



Selective heart rate reduction with ivabradine unloads the left ventricle in heart failure patients

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No conflicts of interest to declare

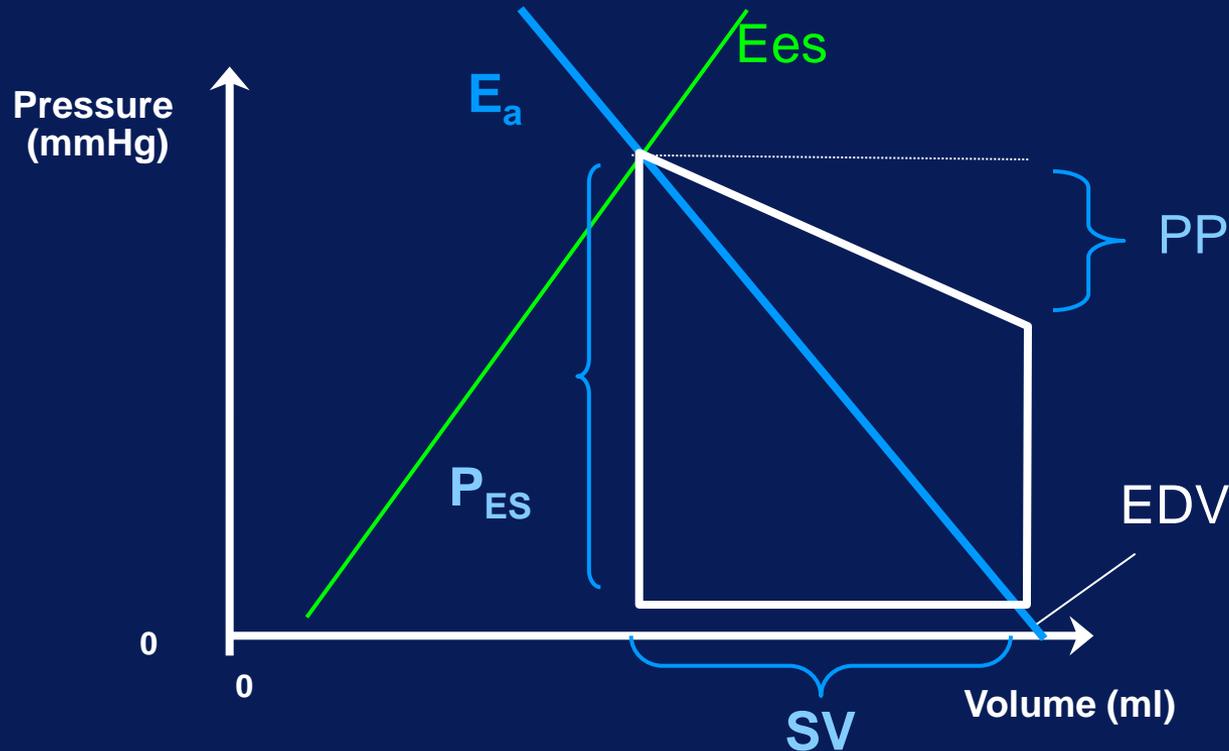
Background

- **SHIFT Trial 2010:** Selective heart rate reduction by ivabradine improved outcome in patients with systolic heart failure (EF \leq 35%).
- Aim of this study was to investigate whether selective heart rate reduction with ivabradine reduces afterload in patients with systolic heart failure thereby possibly contributing to the beneficial outcome of the **SHIFT trial**.

Methods

- **275 patients with systolic heart failure ($EF \leq 35\%$) treated either with placebo ($n=132$) or ivabradine (7.5mg bid; $n=143$) were included and retrospectively analyzed.**
- **Effective arterial elastance (Ea), vascular compliance (VC) and end-systolic elastance (Ees) are important parameters of ventricular-arterial interaction. These parameters were calculated non-invasively at baseline and after 8 months of treatment using Echo data and blood pressure measurements of the SHIFT echocardiographic substudy.**

Definition of the pressure-volume parameters



Effective arterial elastance (E_a) = $P_{es}/SV \approx TPR \times HR$
End-systolic elastance (E_{es}) non-invasive single beat analysis
 according to Sunagawa et al., Ann
 Bio Eng 1984 and Chen et al., JACC 2001
Vascular compliance (VC) = SV / PP
Coupling ratio = E_a/E_{es}

Background II

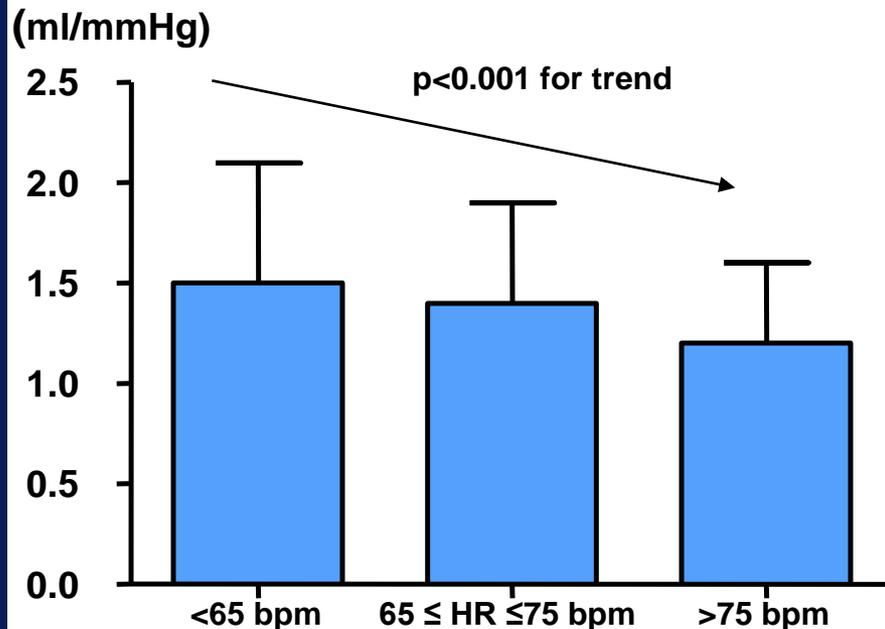
- The effective arterial elastance (E_a) represents resistive and pulsatile load of the heart.
- Theoretically, heart rate can modulate E_a i.e. afterload burden.
- End-systolic elastance (E_{es}) represents cardiac contractility.
- **Aims of the study** →
 - 1.) Does selective heart rate reduction with ivabradine reduce afterload ($E_a \downarrow$) in patients with systolic heart failure ?
 - 2.) Does selective heart rate reduction influence vascular-ventricular interaction?

Baseline demographics of the studied patients

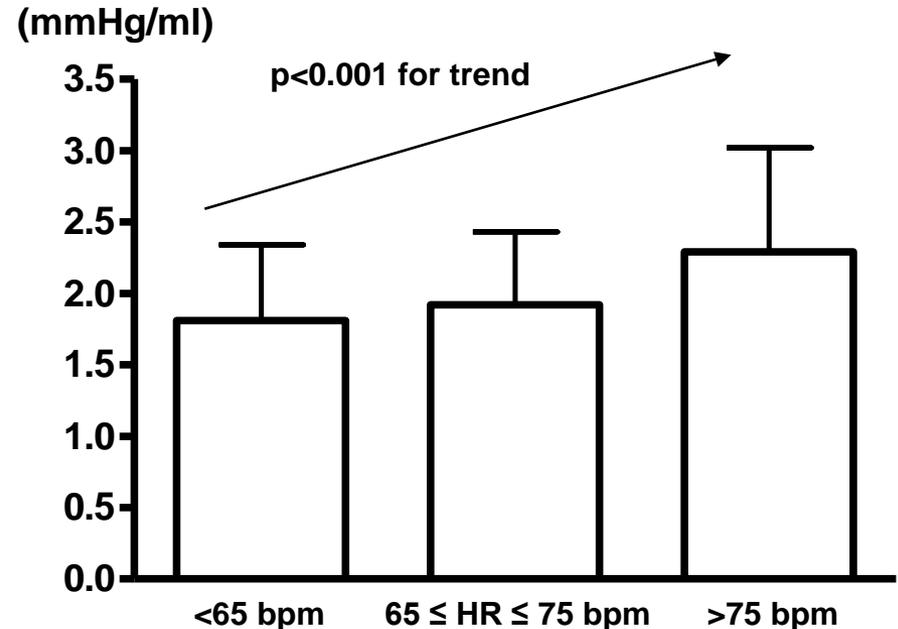
Demographics a. clinical data	All (n=275)	Ivabradine (n=143)	Placebo (n=132)	p-value
Age	59.7 (11.1)	60 (10.8)	59.4 (11.5)	0.65
Male	224 (81.5%)	119 (83.2%)	105 (79.5%)	0.43
NYHA II	153 (55.6 %)	82 (57.3 %)	71 (53.8%)	0.55
NYHA III+IV	122 (44.4%)	61 (42.7%)	61 (46.2%)	
EF (%)	28.6 (5.3)	28.5 (5.2)	28.7 (5.4)	0.55
Heart rate	71 (11.4)	71 (11.8)	71 (11.0)	0.70
Systolic blood pressure (SBP, mmHg)	122 (15)	123 (15.7)	121 (14.2)	0.33
Diastolic blood pressure (DBP, mmHg)	76 (8.6)	76 (9.2)	76 (8.0)	0.81

Effects of heart rate on compliance and Ea by tertiles at baseline (n=275)

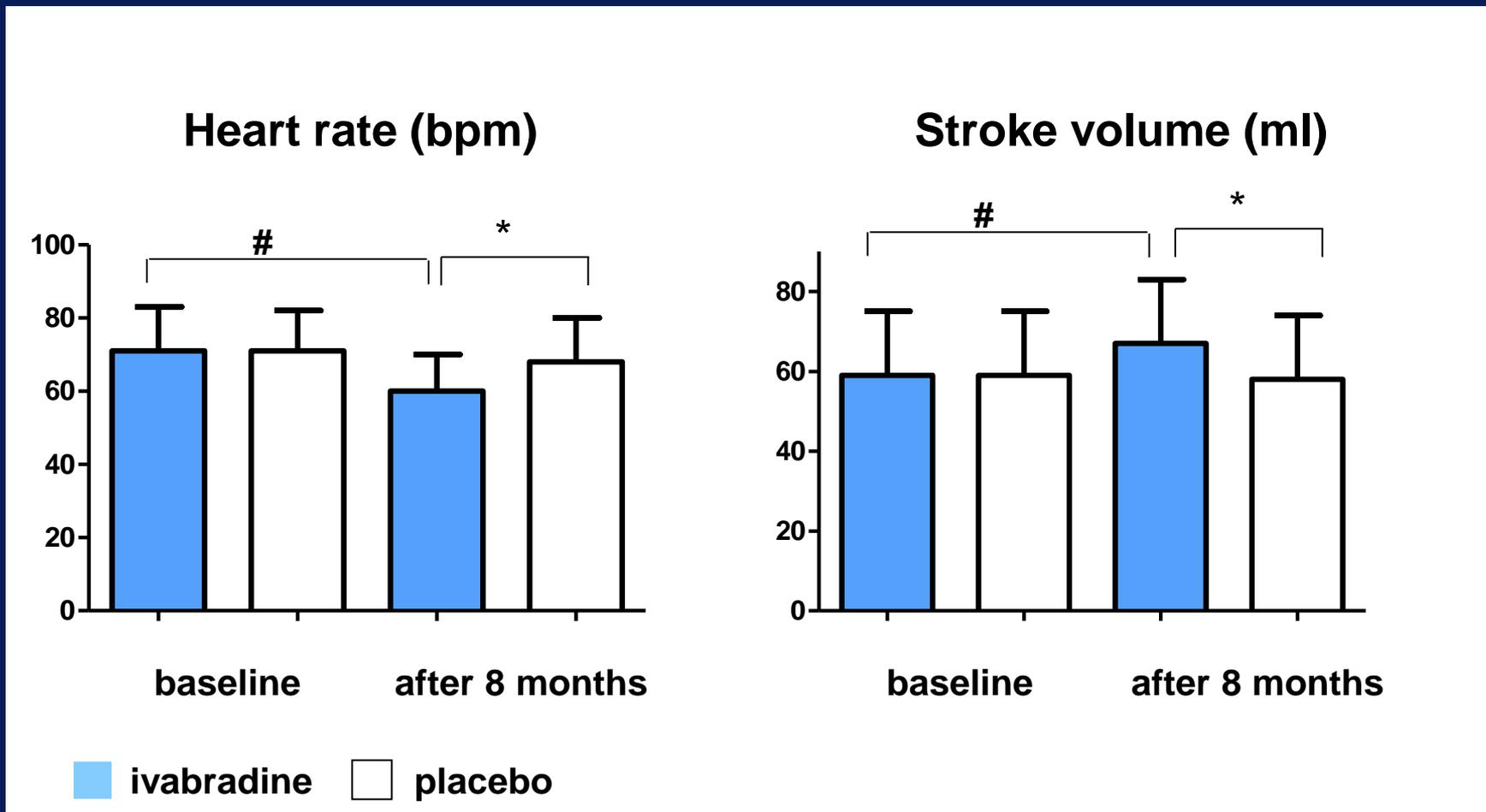
Vascular compliance (VC)



Effective arterial elastance (Ea)

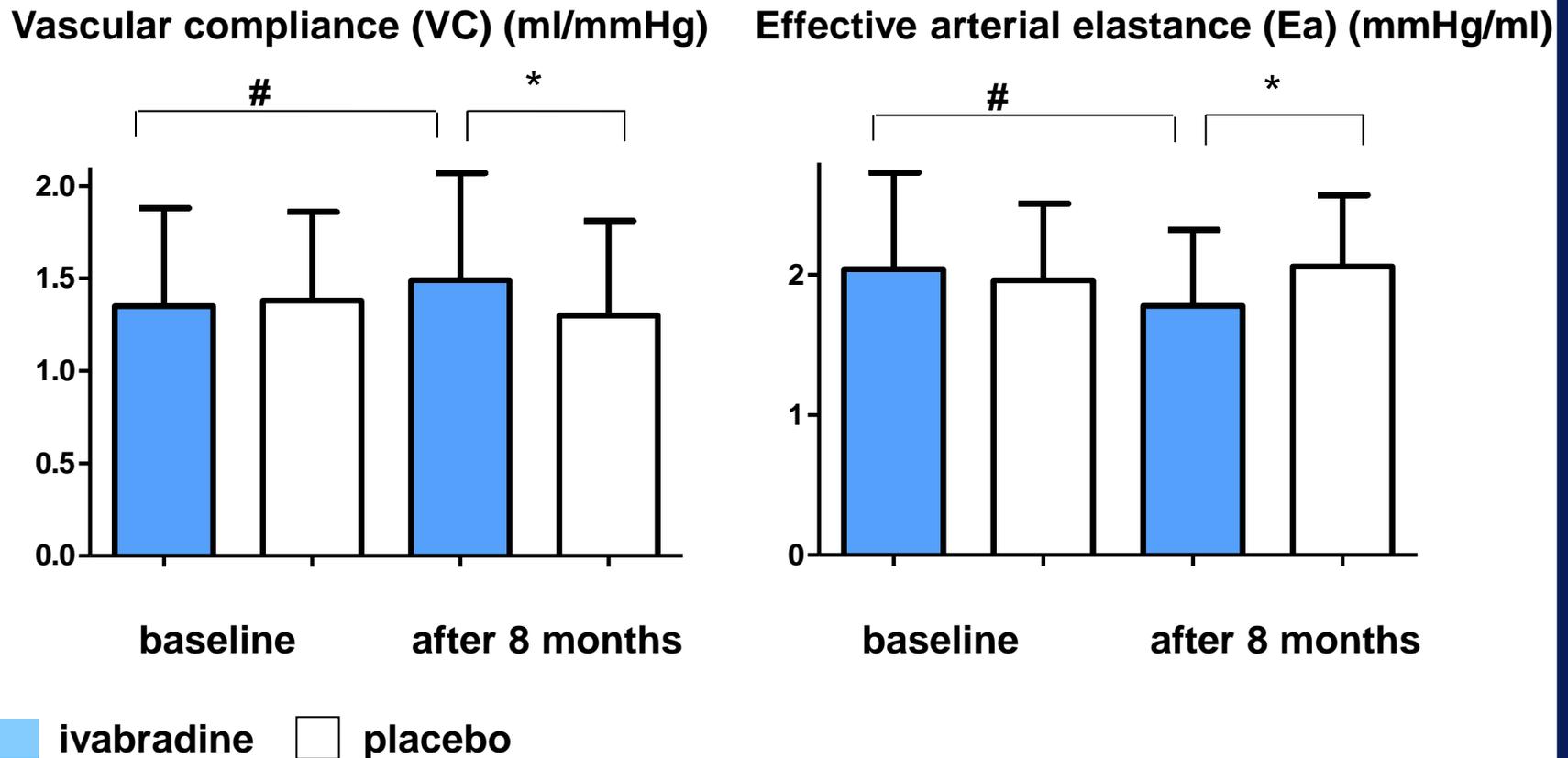


Effect of ivabradine on HR and stroke volume after 8 mths. of treatment



$p < 0.05$ Iva baseline vs. 8 mths. of treatment; * $p < 0.05$ placebo vs. Iva 8 mths.

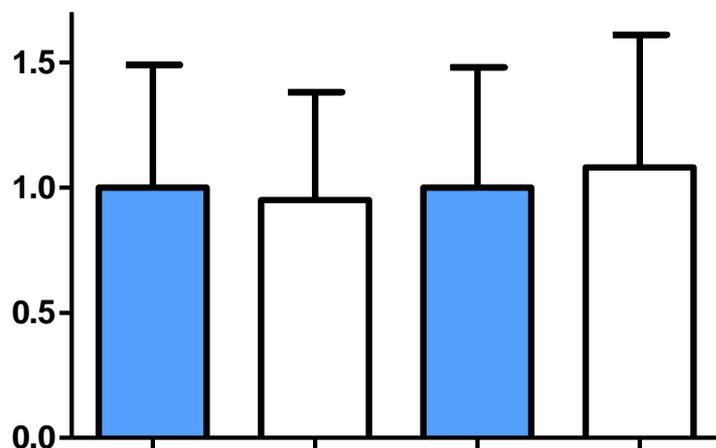
Effect of ivabradine on vascular compliance and Ea after 8 mths. of treatment



p<0.05 Iva baseline vs. 8 mths. of treatment; * p<0.05 placebo vs. Iva 8 mths.

Effect of ivabradine on Ees and coupling ratio Ea/Ees after 8 mths. of treatment

End-systolic elastance (Ees) (mmHg/ml)

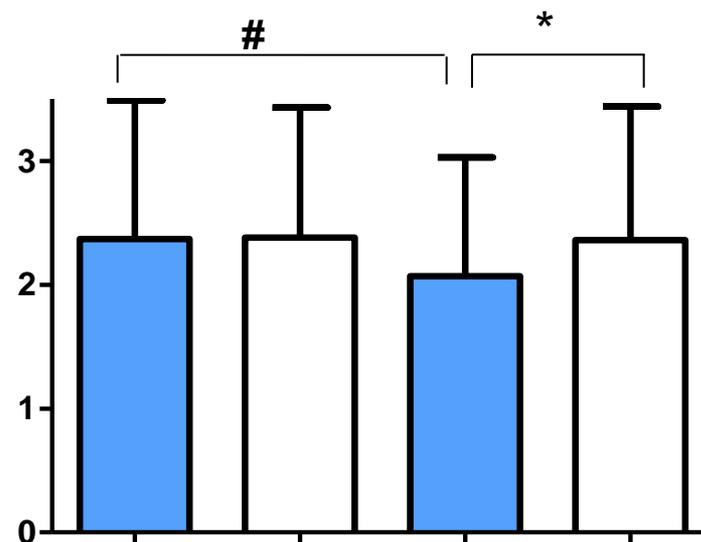


baseline

after 8 months

■ ivabradine □ placebo

Coupling ratio (Ea/Ees)

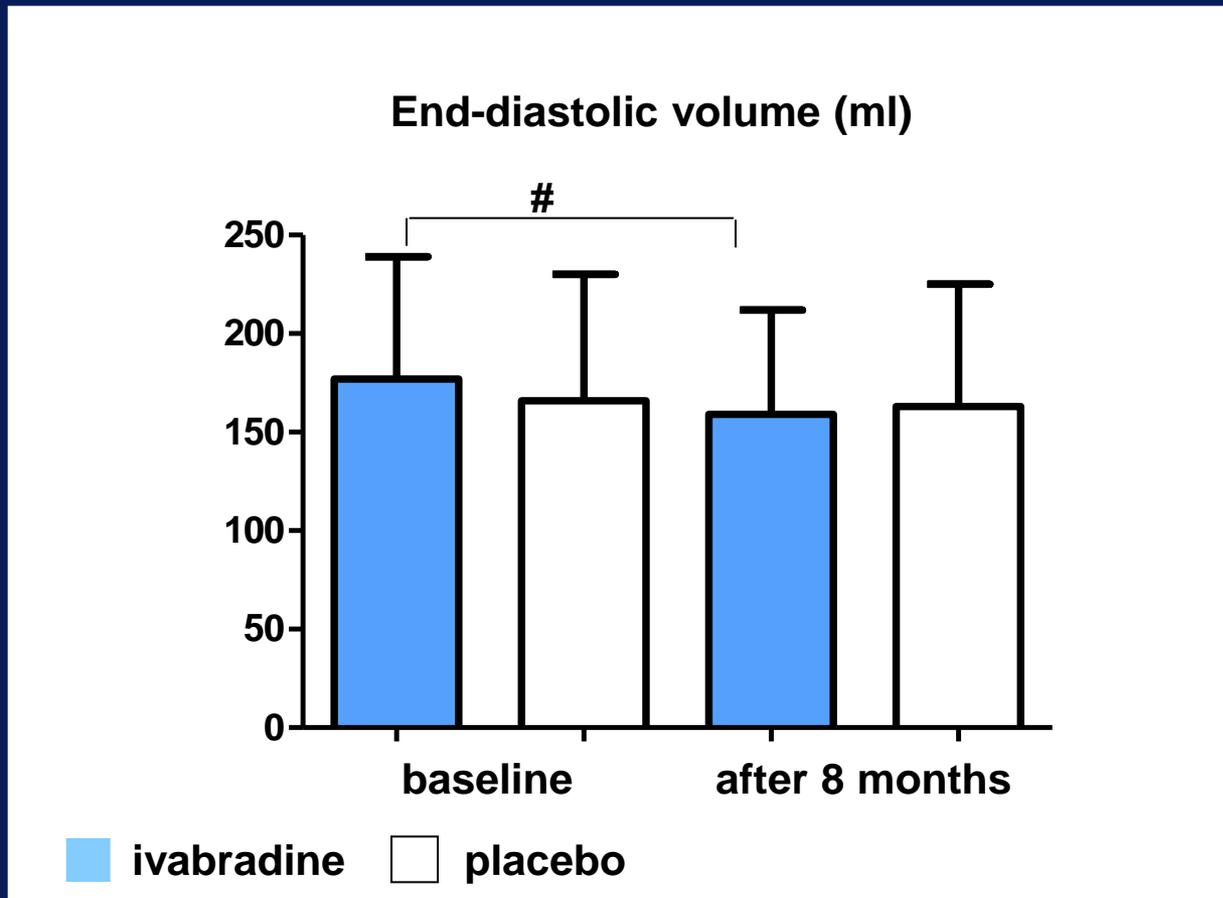


baseline

after 8 months

p<0.05 Iva baseline vs. 8 mths. of treatment; * p<0.05 placebo vs. Iva 8 mths.

Effect of ivabradine on end-diastolic volume (EDV) after 8 mths. of treatment



$p < 0.05$ Iva baseline vs. 8 mths. of treatment

Summary

The studied patients at baseline demonstrated :

a rightward shift in the PV diagram with increased EDV of about 170 ml (normal < 155 ml*)

a marked increase in Ea of 2.0 mmHg/ml (normal 1.2- 1.3#)

a decreased Ees of 1.0 mmHg/ml (normal 1.7#)

an abnormal high coupling ratio (Ea/Ees) of 2.4 (normal 0.7#)

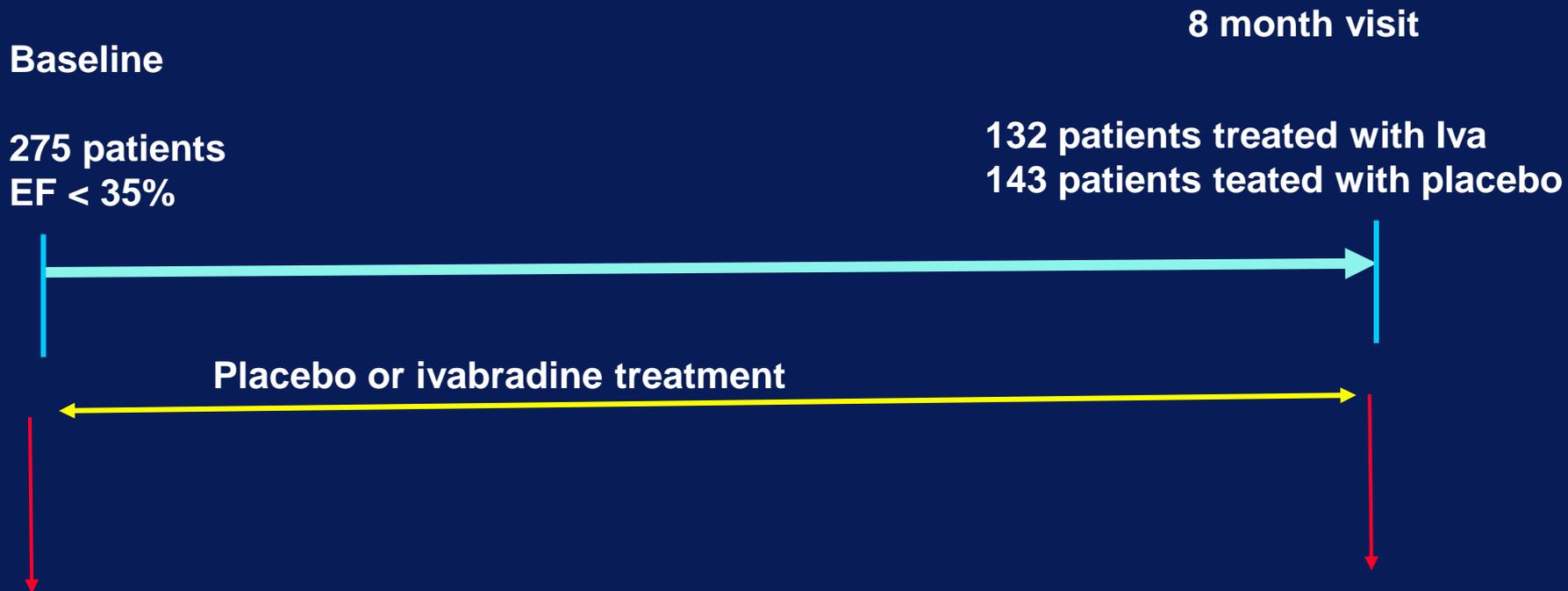
After 8 months ivabradine reduced Ea, increased VC with improvement of the coupling ratio (Ea/Ees) and stroke volume while Ees remained unchanged and EDV was reduced.

* Oh JK, The Echo Manual 3rd Ed. 2006; # Redfield MM et al., Circulation 2005

Conclusion

- Heart rate modulates cardiac afterload indicated by the alterations of effective arterial elastance (E_a).
- Selective heart rate reduction with ivabradine reduced effective arterial elastance mainly by improving vascular compliance (VC).
- Ivabradine did not alter E_{es} , a load-independent marker of left ventricular contractility.
- Higher stroke volumes of the patients of the ivabradine group may therefore depend on improved ventricular-arterial coupling.

Treatment scheme



Baseline

8 month visit

275 patients
EF < 35%

132 patients treated with Iva
143 patients teated with placebo

Placebo or ivabradine treatment

**EA/ VC were
calculated
according to
heart rate tertiles**