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

Effects of heart rate reduction with ivabradine on left ventricular remodeling and function: results of the SHIFT echocardiography substudy

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on behalf of the SHIFT Investigators

Disclosures

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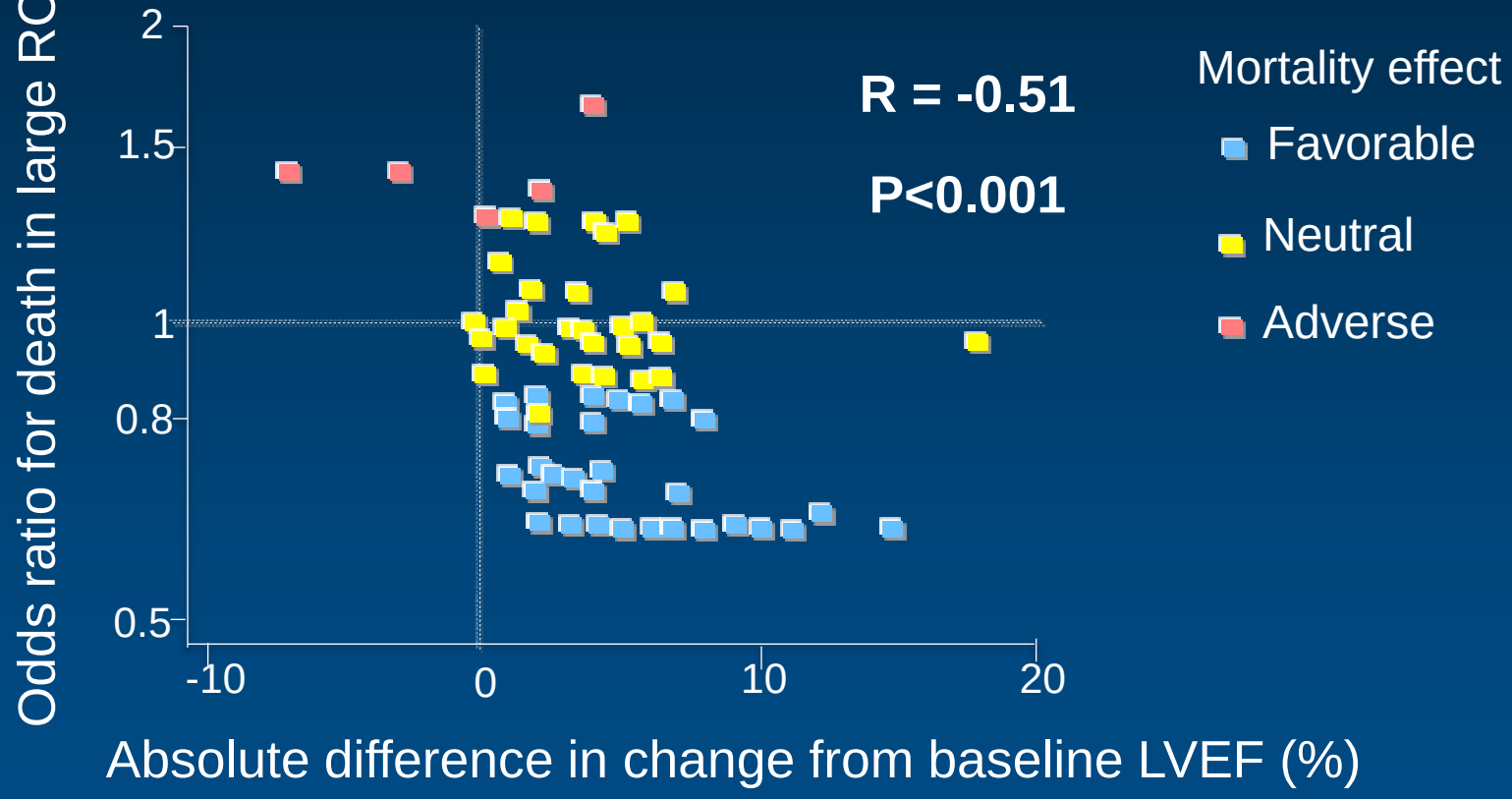
Montreal Heart Institute Coordinating Center | MHICC

Background

- Cardiac remodeling is central to the pathophysiology of heart failure (HF) and is a prognostic factor in patients with HF
- Left ventricular (LV) enlargement and reduced ejection fraction are powerful predictors of outcomes in heart failure
- Therapeutic effects of drugs and devices on LV remodeling are associated with their longer-term effects on mortality
- It is therefore relevant to evaluate the impact of HF therapies on cardiac remodeling

Relationship between drug/device effects on LVEF and prognosis in heart failure

Meta-analysis of 30 mortality trials (69 766 patients)
and 88 remodeling trials (19921 patients)



Kramer DG et al *J Am Coll Cardiol* 2010;56:392–406

Background

- SHIFT is a randomised, double-blind, placebo-controlled, multinational trial in 6505 pts with chronic HF, LVEF ≤ 35%, sinus rhythm and heart rate (HR) ≥ 70 bpm
- Patients were randomly allocated to ivabradine 5 mg bid or placebo and the dosage could be adjusted to 7.5 mg or 2.5 mg bid depending on HR and tolerability
- HR lowering with ivabradine led to an 18% reduction in the primary endpoint of CV death/HF hospitalization (P<0.0001)

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

Objective of the pre-specified echocardiography sub-study

To evaluate the effects of the I_f inhibitor ivabradine on LV remodeling and function:

- **Primary endpoint**: the change in the LV end-systolic volume index (LVESVI) from baseline to 8 months
- **Secondary endpoints**: changes during the same interval in
  - LV end-diastolic volume index (LVEDVI)
  - LV end-systolic, end-diastolic volumes (LVESV, LVEDV)
  - LV ejection fraction (LVEF)

Sub-study population

611 patients included from

89 centers in 21 countries

304 patients
Ivabradine

Excluded (N=96)

52: Poor quality of echo recording

19: No baseline and/or 8-month recording

8: Non-matching biplane or 4-chamber views

13: Withdrawn due to death

4: Consent withdrawn

208 patients
Ivabradine (Full-Analysis Set)

307 patients
Placebo

Excluded (N=104)

52: Poor quality of echo recording

15: No baseline and/or 8- month recording

1: Non-matching biplane or 4-chamber views

23: Withdrawn due to death

13: Consent withdrawn

203 patients
Placebo (Full-Analysis Set)

Median sub-study duration: 8.1 months
Follow-up after 8-month echocardiogram: 16.1 months

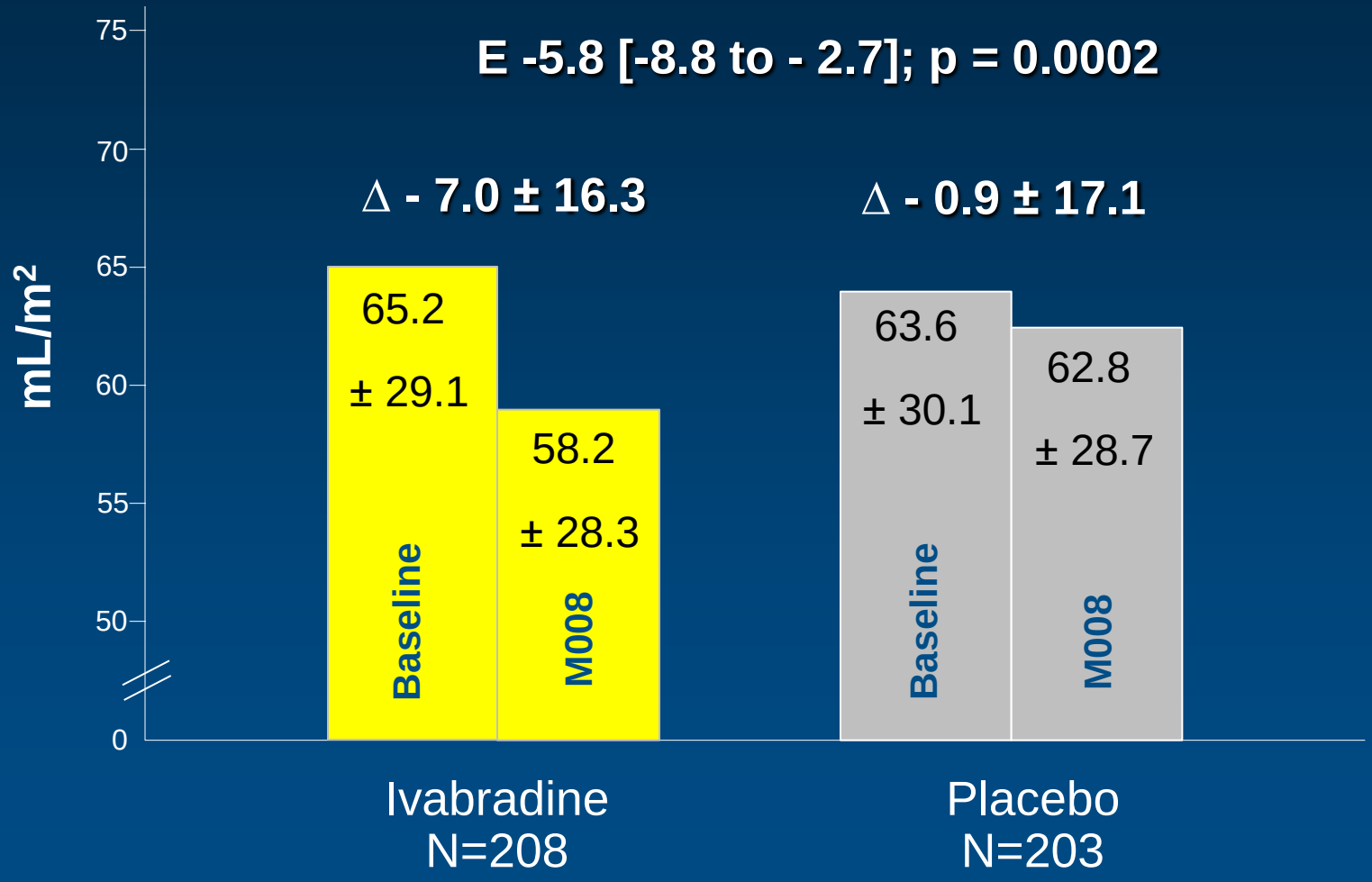
Baseline characteristics

	Ivabradine N=304	Placebo N=307
Mean age, years	60	59
Male, %	80	82
Mean BMI, kg/m^2	28	28
Mean HF duration, years	4	4
HF ischaemic cause, %	67	65
NYHA class II, %	48	46
NYHA class III, %	51	53
Mean LVEF, %	32	32
Mean HR, bpm	78	79
Mean systolic BP, mm Hg	121	119
Mean diastolic BP, mm Hg	75	75

Baseline background treatment

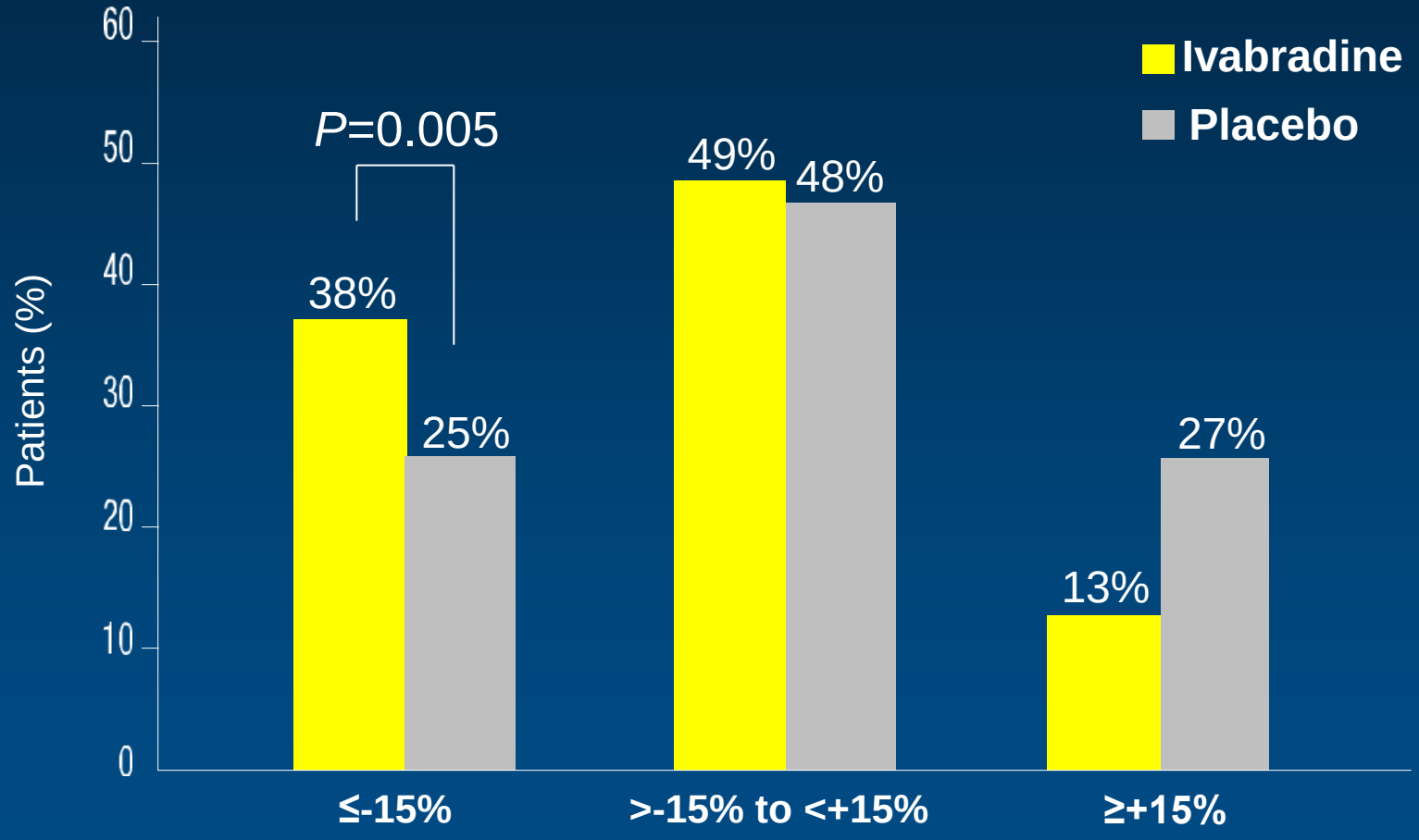
	Ivabradine N=304	Placebo N=307
Beta-blocker, %	92	92
ACE inhibitor, %	80	83
ARB, %	17	12
Diuretic (excluding antialdo), %	87	87
Aldosterone antagonist, %	74	71
Digitalis, %	27	32
Devices, %	3	4

Primary endpoint: change in LVESVI from baseline to 8 months



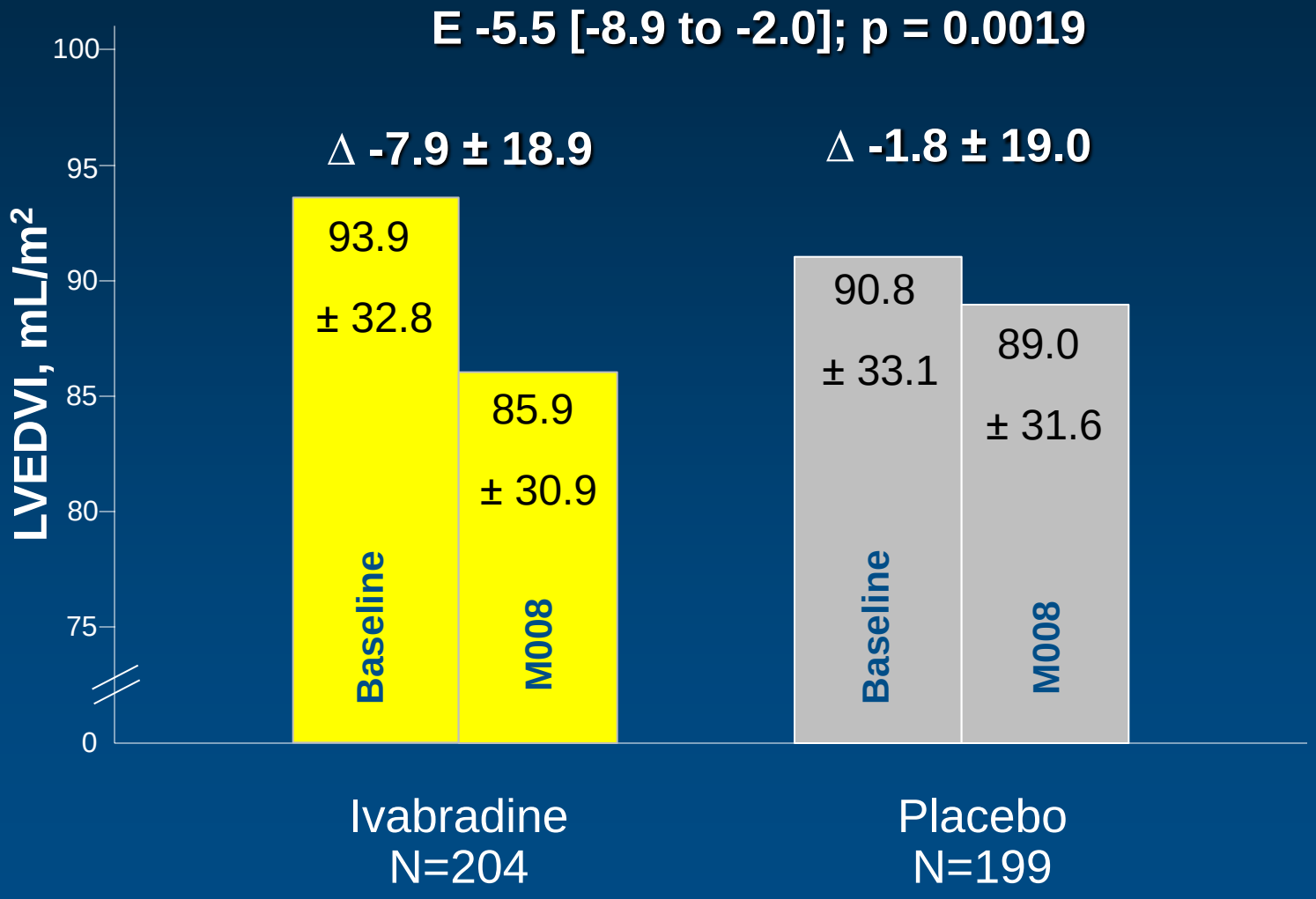
LVESVI: Left ventricular end-systolic volume index

Relative change in LVESVI from baseline to 8 months



LVESVI: Left ventricular end-systolic volume index

Secondary endpoint: change in LVEDVI from baseline to 8 months

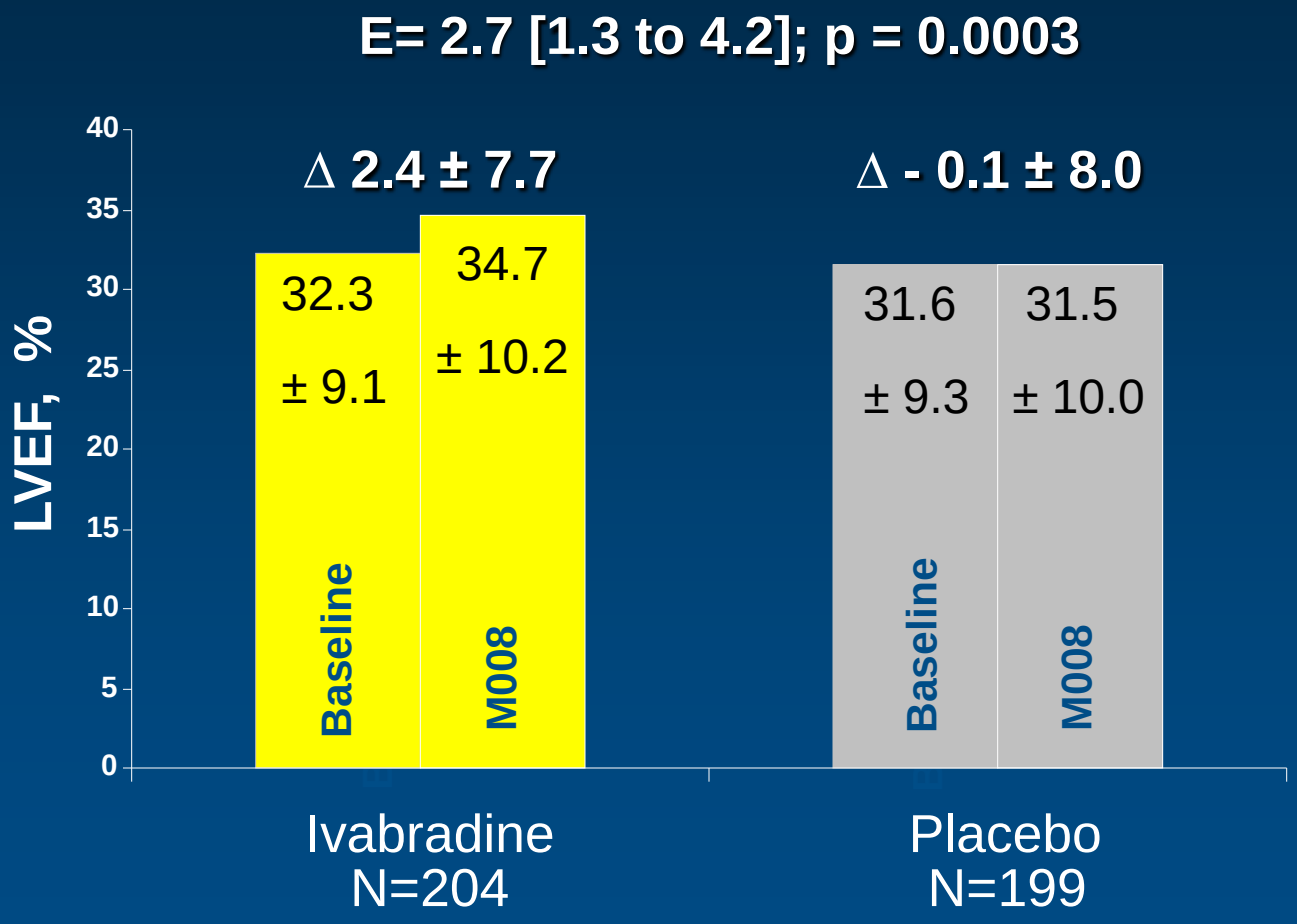


LVEDVI: Left ventricular end-diastolic volume index

Changes in LVESV and LVEDV from baseline to 8 months

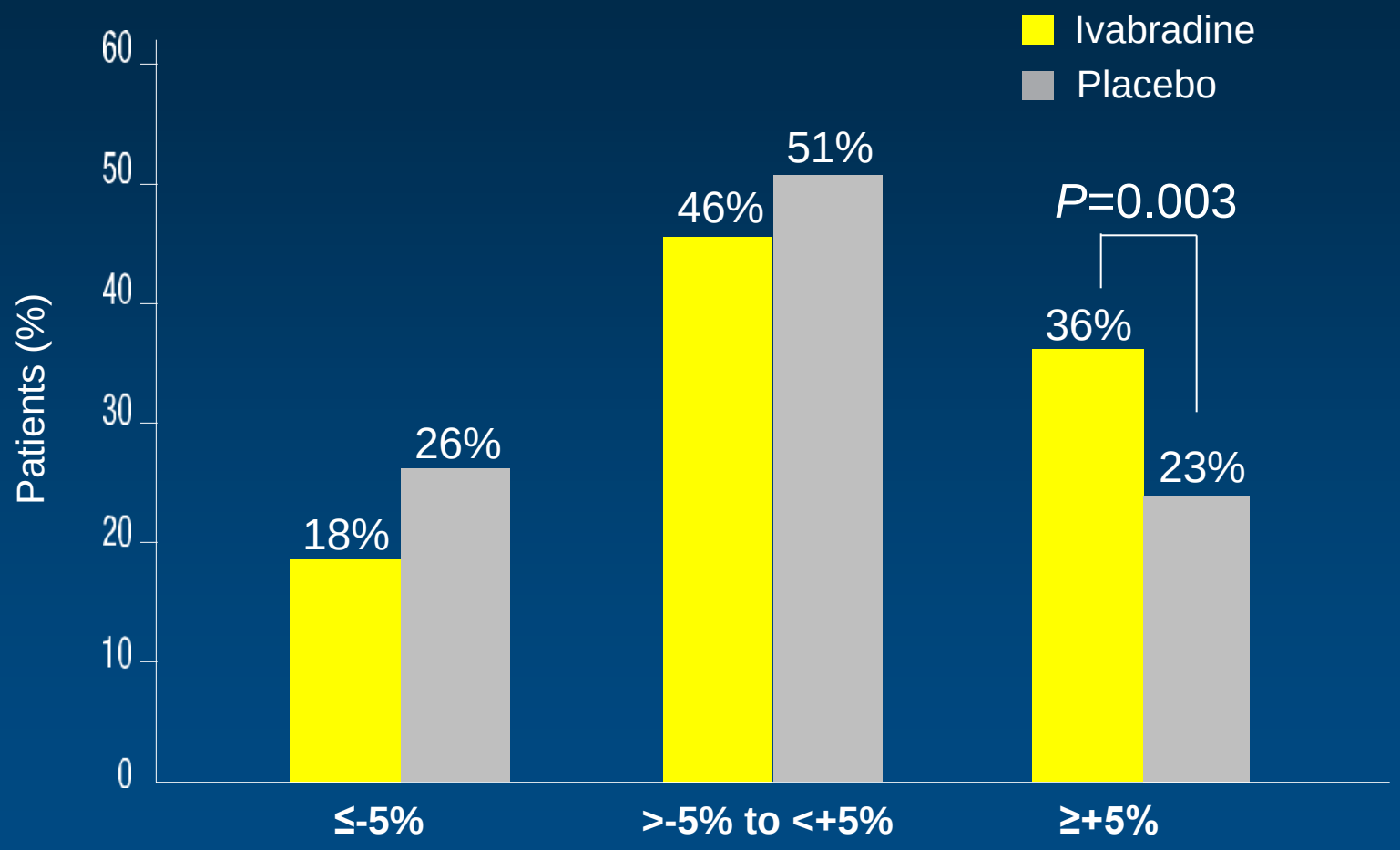
	Baseline	M8 - baseline	E, 95% CI	P value
LVESV, mL				
Ivabradine (N=208)	123.8 ± 55.6	-13.0 ± 31.6		
Placebo (N=203)	122.2 ± 59.8	-1.3 ± 32.8	-11.2 [-17.1 to - 5.4]	<0.001
LVEDV, mL				
Ivabradine (N=204)	178.4 ± 63.4	-14.7 ± 36.4		
Placebo (N=199)	174.7 ± 67.6	-2.9 ± 36.8	-10.9 [-17.6 to - 4.2]	0.0014

Secondary endpoint: change in LVEF from baseline to 8 months



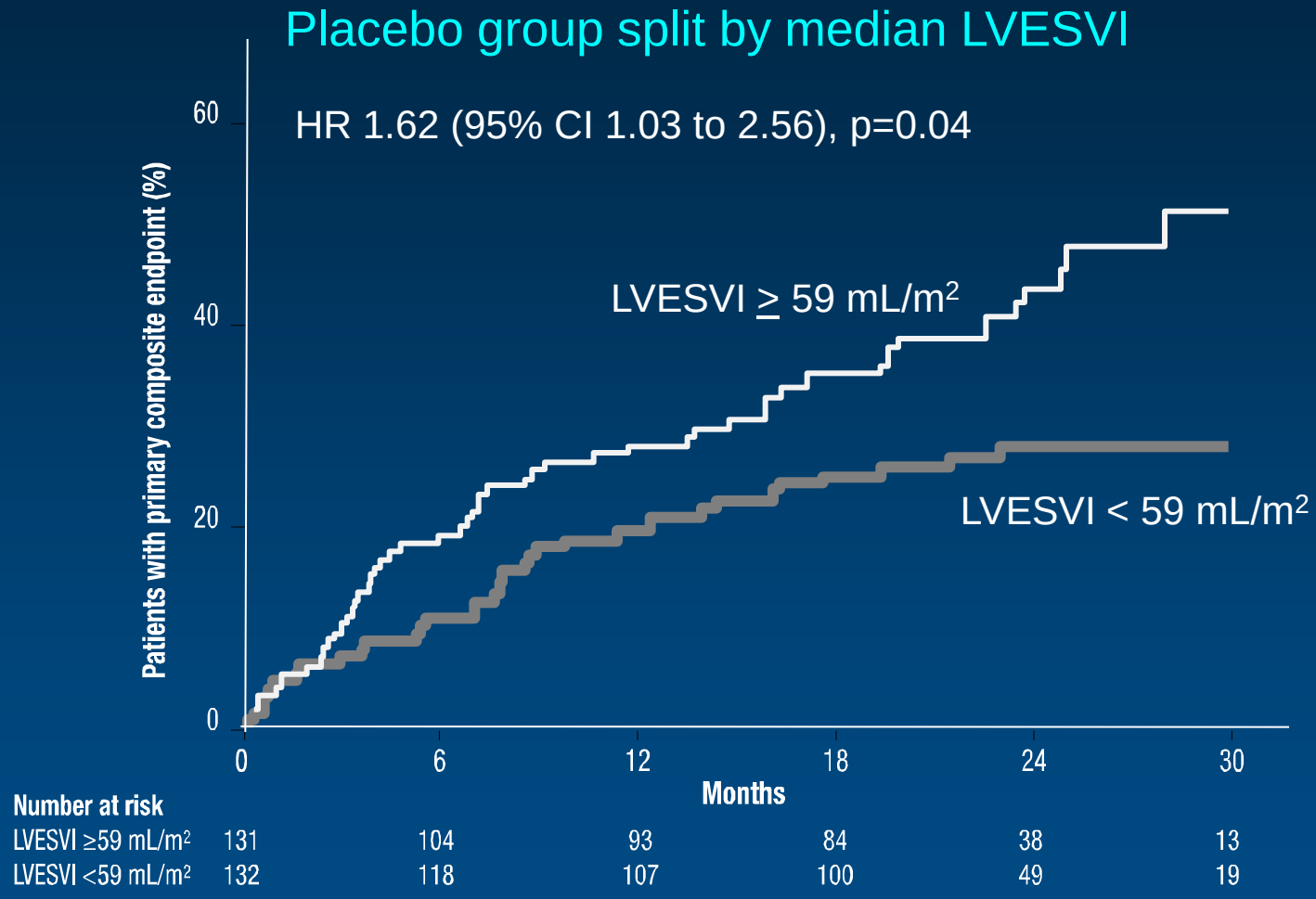
LVEF: Left ventricular ejection fraction

Absolute change in LVEF from baseline to 8 months



LVEF: Left ventricular ejection fraction

LVESVI and the risk of the SHIFT primary composite endpoint



LVESVI: Left ventricular end-systolic volume index

Limitations

- Analysis not designed to clarify the time-course of treatment effects and could not evaluate the acute effect of ivabradine
- The beta-blocker dosage was similar to other recently published data but higher doses can affect LVEF
- Data recorded in patients with HR ≥ 70 bpm, in sinus rhythm and predominantly in men, which may limit generalisation
- One third of patients were excluded from the analysis,usually for reasons related to the quality or collection of recordings

Conclusions

- Ivabradine reverses left ventricular remodeling in patients with heart failure and LV systolic dysfunction:
  - Marked reductions of LV volumes
  - Significant improvement of LVEF

- These results suggest that ivabradine modifies disease progression in patients with HF receiving background therapy

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FASTTRACK
ESC CLINICAL TRIAL UPDATE

Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy

Jean-Claude Tardif[1]*, Eileen O'Meara[1], Michel Komajda[2], Michael Böhm[3], Jeffrey S. Borer[4], Ian Ford[5], Luigi Tavazzi[6], and Karl Swedberg[7], on behalf of the SHIFT Investigators