



Systolic **H**ear**f** failure treatment with
the **I**/**f** inhibitor ivabradine **T**rial

Michel Komajda

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

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



Multinational study

Europe

Belgium
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Finland
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Ireland
Italy
The Netherlands

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Spain
Sweden
Turkey
UK

Bulgaria
Czech Republic
Estonia
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Australia

6505 patients, 37 countries, 677 centres

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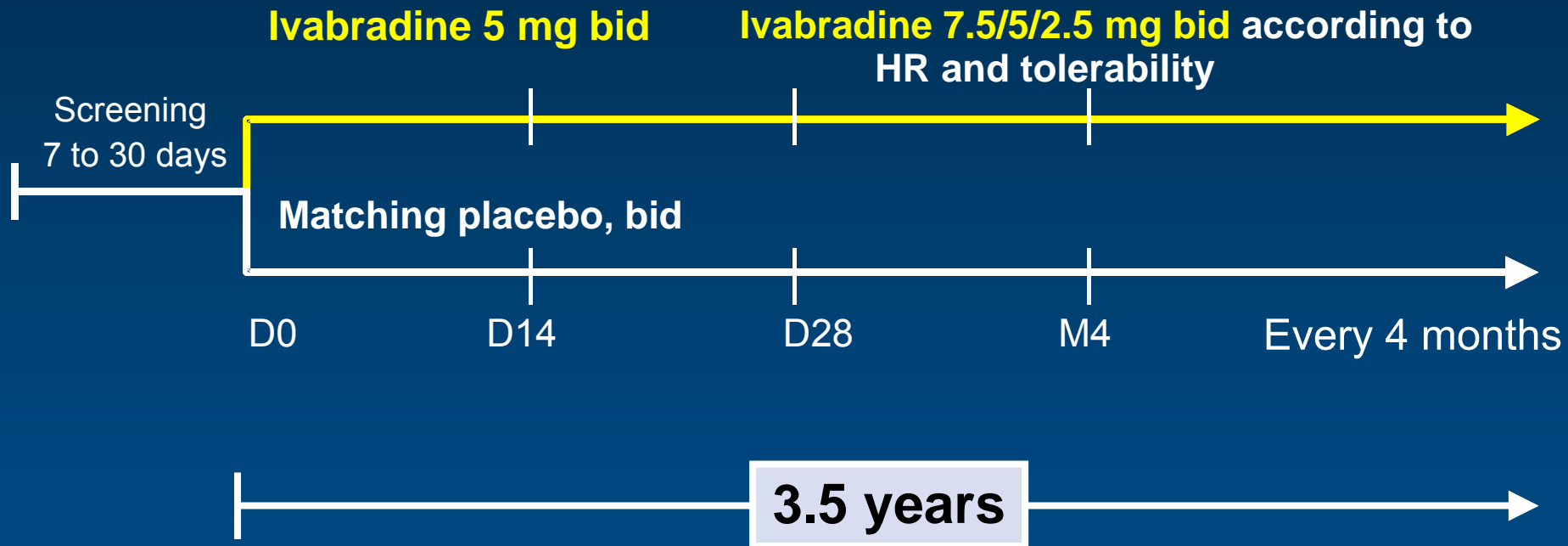
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- ≥ 18 years
- Class II to IV NYHA heart failure
- Ischaemic/non-ischaemic aetiology
- LV systolic dysfunction (EF $\leq 35\%$)
- Heart rate ≥ 70 bpm
- Sinus rhythm
- Documented hospital admission for worsening heart failure ≤ 12 months



Primary composite endpoint

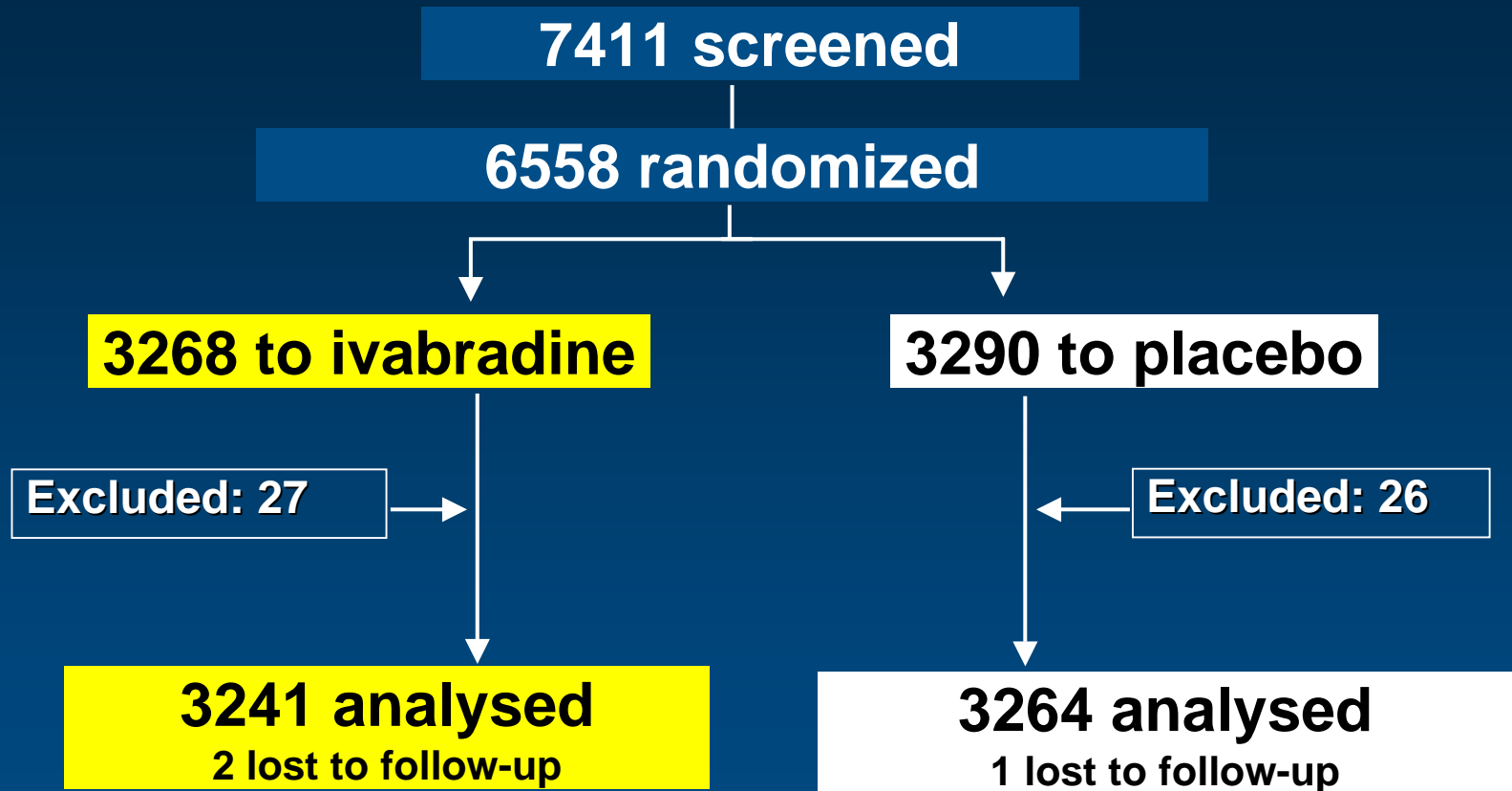
- Cardiovascular death
- Hospitalization for worsening heart failure

Other endpoints

- All-cause / CV / HF death
- All-cause / CV / HF hospitalization
- Composite of CV death, hospitalization 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



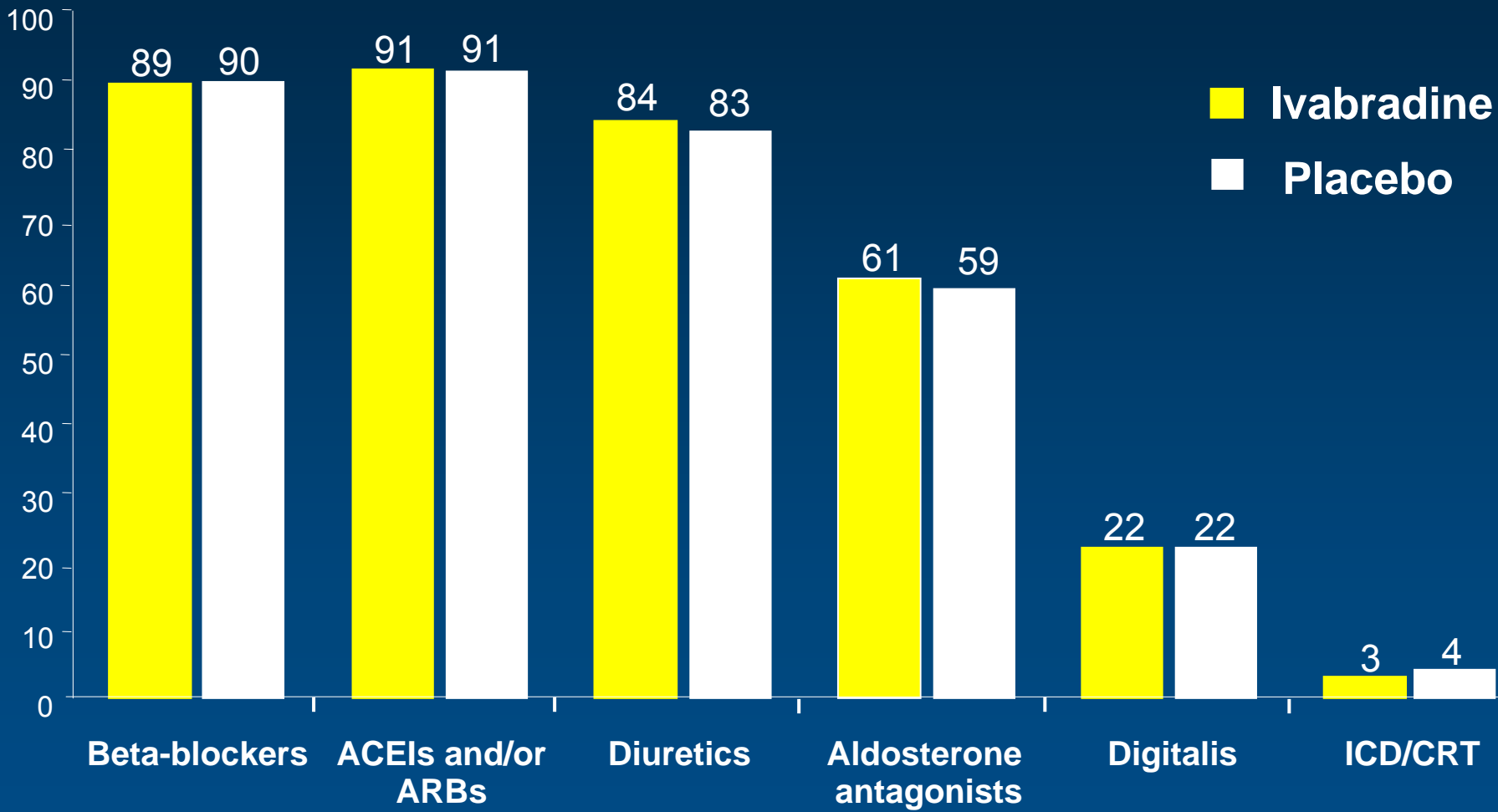
Baseline characteristics

	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



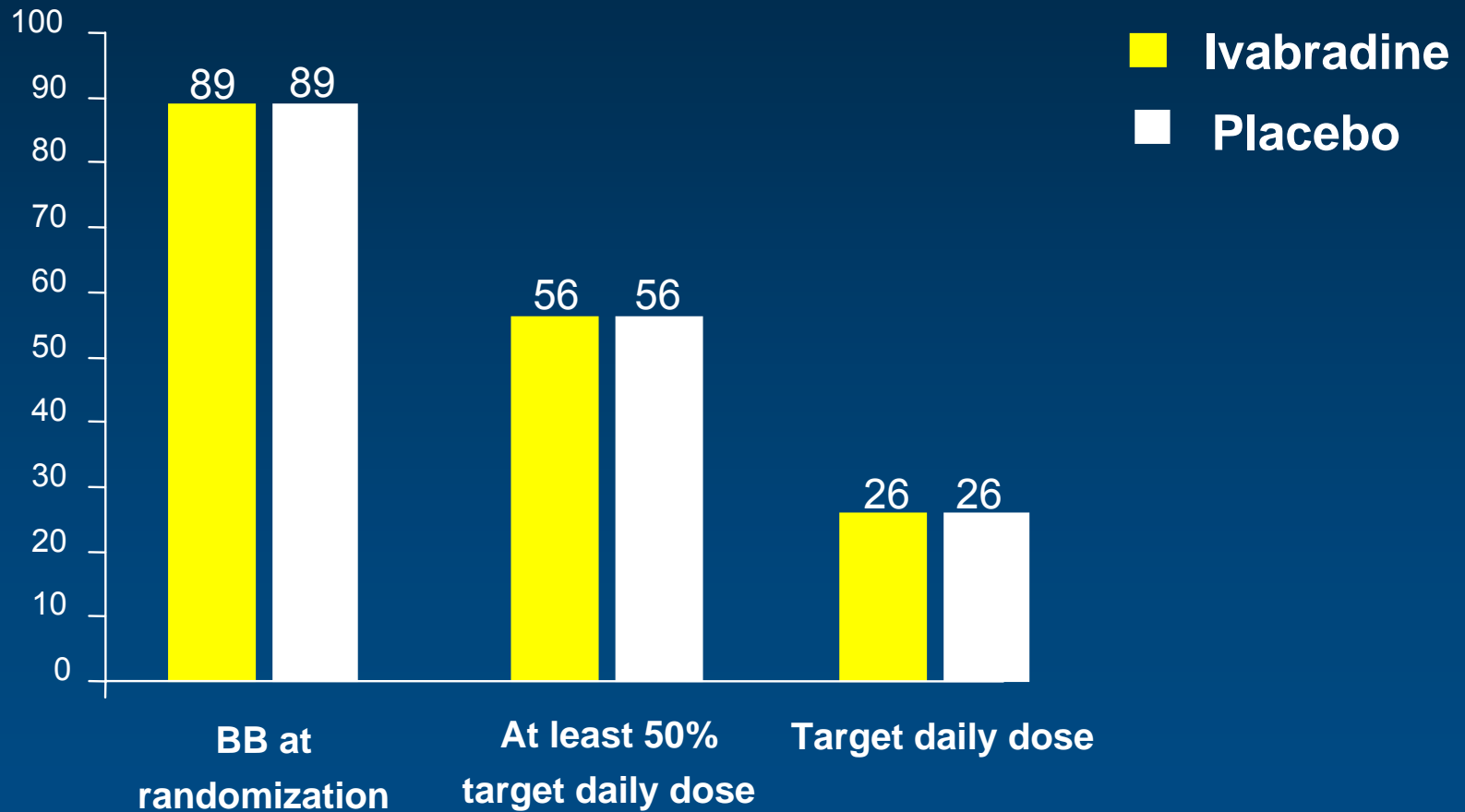
Chronic HF background treatment

Patients (%)



Background beta-blocker treatment

Patients (%)



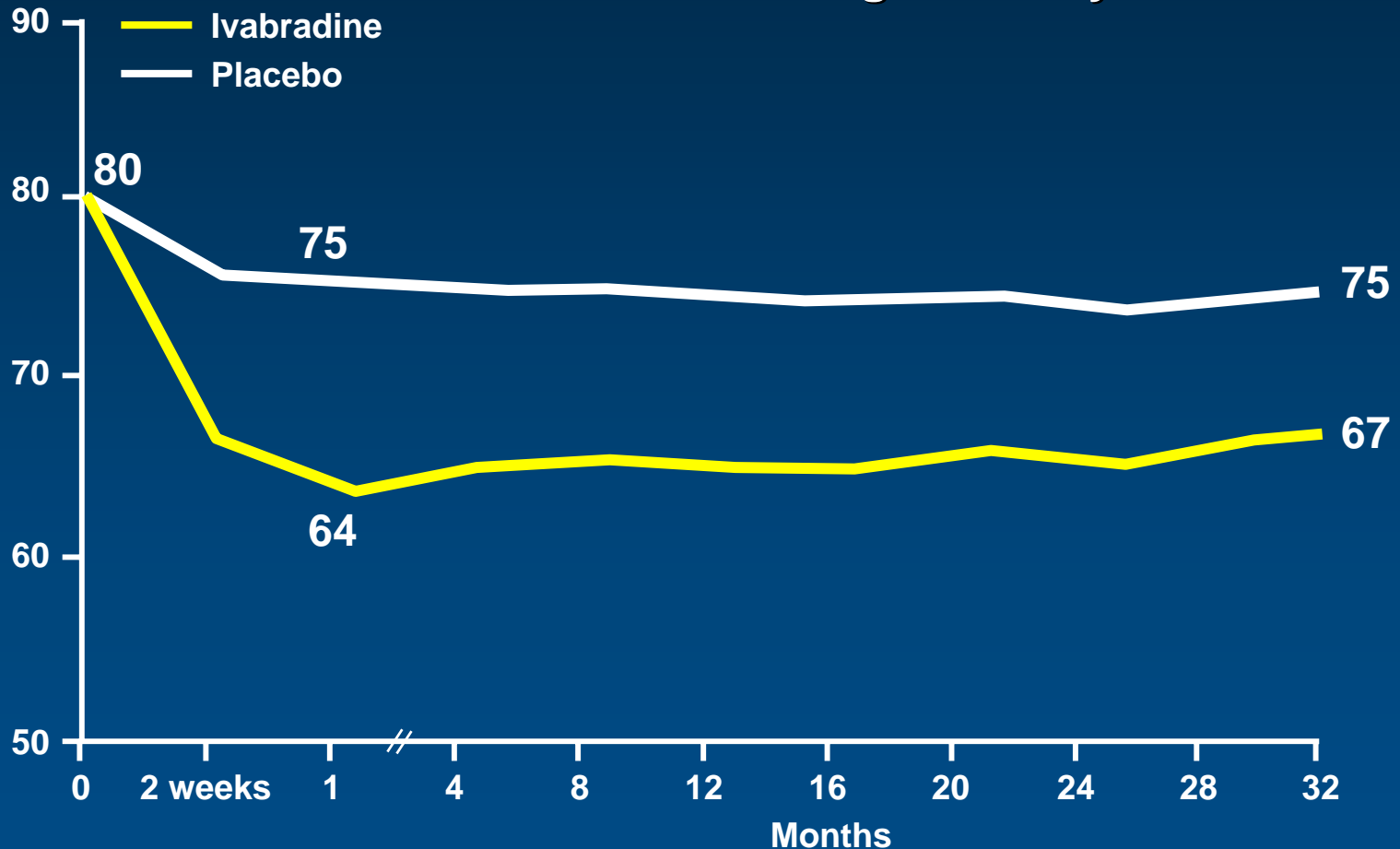


Mean heart rate reduction

Mean ivabradine dose: 6.4 mg bid at 1 month

6.5 mg bid at 1 year

Heart rate (bpm)





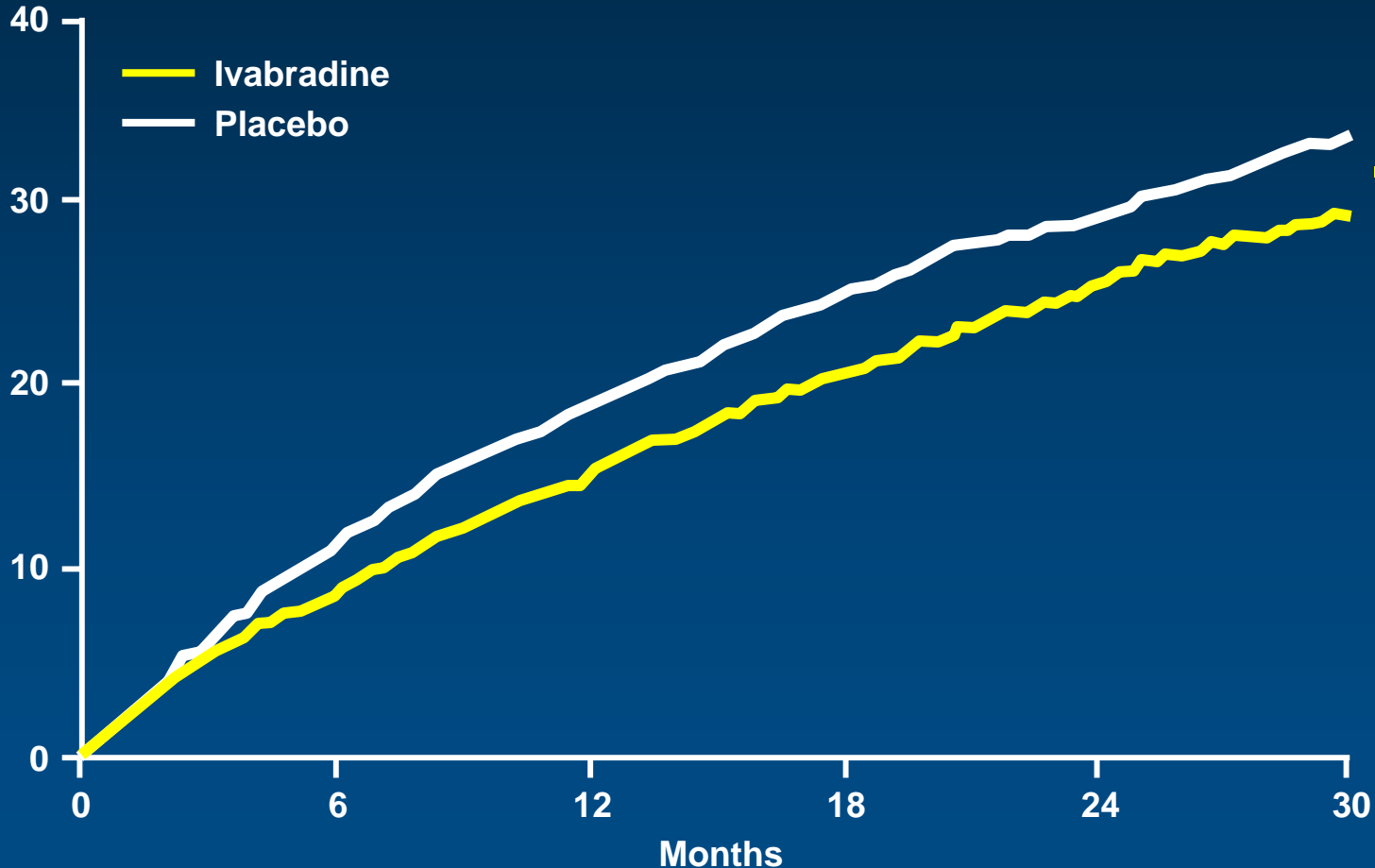
Primary composite endpoint

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 (%)



- 18%



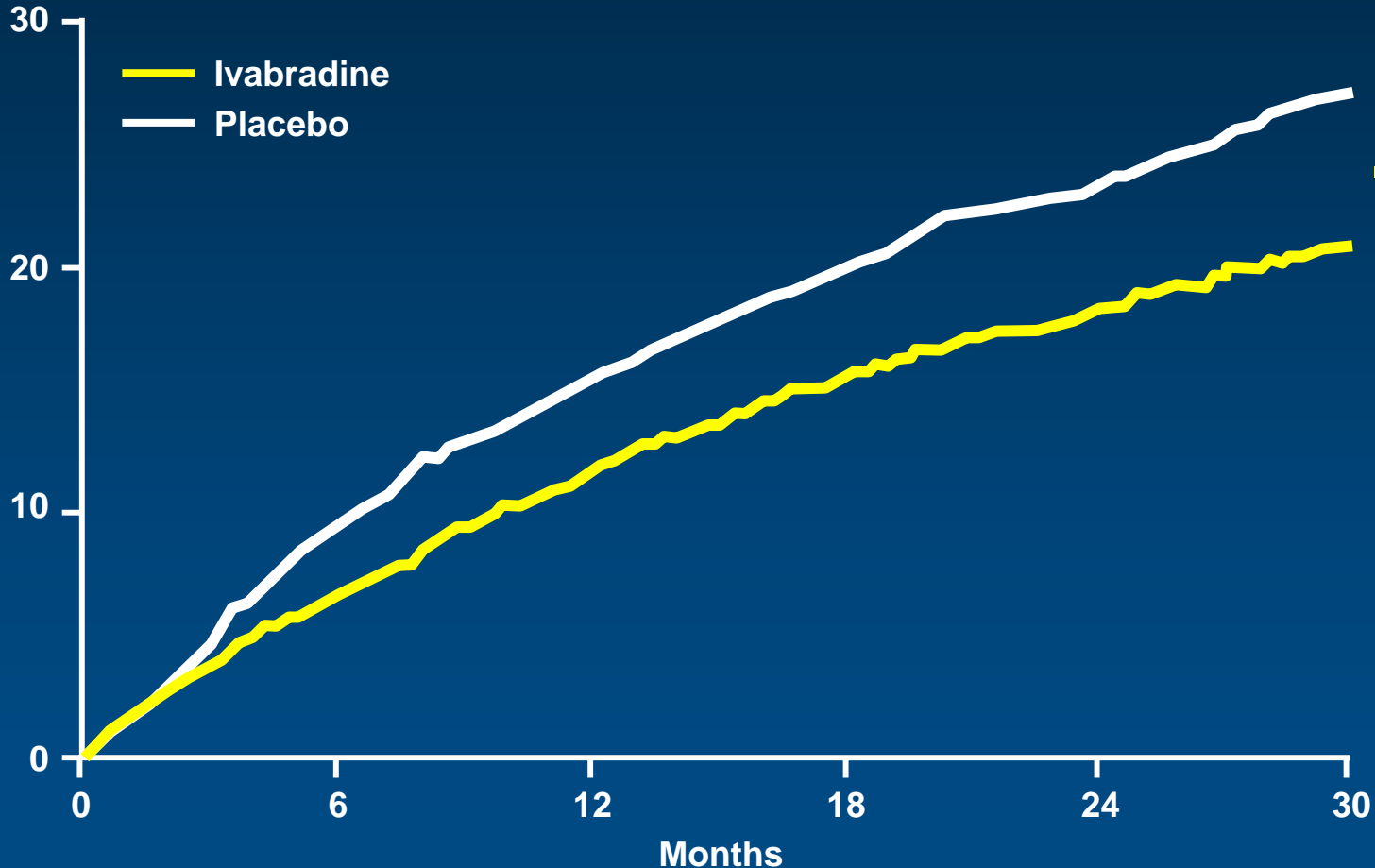
Hospitalization for heart failure

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

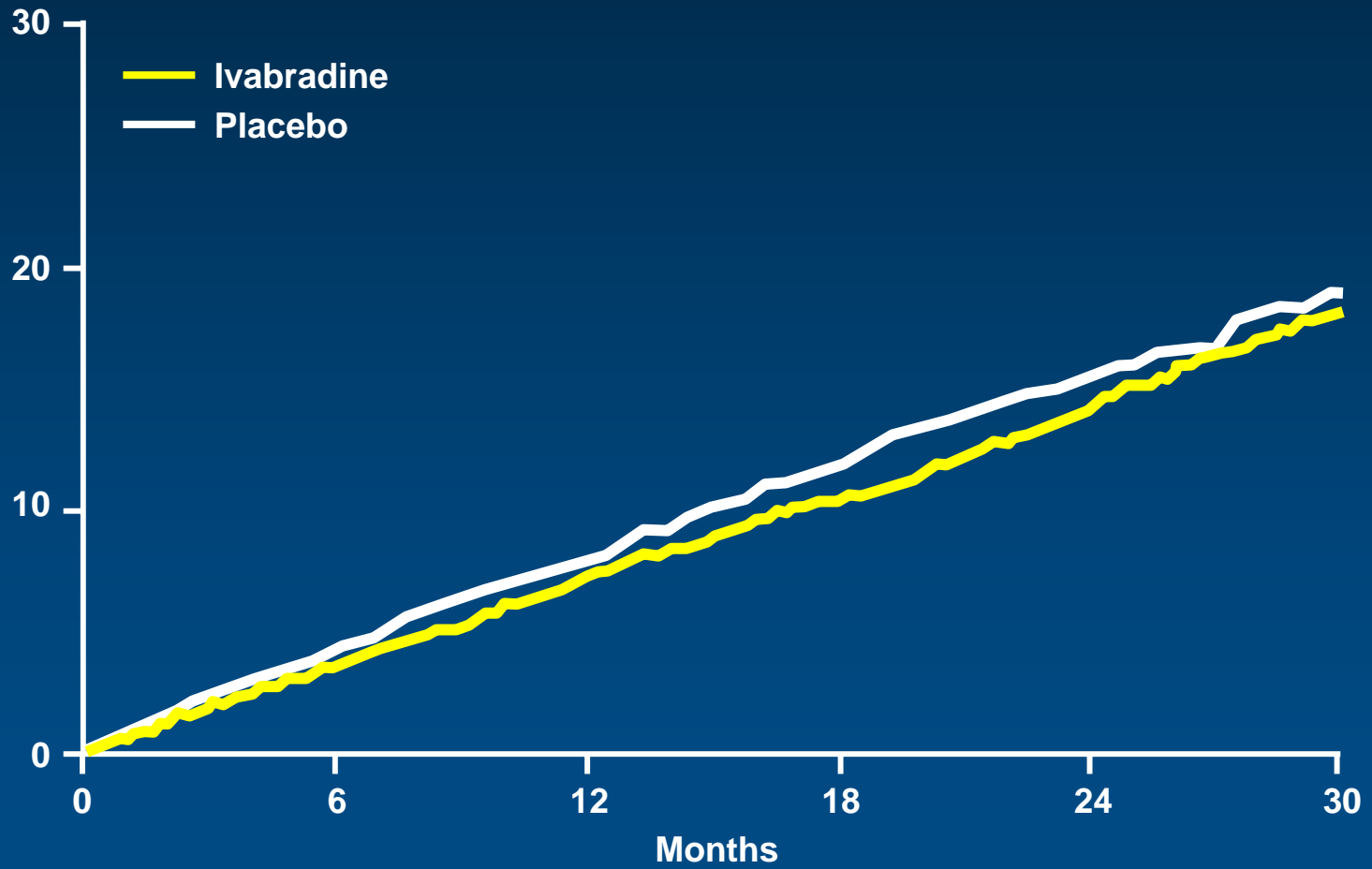
Ivabradine n=449 (7.5%PY)

Placebo n=491 (8.3%PY)

HR = 0.91

p=0.128

Cumulative frequency (%)

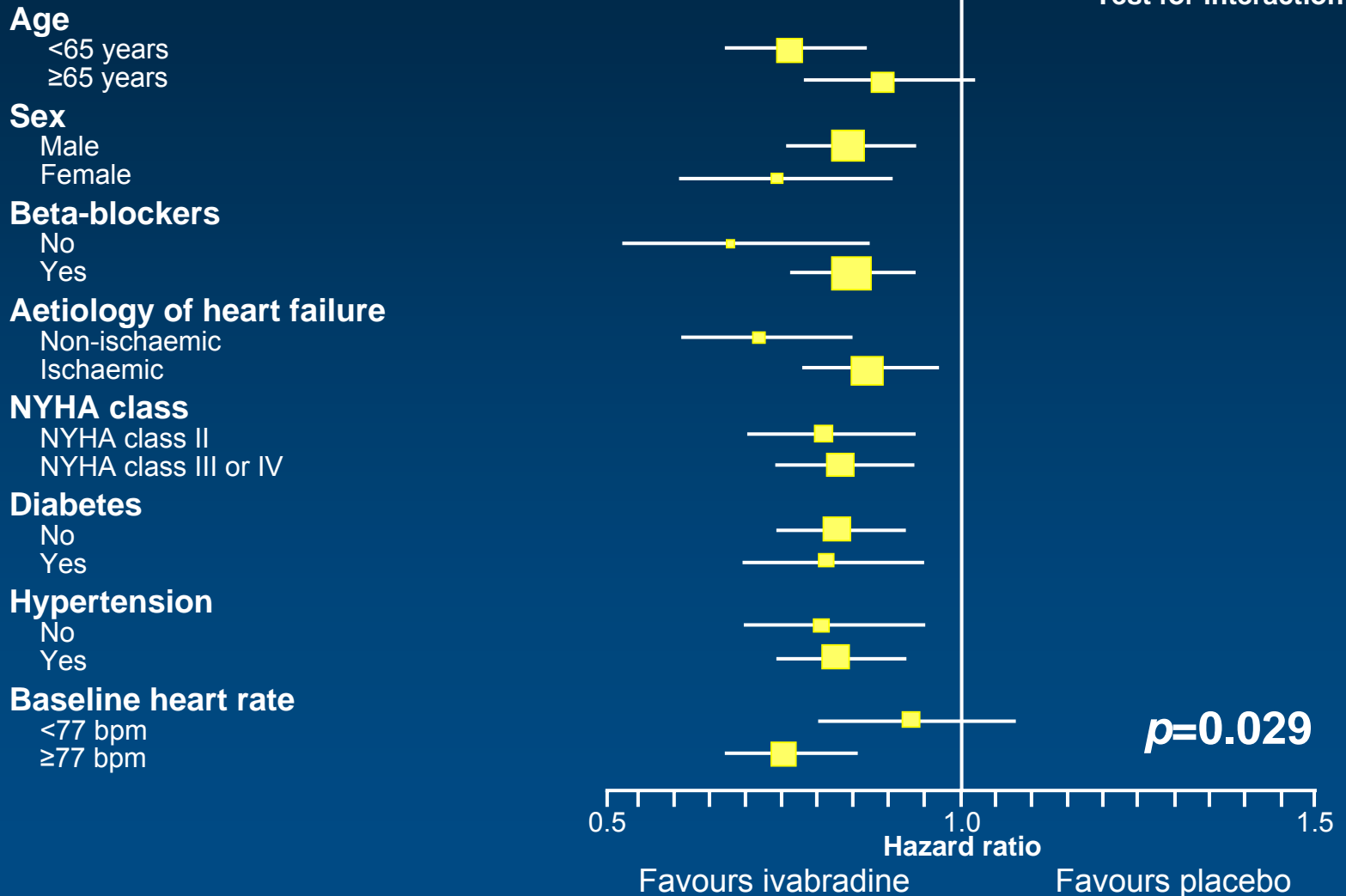




Effect of ivabradine on outcomes

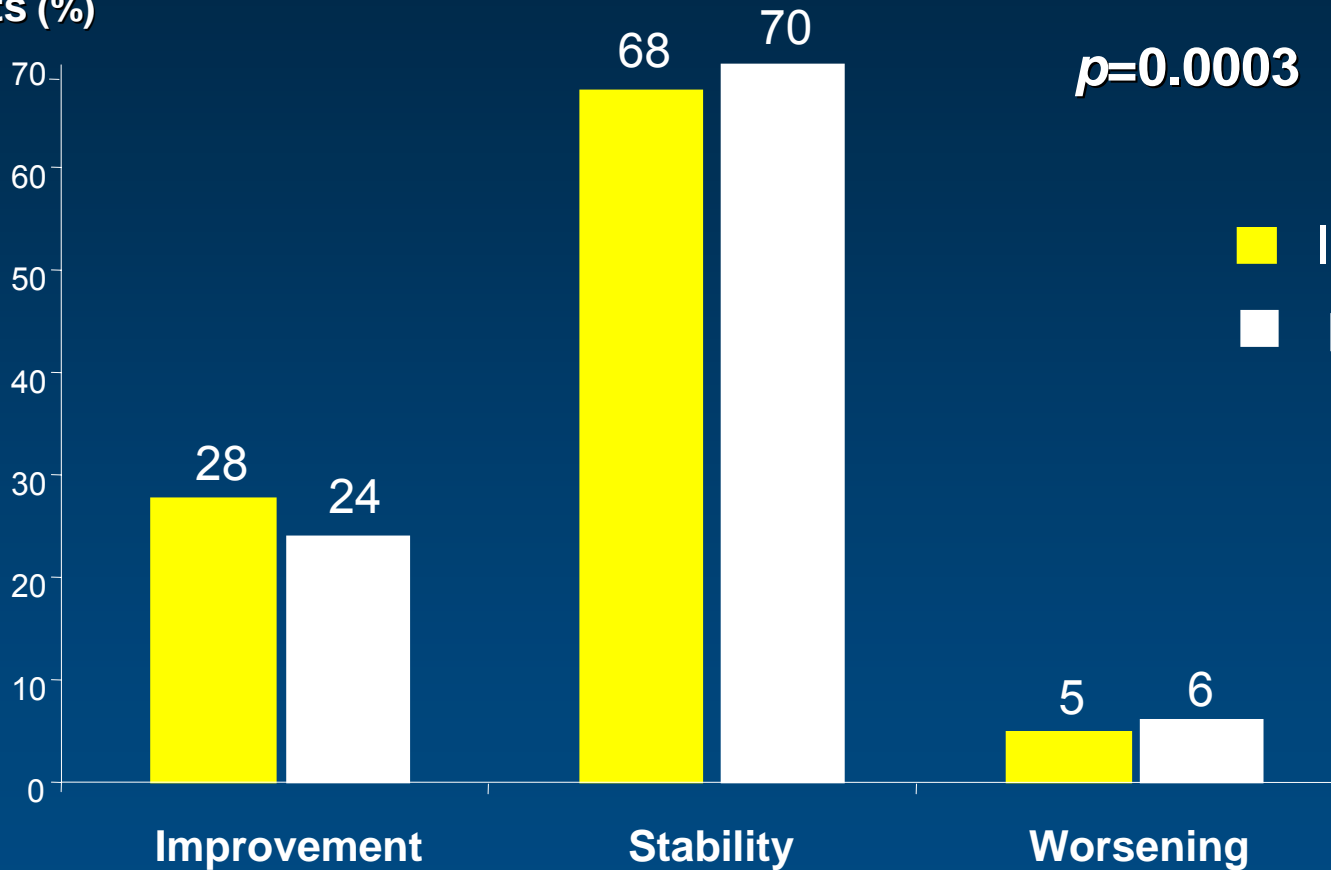
Endpoints	Hazard ratio	95% CI	<i>p</i> value
Primary composite endpoint	0.82	[0.75;0.90]	<i>p</i> <0.0001
All-cause death	0.90	[0.80;1.02]	<i>p</i> =0.092
Death from HF	0.74	[0.58;0.94]	<i>p</i> =0.014
Hospitalisation for any cause	0.89	[0.82;0.96]	<i>p</i> =0.003
Hospitalisation for CV reason	0.85	[0.78;0.92]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



$p=0.0003$

■ 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

- 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 hospitalization by 18% ($p < 0.0001$). The absolute risk reduction was 4.2%
- This beneficial effect was mainly driven by a favourable effect on heart failure death/hospital admission (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 hospitalization for heart failure is 27

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Articles

LB

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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**

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- **677** centres
- More than **700** investigators and staff
- Study supported by



**Learn more about SHIFT on Monday 30 August
during the Clinical Trial Update II (14h13, Stockholm, Zone K)**