Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial

Effect of ivabradine on recurrent hospitalization for worsening heart failure: findings from SHIFT

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on behalf of

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Disclosures

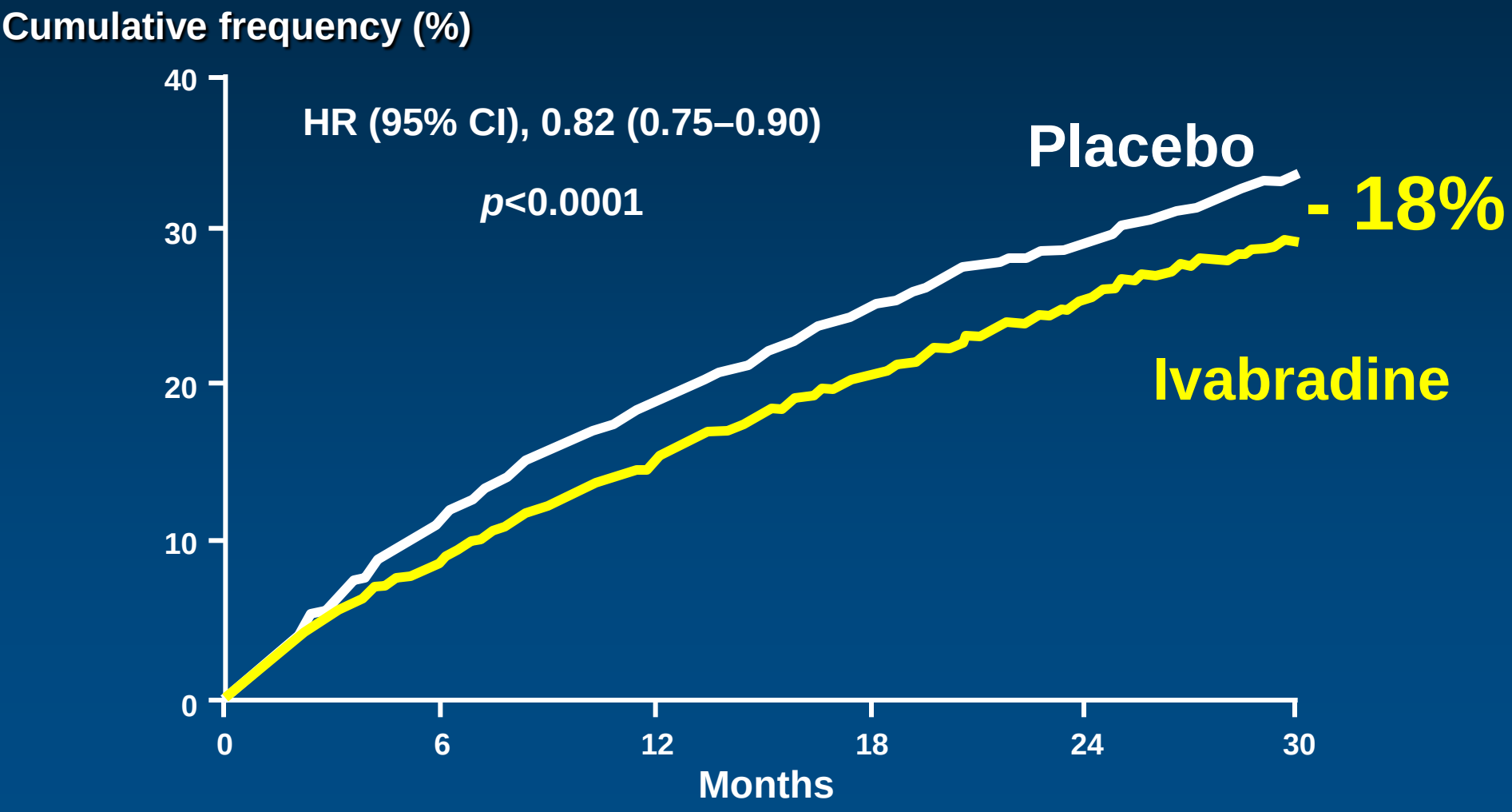
- All authors have received honoraria or research grants from Servier
- The study was supported by Servier, France

Trial design

- Randomized, double-blind, placebo-controlled trial in 6505 patients to test the hypothesis that heart rate slowing with the I_f inhibitor ivabradine improves cardiovascular outcomes in patients with:
  - Moderate to severe chronic heart failure (HF)
  - Hospitalization for worsening HF within the 12 months prior to randomization
  - Left ventricular ejection fraction ≤35%
  - Sinus rhythm and heart rate ≥70 bpm
  - Receiving guidelines-based background HF therapy

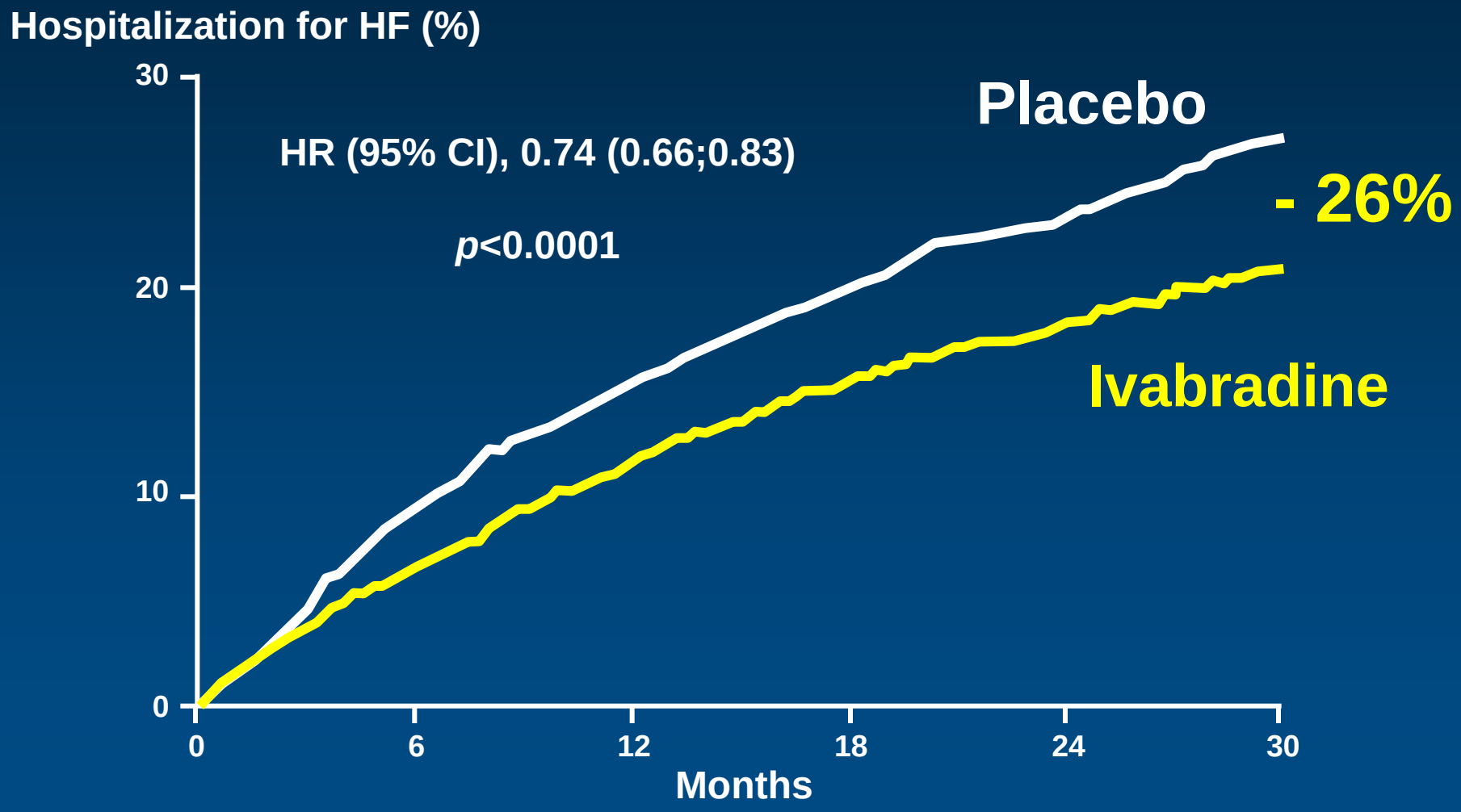
Swedberg K, et al. *Lancet* 2010;376: 875-885.

Primary endpoint: composite of CV death or hospitalization for heart failure



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

Secondary pre-specified endpoint: hospitalization for heart failure

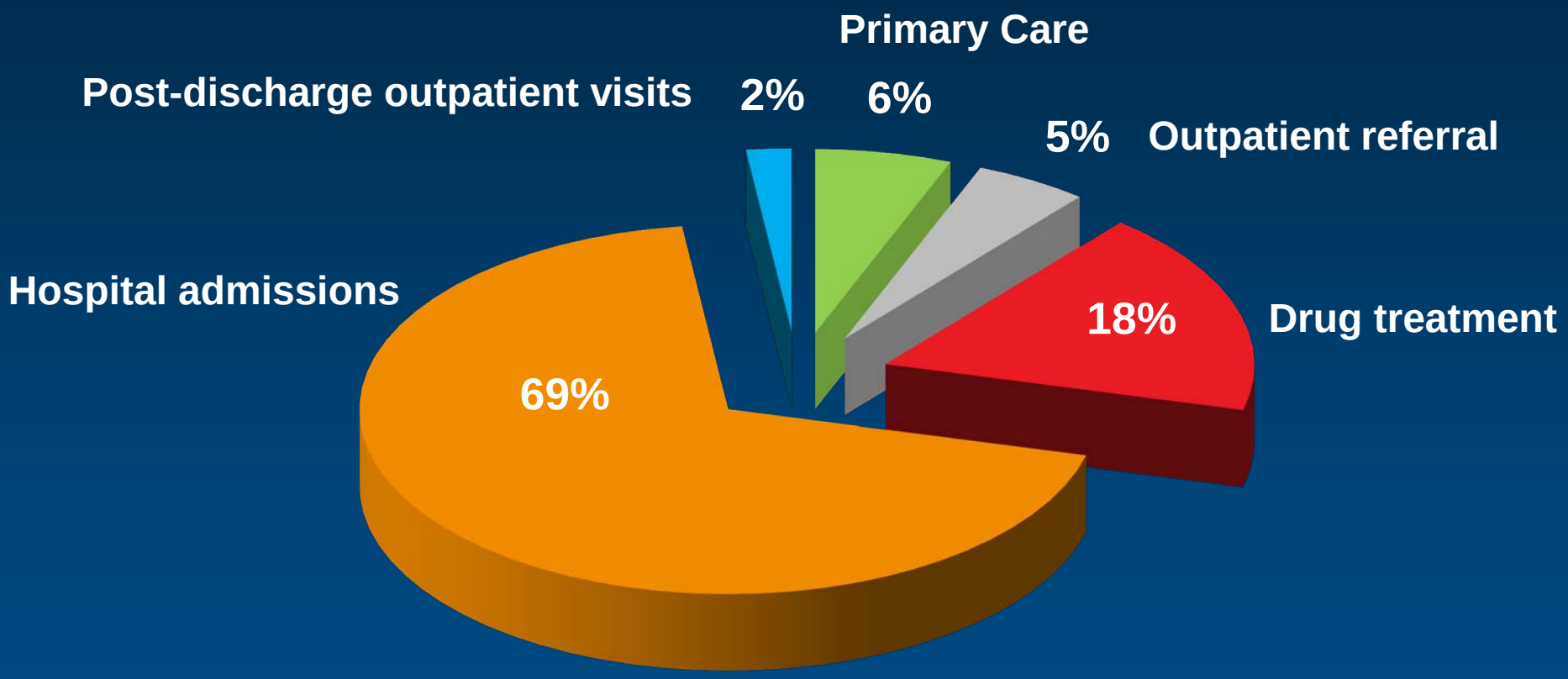


Swedberg K, et al. *Lancet* 2010;376: 875-885.

Objective of the current analysis

To assess the effect of heart rate slowing with ivabradine on recurrent hospitalizations for worsening heart failure

Economic burden of chronic HF



Hospitalization accounts for most CHF-associated costs

Stewart S et al. *Eur J Heart Fail* 2002;4:361–71.

Analysis plan

- Effect of ivabradine on
  - ***total hospitalizations***: incidence rate ratio vs placebo
  - ***repeated hospitalizations***:
    - total-time approach (time from randomization to 1st, 2nd and 3rd hospitalization)
    - gap-time approach (time from 1st to 2nd hospitalization)

- All approaches adjusted for protocol-specified prognostic factors present pre-randomization (beta-blocker intake, NYHA class, ischaemic cause of HF, LVEF, age, SBP, HR, creatinine clearance)

Pre-randomization characteristics

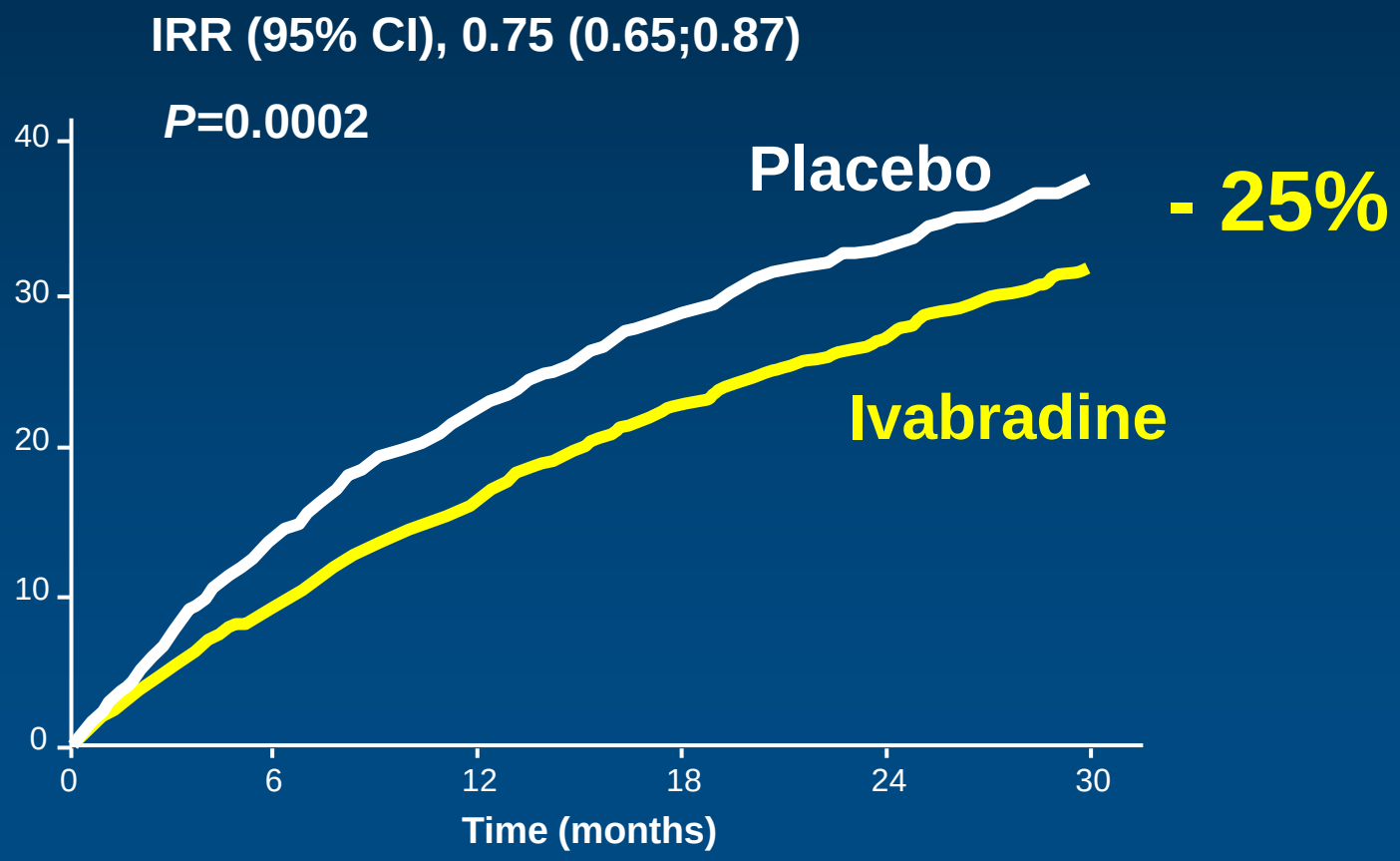
	Number of hospitalizations for HF during trial				
	None (n=5319)	**One** (n=714)	**Two** (n=254)	**Three or >** (n=218)	*p*-value
Age (years)	60.0	62.3	61.8	62.4	<0.0001
Male (%)	77	74	77	81	0.18
Heart rate (bpm)	79.3	82.2	83.4	82.2	<0.0001
SBP (mmHg)	122.3	119.8	118.1	117.6	<0.0001
DBP (mmHg)	76.0	75.0	73.4	73.3	<0.0001
LVEF (%)	29.3	27.6	27.8	27.1	<0.0001
NYHA class II (%)	51	38	38	34	<0.0001
NYHA class III/IV (%)	49	62	62	66	
Duration of HF (years)	3.3	4.2	4.3	4.6	<0.0001
Diabetes (%)	29	35	35	40	<0.0001

Pre-randomization background treatment

	Number of hospitalizations for HF during trial				
	None (n=5319)	**One** (n=714)	**Two** (n=254)	**Three or >** (n=218)	*p*-value
Beta-blockers (%)	90	89	80	86	<0.0001
ACEI and/or ARB (%)	91	89	90	93	0.13
MRA (%)	58	69	67	73	<0.0001
Diuretics (%)	82	90	90	95	<0.0001
Digitalis (%)	20	30	33	35	<0.0001

Effect of ivabradine on total HF hospitalizations

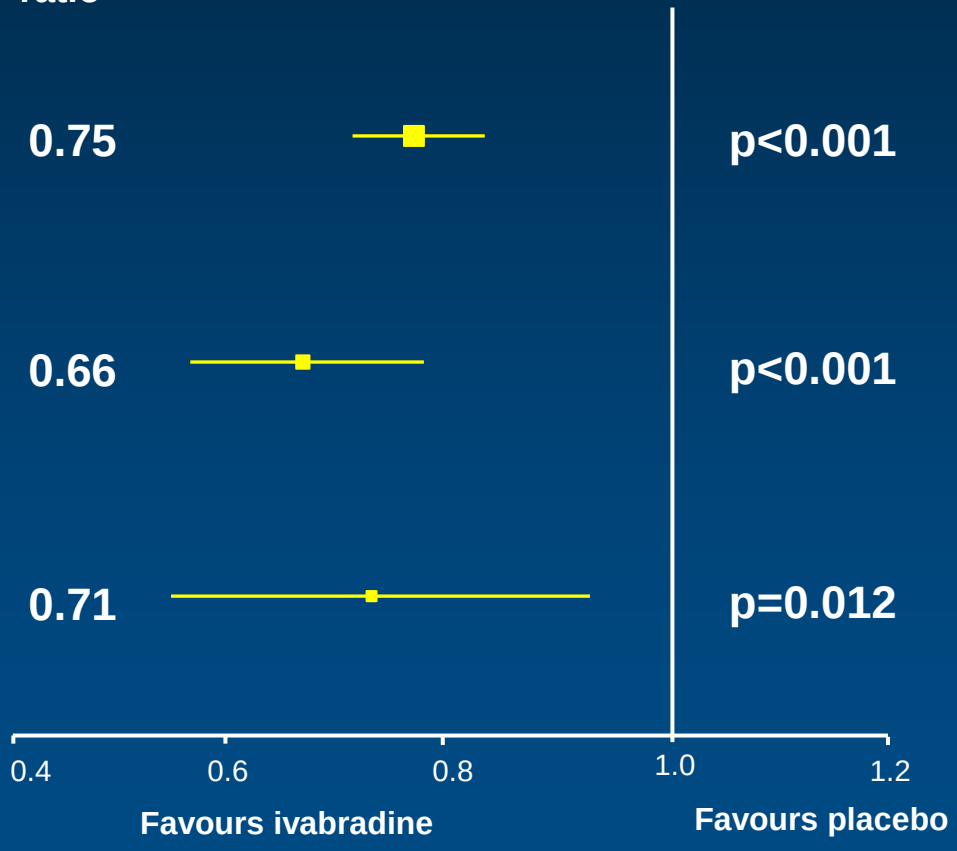
Cumulative incidence of HF hospitalizations (first and repeated)



Recurrence of HF hospitalization

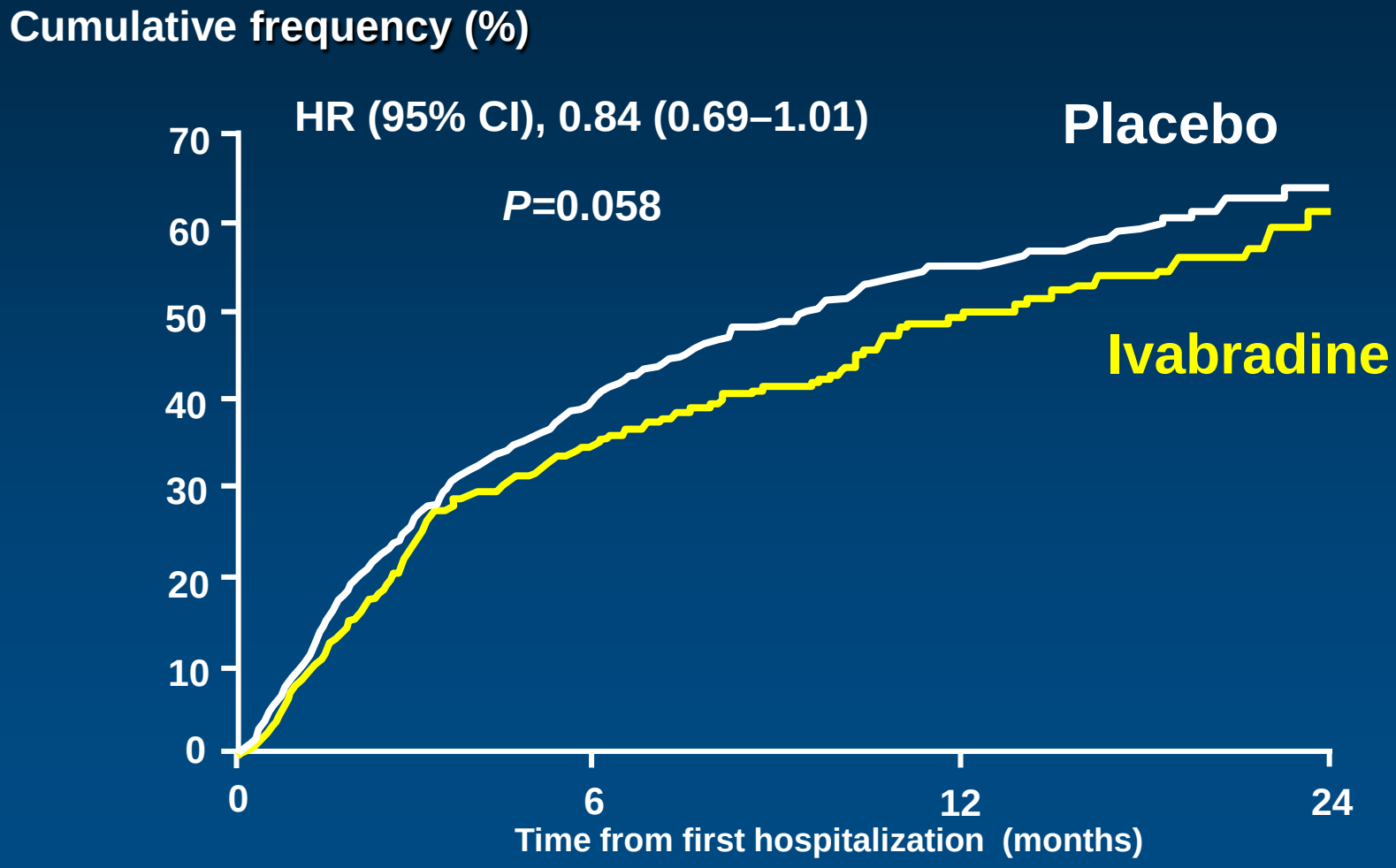
Total-time approach

	Ivabradine (n=3241)	Placebo (n=3264)	Hazard ratio	*p*-value
First hospitalization	514 (16%)	672 (21%)	0.75	p<0.001
Second hospitalization	189 (6%)	283 (9%)	0.66	p<0.001
Third hospitalization	90 (3%)	128 (4%)	0.71	p=0.012



Recurrence of HF hospitalizations

Gap-time approach **= Time from 1st to 2nd hospitalization**



472 patients with at least a first and second hospitalisation for worsening HF

Total number of hospitalizations

	Ivabradine (N=3241)	Placebo (N=3264)	IRR	95% CI	*p*-value
Hospitalization for worsening HF	902	1211	0.75	0.65-0.87	0.0002
Hospitalization for any cause	2661	3110	0.85	0.78-0.94	0.001
Cardiovascular hospitalisation	1909	2272	0.84	0.76-0.94	0.002
Hospitalization for other than worsening of HF	1759	1899	0.92	0.83-1.02	0.12

Limitations

- Both of the statistical models have well known limitations
  - ✓ total-time approach: treatment effect dependent on previous hospitalizations (cumulative effect)
  - ✓ gap-time approach: restricted set of patients; therefore, randomization not preserved
- Data on hospitalization burden may be influenced by differences between health care systems in different countries

Conclusion

- Heart rate reduction with ivabradine in patients with chronic HF, in sinus rhythm, with heart rate ≥70 bpm and already receiving guidelines-suggested therapies substantially decreases the risk of clinical deterioration as reflected by:
  - reduction in the total hospitalizations for worsening HF
  - reduction in the incidence of recurrent HF hospitalizations
  - increase in time to first and subsequent hospitalizations

- This benefit reduces the total burden of HF for the patient and can be expected to substantially reduce health care costs

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

Jeffrey S. Borer[1*], Michael Böhm[2], Ian Ford[3], Michel Komajda[4], Luigi Tavazzi[5], Jose Lopez Sendon[6], Marco Alings[7], Esteban Lopez-de-Sa[6], and Karl Swedberg[8], on behalf of the SHIFT Investigators