ESC Heart Failure 2020
Late breaking clinical trials virtual session, June 5, 2020

Effects of Vericiguat on Left Ventricular Structure and Function in Patients with Heart Failure with Reduced Ejection Fraction: The VICTORIA Echocardiographic Substudy

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for the VICTORIA study group

Disclosures

Speaker Bureau, Consultancy, Advisory Board/Committee for:

Bayer Healthcare, MSD, Novartis, Astra-Zeneca, Stealth, Servier, Daiichi-Sankyo, Biotronic, Abbott Vascular, BMS

B.P. was Co-PI of the VICTORIA study.

The VICTORIA main trial and the VICTORIA Echo substudy was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co, and Bayer AG

Background: Targeting sGC in HFrEF

Heart failure with reduced ejection fraction (HFrEF) is characterized by impaired activity of soluble guanylate cyclase (sGC), resulting in reduced cyclic GMP availability

Vericiguat is a new oral sGC stimulator that restores cGMP levels

VICTORIA (n=5050, median follow-up 10.8 months) demonstrated the clinical benefit of Vericiguat vs. Placebo in HFrEF after a recent worsening heart failure event *(Armstrong, Pieske et al., NEJM 2020; 382:1883-1893)*

VICTORIA Echo substudy: Aims

1. Describe cardiac functional and structural features of patients recruited into VICTORIA

2. Assess the natural course of cardiac function and structure after a worsening heart failure event

3. Characterize the effects of Vericiguat vs. Placebo on cardiac function and structure over 8 months of therapy

VICTORIA Echo substudy: Methods

1. Patients were recruited at 102 sites from 29 countries worldwide

2. Echocardiograms performed according to a VICTORIA echo manual by certified sonographers

3. Quality control and central reading by the Academic Imaging Core Laboratory, Charité University Medicine Berlin, Germany

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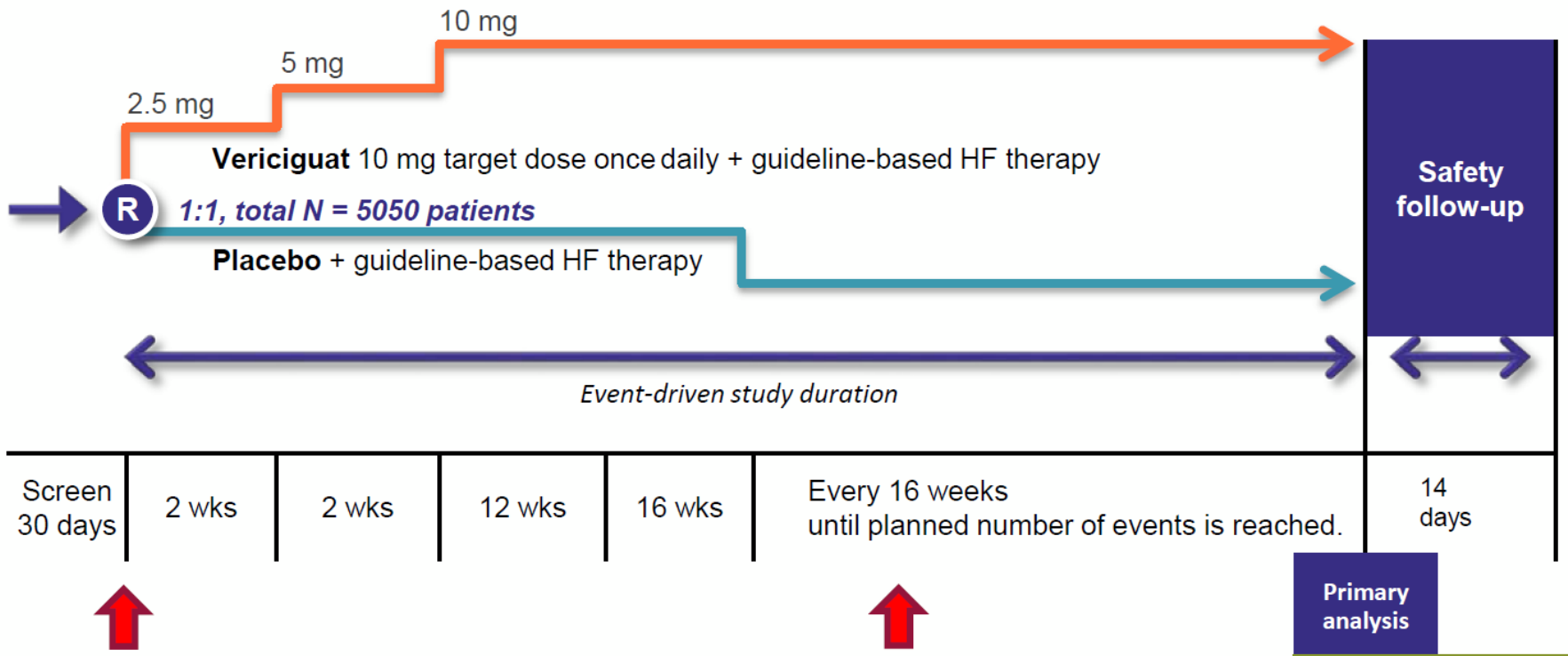
VICTORIA Echo substudy: Design



Baseline Echo

8 months Follow-Up Echo

Primary readouts:
Change in LVEF and LVESVI from baseline to 8 months follow-up

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Armstrong PW et al. N Engl J Med. 2020 DOI: 10.1056/NEJMoa1915928

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VICTORIA Echo substudy: Statistical analysis plan

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- Sample size calculation*: 410 paired BL-FU echocardiograms (205 per arm)

  Power of ≥80% to detect a difference of 6.5ml/m² change in LVESVI and 2.3 % change in LVEF from baseline to 8 month follow-up between both groups (1-sided α=0.05)

- All statistical analyses performed according to prespecified statistical analysis plan

*SHIFT; Tardif JC et al., Eur Heart J 2011;32:2507-2515

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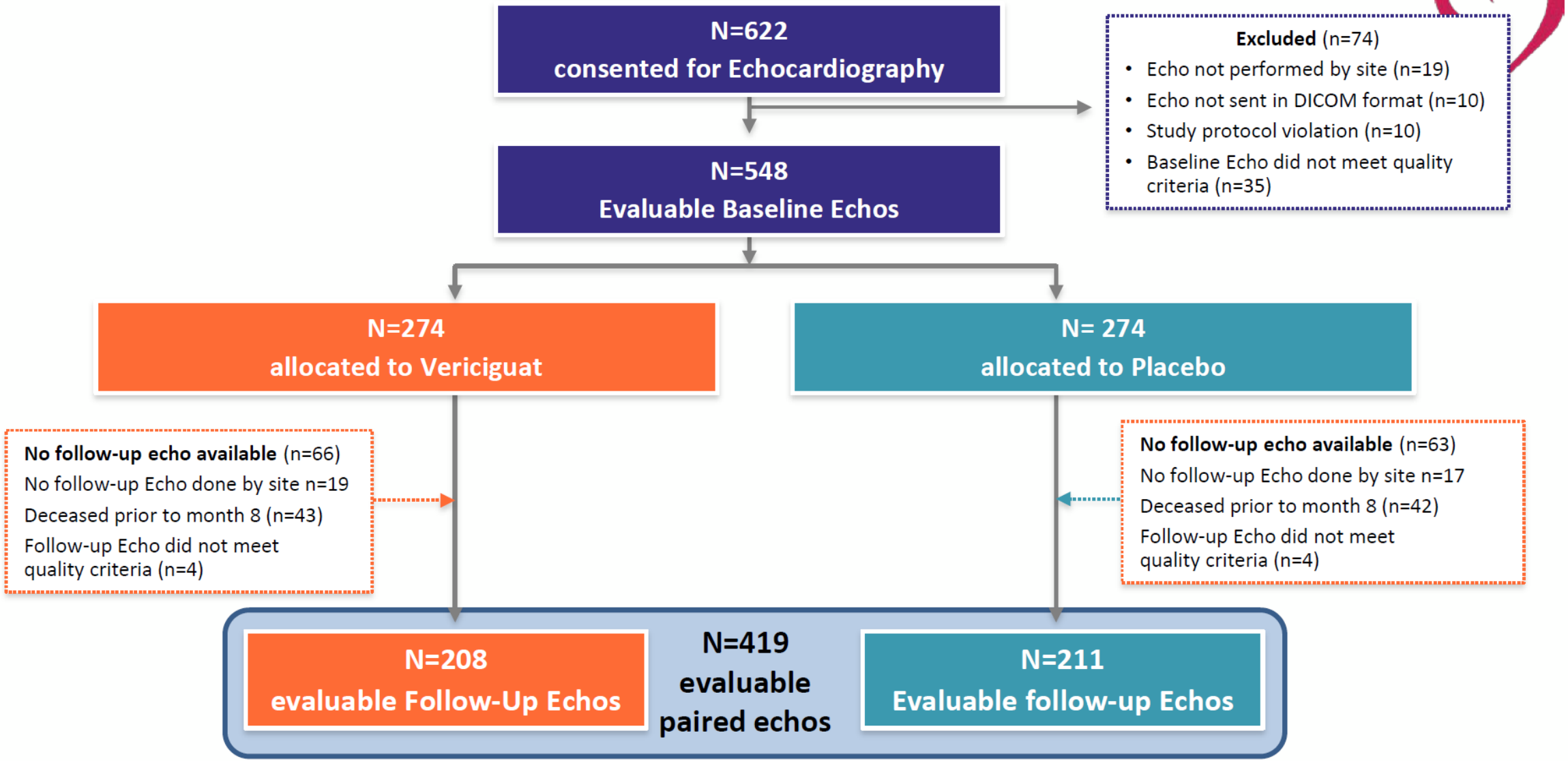
Patient recruitment into VICTORIA Echocardiography Substudy



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Selected clinical characteristics at baseline

	Placebo (n=211)	Vericiguat (n=208)	Overall Trial (n=5050)
Age (yrs; SD)	64.9 ± 11.8	64.3 ± 12.2	67.3±12.2
Female Sex (%)	28.0	26.9	23.9
LVEF (%; SD; site measure)	28.0 ± 8.4	29.5 ± 8.3	28.9±8.3
HFH within 3 mo (%)	73.0	64.9	66.9
NYHA class II/III (%)	63.0/34.1	59.6/38.9	59.0/39.7
NTproBNP (Median, 25th, 75th)	2424 (1290,4395)	2694 (1449,4570)	2816 (1556, 5314)

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Baseline echocardiographic measurements

Measurement	Placebo (n=211)	Vericiguat (n=208)	P-value*
LVEF (%)	**31.8 (8.2)**	**33.0 (9.4)**	**0.172**
LVESVI (mL/m^2)	**68.2 (31.0)**	**60.7 (26.8)**	**0.009**
LVEDVI (mL/m^2)	97.7 (35.3)	88.7 (31.7)	0.006
LAVI (mL/m^2)	49.7 (21.2)	50.5 (21.7)	0.704
LVMI (g/m^2)	140.5 (41.8)	140.1 (39.9)	0.942
LV SVI (mL)	29.6 (8.7)	28.1 (9.5)	0.090
LV-GLS (%)	-6.4 (3.1)	-7.0 (3.1)	0.087

Values are Mean (SD); ** t-test*

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Echo substudy patients: lower risk for events, but evidence of clinical benefit

Primary VICTORIA outcome events (CV death or HF hospitalisation)

	Placebo	Vericiguat	P-value
Overall trial cohort (n=5050)	38.5%	35.5%	0.02
Echo substudy (n=419)	22.3%	15.4%	0.071

By definition, events until 8 months FU only consist of HF hospitalisation, and CV death and HF hospitalisation only after 8 months follow-up.

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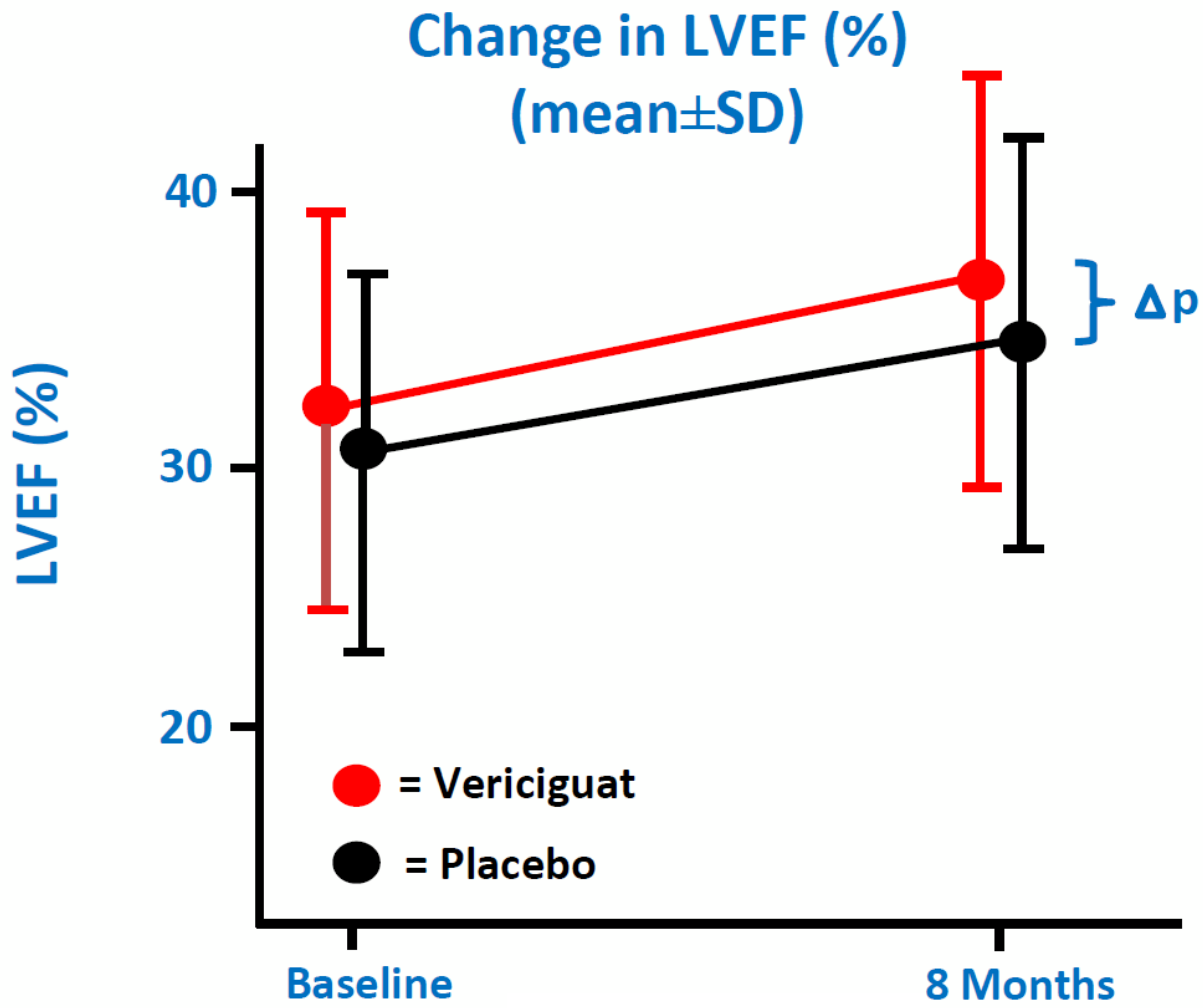
VICTORIA Echo endpoints: LVEF



33.0 ± 9.4 to 36.1 ± 10.2%, p<0.001

31.8 ± 8.2% to 34.2 ± 9.5%, p<0.001

*Treatment comparison for absolute change:adjusted for baseline value and BB use, stratified for region and race

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VICTORIA Echo endpoints: LVESVI

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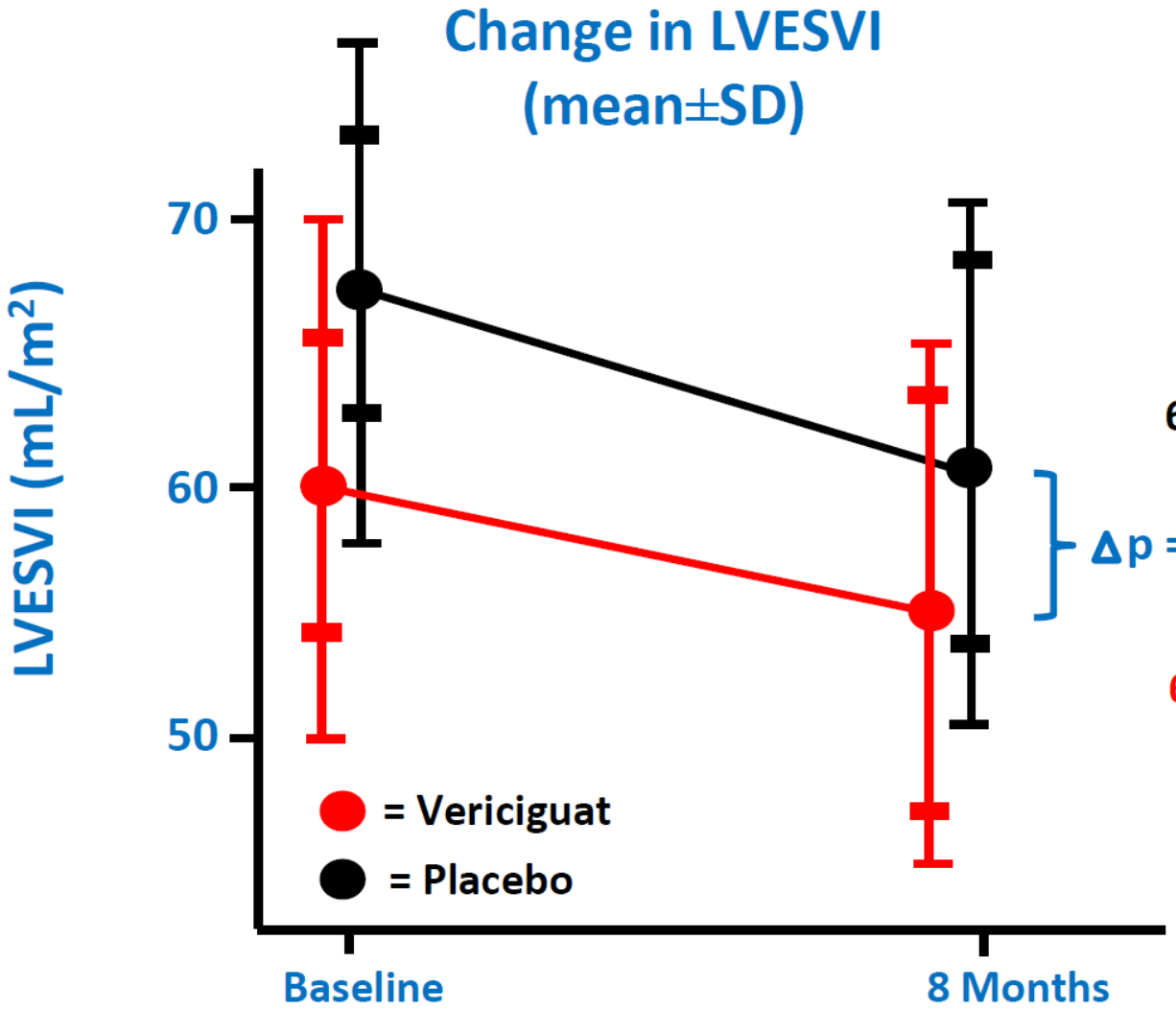

68.2 ± 31.0 to 61.1 ± 29.9 ml/m², p<0.001

Δp = 0.21*

60.7 ± 26.8 to 56.8 ± 30.4 ml/m², p<0.001

* Treatment comparison for absolute change: adjusted for baseline value and BB use, stratified for region and race

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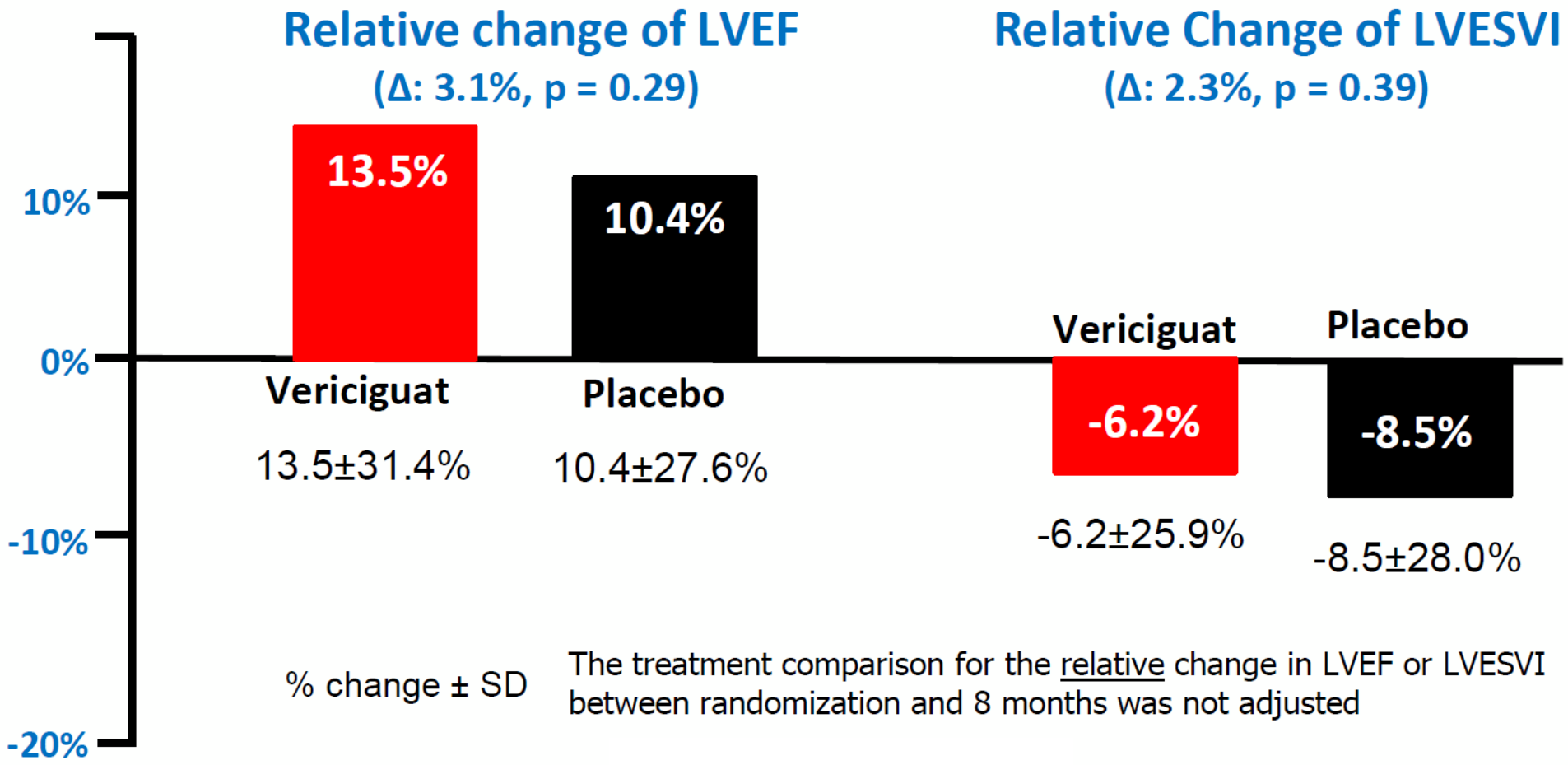
Relative change in primary endpoints after 8 months



% change ± SD

The treatment comparison for the relative change in LVEF or LVESVI between randomization and 8 months was not adjusted

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Echo substudy: Potential limitations

- VICTORIA required excellent SOC in both groups and the close follow up/ medical oversight may have accelerated cardiac recovery during FU
- Our selected ECHO sample size represents <10% of 5050 pts and there were some imbalances at baseline
- Volumes in the vericiguat group start from lower baseline, making it harder to demonstrate a larger decrease with vericiguat.
- Additional imaging parameters including RV function as well as biomarkers will be part of future analyses

Summary and Conclusions

1. VICTORIA Echo investigated a subgroup of patients that survived to 8 months follow-up and had event rate reductions in line with overall trial results.
2. Baseline imaging parameters consistent with HFrEF and a recent worsening event
3. LV EF and ESVI significantly improved from baseline to 8 months irrespective of treatment assignment
4. Vericiguat had no additional significant effect on LV EF or ESVI
5. Further studies are needed to understand the mechanistic basis for the clinical benefits of Vericiguat.

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Many thanks for your attention!

My thanks go also to the VICTORIA trial teams behind the scenes, the trial site sonographers,
the echo core lab readers, and the VICTORIA patients who participated in this substudy.

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