



Systolic **H**ear failure treatment with
the **If** inhibitor ivabradine **T**rial

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on behalf of the **SHIfT** Investigators



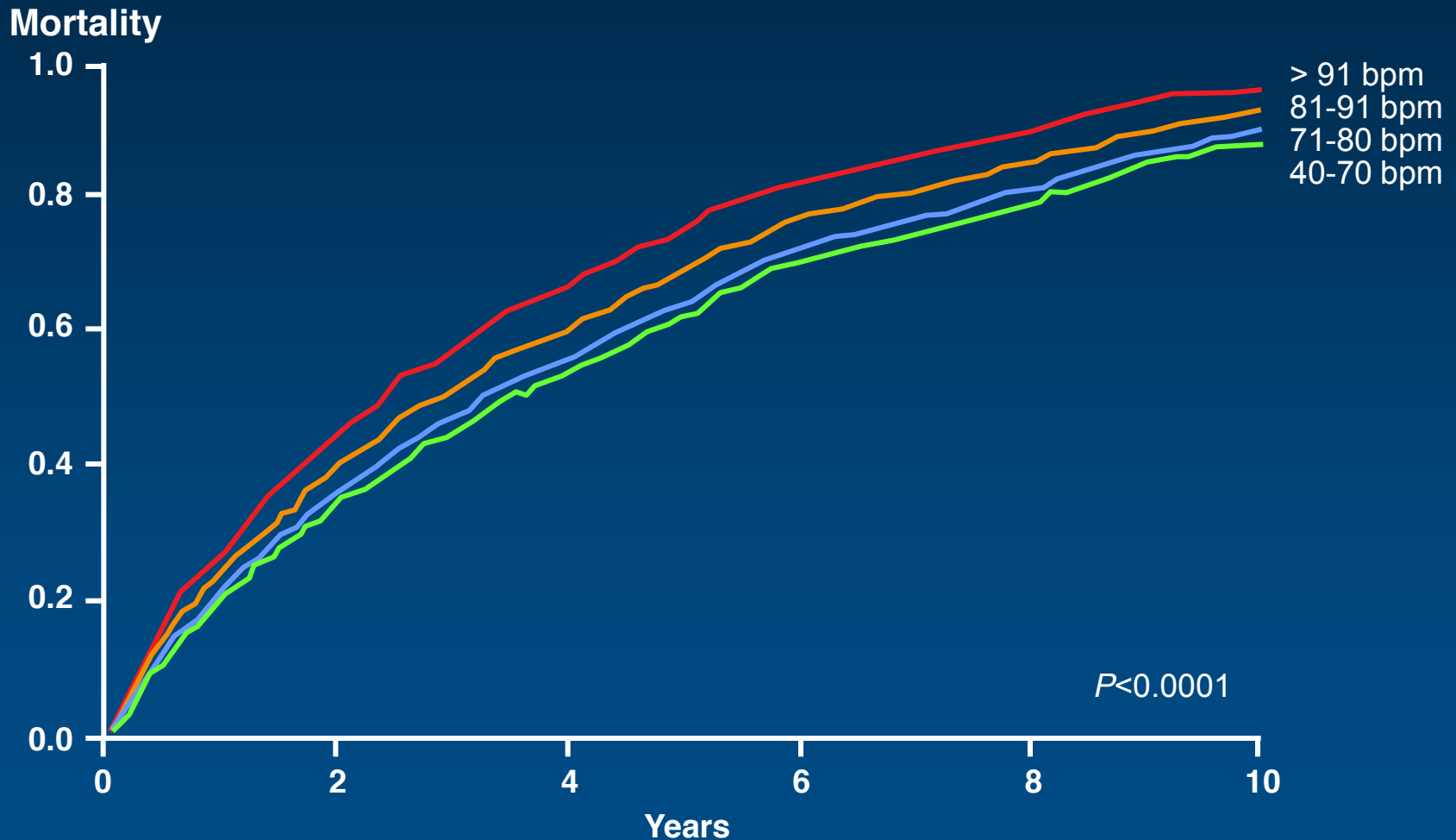
Disclosures

SHIFT Executive Committee members received fees, research grants, or both from Servier, as well as fees for speaking or consulting from other major cardiovascular pharmaceutical companies

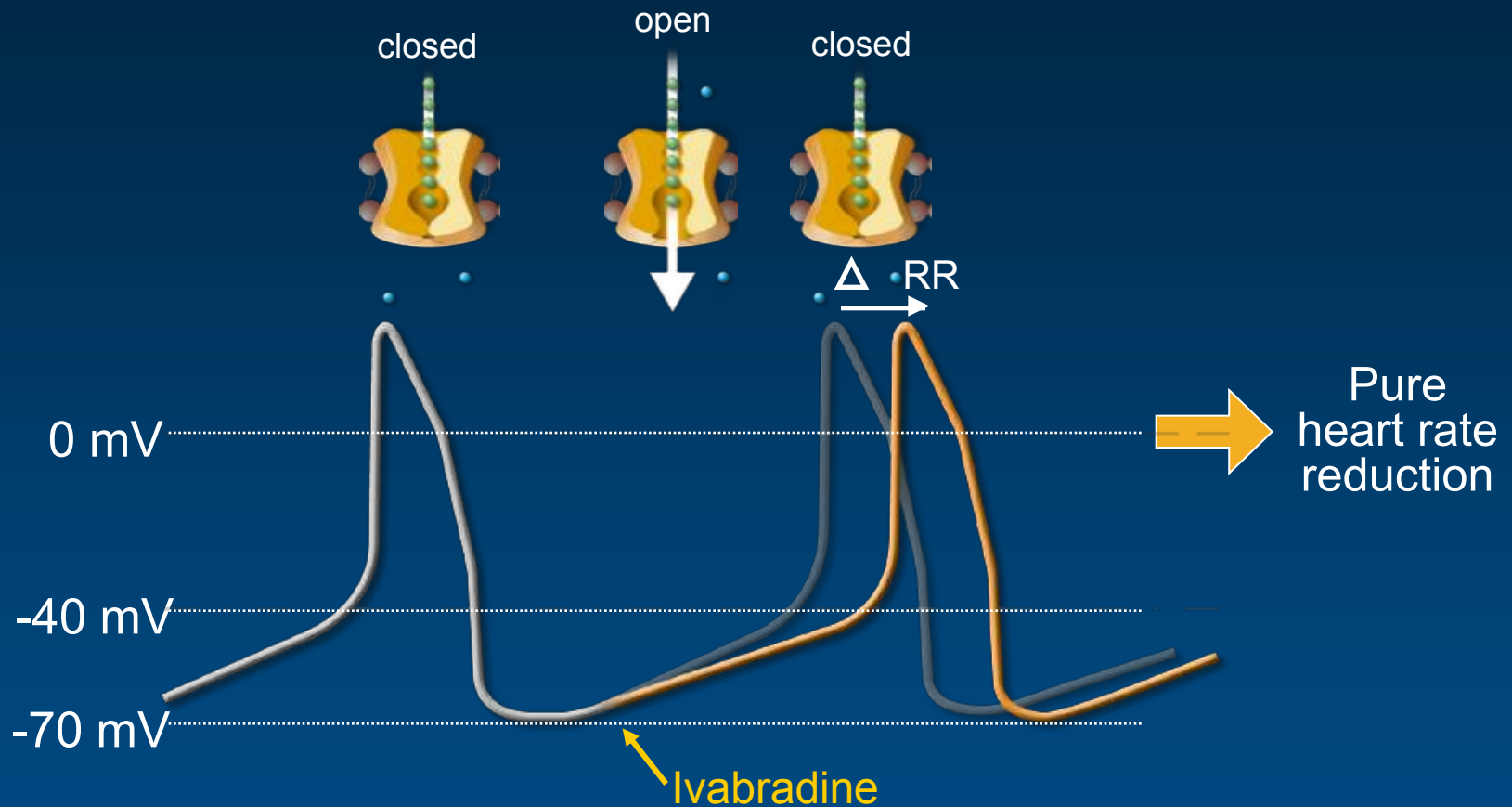
- Elevated heart rate is associated with poor outcome in a number of cardiovascular conditions including heart failure
- Heart rate remains elevated in many heart failure patients despite treatment by beta-blockers
- Ivabradine is a novel heart rate-lowering agent acting by inhibiting the I_f current in the sino-atrial node
- We hypothesized that the addition of ivabradine to recommended therapy would be beneficial in heart failure patients with elevated heart rate

Resting heart rate and mortality in HF post MI patients

DIAMOND study; 1518 patients with HF post MI, 10 years follow up



Ivabradine: pure heart rate reduction



I_f inhibition reduces the diastolic depolarization slope, thereby lowering heart rate

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 ≥ 70 bpm and
4. Recommended therapy

Europe

Belgium
Denmark
Finland
France

Germany
Greece
Ireland
Italy
The Netherlands

Portugal
Spain
Sweden
Turkey
UK

Bulgaria
Czech Republic
Estonia
Hungary

Latvia
Lithuania
Norway
Poland
Romania

Russia
Slovakia
Slovenia
Ukraine

North America

Canada

South America

Argentina
Brazil
Chili

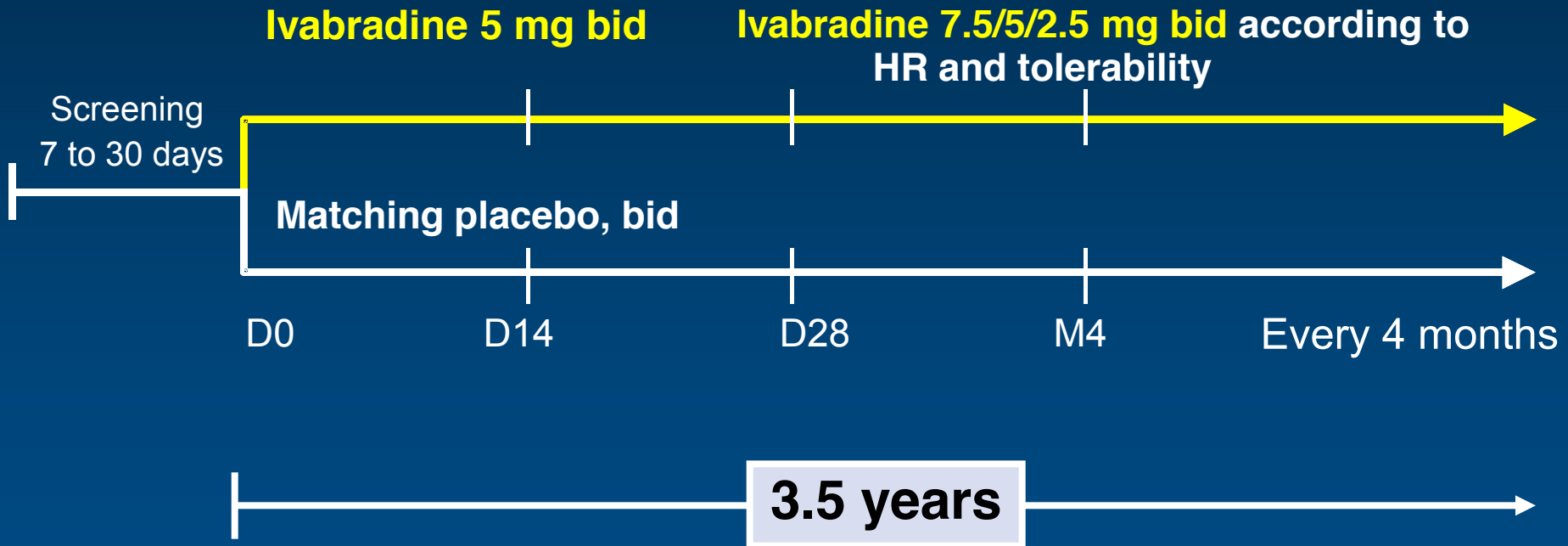
Asia

China
Hong Kong
India
South Korea
Malaysia

Australia

6505 patients, 37 countries, 677 centres

- ≥ 18 years
- Class II to IV NYHA heart failure
- Ischaemic/non-ischaemic aetiology
- LV systolic dysfunction (EF $\leq 35\%$)
- Heart rate ≥ 70 bpm
- Sinus rhythm
- Documented hospital admission for worsening heart failure ≤ 12 months



Primary composite endpoint

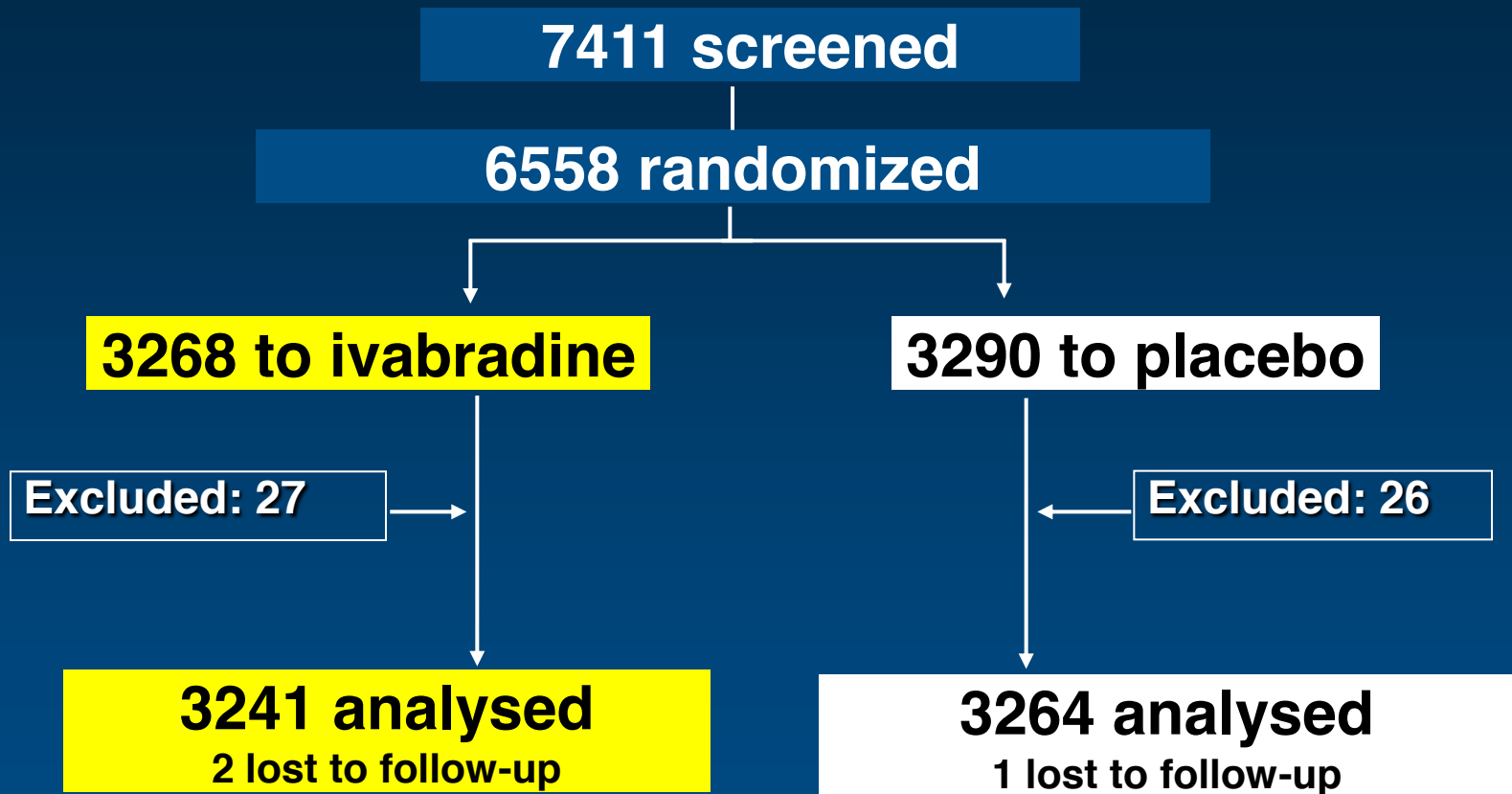
- Cardiovascular death
- Hospitalisation for worsening heart failure

Other endpoints

- All-cause / CV / HF death
- All-cause / CV / HF hospitalisation
- Composite of CV death, hospitalisation for HF or non-fatal MI
- NYHA class / Patient & Physician Global Assessment

In total population and in patients with at least 50% target dose of beta-blockers

Patients and follow-up



Median study duration: 22.9 months; maximum: 41.7 months



Baseline characteristics

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



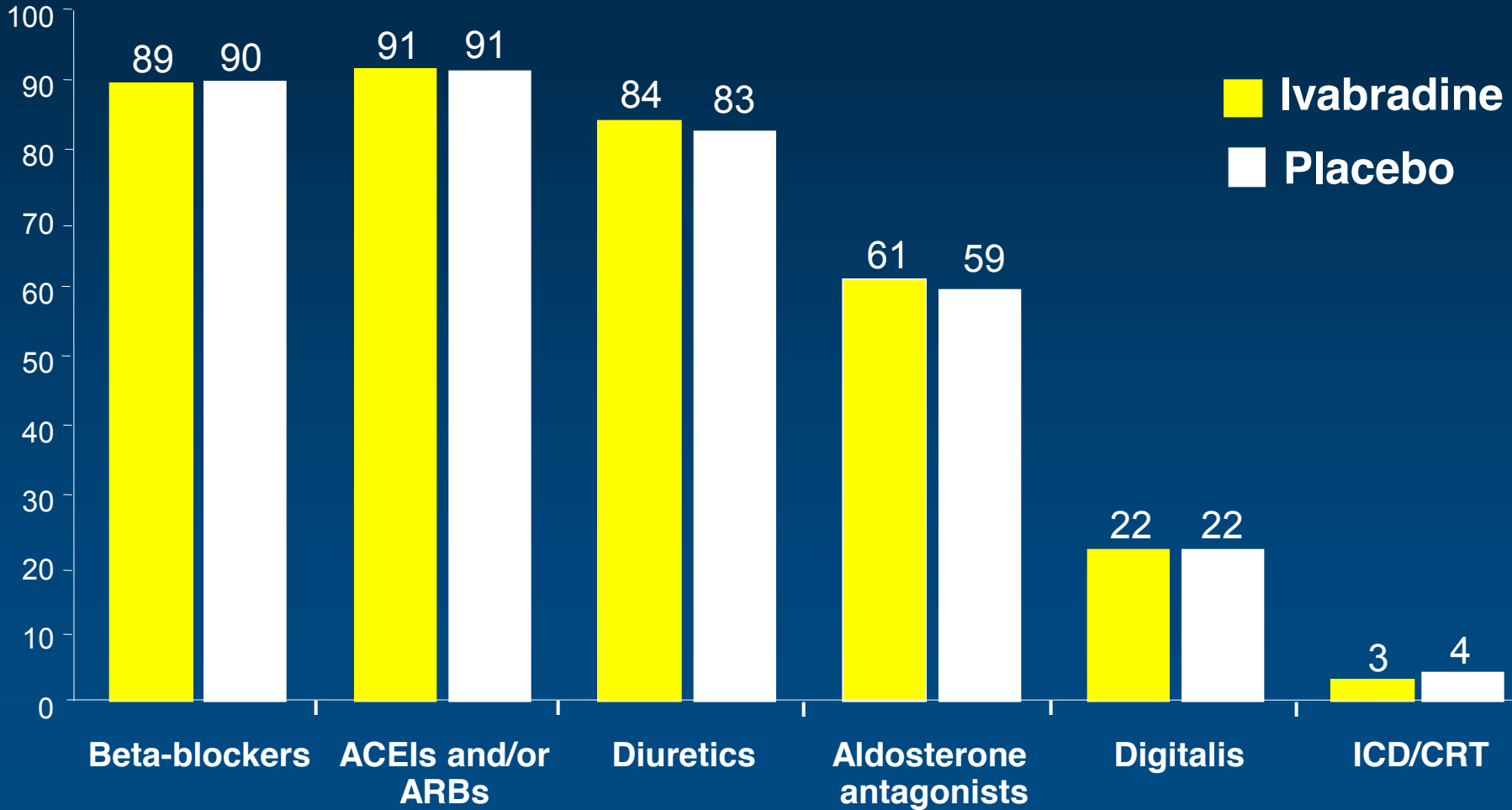
Baseline characteristics

	Ivabradine	Placebo
	3241	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 m²	75	75



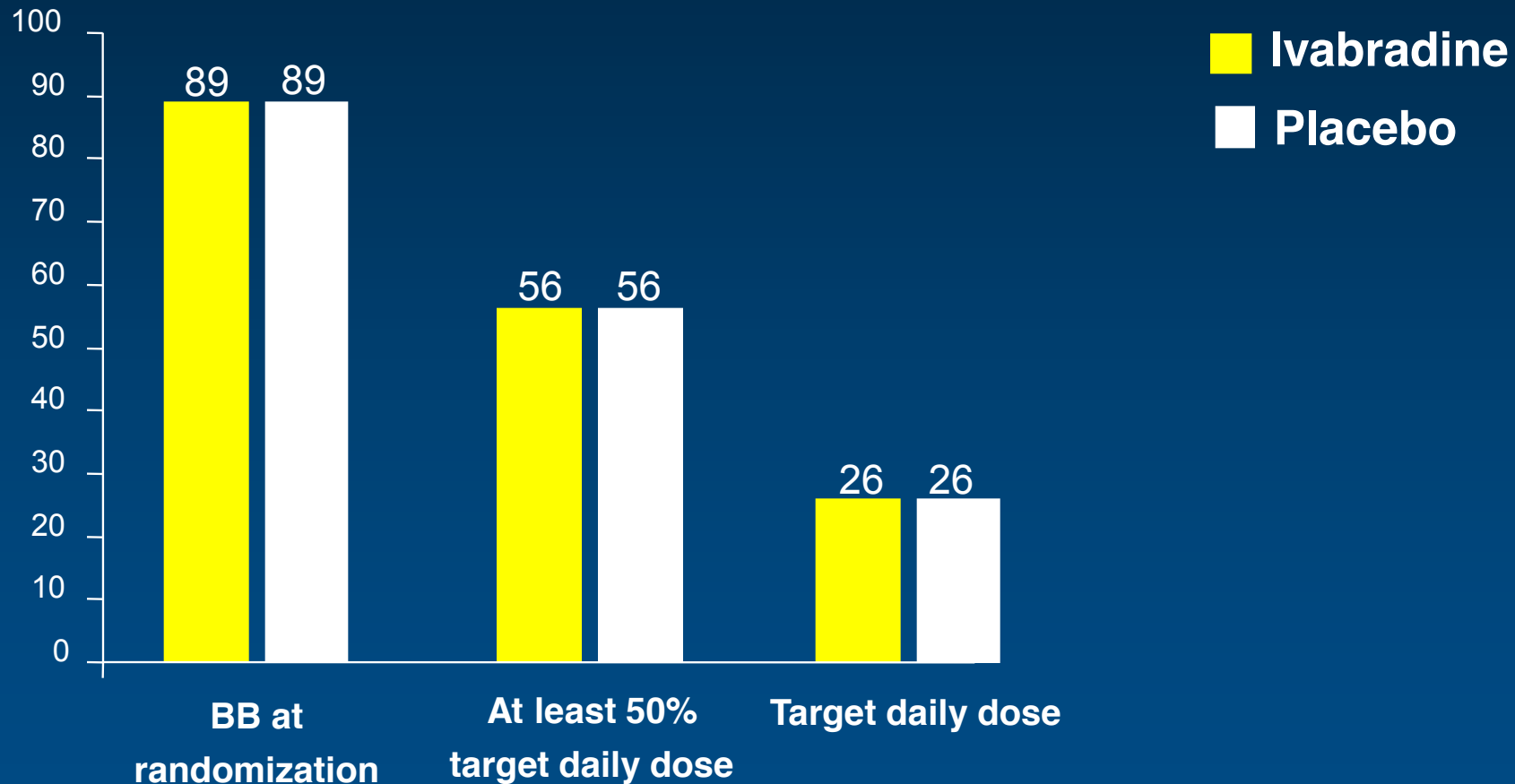
Chronic HF background treatment

Patients (%)



Background beta-blocker treatment

Patients (%)





Background beta-blocker treatment

Main reasons for not prescribing BB, %

	Ivabradine n=344	Placebo n=341
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COPD	37	32
Hypotension	17	20
Asthma	10	11
Cardiac decomp.	7	9
Fatigue	5	6

Main reasons for not achieving BB target dose, %

	Ivabradine n=2099	Placebo n=2126
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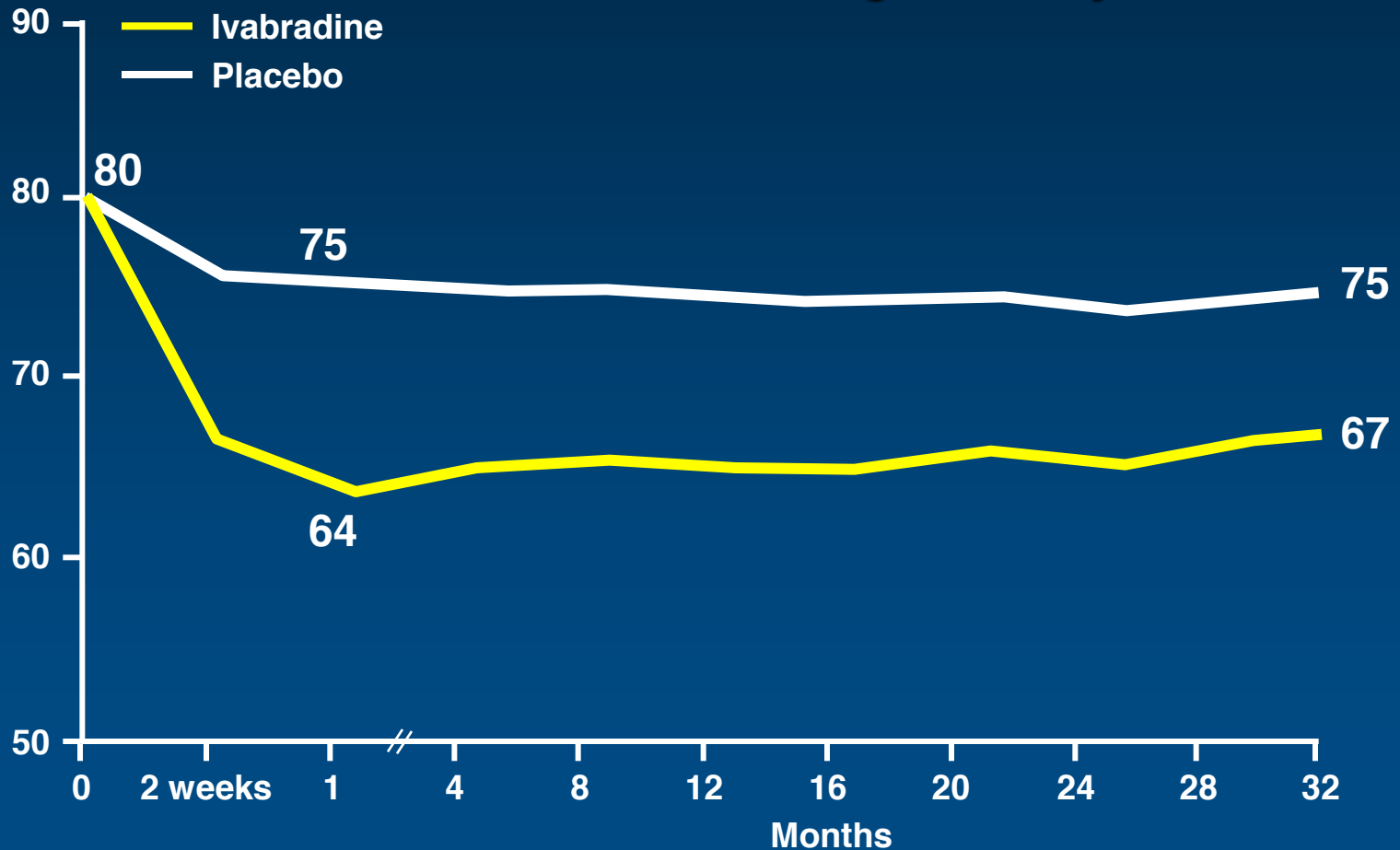
Hypotension	44	45
Fatigue	32	32
Dyspnea	14	14
Dizziness	13	12
Bradycardia	6	6

Mean heart rate reduction

Mean ivabradine dose: 6.4 mg bid at 1 month

6.5 mg bid at 1 year

Heart rate (bpm)





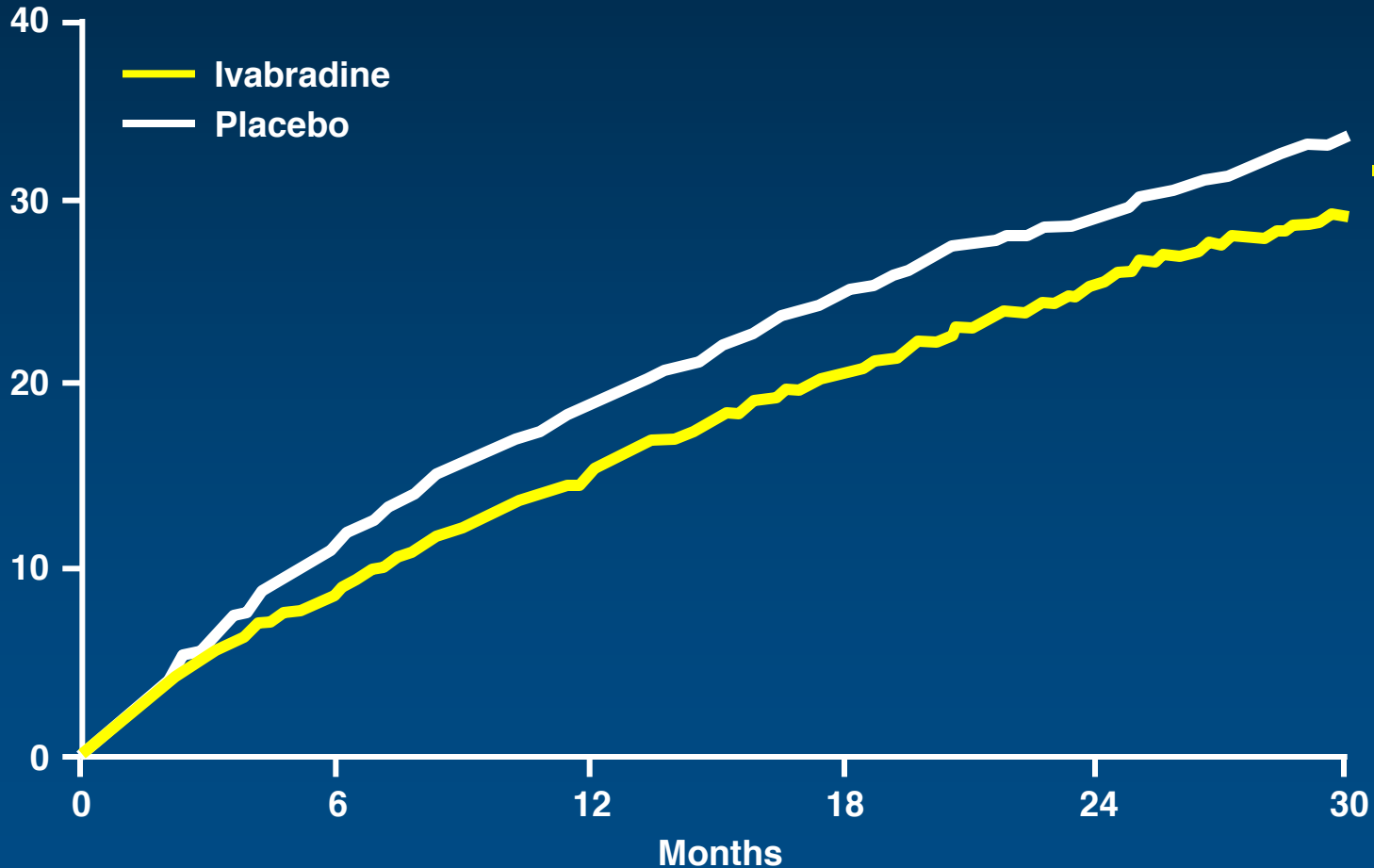
Primary composite endpoint

Ivabradine n=793 (14.5%PY)

Placebo n=937 (17.7%PY)

HR = 0.82 [95% CI 0.75-0.90] $p < 0.0001$

Cumulative frequency (%)





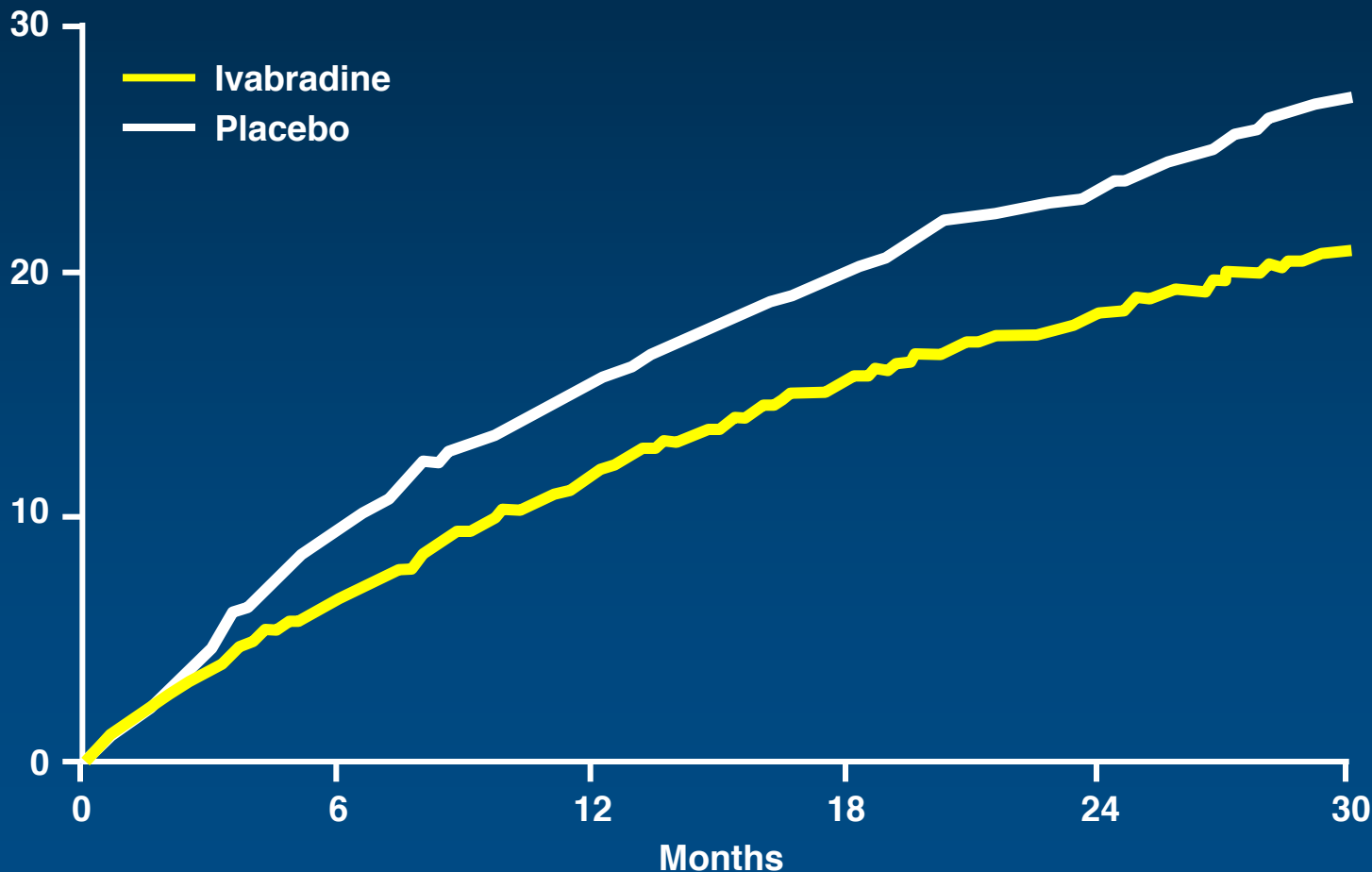
Hospitalisation for heart failure

Ivabradine n=514 (9.4%PY)

Placebo n=672 (12.7%PY)

HR = 0.74 [95% CI 0.66-0.83] $p < 0.0001$

Cumulative frequency (%)



- 26%

Cardiovascular death

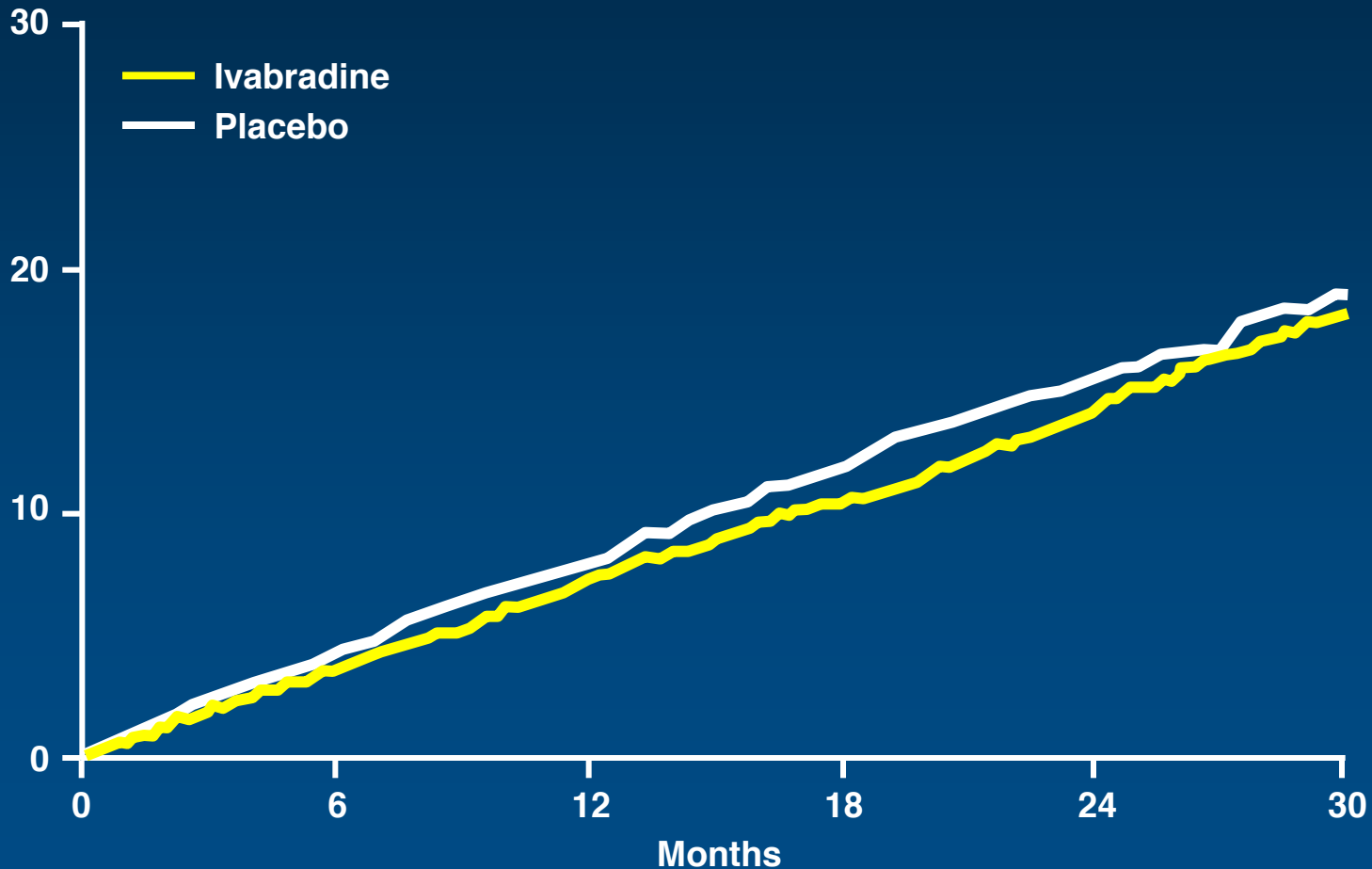
Ivabradine n=449 (7.5%PY)

Placebo n=491 (8.3%PY)

HR = 0.91

p=0.128

Cumulative frequency (%)

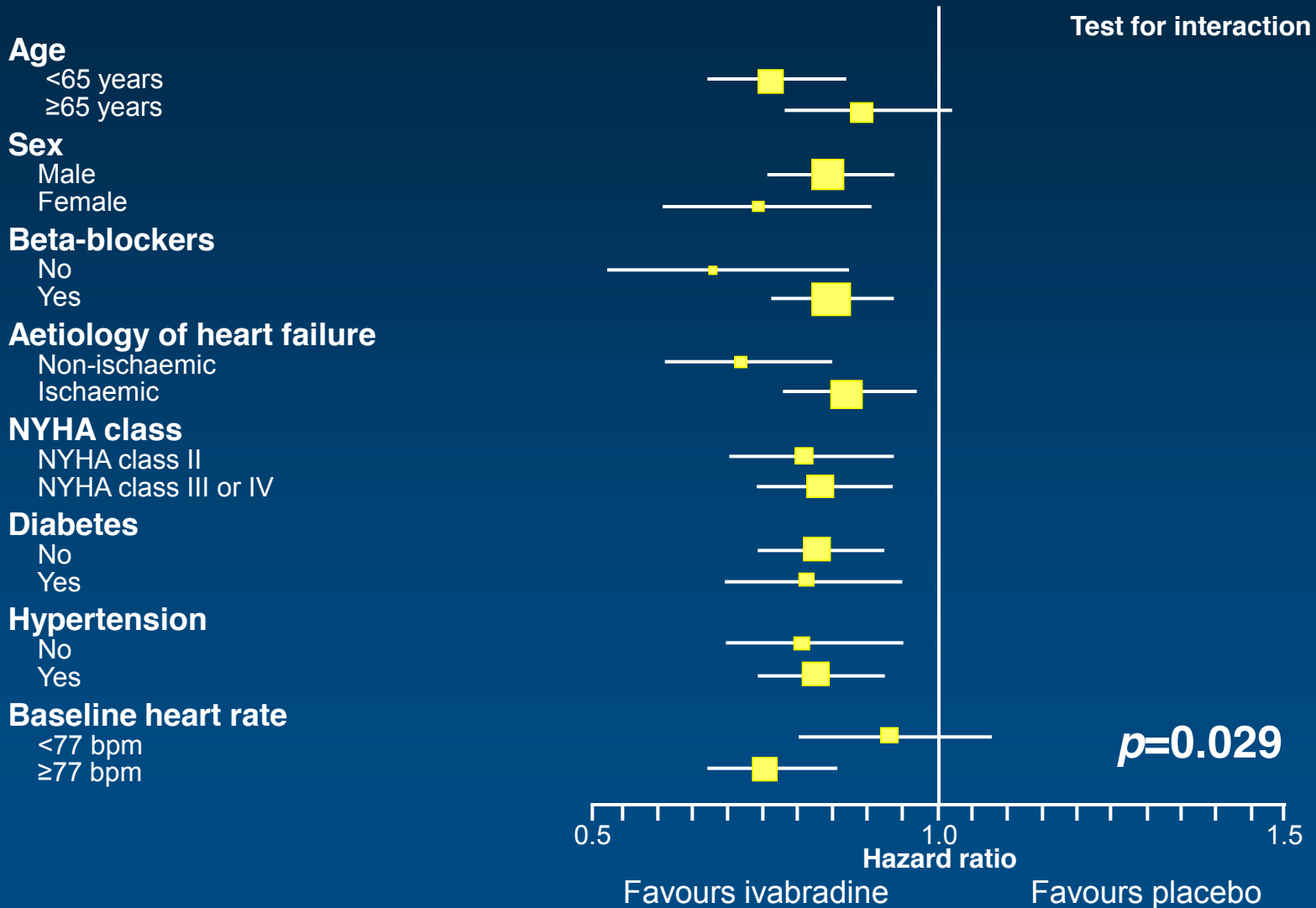




Effect of ivabradine on outcomes

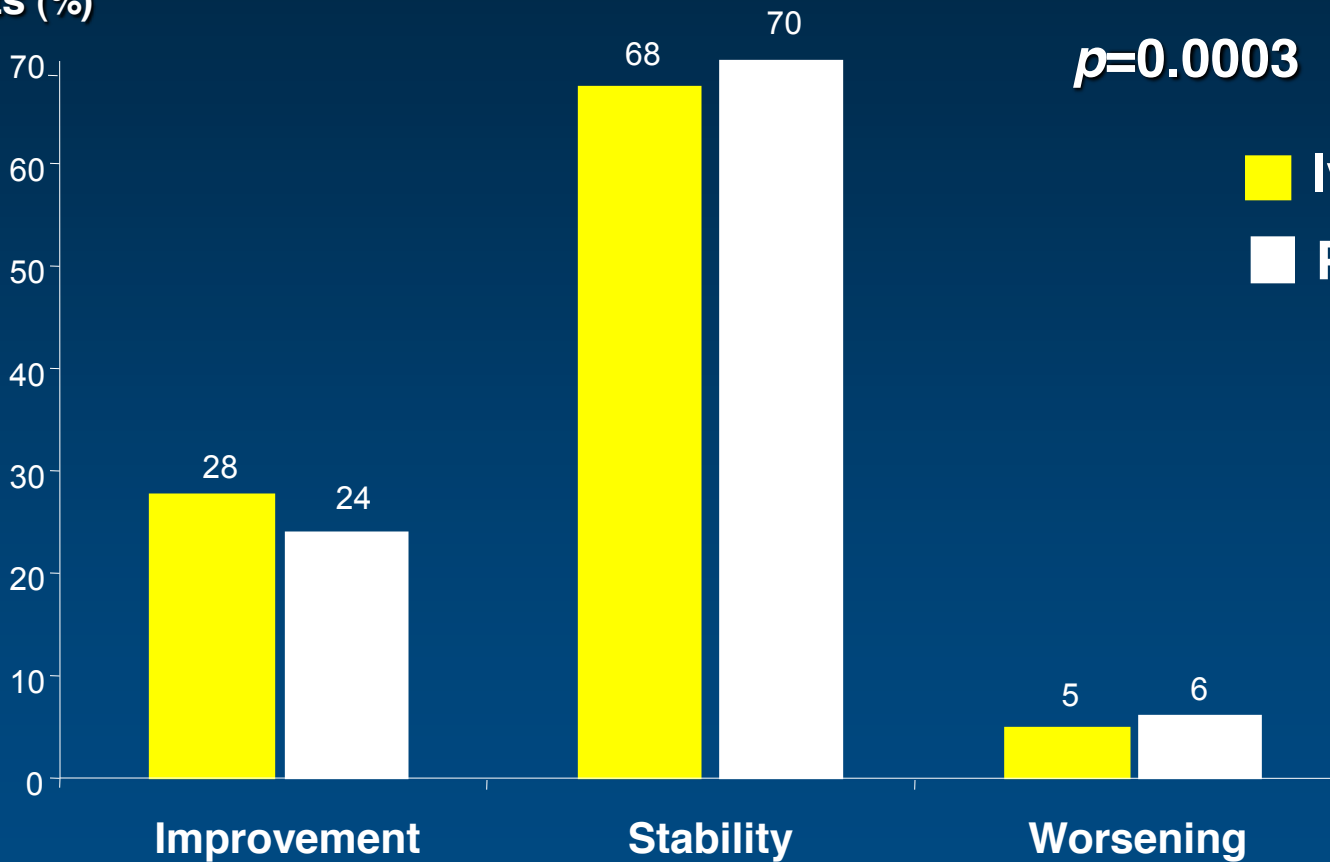
Endpoints	Hazard ratio	95% CI	<i>p</i> value
Primary composite endpoint	0.82	[0.75;0.90]	<i>p</i> <0.0001
All-cause death	0.90	[0.80;1.02]	<i>p</i> =0.092
Death from HF	0.74	[0.58;0.94]	<i>p</i> =0.014
Hospitalisation for any cause	0.89	[0.82;0.96]	<i>p</i> =0.003
Hospitalisation for CV reason	0.85	[0.78;0.92]	<i>p</i> =0.0002
CV death/hospitalisation for HF or non-fatal MI	0.82	[0.74;0.89]	<i>p</i> <0.0001

Effect of ivabradine in prespecified subgroups



NYHA class changes

Patients (%)



Ivabradine
Placebo



Incidence of selected adverse events (N = 6492)

Patients with an event

	Ivabradine N=3232, % (n)	Placebo N=3260, % (n)	p value
All serious adverse events	45% (1450)	48% (1553)	0.025
All adverse events	75% (2439)	74% (2423)	0.303
Heart failure	25% (804)	29% (937)	0.0005
Symptomatic bradycardia	5% (150)	1% (32)	<0.0001
Asymptomatic bradycardia	6% (184)	1% (48)	<0.0001
Atrial fibrillation	9% (306)	8% (251)	0.012
Phosphenes	3% (89)	1% (17)	<0.0001
Blurred vision	1% (17)	< 1% (7)	0.042



Incidence of serious adverse events

	Patients with an event		<i>p</i> value
	Ivabradine N=3232, % (n)	Placebo N=3260, % (n)	
All serious adverse events	45% (1450)	49% (1553)	0.025
Cardiac disorders	28% (920)	30% (991)	0.091
General disorders, administration conditions	7% (240)	8% (254)	0.617
Infection and infestations	7% (216)	7% (236)	0.381
Respiratory, thoracic, mediastinal disorders	3% (107)	4% (122)	0.347
Surgical and medical procedures	3% (102)	4% (122)	0.197
Gastrointestinal disorders	3% (89)	3% (103)	0.342
Neoplasm benign, malignant and unspecified	2% (68)	2% (61)	0.534
Renal and urinary disorders	2% (51)	1% (47)	0.685
Hepatobiliary disorders	1% (29)	1% (39)	0.273
Eyes disorders	1% (18)	<1% (13)	0.374



Treatment discontinuation

Patients with an adverse event,
leading to withdrawal

	Ivabradine N=3232, % (n)	Placebo N=3260, % (n)	p value
All	14% (467)	13% (416)	0.051
Heart failure	2% (70)	3% (82)	0.367
Symptomatic bradycardia	1% (20)	<1% (5)	0.002
Asymptomatic bradycardia	1% (28)	<1% (5)	<0.0001
Atrial fibrillation	4% (135)	3% (113)	0.137
Phosphenes	<1% (7)	<1% (3)	0.224
Blurred vision	<1% (1)	<1% (1)	1.000

- Heart failure with systolic dysfunction and elevated heart rate is associated with poor outcomes (primary composite endpoint in the placebo group is 18%/year)
- Ivabradine reduced CV mortality or heart failure hospitalisation by 18% ($p < 0.0001$). The absolute risk reduction was 4.2%
- This beneficial effect was mainly driven by a favourable effect on HF death/hospitalisation (RRR 26%)
- Overall, treatment with ivabradine was safe and well tolerated

- The addition of ivabradine to recommended therapy significantly reduces death and hospitalisations related to heart failure in patients with heart rate ≥ 70 bpm
- The NNT for 1 year to prevent ...
 - ✓ One primary endpoint is 26
 - ✓ One hospitalisation for heart failure is 27



KEY Questions & Answers

**Are the BEAUTIFUL and the
SHIFT populations similar?**

BEAUTIFUL versus SHIFT

	BEAUTIFUL	SHIFT
	Differences	
	All documented CAD	All documented CHF
LV ejection fraction	<40%	≤35%
NYHA	Classes I, II, & III	Classes II, III, & IV
Heart rate	>60 bpm	≥70 bpm
	Primary endpoint	
	CV death + hospitalisation for AMI + new onset/worsening HF	CV death + hospitalisation for worsening HF

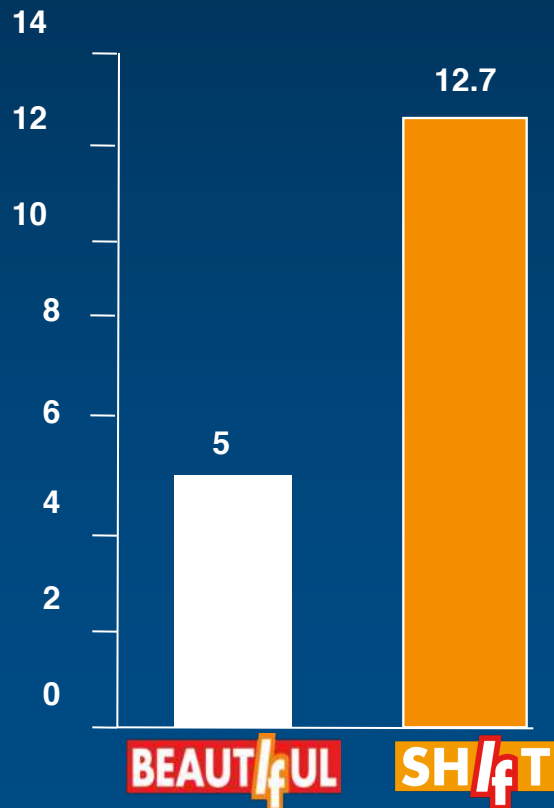
BEAUTIFUL versus SHIFT

Baseline population	BEAUTIFUL	SHIFT
Age (y)	65	60
Gender (male/female)	83/17	77/23
Heart rate (bpm)	72	80
NYHA I (%)	15	-
NYHA II (%)	62	49
NYHA III (%)	23	51
NYHA IV (%)	-	2
Ejection fraction (%)	32	29

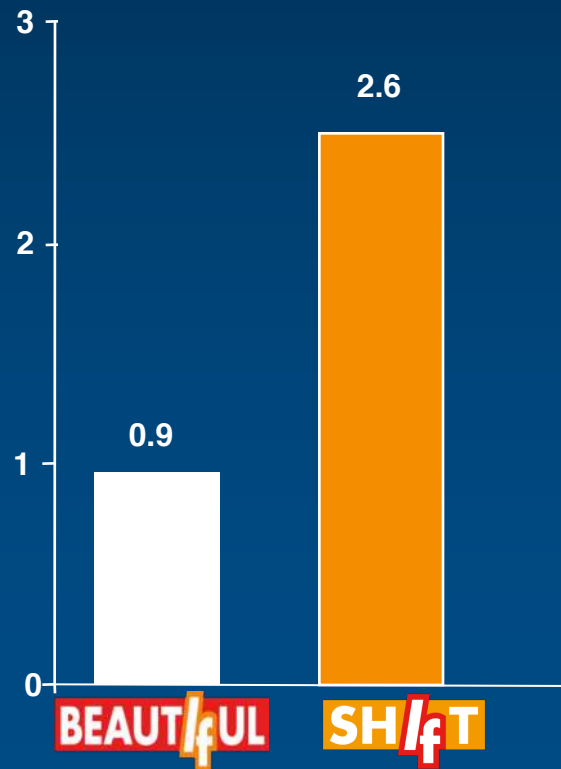
SH/fT versus BEAUT/fUL event rate in placebo arm

Event rates in the placebo group per patient-year of follow-up (%)

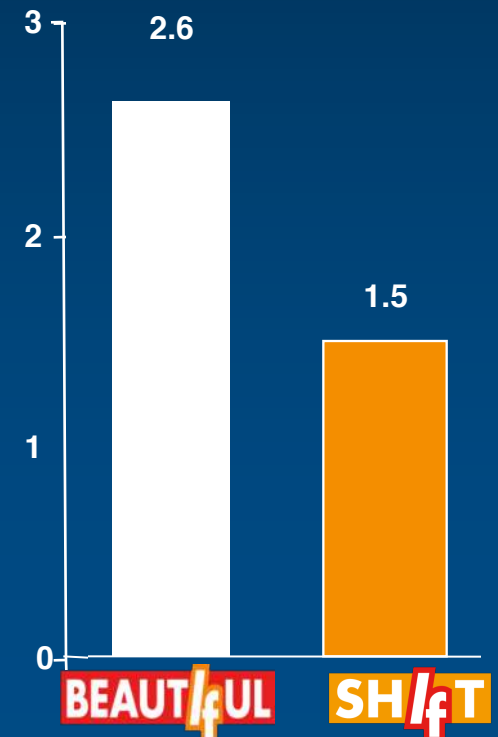
HF hospitalisation



HF death



MI hospitalisation



SH/fT versus BEAUT/fUL effect of ivabradine

Event rates per patient-year of follow-up (%)

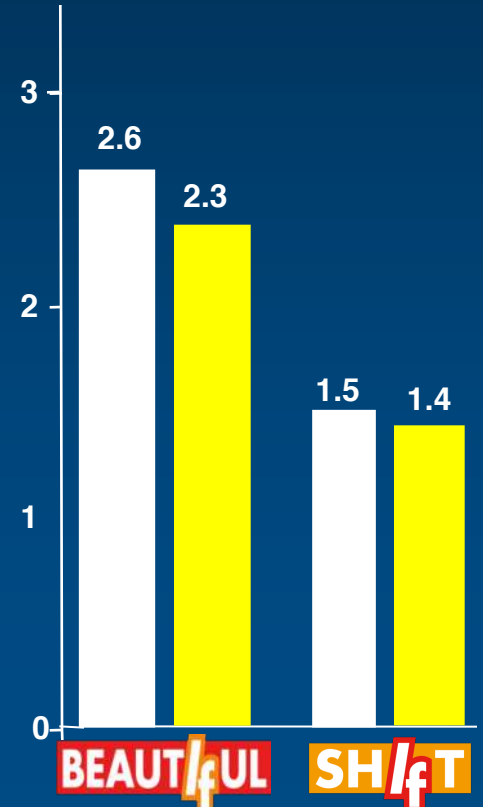
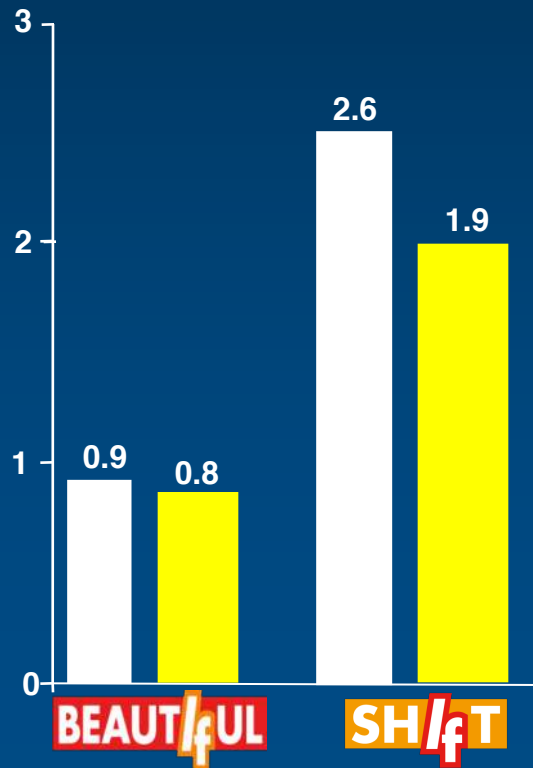
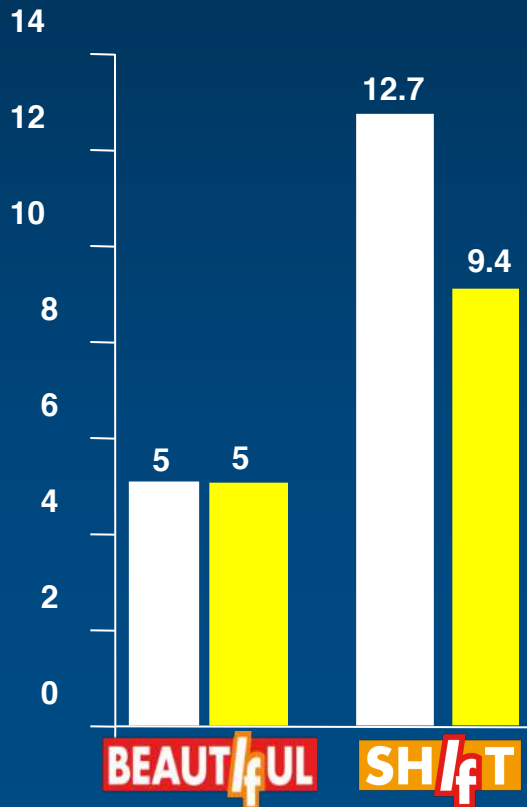
Ivabradine

Placebo

HF hospitalisation

HF death

MI hospitalisation



SHIFT versus BEAUTIFUL (HR ≥ 70 bpm): effect of ivabradine

Event rates per patient-year of follow-up (%)

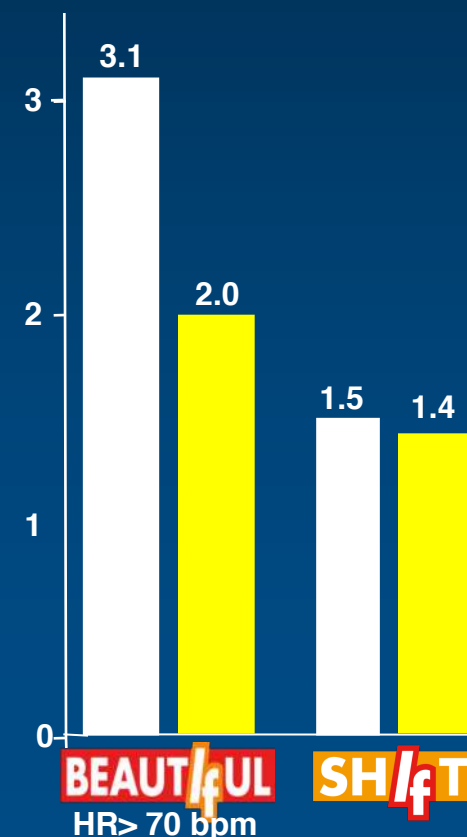
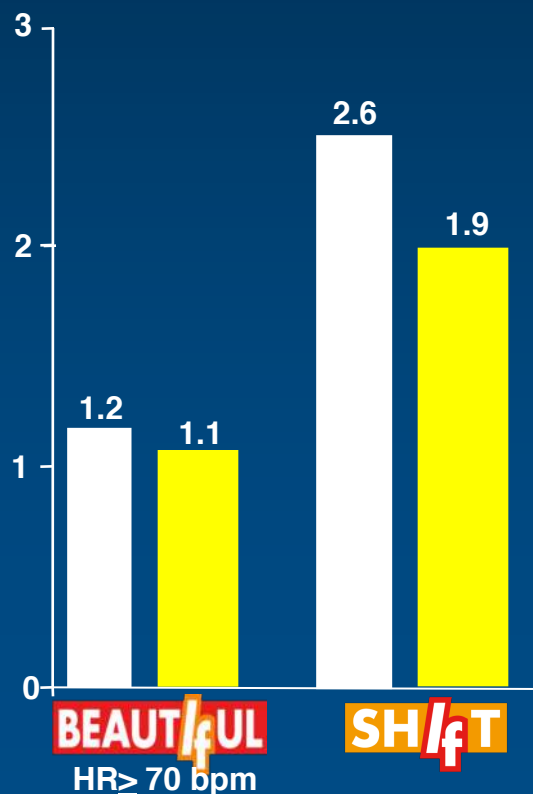
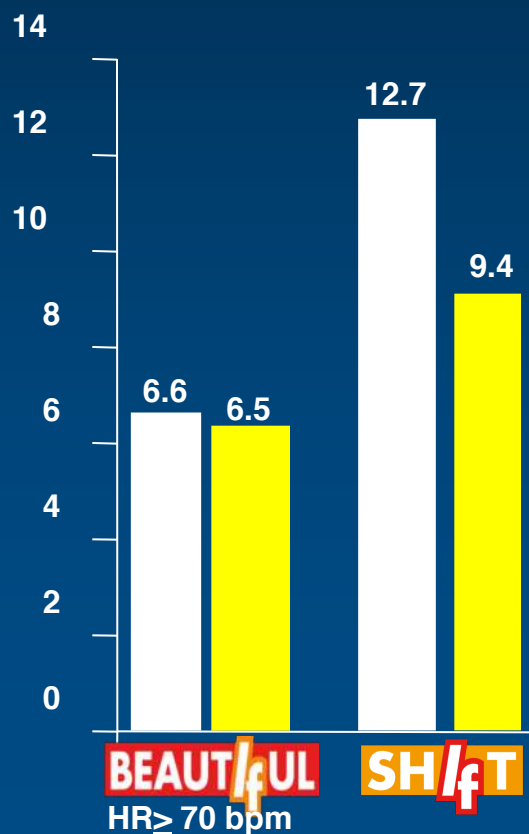
Ivabradine

Placebo

HF hospitalisation

HF death

MI hospitalisation



**Do HF patients frequently have
heart rate ≥ 70 bpm?**

HF registries: more than 50% of patients have heart rate ≥ 70 bpm

IMPACT RECO III

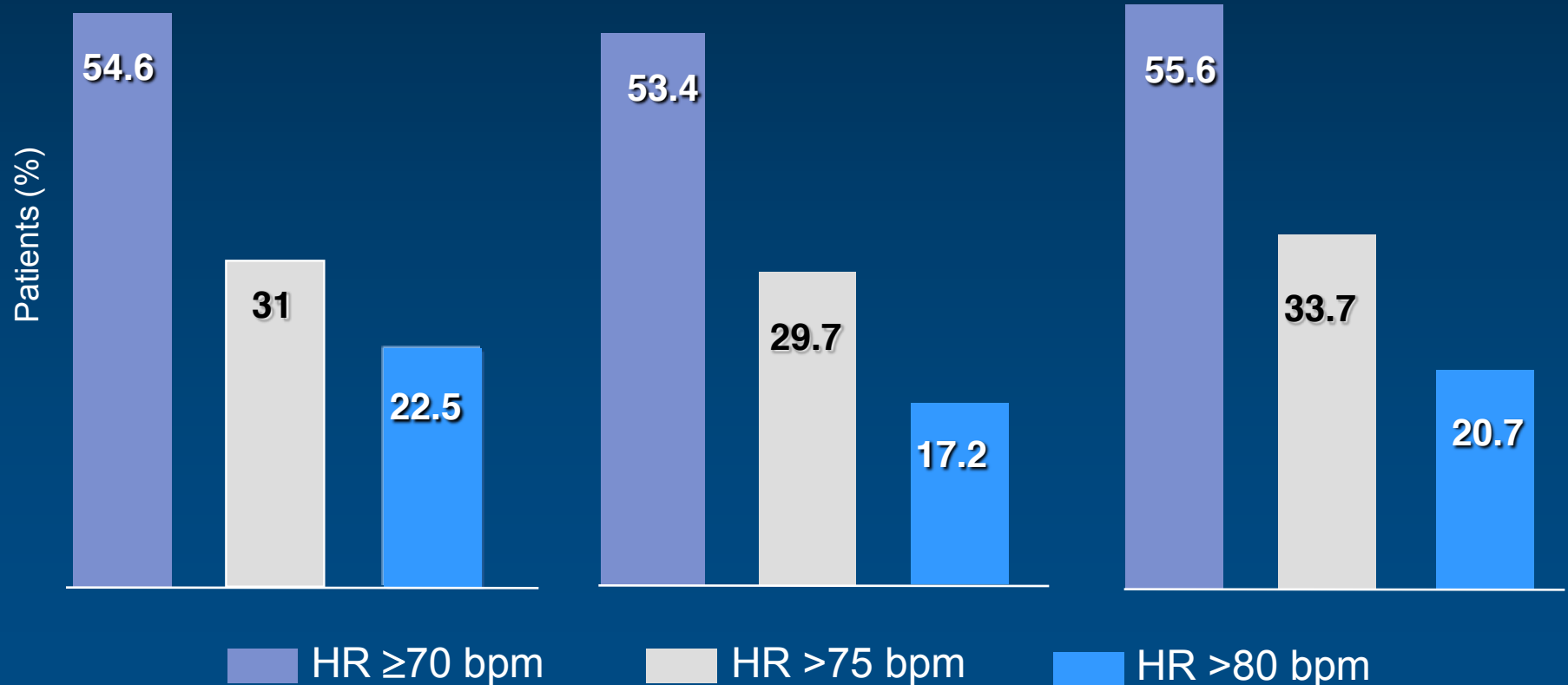
1407 patients

HF OUTCOME*

3480 patients

ESC PILOT HF**

2450 patients

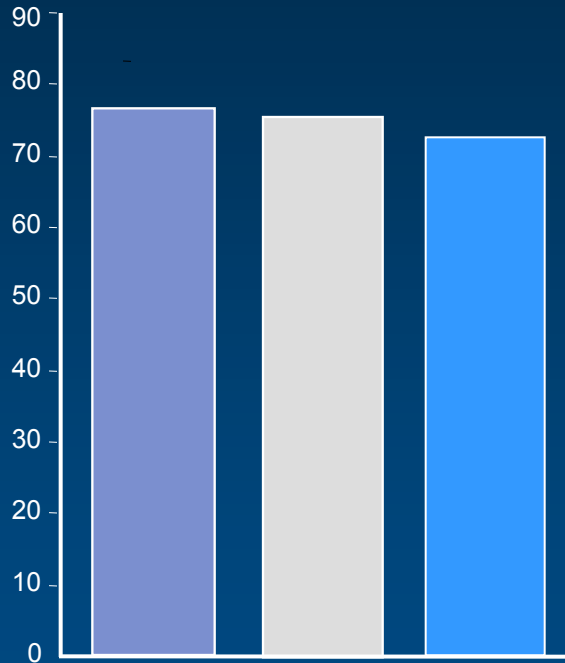


*Courtesy of Prof Tavazzi
**Courtesy of Prof Maggioni

Heart rate in European surveys: beta-blocker therapy

HF OUTCOME*

Beta-blocker (%)

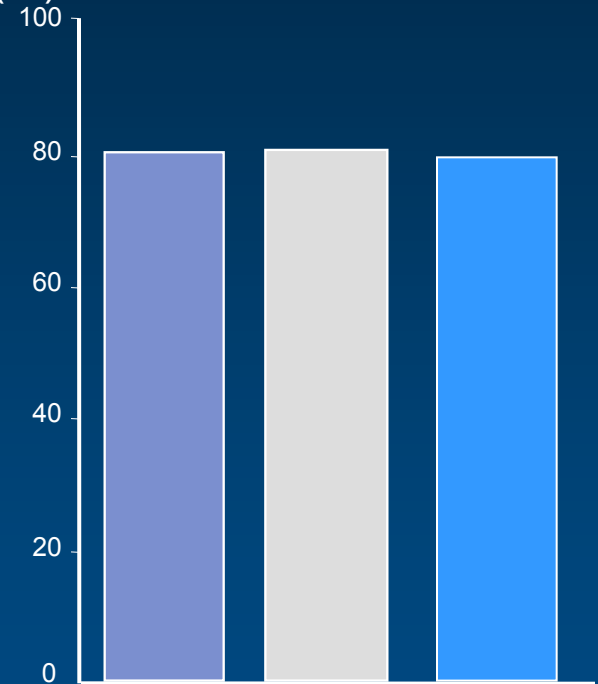


HR ≥70 bpm

HR >75 bpm

ESC HF PILOT**

Beta-blocker (%)



HR >80 bpm

*Courtesy of Prof Tavazzi

**Courtesy of Prof Maggioni

**Are HF patients with heart rate
 ≥ 70 bpm at elevated CV risk?**



Are HF patients with heart rate ≥ 70 bpm at elevated CV risk?

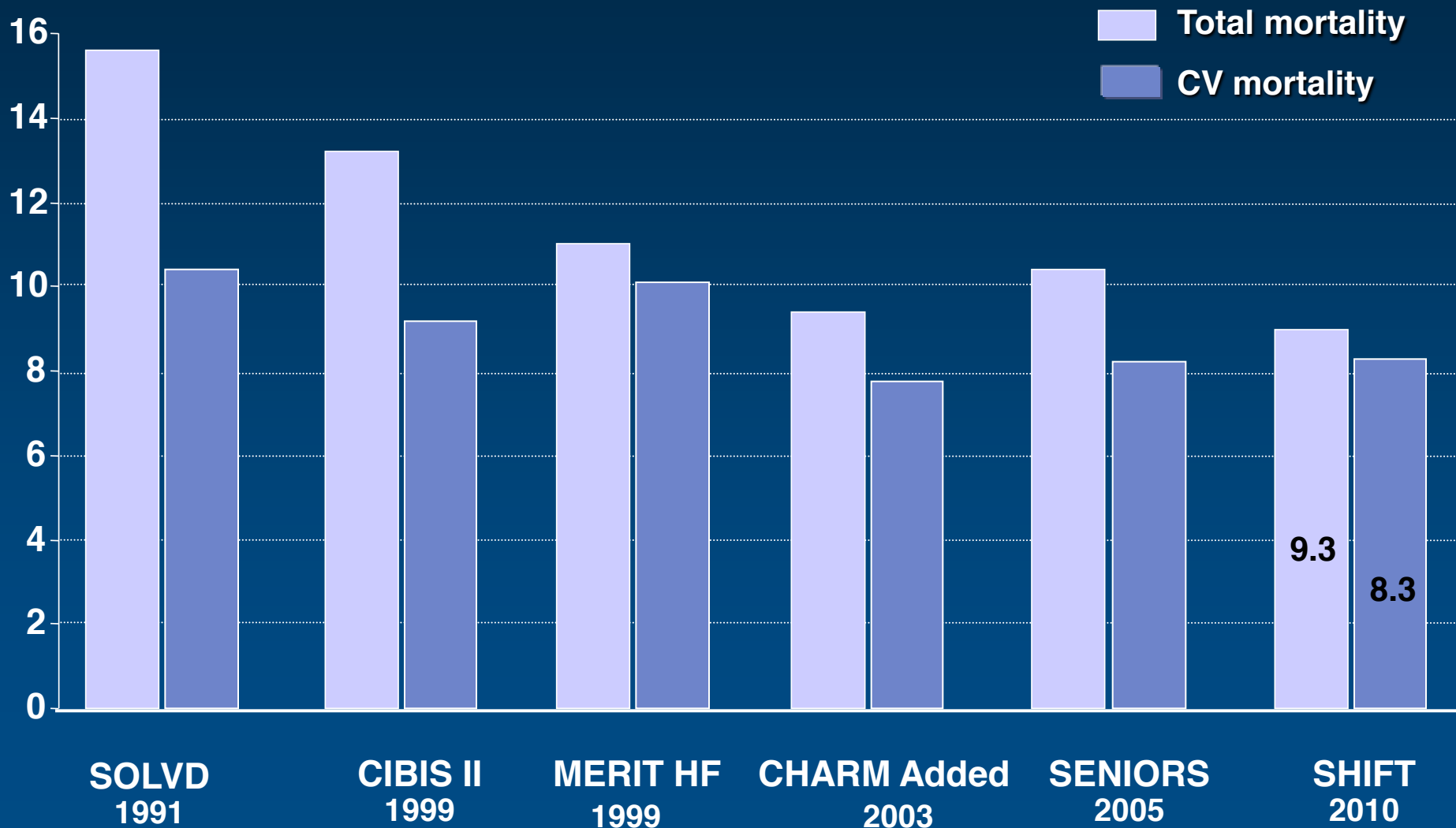
YES

High CV risk despite recommended therapy:

PEP in the placebo group was 18% / year

Annual risk of mortality in placebo group in HF trials

Rate of mortality in the placebo group per patient-year of follow-up (%)



Annual risk of HF death in major HF trials

HF death rate per patient-year of follow-up (%)

