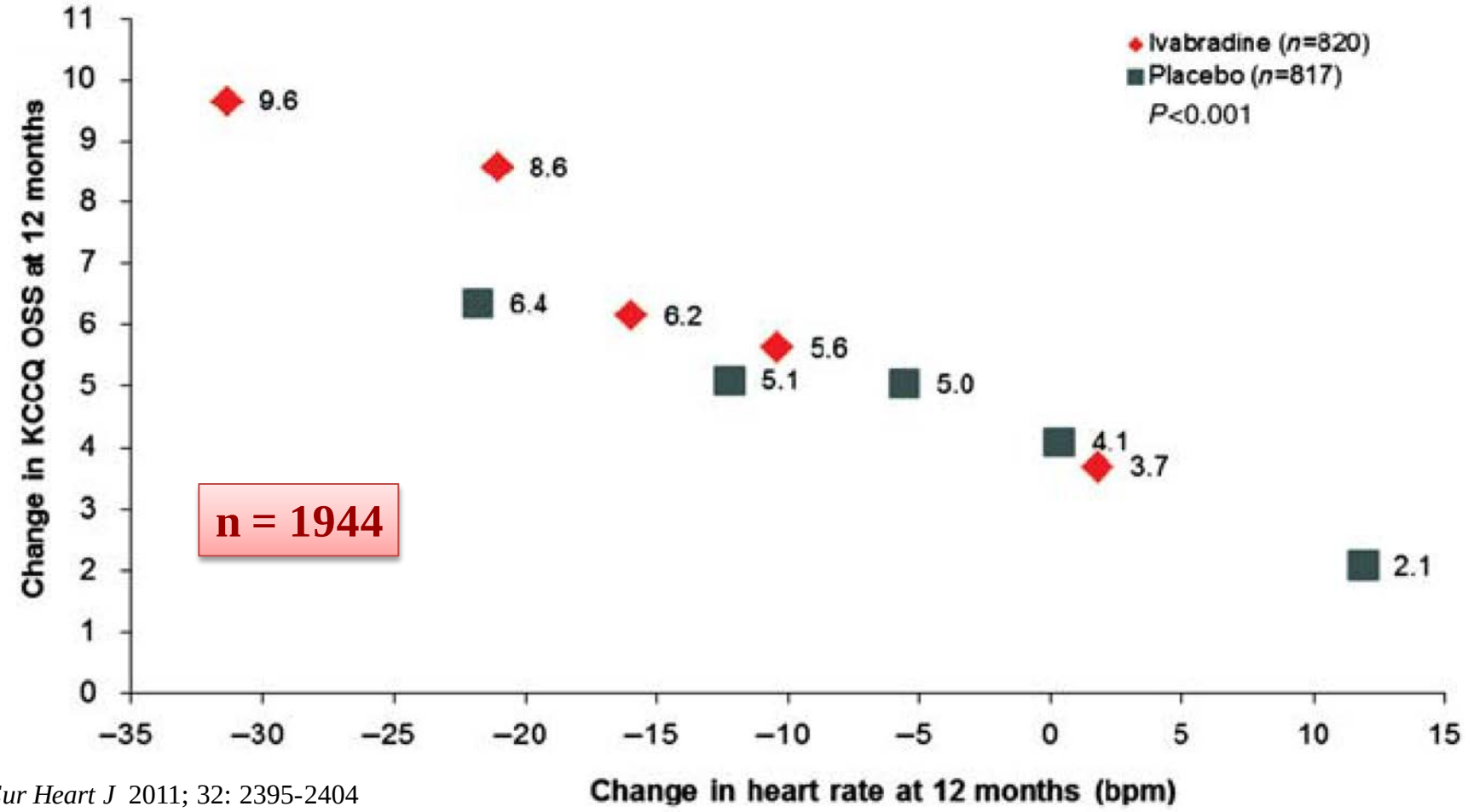
Main SHIFT Criticisms

- **Patients with resting heart rate > 70 bpm**
  (data from recent HF trials and registries suggest that 50% of patients have HR>70 bpm and ≈ 40% have HR>77 bpm)

- **Only 26% of patients were prescribed target doses of β-blockers by the investigators**
  43% in CIBIS-II, 64% in MERIT-HF, 65% in COPERNICUS

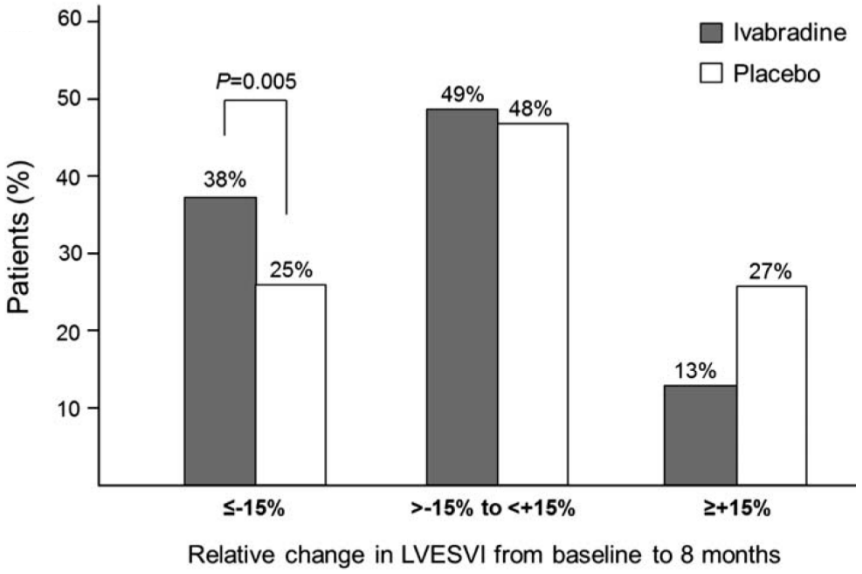
Effect of ivabradine on Quality of Life

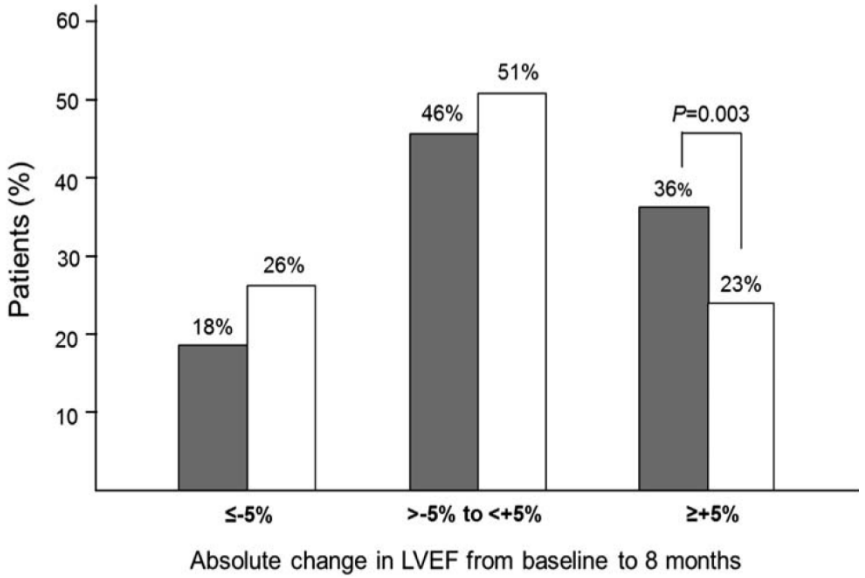
- Qol assessed by means of the Kansas City Cardiomyopathy Questionnaire (the higher the score the better the QoL)



Eur Heart J 2011; 32: 2395-2404

Effect of ivabradine on LV remodelling
(Echo Substudy, n=411)

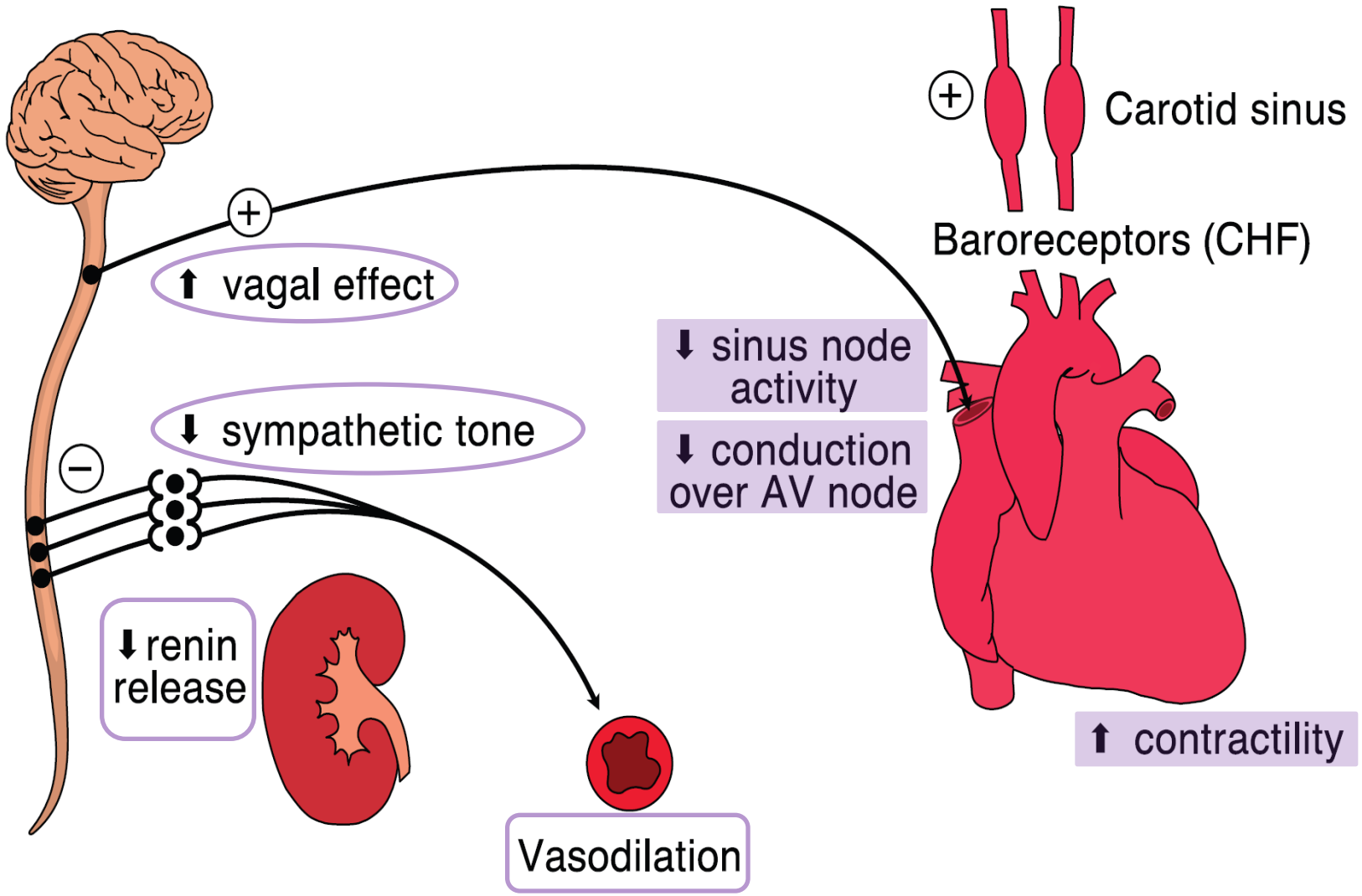




- Treatment with ivabradine **reduced LVESVI** compared with placebo (-5.8 ml/m^2, CI -8.8 to -2.7 ml/m^2, p<0.001)
- The reduction in LVESVI was independent of beta-blocker use
- Ivabradine also significantly improved LVEDVI and LVEF

Eur Heart J 2011; 32: 2507-2515

Digitalis


Carotid sinus
Baroreceptors (CHF)
⬆ vagal effect
⬇ sympathetic tone
⬇ sinus node activity
⬇ conduction over AV node
⬇ renin release
⬆ contractility
Vasodilation