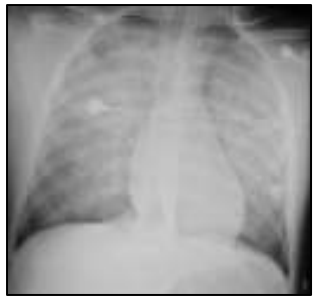
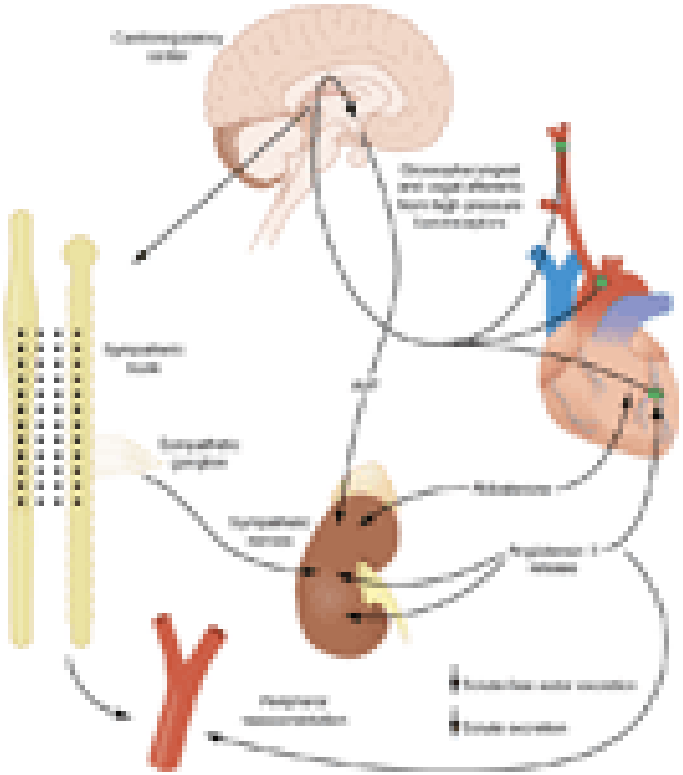
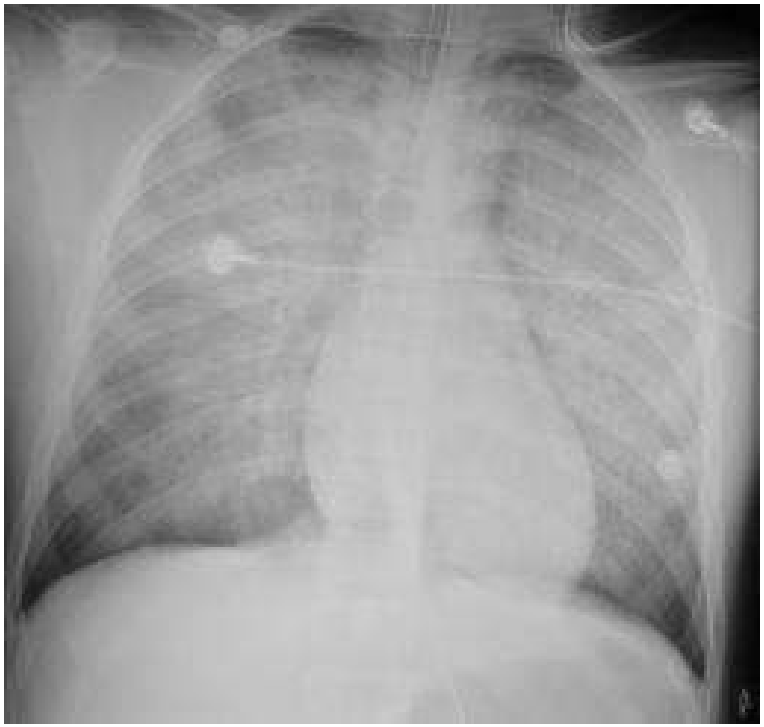


State of the art in heart failure treatment

Martin R Cowie
Professor of Cardiology
Imperial College London (Brompton Hospital)
m.cowie@imperial.ac.uk

Neurohormonal activation





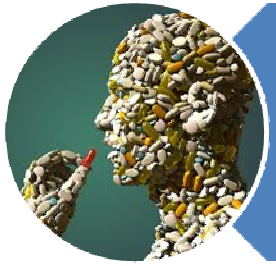
Heart Failure spectrum

ACE-I	AIRE/SAVE/TRACE (ramipril/captopril/trando)	SOLVD Treatment (enalapril)	CONSENSUS (enalapril)
Beta Blocker	CAPRICORN (carvedilol)	US Carvedilol/MERIT/CIBIS (carvedilol/metoprolol/biso)	COPERNICUS (carvedilol)
Aldosterone Blocker	EPHESUS (eplerenone)	EMPHASIS-HF (eplerenone) NYHA II mild CHF	RALES (spironolactone) Moderate-Severe HF NYHA III/IV
ARB	OPTIMAAL (Losartan) VALIANT (Valsartan)	ELITE (Losartan) Valheft/CHARM (Valsartan/Candesartan)	

ACE-I: Angiotensin Converting Enzyme-Inhibitor
ARB: Angiotensin II Receptor Blocker

Ever increasing evidence base....

EMPHASIS



SHIFT

Remote monitoring

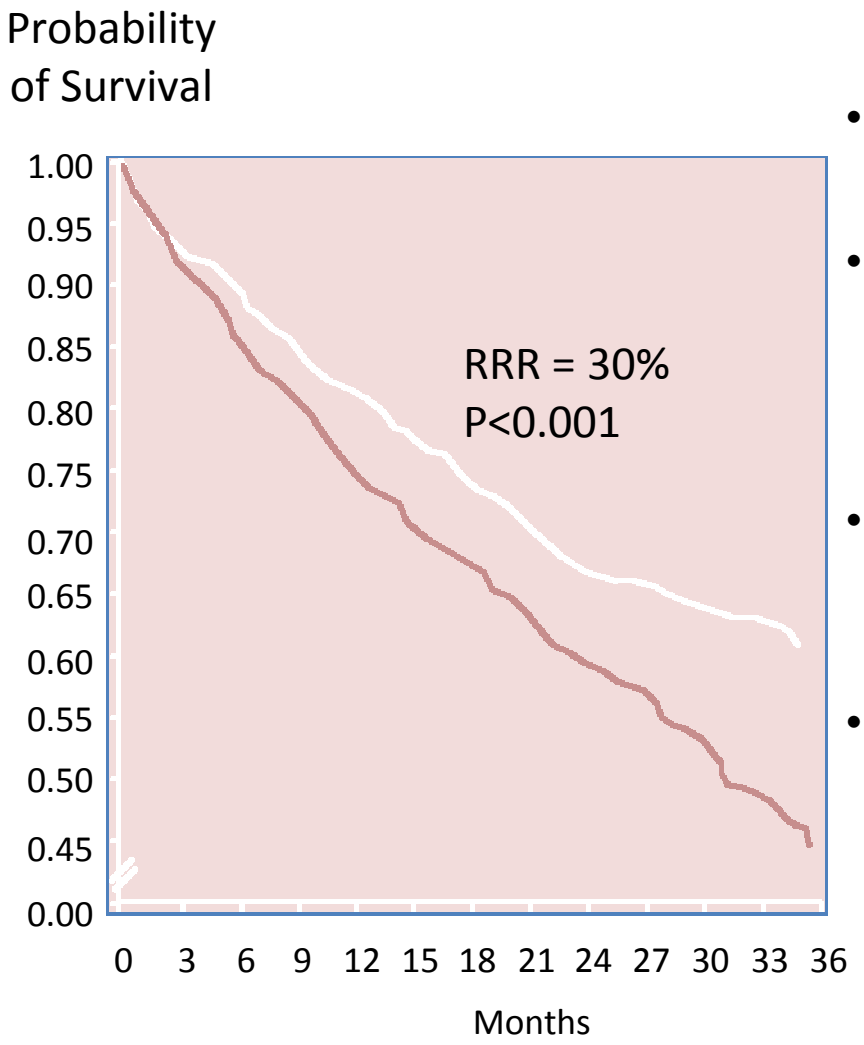
Ever increasing evidence base....

EMPHASIS

SHIFT

RAFT

Aldosterone antagonist therapy for heart failure due to LVSD



- The Randomised Aldactone Evaluation Study (RALES)
- 1663 patients with NYHA III or IV heart failure and ejection fraction $\leq$35% who were already treated with ACE inhibitor, diuretic $\pm$ digoxin
- Spironolactone 25mg od vs placebo, with patients followed for an average of 2 years
- 30% reduction in the risk of death ($p<0.001$) and 35% reduction in risk of hospitalisation ($p<0.001$) among patients randomised to spironolactone

Pitt et al, N Engl J Med, 1999

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D, Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D., for the EMPHASIS-HF Study Group*

NEJM 2011; 364: 11-21

METHODS

In this randomized, double-blind trial, we randomly assigned 2737 patients with New York Heart Association class II heart failure and an ejection fraction of no more than 35% to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

RESULTS

The trial was stopped prematurely, according to prespecified rules, after a median follow-up period of 21 months. The primary outcome occurred in 18.3% of patients in the eplerenone group as compared with 25.9% in the placebo group (hazard ratio, 0.63; 95% confidence interval [CI], 0.54 to 0.74; P<0.001).

NEJM 2011; 364: 11-21

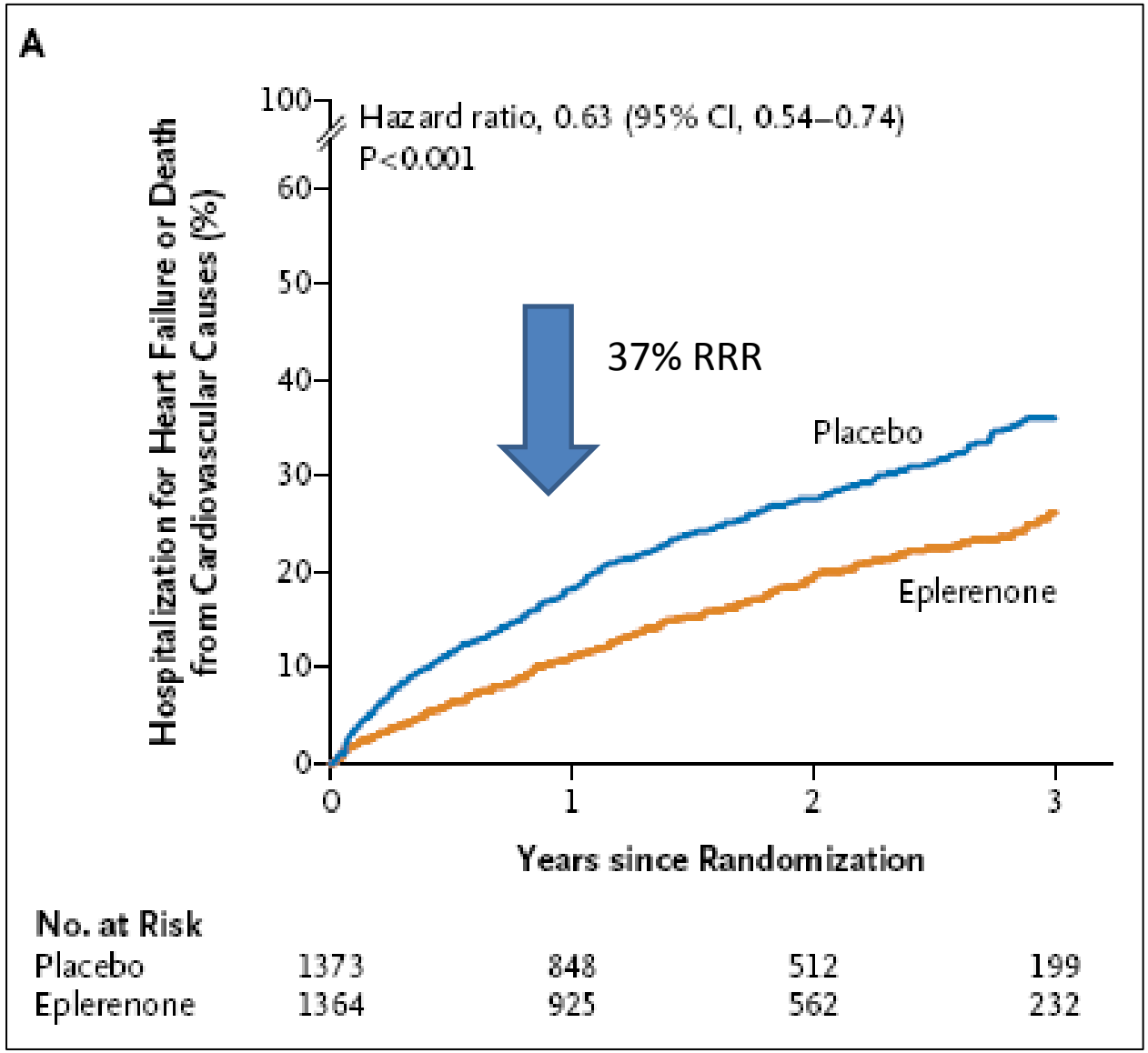
Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	Eplerenone (N=1364)	Placebo (N=1373)
Age — yr	68.7±7.7	68.6±7.6
Female sex — no. (%)	309 (22.7)	301 (21.9)
Race — no. (%)†		
White	1127 (82.6)	1141 (83.1)
Black	37 (2.7)	30 (2.2)
Asian	158 (11.6)	158 (11.5)
Other	42 (3.1)	44 (3.2)
Heart rate — beats/min	72±12	72±13
Blood pressure — mm Hg		
Systolic	124±17	124±17
Diastolic	75±10	75±10
Left ventricular ejection fraction — %	26.2±4.6	26.1±4.7
QRS duration — msec	121±45	122±44
QRS duration >130 msec in nonpaced baseline ECG — no./total no. (%)	298/1167 (25.5)	305/1158 (26.3)
Body-mass index‡	27.5±4.9	27.5±4.9
Principal cause of heart failure — no. (%)		
Ischemic heart disease	951 (69.7)	935 (68.1)
Nonischemic heart disease	410 (30.1)	436 (31.8)
Unknown	3 (0.2)	2 (0.1)
Duration of heart failure — yr	4.8±5.9	4.6±5.5

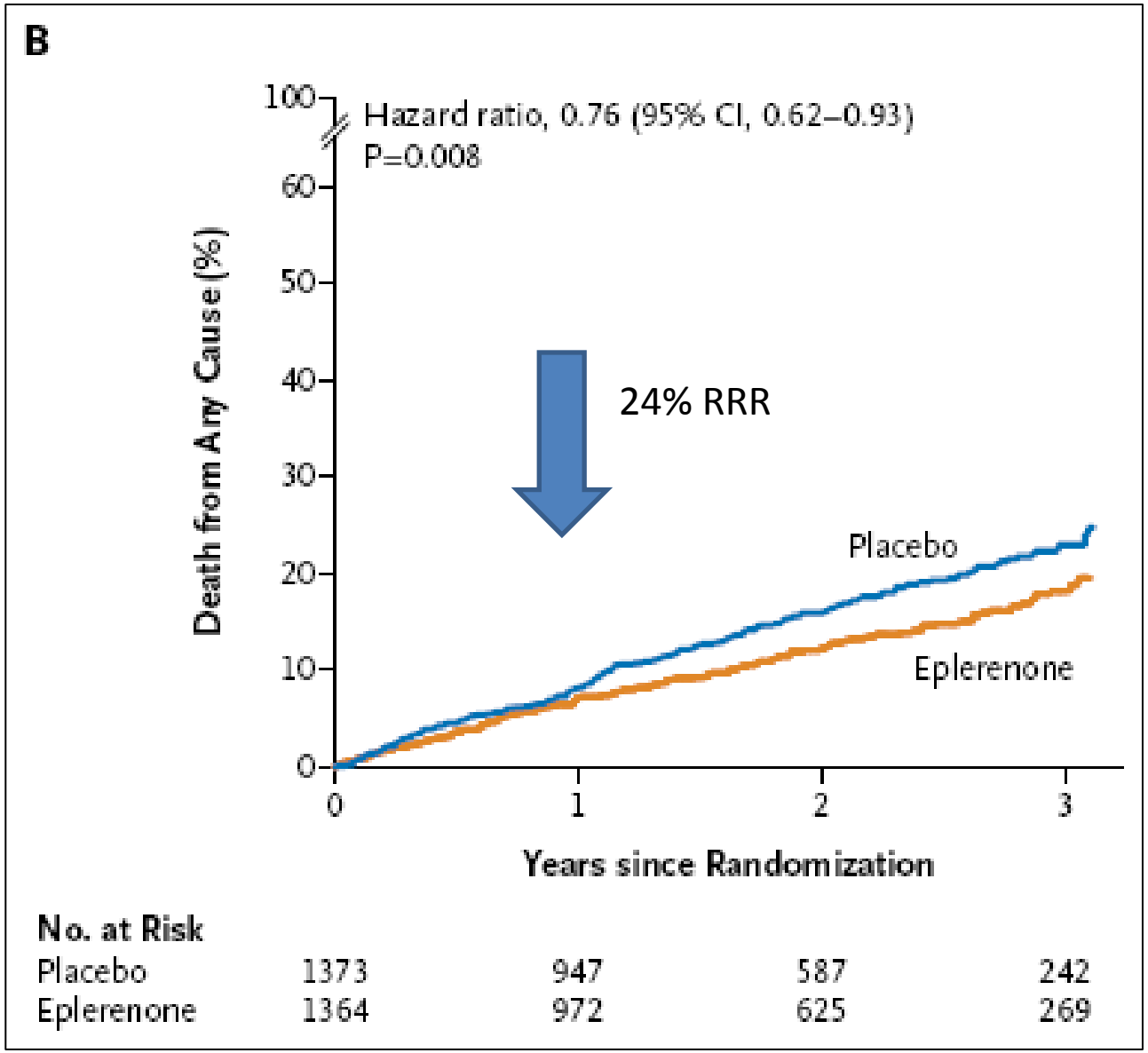
Concomitant medication

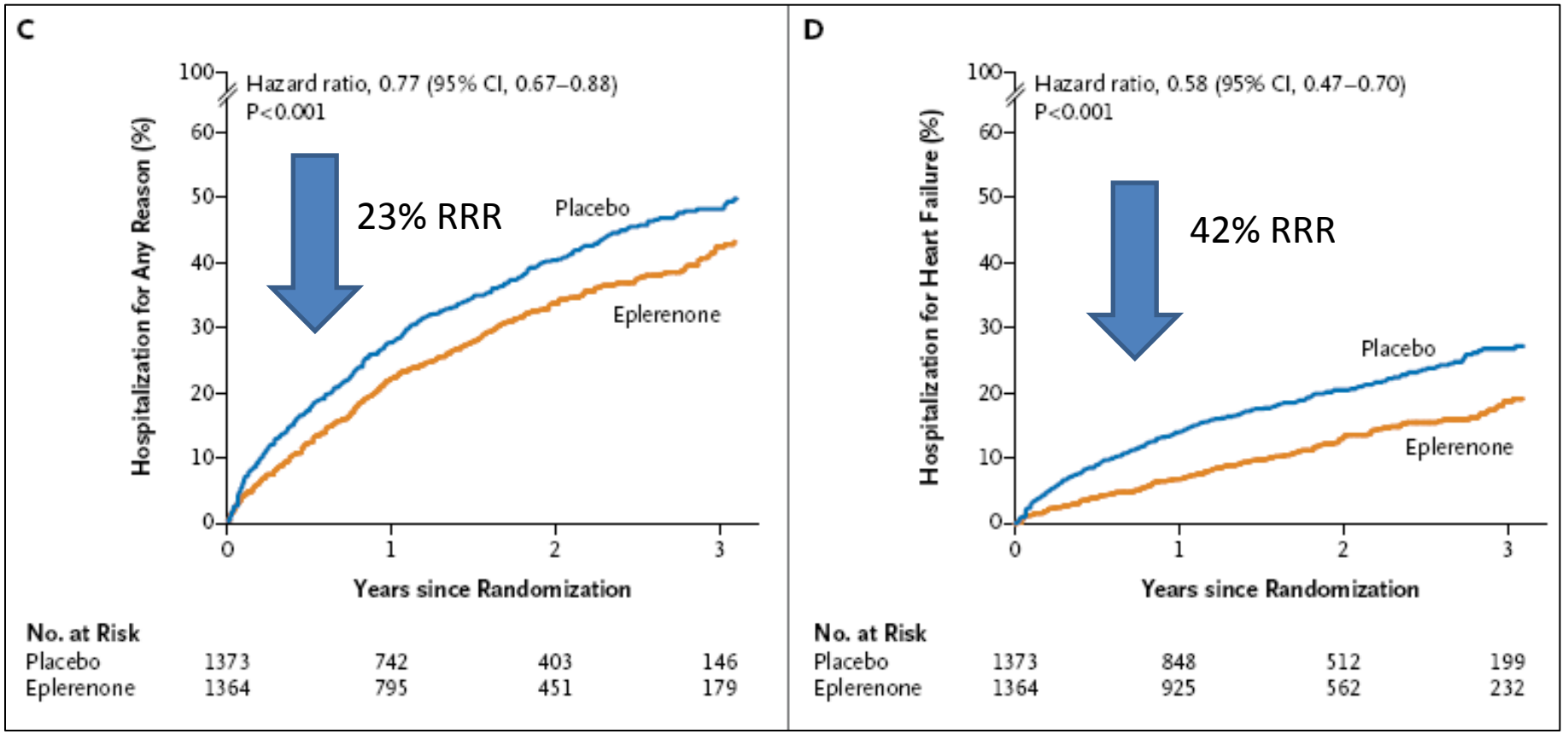
Medication — no. (%)		
Diuretic	1150 (84.3)	1176 (85.7)
ACE inhibitor	1068 (78.3)	1057 (77.0)
ARB	262 (19.2)	267 (19.4)
ACE inhibitor, ARB, or both	1282 (94.0)	1275 (92.9)
Beta-blocker	1181 (86.6)	1193 (86.9)
Digitalis glycosides	363 (26.6)	377 (27.5)
Antiarrhythmic drug	196 (14.4)	192 (14.0)
Antithrombotic drug (antiplatelet or oral anticoagulant)	1205 (88.3)	1214 (88.4)
Lipid-lowering agent	857 (62.8)	856 (62.3)

NEJM 2011; 364: 11-21



NEJM 2011; 364: 11-21


B
100
60
50
40
30
20
10
0
Hazard ratio, 0.76 (95% CI, 0.62–0.93)
P=0.008
Death from Any Cause (%)
24% RRR
Placebo
Eplerenone
0
1
2
3
Years since Randomization
No. at Risk
Placebo 1373 947 587 242
Eplerenone 1364 972 625 269


C
Hazard ratio, 0.77 (95% CI, 0.67–0.88)
P<0.001
23% RRR
Placebo
Eplerenone
Hospitalization for Any Reason (%)
100
60
50
40
30
20
10
0
0
1
2
3
Years since Randomization
No. at Risk
Placebo 1373 742 403 146
Eplerenone 1364 795 451 179
D
Hazard ratio, 0.58 (95% CI, 0.47–0.70)
P<0.001
42% RRR
Placebo
Eplerenone
Hospitalization for Heart Failure (%)
100
60
50
40
30
20
10
0
0
1
2
3
Years since Randomization
No. at Risk
Placebo 1373 848 512 199
Eplerenone 1364 925 562 232

EMPHASIS-HF Study

SAFETY ADVERSE EVENTS

Patients with an adverse event (AE)*

Outcome	Eplerenone (N=1360)	Placebo (N=1373)	P Value
All	979 (72)	1007 (73.6)	0.37
Hyperkalemia – n (%)	109 (8)	50 (3.7)	<0.001
Hypokalemia – n (%)	16 (1.2)	30 (2.2)	0.05
Renal failure – n (%)	38 (2.8)	41 (3.0)	0.82
Hypotension – n (%)	46 (3.4)	37 (2.7)	0.32
Gynecomastia and other breast disorders – n (%)	10 (0.7)	14 (1.0)	0.54

*Investigator reported adverse events

EMPHASIS-HF Study

SAFETY: DRUG DISCONTINUATIONS DUE TO AE

Outcome	Patients with an adverse event* leading to drug withdrawal — no. (%)		
	Eplerenone (N=1360)	Placebo (N=1373)	P Value
All	188 (13.8)	222 (16.2)	0.09
Hyperkalemia – n (%)	15 (1.1)	12 (0.9)	0.57
Hypokalemia – n (%)	0	3 (0.2)	0.25
Renal failure – n (%)	4 (0.3)	6 (0.4)	0.75
Hypotension – n (%)	0	3 (0.2)	0.25
Gynecomastia and other breast disorders – n (%)	2 (0.1)	2 (0.1)	1.00

*Investigator reported adverse events

EMPHASIS-HF Study

SAFETY: PRESPECIFIED ADJUDICATED EVENTS

Outcome	Eplerenone (N=1364)	Placebo (N=1373)	Hazard Ratio (95% CI)	P Value
Hospitalization for worsening renal failure*	9 (0.7)	8 (0.6)	0.97 (0.37, 2.58)	0.95
Hospitalization for hyperkalemia*	4 (0.3)	3 (0.2)	1.15 (0.25, 5.31)	0.85

EMPHASIS HF study results presentation. Presented at AHA congress 2010.
http://click.heartemail.org/?qs=c809010216325f9c50c94e221d4e3fd62e92e966356857c348c68a0675e1e1a3. Accessed November 21, 2010

Important addition to therapy....
For mild HF with low EF

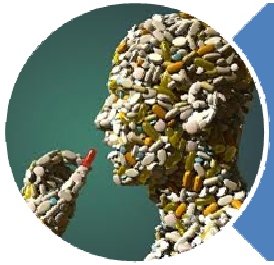
NNT

- To prevent one patient experiencing the primary endpoint, per year of follow up, is 19
- To postpone one death, per year of follow up, is 51

NB Eplerenone not yet licensed for treatment of EMPHASIS population

Ever increasing evidence base....

EMPHASIS

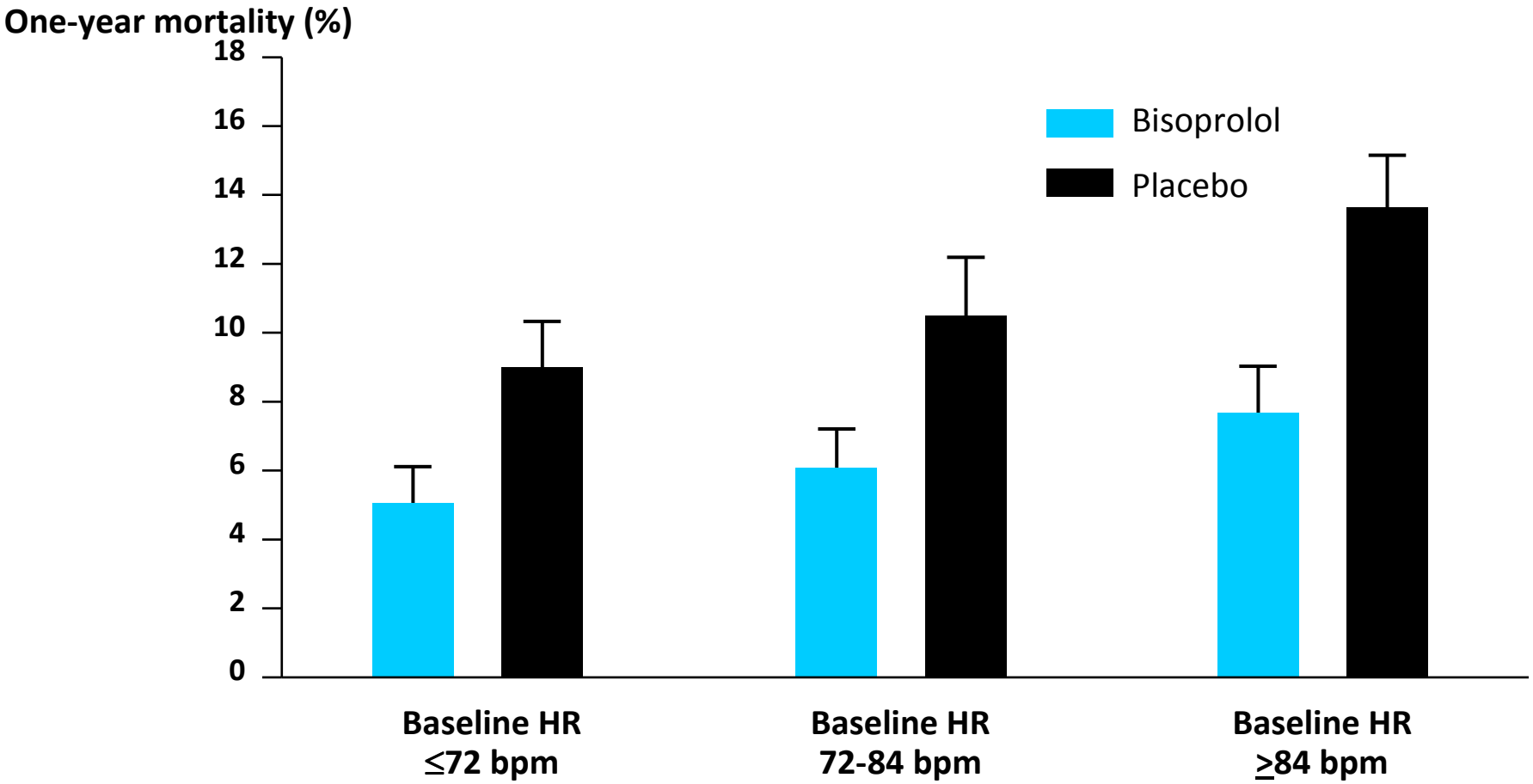


SHIFT

RAFT

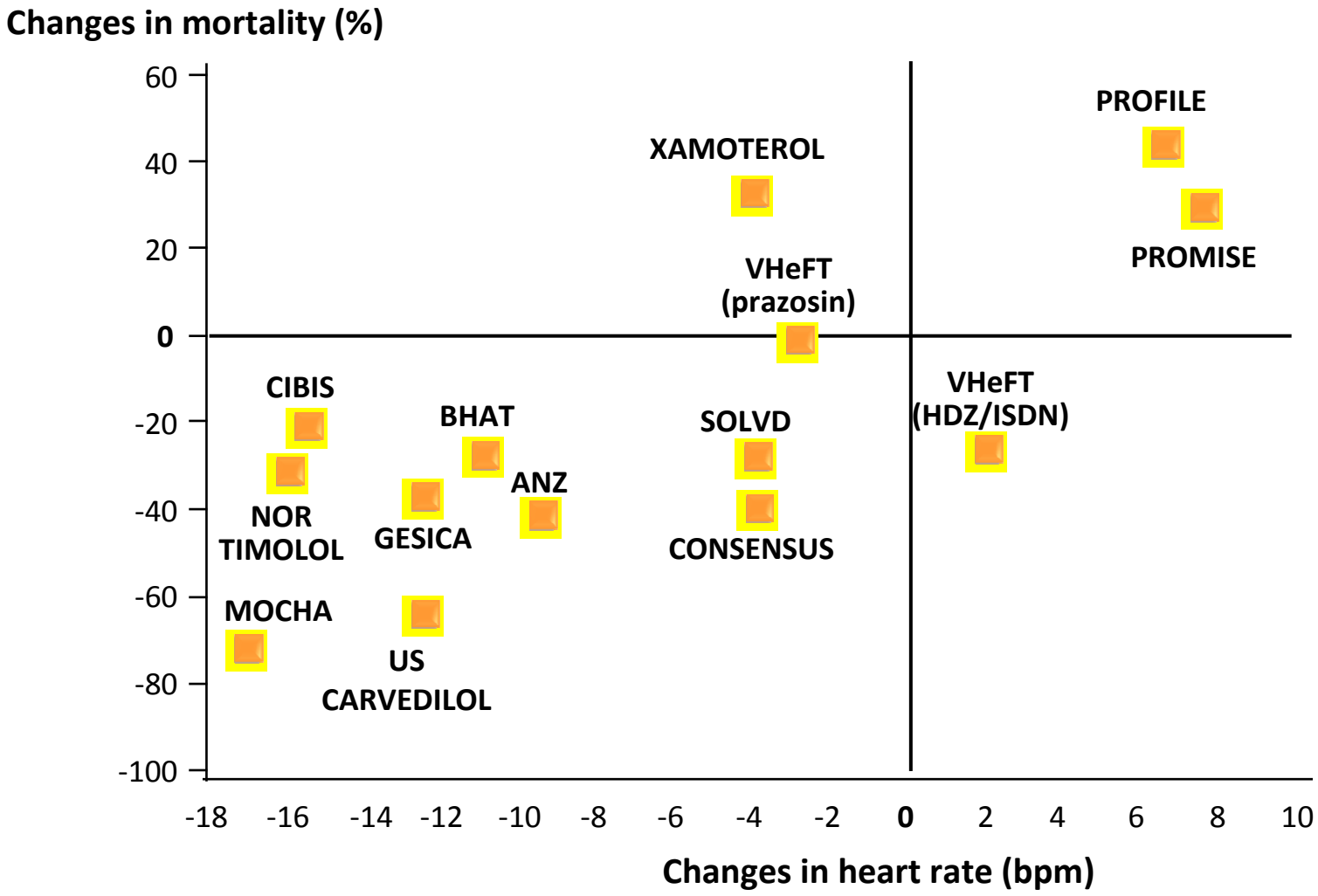
Heart rate strongly associated with mortality

The CIBIS-2 study (n=2539)



Lechat P, et al. *Circulation*. 2001;103:1428-1433.

Reduction of heart rate and outcomes in CHF trials



Kjekshus J, et al. *Eur Heart J*. 1999;1(suppl.H):H64-H69.

Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial

Primary objective

To evaluate whether the I_f inhibitor ivabradine improves cardiovascular outcomes in patients with:

1. Moderate to severe chronic heart failure
2. Left ventricular ejection fraction $\leq$ 35%
3. Heart rate $\geq$ 70 bpm in sinus rhythm
4. Best recommended therapy

Ivabradine 5mg bd or placebo, titrated to 7.5mg/5mg/2.5mg according to tolerability

Study end points

Primary composite end point

- Cardiovascular death
- Hospitalization for worsening heart failure

Other end points

- All-cause / CV / HF death
- All-cause / CV / hospitalization for heart failure
- Composite of CV death, hospitalization for HF or nonfatal MI
- NYHA class / Patient & Physician Global Assessment

Median study duration 22.9 months, maximum 41.7 months

Swedberg K, et al. *Eur J Heart Fail.* 2010;12:75-81.

Baseline characteristics

	Ivabradine 3241	Placebo 3264
Mean age (y)	60.7	60.1
Male (%)	76	77
Ischemic etiology (%)	68	67
NYHA II (%)	49	49
NYHA III/IV (%)	51	51
Previous MI (%)	56	56
Diabetes (%)	30	31
Hypertension (%)	67	66

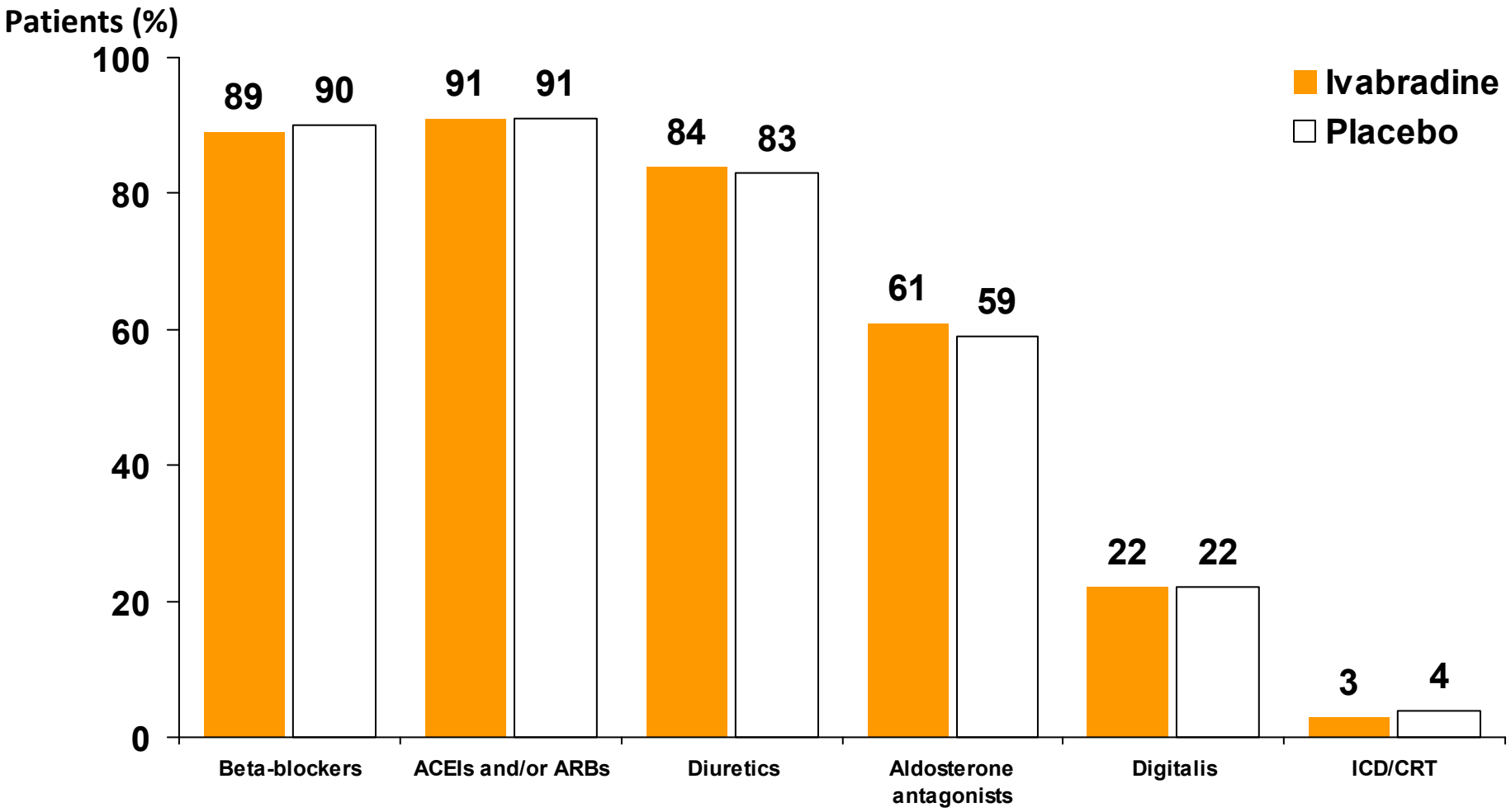
Swedberg K, et al. *Lancet*. 2010;376:875-885.

Baseline characteristics

	Ivabradine 3241	Placebo 3264
Mean heart rate (bpm)	80	80
Mean LVEF (%)	29	29
Mean SBP (mm Hg)	122	121
Mean DBP (mm Hg)	76	76
eGFR (mL/min/1.73 $m^{2)}$	75	75

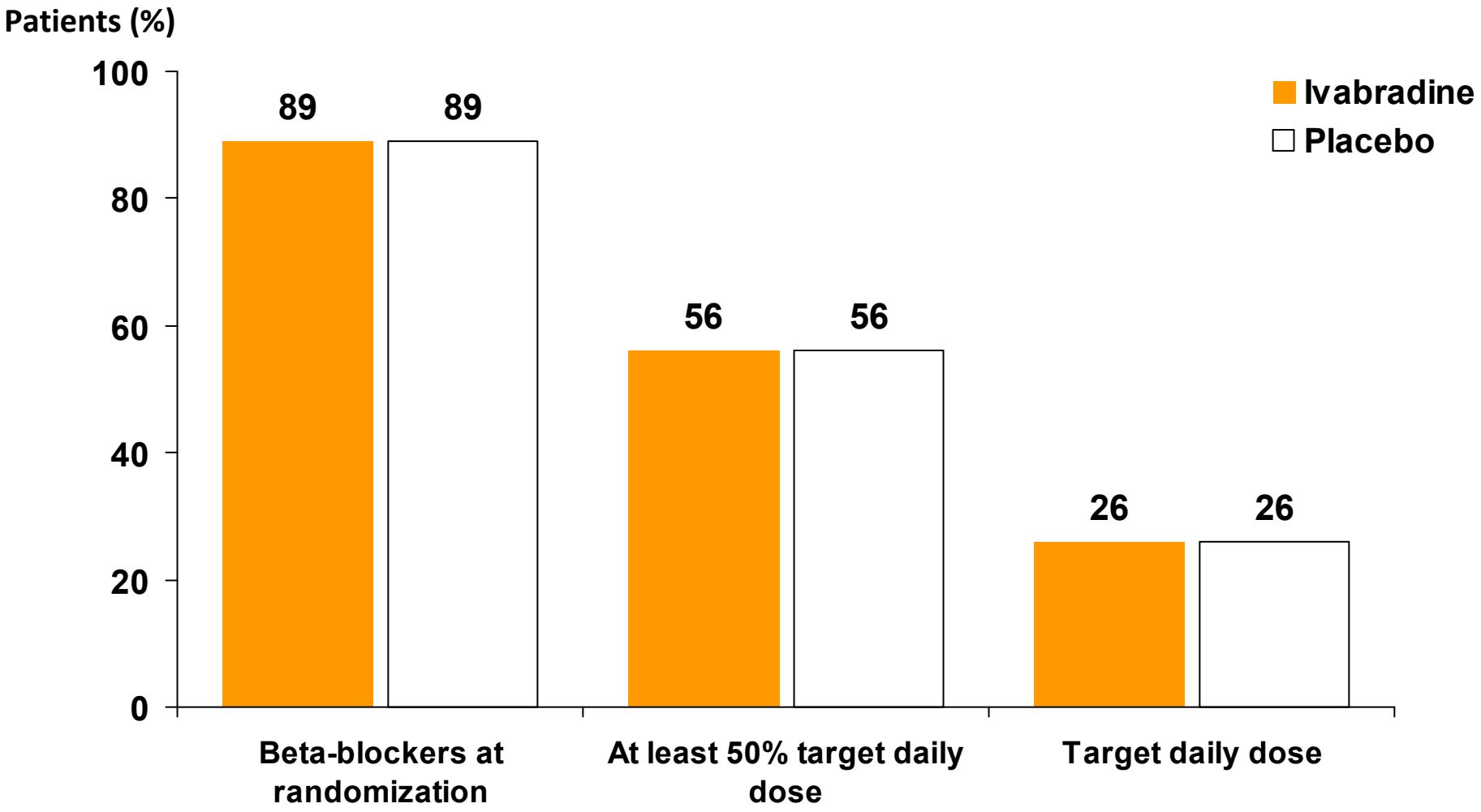
Swedberg K, et al. *Lancet*. 2010;376:875-885.

Chronic heart failure background treatment



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

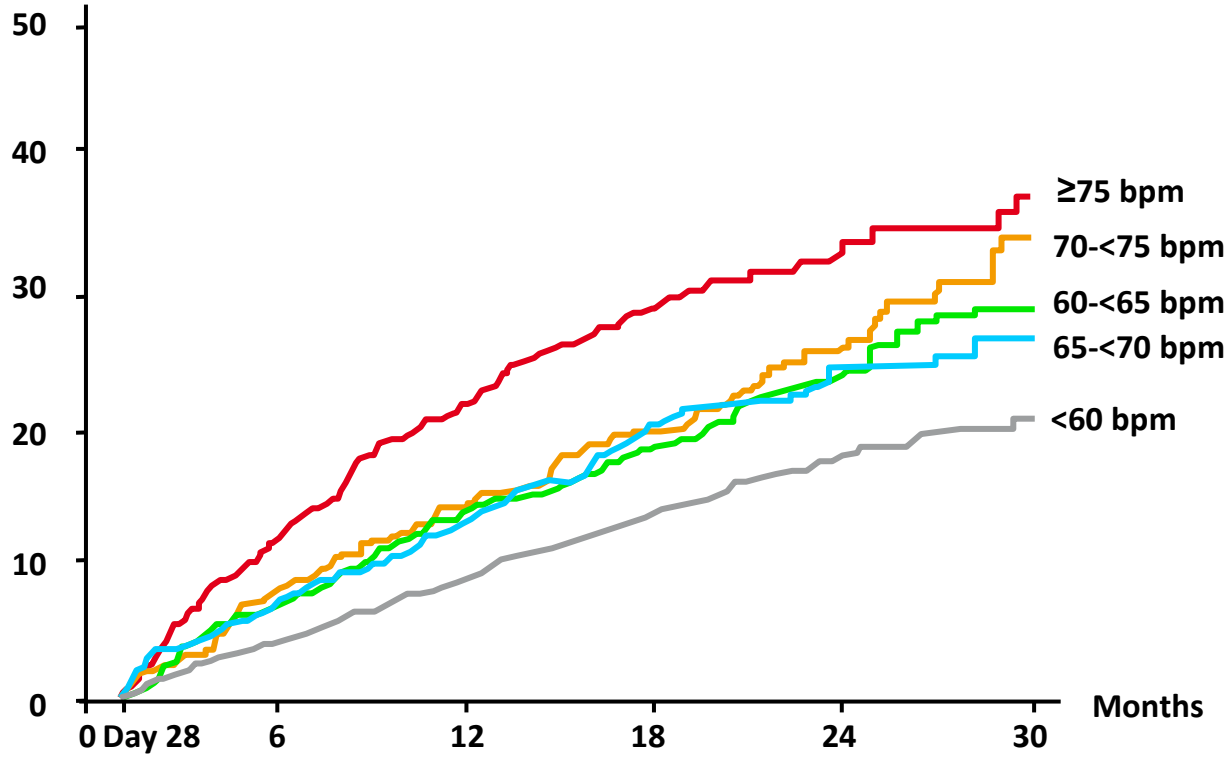
Background beta-blocker treatment



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

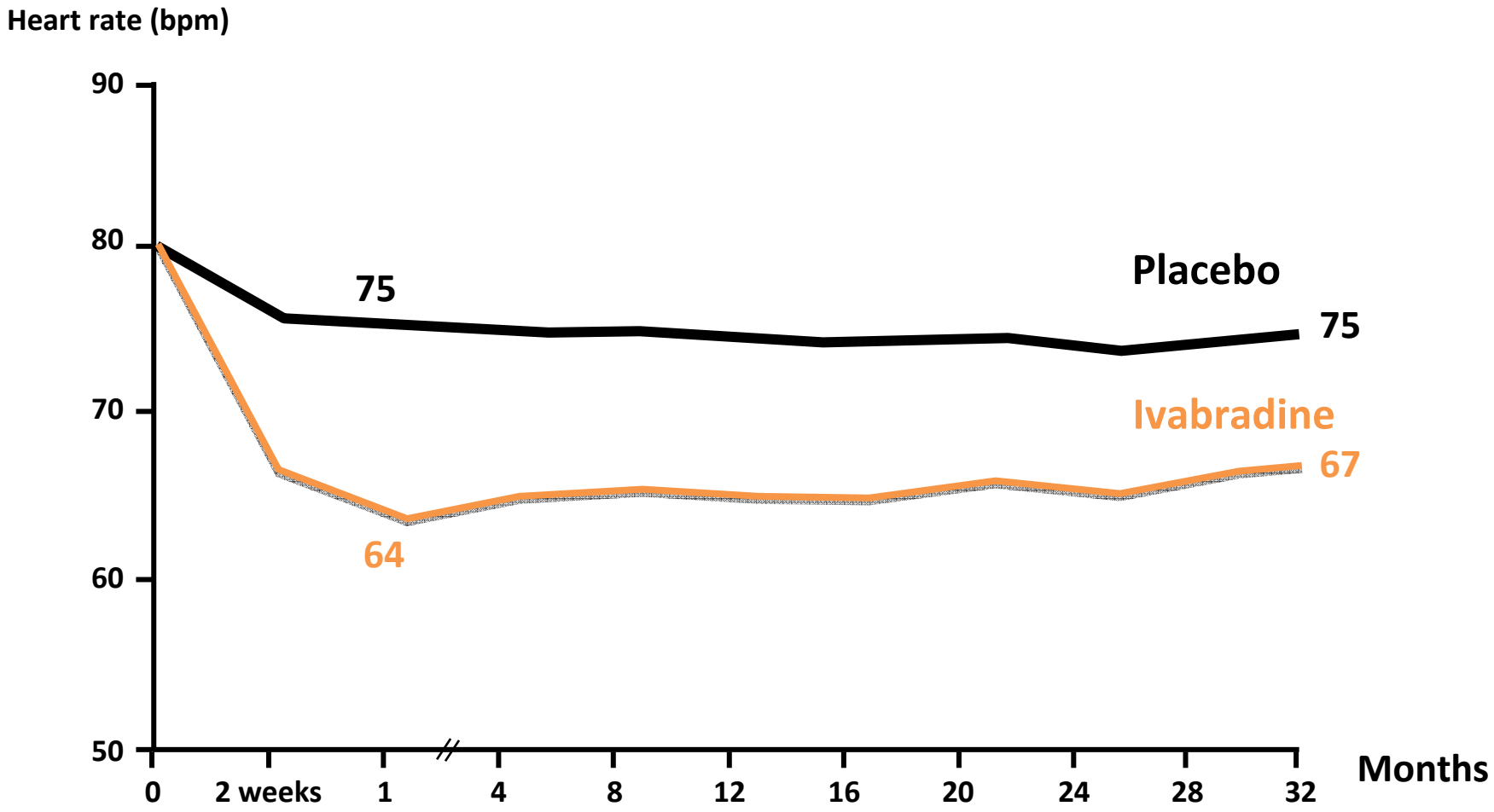
Primary composite endpoint according to heart rate achieved at D28*

Patients with primary composite endpoint in the ivabradine group (%)



*Data exclude patients reaching primary composite endpoint in the first 28 days

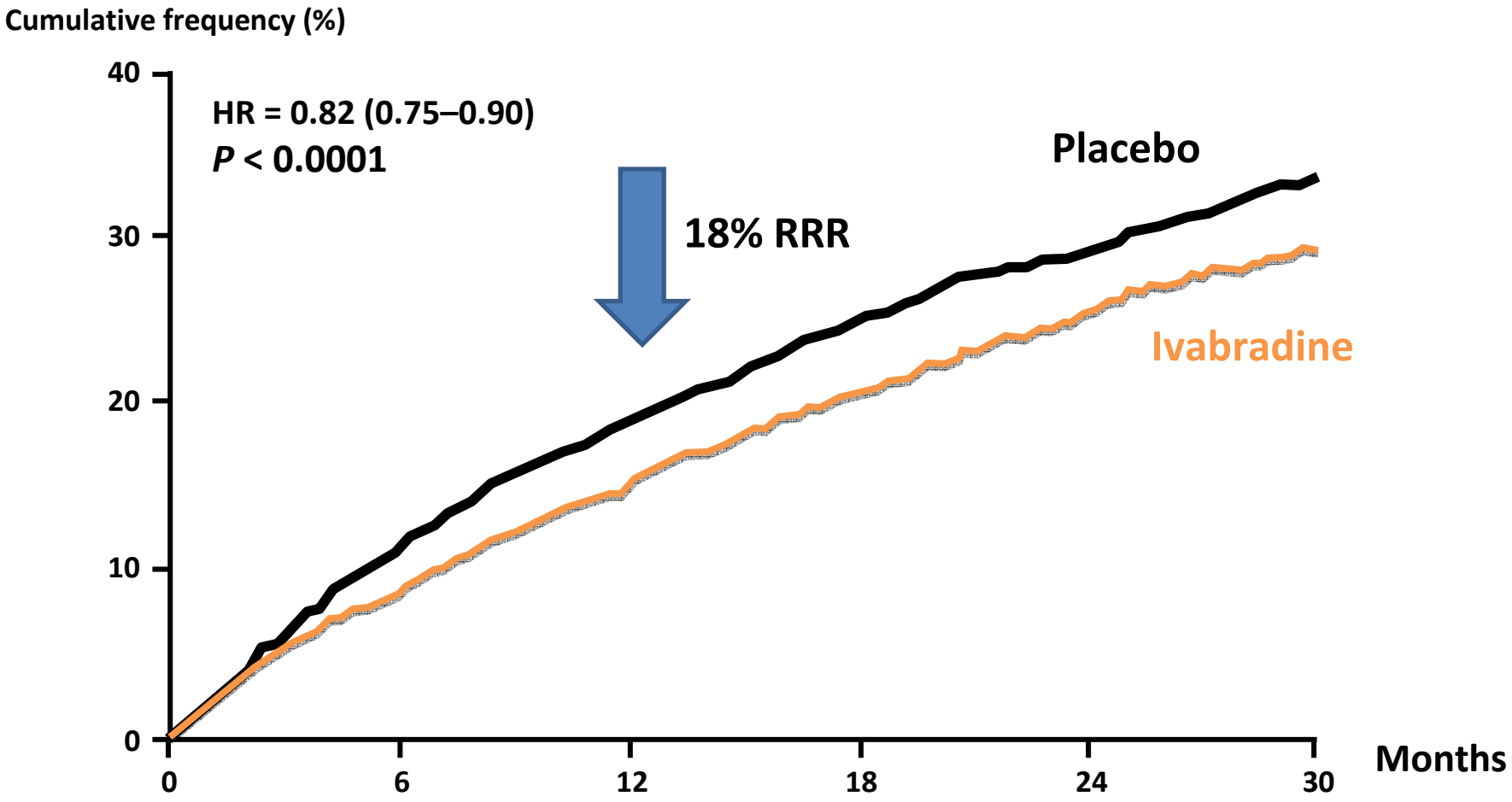
Mean heart rate reduction



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

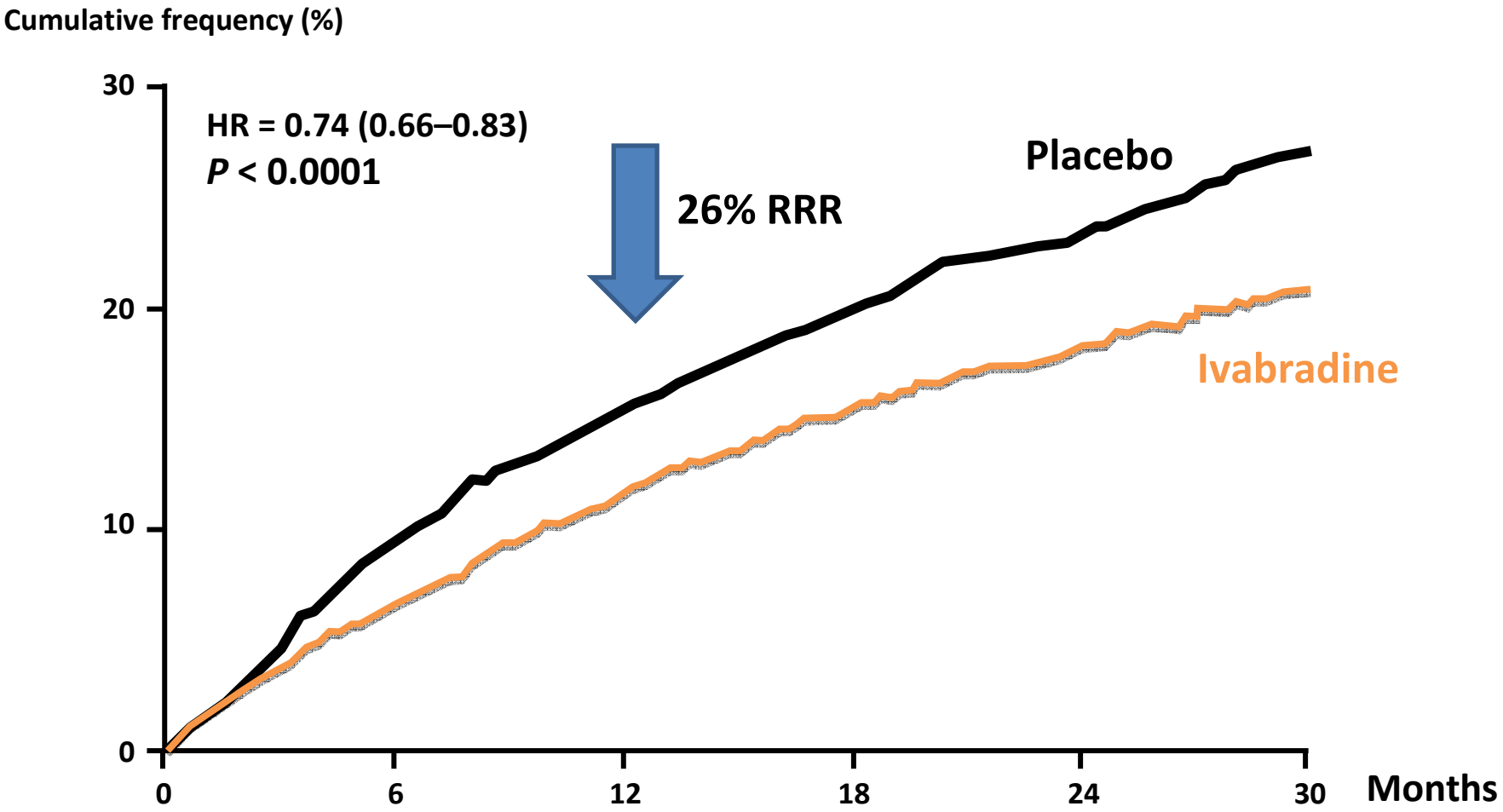
Primary composite end point

(CV death or hospital admission for worsening HF)



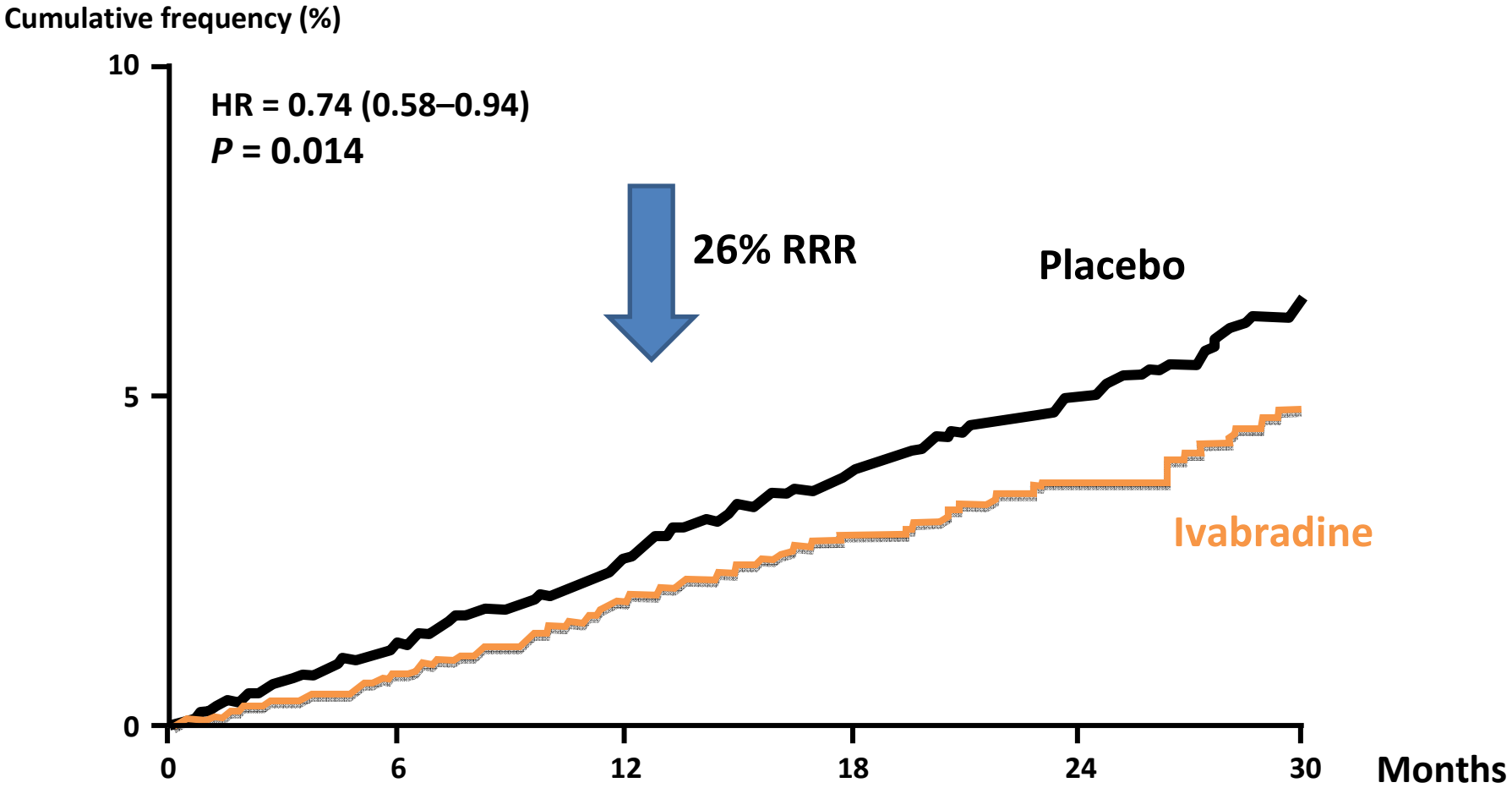
Swedberg K, et al. *Lancet*. 2010;376:875-885.

Hospitalization for worsening heart failure



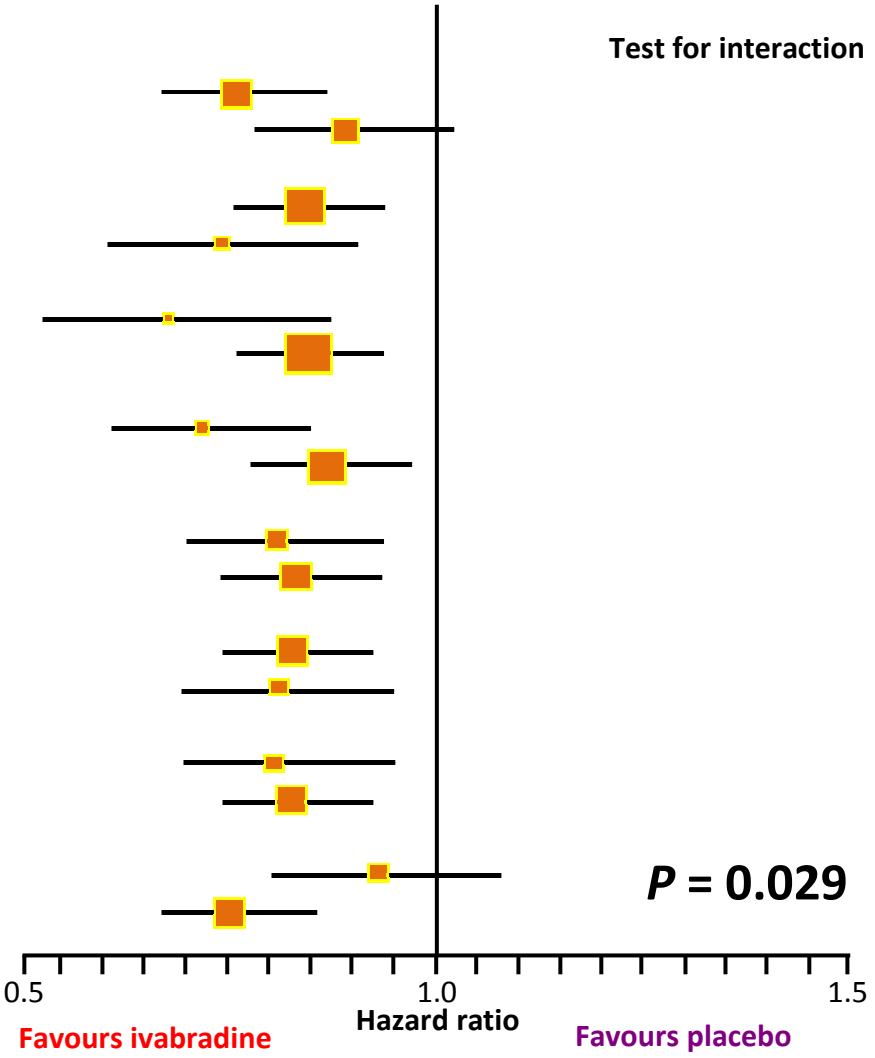
Swedberg K, et al. *Lancet*. 2010;376:875-885.

Death from heart failure



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

Effect of ivabradine in prespecified subgroups



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

Incidence of selected adverse events

	Patients with an event n= 6492		
	Ivabradine n=3232, n (%)	**Placebo n=3260, n (%)**	***P* value**
All serious adverse events	**1450** (45%)	**1553** (48%)	**0.025**
All adverse events	2439 (75%)	2423 (74%)	0.303
Symptomatic bradycardia	150 (5%)	32 (1%)	<0.0001
Asymptomatic bradycardia	184 (6%)	48 (1%)	<0.0001
Atrial fibrillation	306 (9%)	251 (8%)	0.012
Phosphenes	89 (3%)	17 (1%)	<0.0001
Blurred vision	17 (1%)	7 (<1%)	0.042

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

Treatment discontinuation

	Patients with an adverse event, leading to withdrawal		
	Ivabradine n=3232, n (%)	**Placebo** n=3260, n (%)	***P* value**
All adverse events	467 (14%)	416 (13%)	0.051
Symptomatic bradycardia	20 (1%)	5 (<1%)	0.002
Asymptomatic bradycardia	28 (1%)	5 (<1%)	<0.0001
Atrial fibrillation	135 (4%)	113 (3%)	0.137
Phosphenes	7 (<1%)	3 (<1%)	0.224
Blurred vision	1 (<1%)	1 (<1%)	1.000

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

Important addition to therapy....
For those in sinus rhythm with HR > 70bpm and low EF

NNT

- To prevent one patient experiencing the primary endpoint, per year of follow up, is 26
- To postpone one hospitalisation for HF, per year of follow up, is 27

NB Ivabradine not yet licensed for treatment of SHIFT population

Ever increasing evidence base….

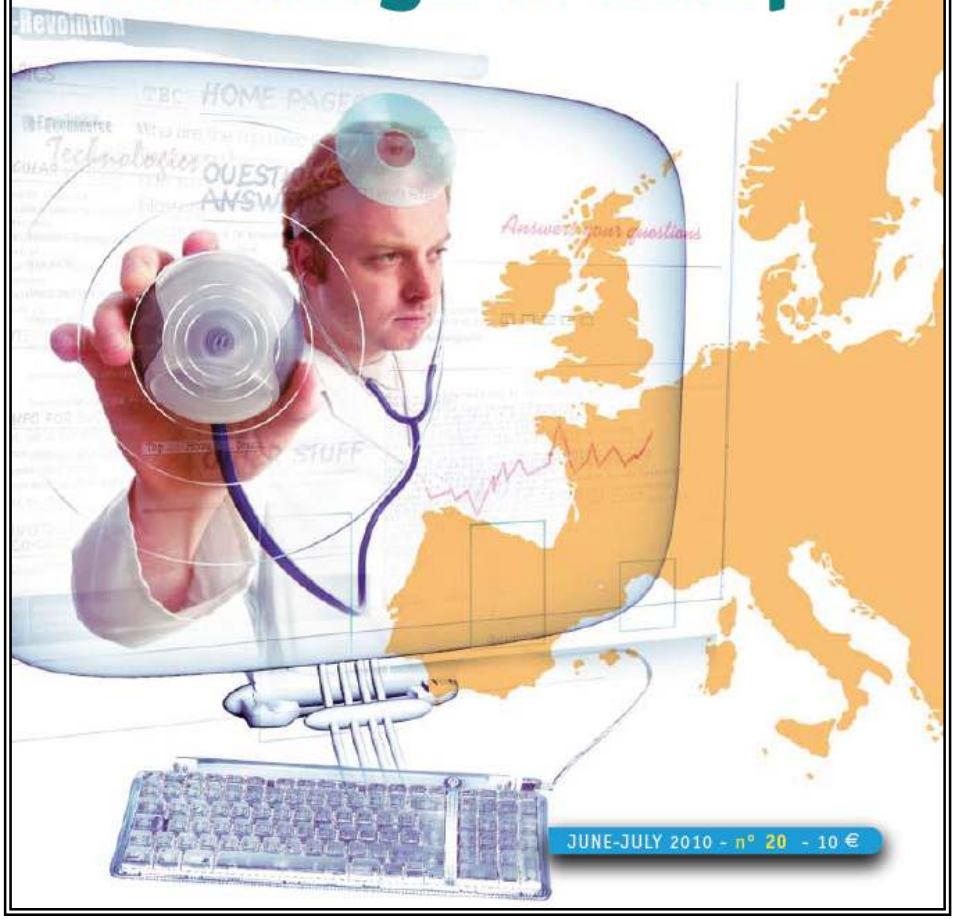
EMPHASIS

SHIFT

Remote monitoring

THE EUROPEAN FILES

The Telemedicine challenge in Europe



JUNE-JULY 2010 - n° 20 - 10 €

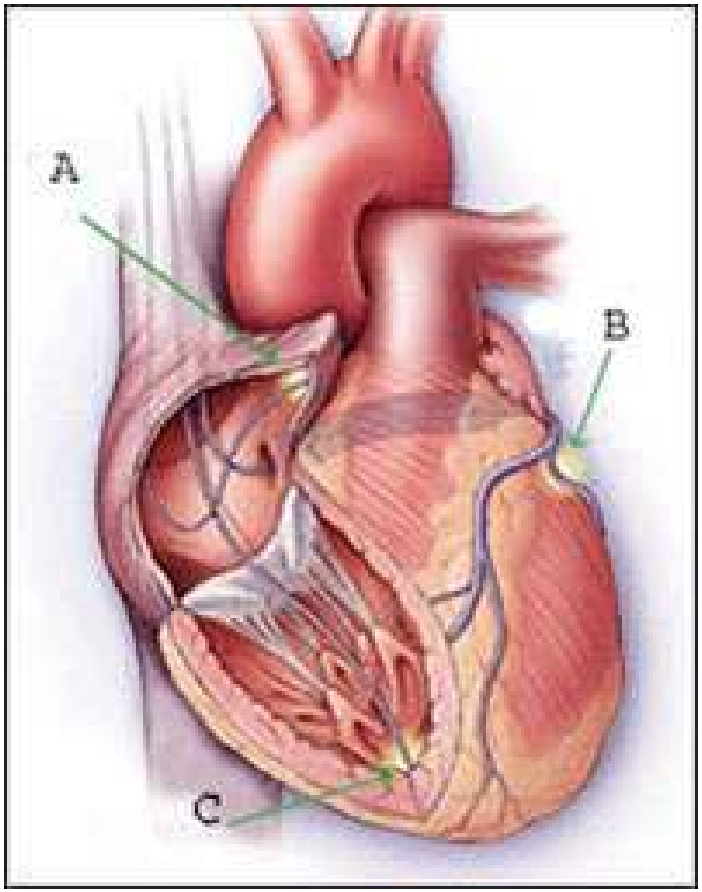
Remote monitoring

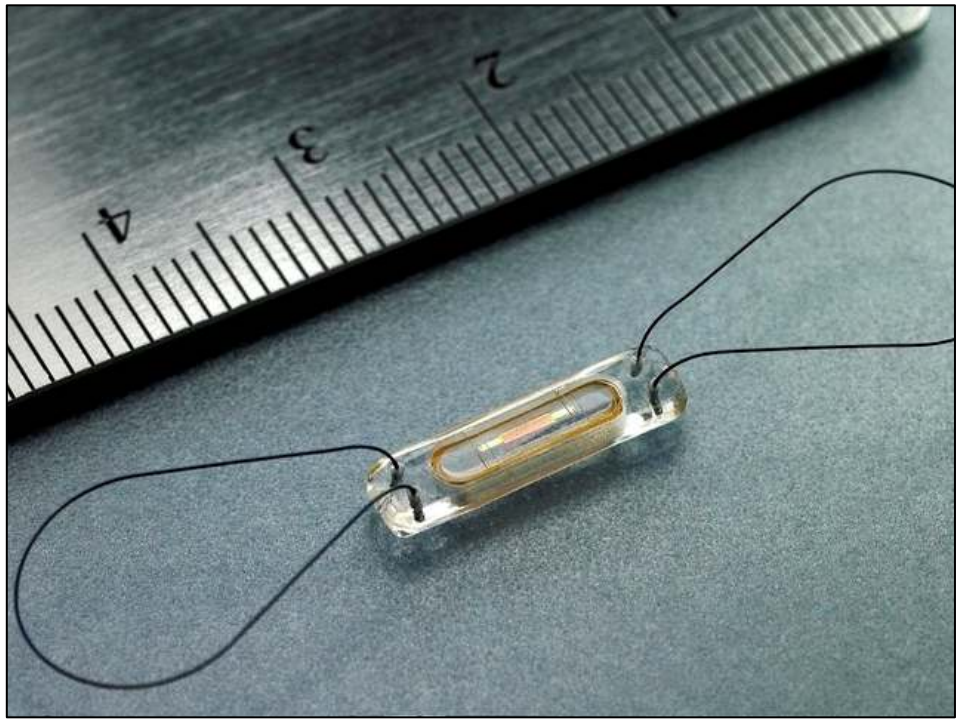
- Initially, telephone monitoring of patients
- Then, patient-initiated monitoring using stand alone equipment
- More recently, data can be transmitted often without patient needing to do anything – usually from implanted device
  - Some devices implanted for therapeutic indications
  - In future, perhaps implantation of monitoring-only devices

Stand alone system

Implanted systems

Implanted systems





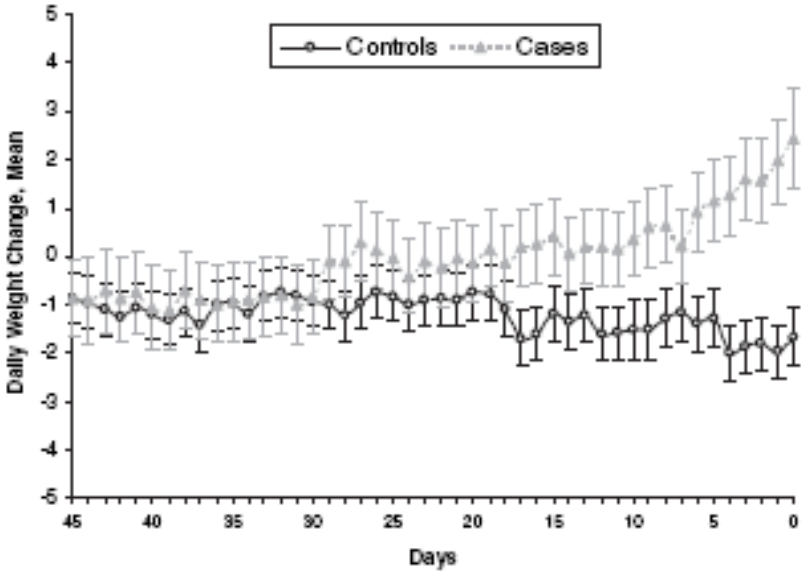
What can be monitored?

- Symptoms
- Body weight
- Pulse rate, Blood pressure, oxygen saturation, ECG
- Patient activity
- Heart rate variability
- Arrhythmic episodes (atrial fibrillation; ventricular tachycardia/fibrillation)
- Transthoracic impedance
- Right ventricular or pulmonary artery pressure
- Left atrial pressure
- And on and on……

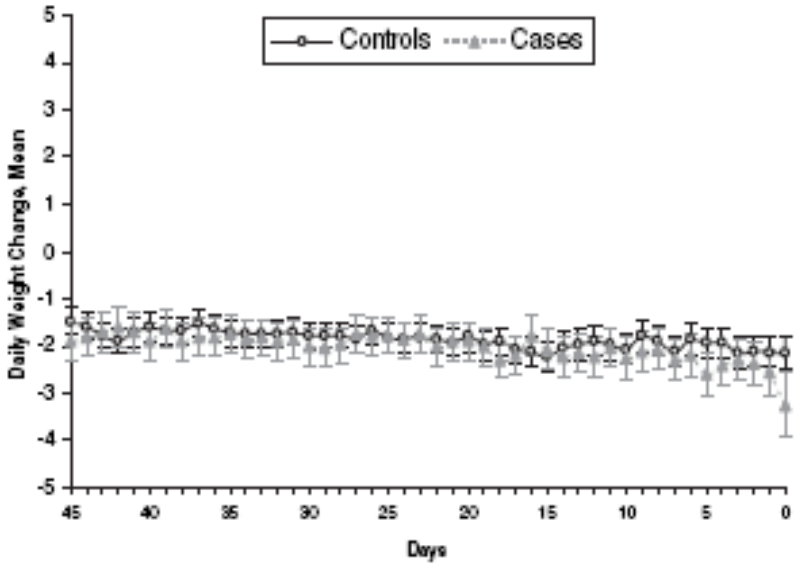
What is the rationale?

- Frequent monitoring by a health professional may enable earlier intervention to treat deterioration in e.g. heart failure
- The intervention can be:
  - Reminders about lifestyle and diet
  - Advice about medication (e.g. adjustment of diuretic dose)
  - Recall for early clinic review (primary or secondary care)
  - Home visit
  - Urgent hospitalisation
- Remote monitoring usually (but not always) builds on self-monitoring, and helps reinforce educational messages
- Finding the best method of telemonitoring, and what to monitor has been a challenge

The potential of monitoring



Daily weight change preceding HF hospitalisation



Daily weight change preceding non-HF hospitalisation

Chaudhry SI et al. Circulation 2007; 116: 1549-54

THE COCHRANE COLLABORATION®

Structured telephone support or telemonitoring programmes for patients with chronic heart failure (Review)

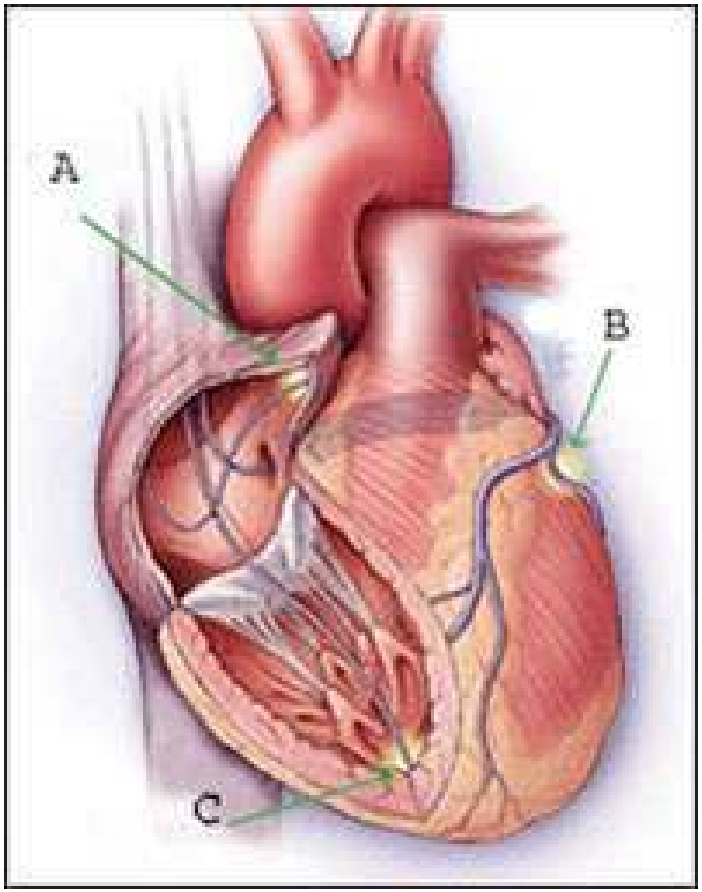
- Studies: telephone support (16), telemonitoring (11), both (2)

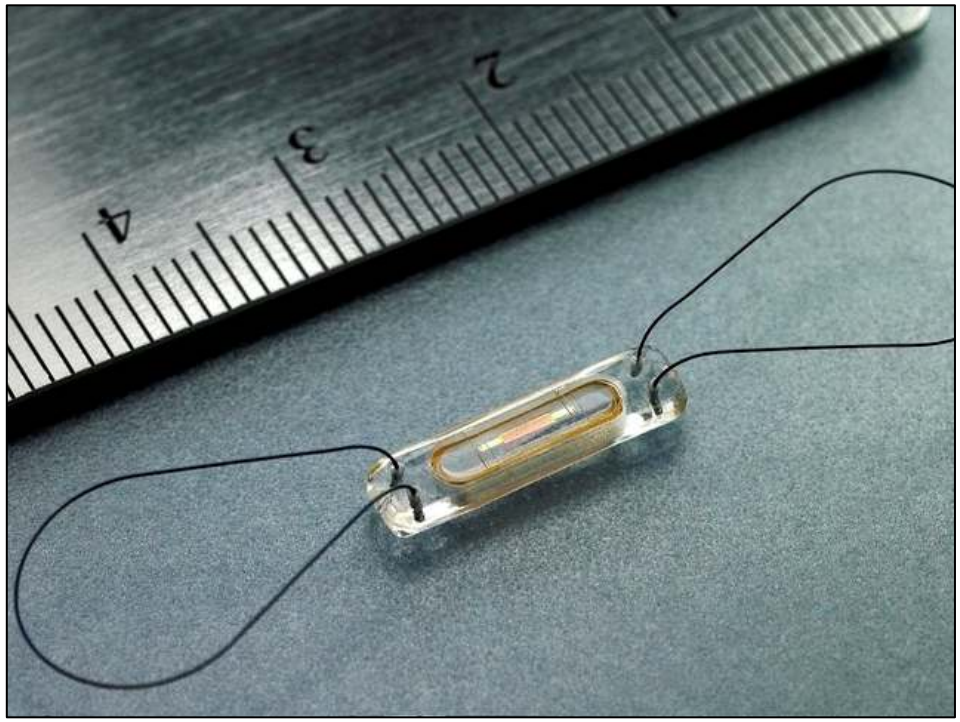
- Structured telephone support:
  - Mortality RR 0.88 [0.76-1.01] P=0.08
  - HF hospitalisation RR 0.77 [0.68-0.87] P < 0.00001

- Telemonitoring:
  - Mortality RR 0.66 [0.54-0.81] P<0.0001
  - HF hospitalisation RR 0.79 [0.67-0.94] P=0.008

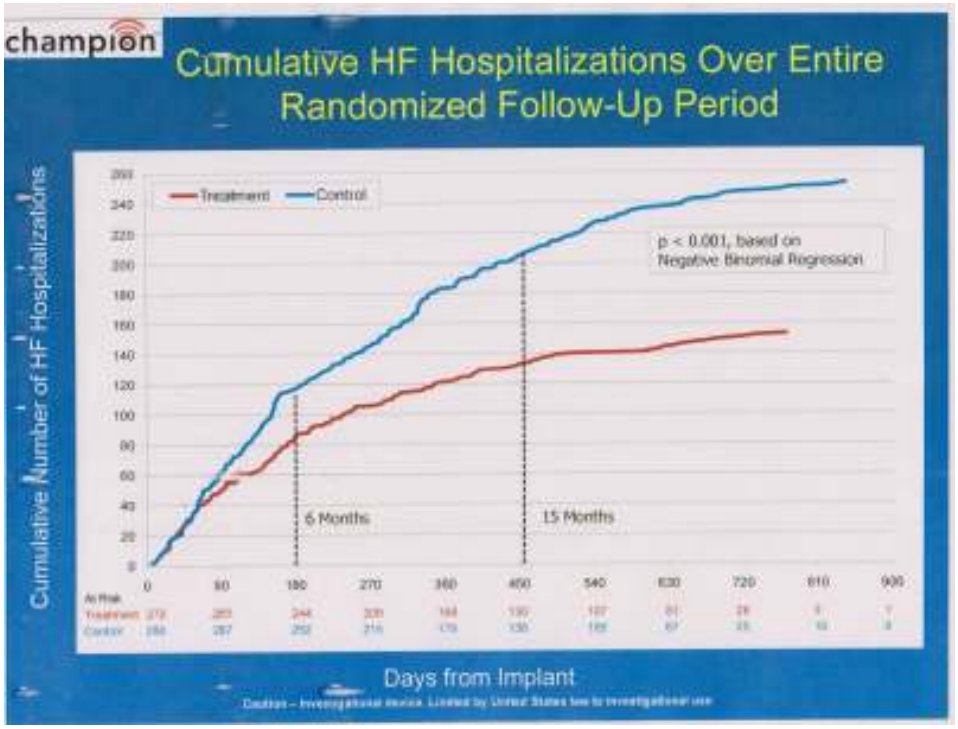
Inglis SC et al. Cochrane Database of Reviews 2010; 8 (CD007228)

Implanted systems





CardioMEMS



- 550 patients (NYHA III), with HF hospitalisation in preceding 12 months
- All patients had implant
- 1:1 randomisation to blinding or not to monitored data
- 6 months:
  - 83 hospitalisation in 54 patients versus 120 hospitalisations in 80 patients
  - RRR 30% (P<0.001)

Abraham WT et al. Presentation at HF2010 (Berlin)

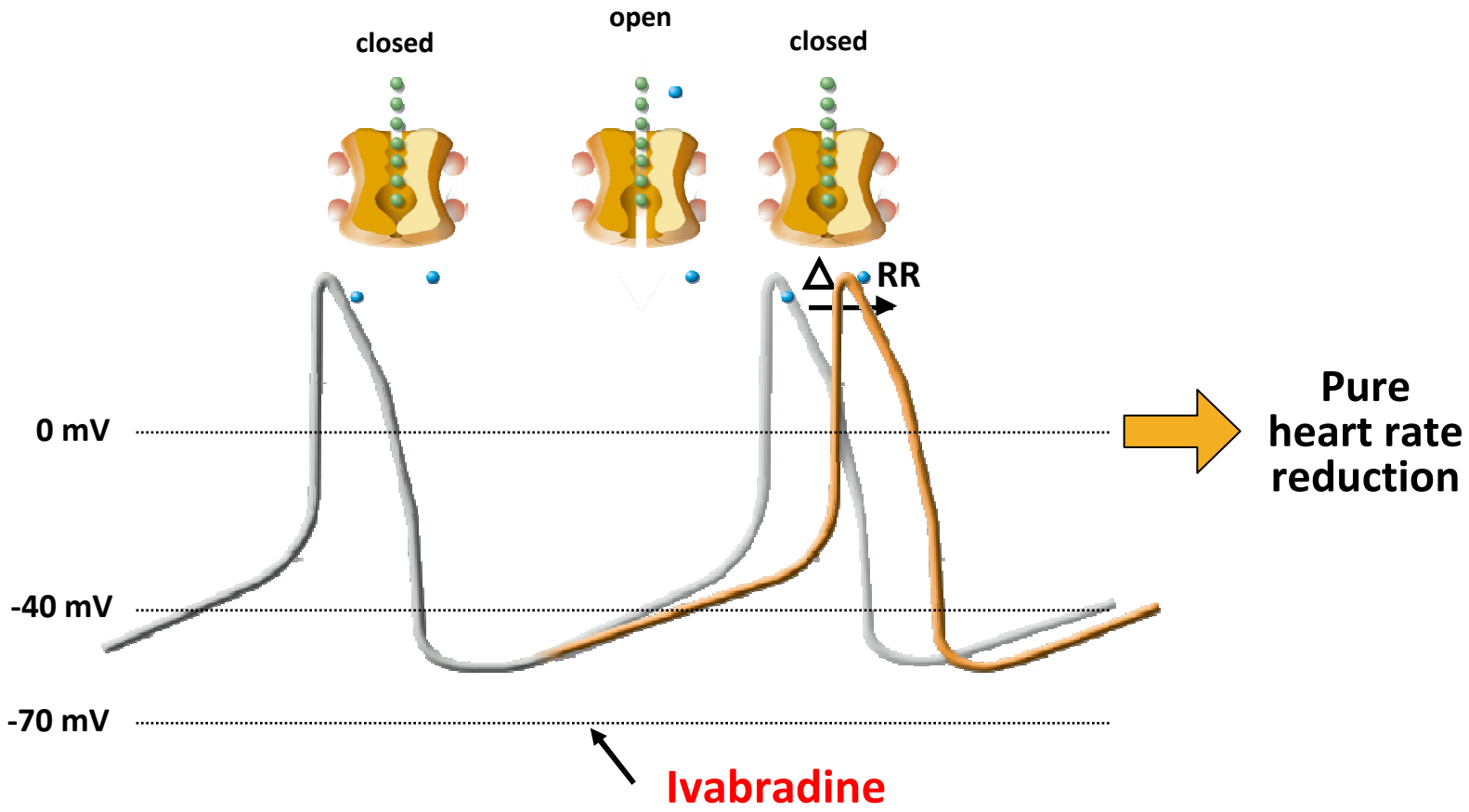
How should the data be presented?

And how often? And to whom?

Conclusions

- Evidence base rapidly moves forward
- ACEI, beta-blocker and aldosterone antagonist should be aim for those with HF and LVSD
- If in sinus rhythm, and HR > 70bpm consider ivabradine for extra benefit
- Disease management is changing: technology supporting expert management closer to home

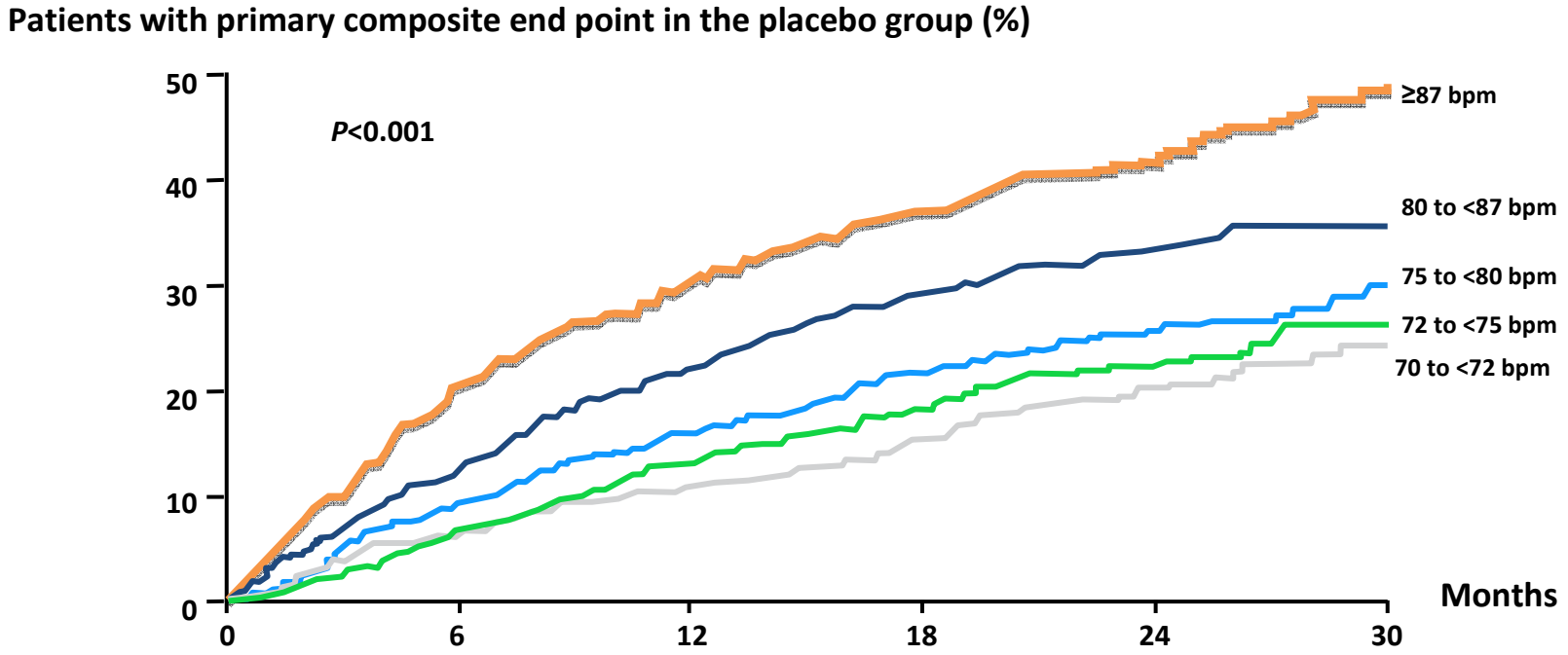
Ivabradine: ‘pure’ heart rate reduction



I_f inhibition reduces the diastolic depolarization slope, and thereby lowers heart rate

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

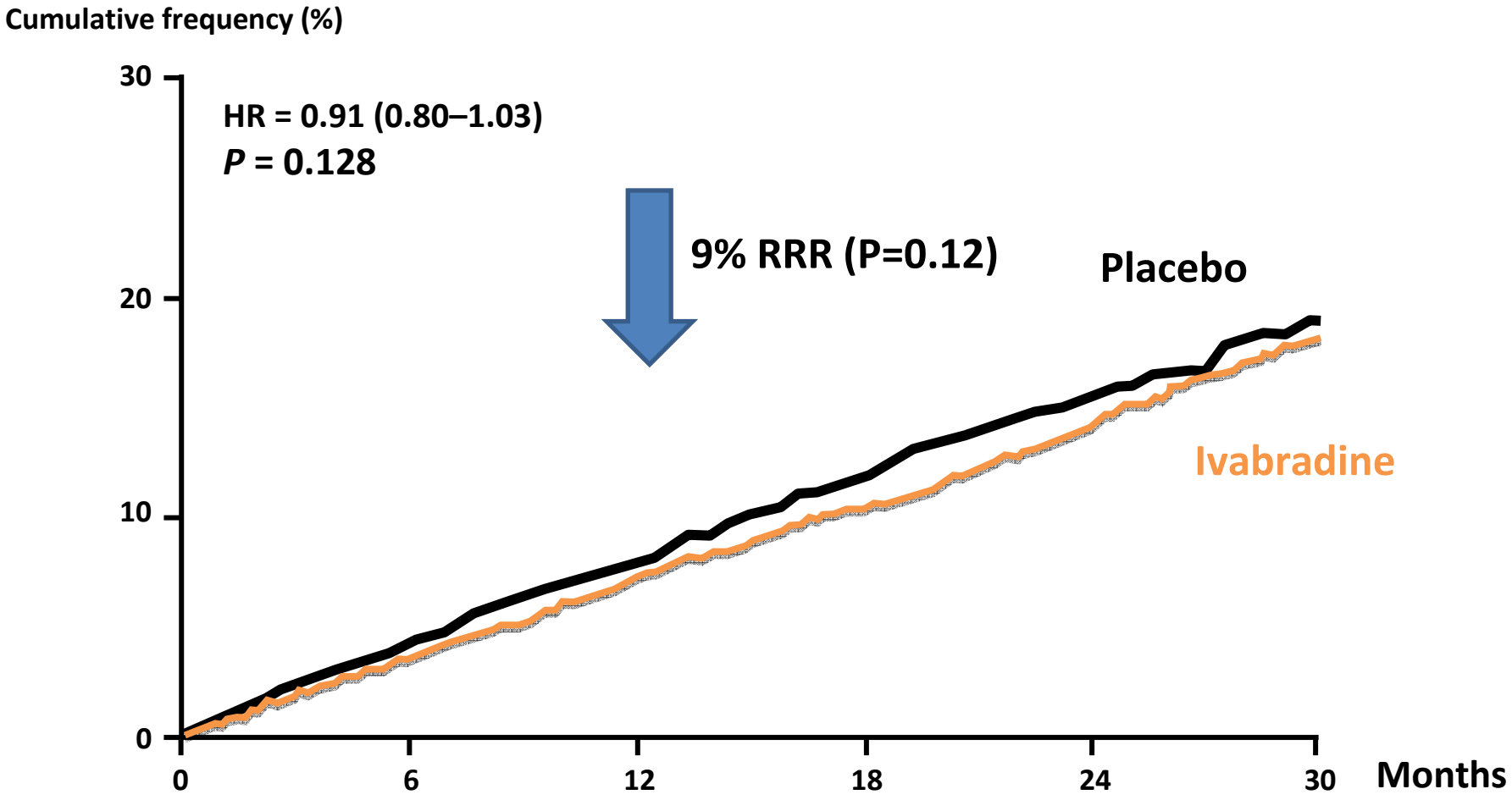
Heart rate is a predictor of CV death and/or hospitalizations for HF



Risk increases by 3% per 1 bpm increase, and by 16% per 5 bpm increase

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

Cardiovascular death



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