

# ACC.24

A Double-blind, Randomized  
Placebo-Procedure-Controlled Trial  
of an Interatrial Shunt In Patients  
with HFrEF and HFpEF: **Principal  
Results from the RELIEVE-HF Trial**

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for the RELIEVE-HF study group

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# Background

- Heart failure (HF) is characterized by increased left atrial pressure and pulmonary venous congestion
- Left atrial pressure rises with exercise and fluid overload and may be difficult to regulate pharmacologically
- An inter-atrial shunt (IAS) may provide an autoregulatory mechanism to decrease left atrial pressure and improve HF symptoms and prognosis
- In pilot studies, the **Ventura IAS (V-Wave Ltd.)** reduced filling pressures, improved cardiac structure and function, and provided symptomatic relief and functional improvement in patients with HFrEF and HFpEF

# Objectives and Trial Design

- We therefore sought to determine the safety and effectiveness of the V-Wave Ventura IAS device in symptomatic HF patients with any LVEF in a randomised, double-blind, placebo-procedure-controlled, multicenter trial
- Given uncertainty as to whether the response to an IAS would vary according to systolic function, **stratified randomizations were performed in patients with reduced ( $\leq 40\%$ ) and preserved ( $> 40\%$ ) LVEF**



# V-Wave Ventura Inter-atrial Shunt

**14F delivery system**  
Over-the-wire, retrievable

**Right Atrium**

**Exit hood**

- Blocks route of paradoxical emboli transit in RA

• **DAPT 6 months**

Fossa ovalis

**Nitinol frame**

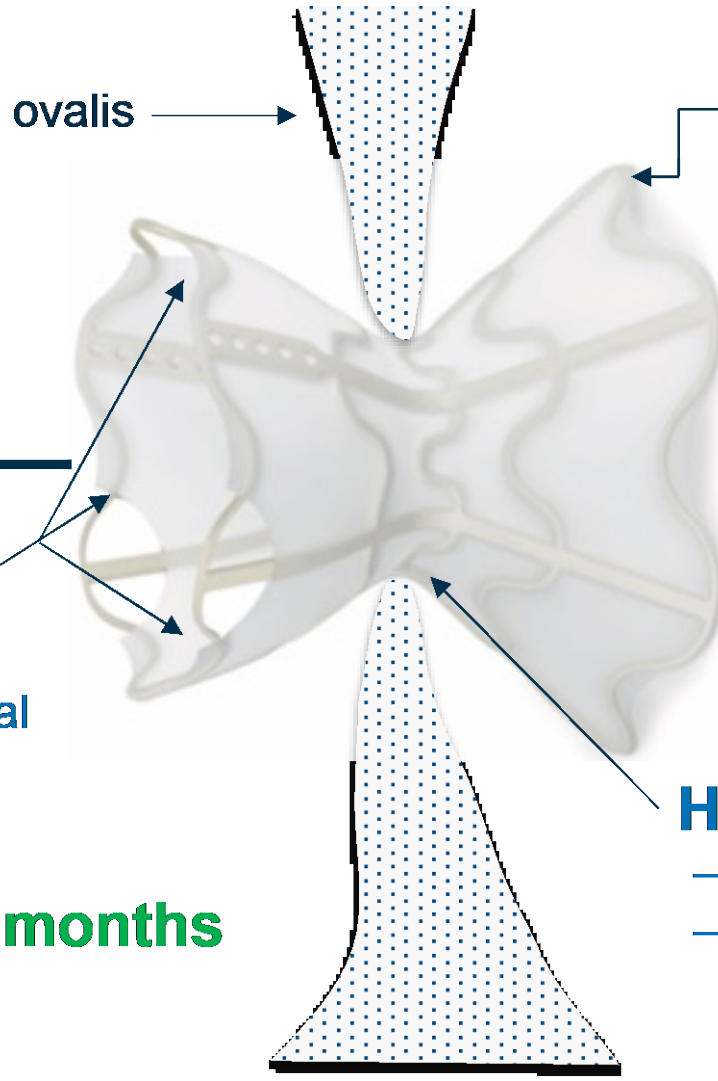
**Full ePTFE encapsulation**

- Channels flow
- Prevents late lumen loss

**Left Atrium**

**Hourglass shape**

- Secure and atraumatic retention
- 5.1 mm orifice, Venturi efficiency





# Key Inclusion Criteria

1. Ischemic or non-ischemic cardiomyopathy with **any LVEF** and documented HF for at least 6 months
2. NYHA class II, III, or ambulatory IV functional class despite maximally-tolerated class I GDMT and cardiac rhythm management device therapy for HF as assessed by a central eligibility committee
3. HF hospitalization within the prior 12 months and/or an elevated (BMI-adjusted) BNP/NT-proBNP (both required for NYHA II)
4. 6MWT  $\geq 100$  meters -  $\leq 450$  meters
5. Written, informed consent

# Key Clinical Exclusion Criteria

1. Resting SBP  $<90$  or  $>160$  mmHg or intractable HF
2. Severe pulmonary hypertension defined as PASP  $>70$  mmHg by echo/Doppler or PVR  $>4.0$  WU on RHC that cannot be reduced by vasodilator therapy
3. RV dysfunction defined as TAPSE  $<12$  mm or RVFAC  $\leq 25\%$  on TTE
4. LVEDD  $>8$  cm on TTE
5. ASD, PFO, APVR, corrected CHD, severe valve lesions
6. Transseptal procedure for another indication planned within 6 months



# Final Key Exclusion Criteria After RHC and TEE/ICE

- performed just prior to randomization -

1. Anatomical anomaly that precludes implanting the IAS across the fossa ovalis (FO) including:

**Minimal FO thickness >6 mm or length <10 mm; ASD or PFO with >trace shunting; atrial septal aneurysm; intracardiac thrombus**

2. Hemodynamic, heart rhythm, or respiratory instability including:

**Mean PCWP <7 mmHg or >35 mmHg; RAP  $\geq$  LAP (or PCWP) when LAP (PCWP) is  $\geq$ 7 mmHg; CI <1.5 L/min/m<sup>2</sup>; severe pulmonary HTN as previously defined, SBP <90 or >160 mmHg; need for IV vasopressor or inotrope medication; malignant arrhythmias; acute respiratory distress or hypoxemia**





# RELIEVE-HF Primary Effectiveness Endpoint

- **Comparison between groups of the hierarchical composite ranking of:**
  - All-cause death
  - Cardiac transplantation or left ventricular assist device (LVAD) implantation
  - All HF hospitalizations
  - All outpatient worsening HF events
  - Change in KCCQ-OS from baseline to 12 months (5-point minimum difference)
- **Analyzed by the Finkelstein-Schoenfeld method when the last enrolled patient reaches 12 months with longest FU to 24 months, expressed as the win ratio**
- A single interim analysis of the primary effectiveness outcome with adaptive sample size re-estimation by an independent third party was planned when 200 enrolled patients completed 6-month follow-up. To prevent inflation of type-1 error the final FS statistic is derived from data weighted differently before and after the interim analysis.\*





## RELIEVE-HF Primary Safety Endpoint

- Device-related or procedure-related MACNE (all-cause death, stroke, systemic embolism or need for open cardiac surgery or major endovascular surgical repair) at 30 days in the IAS group, compared against an OPC of 11%
- Numerous additional secondary safety and effectiveness endpoints were pre-specified
- All primary and secondary endpoints will be tested in the randomized strata of patients with reduced and preserved LVEF

# Patient Flow

**1136 patients** were screened for enrollment at **113 sites** in **11 countries** (USA, Canada, Israel, Germany, Spain, Switzerland, Belgium, Poland, The Netherlands, Australia, and New Zealand)

Roll-in cases  
N=97  
Shunt implanted

Enrolled  
N=605  
at 101 sites

**Ineligible N= 531**

- All inclusion criteria not met (n=212)
- Exclusion criteria present (n=182)
- Not approved by eligibility committee (n=17)
- Failed final eligibility assessment in the cath lab (n= 60)
- Withdrew consent during screening (n=33)
- Incomplete screening or other (n= 24)
- Death during screening (n=3)

Randomized  
N=508  
at 94 sites  
between Oct 24, 2018 and Oct 19, 2022

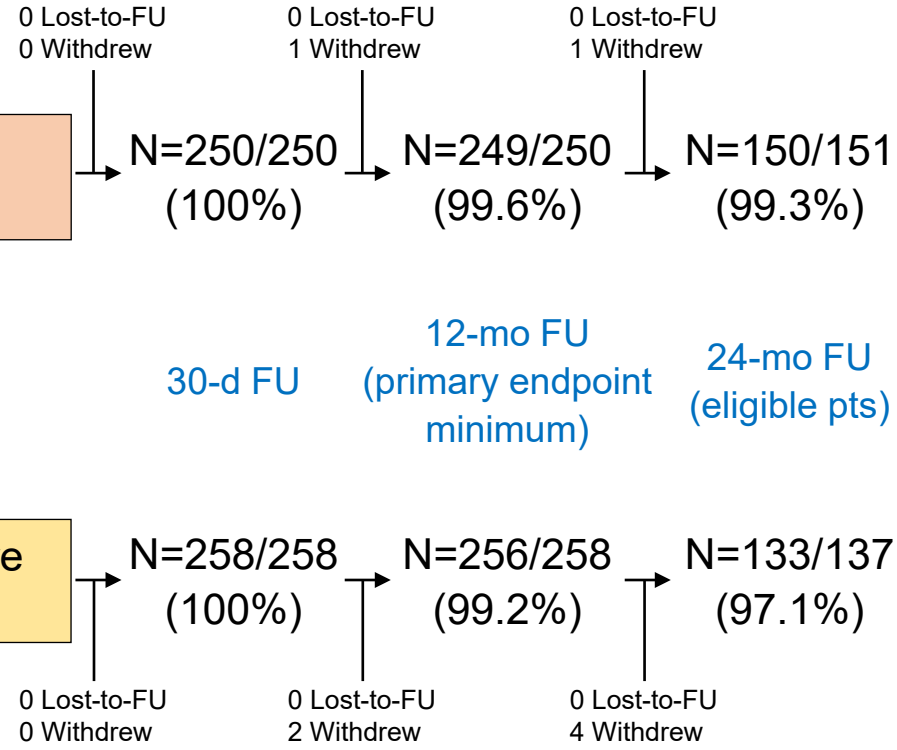
**Randomized 1:1**  
Stratified by core lab LVEF ≤40% vs. >40% and site

Inter-atrial shunt  
N=250

Placebo-procedure  
N=258

Patients and all post-cath lab personnel were blinded

Post-procedure patients not on OAC were treated with open-label aspirin (75-100 mg per day) for 2 years + study drug clopidogrel (75 mg per day in the IAS group vs. matching placebo in the control group) for 6 months



**Median follow-up 22.0 (13.3, 23.9) months**

# Baseline Characteristics (1)

	Shunt group (N=250)	Placebo group (N=258)
<b>Age, years</b>	74.0 (67.0, 79.0)	72.0 (65.0, 78.0)
<b>Sex, male</b>	162 (64.8%)	157 (60.9%)
<b>Body mass index, kg/m<sup>2</sup></b>	30.0 (25.6, 34.9)	30.3 (26.2, 36.0)
<b>Diabetes mellitus</b>	124 (49.6%)	125 (48.4%)
<b>Hypertension</b>	209 (83.6%)	216 (83.7%)
<b>Hyperlipidemia</b>	201 (80.4%)	195 (75.6%)
<b>Current or previous smoker</b>	133 (53.2%)	137 (53.1%)
<b>Prior stroke or TIA</b>	43 (17.2%)	48 (18.6%)
<b>COPD</b>	43 (17.2%)	52 (20.2%)
<b>Ischemic cardiomyopathy</b>	114 (45.6%)	120 (46.5%)
<b>Non-ischemic cardiomyopathy</b>	136 (54.4%)	138 (53.5%)
<b>At least one HFH in the prior year</b>	128 (51.2%)	127 (49.2%)
<b>Known CAD</b>	169 (67.6%)	160 (62.0%)
<b>Prior MI</b>	104 (41.6%)	103 (39.9%)
<b>Prior PCI</b>	103 (41.2%)	96 (37.2%)
<b>Prior CABG</b>	65 (26.0%)	58 (22.5%)



# Baseline Characteristics (2)

	Shunt group (N=250)	Placebo group (N=258)
History of atrial fibrillation or flutter	170 (60.8%)	159 (61.2%)
- Baseline rhythm is atrial fib or flutter	76 (30.4%)	64 (24.8%)
ICD or CRT-D	115 (46.0%)	123 (47.7%)
CRT-D or CRT-P	70 (28.0%)	59 (22.9%)
NYHA class II	9 (3.6%)	7 (2.7%)
NYHA class III	239 (95.6%)	251 (97.3%)
NYHA class IV	2 (0.8%)	0 (0.0%)
KCCQ overall summary score	52.1 (35.4, 66.9)	50.8 (34.6, 66.4)
Six-minute walk distance, m	264.8 (195.5, 325.0)	270.9 (198.0, 330.0)
LVEF (biplane, core lab assessment), %	45.4 (33.4, 58.9)	45.3 (33.3, 57.4)
- ≤40% (reduced LVEF)	101/250 (40.4%)	105/258 (40.7%)
- >40% (preserved LVEF)	149/250 (59.6%)	153/258 (59.3%)
BNP (pg/mL)	237.9 (117.2, 412.5)	221.0 (101.0, 518.3)
NT-proBNP(pg/mL)	1939.4 (1066.0, 3259.0)	1596.6 (852.0, 2868.1)
eGFR, mL/min/1.73 m <sup>2</sup>	45.5 (37.5, 59.8)	48.5 (37.2, 60.8)
- <60 mL/min/1.73 m <sup>2</sup>	188 (75.2%)	188 (72.9%)

# Baseline TTE (core-lab)

	Shunt group (N=250)	Placebo group (N=258)
<b>LVEDV (biplane), mL</b>	123.3 (87.0, 175.5)	126.0 (96.0, 181.5)
<b>LVESV (biplane), mL</b>	66.3 (37.5, 115.5)	70.0 (40.5, 117.0)
<b>LAV (biplane), mL</b>	78.5 (63.5, 103.0)	76.0 (59.5, 101.0)
<b>SV, mL</b>	54.0 (41.0, 67.0)	54.0 (44.0, 67.0)
<b>SVI, mL/m<sup>2</sup></b>	26.7 (21.7, 31.9)	27.5 (21.8, 33.0)
<b>CO, L/min</b>	3.7 (2.9, 4.6)	3.8 (3.1, 4.7)
<b>CI, L/min/m<sup>2</sup></b>	1.8 (1.5, 2.2)	1.9 (1.5, 2.3)
<b>RV FAC, %</b>	37.7 (33.3, 42.9)	37.5 (33.3, 42.9)
<b>TAPSE, mm</b>	16.5 (14.0, 20.0)	17.0 (14.0, 19.0)
<b>PASP, mmHg</b>	32.0 (24.0, 41.0)	32.0 (25.0, 40.0)
<b>RVEDAI, cm<sup>2</sup>/m<sup>2</sup></b>	9.8 (8.2, 11.9)	10.4 (8.4, 12.4)
<b>IVC diameter max, cm</b>	1.6 (1.2, 2.0)	1.6 (1.2, 1.9)
<b>MR moderate or greater</b>	49 (19.6%)	38 (14.7%)
<b>TR moderate or greater</b>	50/247 (20.2%)	45/257 (17.5%)

# Baseline Right Heart Catheterization

	Shunt group (N=250)	Placebo group (N=258)
<b>HR, bpm</b>	67.0 (60.0, 75.0)	68.0 (60.0, 77.0)
<b>SBP, mmHg</b>	116.0 (104.0, 133.0)	115.0 (103.0, 134.0)
<b>DBP, mmHg</b>	64.0 (57.0, 73.0)	65.0 (59.0, 73.0)
<b>Mean RAP, mmHg</b>	9.0 (6.0, 12.0)	9.0 (6.0, 11.0)
<b>Systolic PAP, mmHg</b>	37.0 (30.0, 45.0)	37.0 (31.0, 44.0)
<b>Mean PAP, mmHg</b>	25.0 (21.0, 31.0)	25.0 (20.0, 30.0)
<b>PVR, WU</b>	2.1 (1.5, 3.1)	2.0 (1.4, 2.8)
<b>PCWP, mmHg</b>	15.5 (12.0, 20.0)	16.0 (12.0, 21.0)
<b>CO, L/min</b>	4.2 (3.4, 5.3)	4.3 (3.6, 5.3)
<b>CI, L/min/m<sup>2</sup></b>	2.1 (1.8, 2.6)	2.2 (1.8, 2.6)



# Procedural Details

	Shunt group (N=250)	Placebo group (N=258)	Difference [95% CI]
<b>Procedure duration, minutes</b>	80 (59, 100)	43 (30, 55)	35.5 [31.0, 40.0]
<b>Fluoroscopy time, minutes</b>	14 (10, 21)	4 (2, 7)	9.9 [8.9, 10.9]
<b>Contrast administered, mL</b>	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
<b>Heparin administered, units</b>	9000 (7000, 12,000)	-	-
<b>Activated clotting time, secs</b>	291 (246, 342)	-	-
<b>Shunt implant attempt</b>	250 (100%)	1 (0.4%)*	-
<b>- Shunt implanted successfully</b>	250 (100%)	1 (0.4%)	-
<b>Hospital duration post procedure, days</b>	1 (1, 1)	1 (1, 1)	0.0 [0.0, 0.0]



## RELIEVE-HF Primary Safety Endpoint

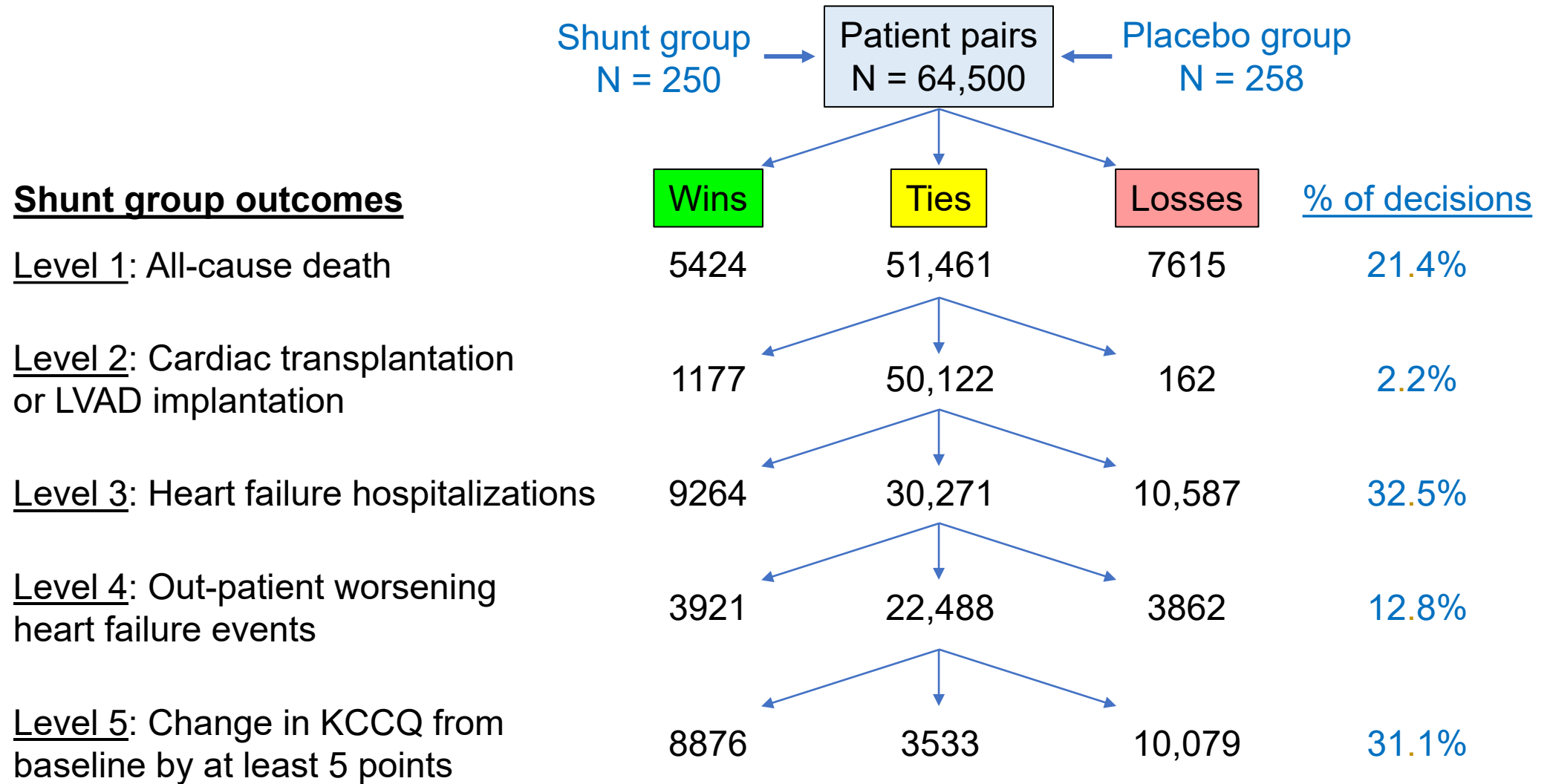
- Device-related or procedure-related MACNE (all-cause death, stroke, systemic embolism or need for open cardiac surgery or major endovascular surgical repair) at 30 days in the IAS group, compared against an OPC of 11%

Within 30 days, **MACNE occurred in 0 (0.0%) of 250 patients** in the IAS group (upper 1-sided 97.5% CL = 1.5%), which is below the 11% performance goal,  **$P < 0.0001$**  using an exact binomial test

MACNE occurred in 0 (0.0%) IAS-treated patients through 2-year FU



# RELIEVE-HF Primary Effectiveness Endpoint



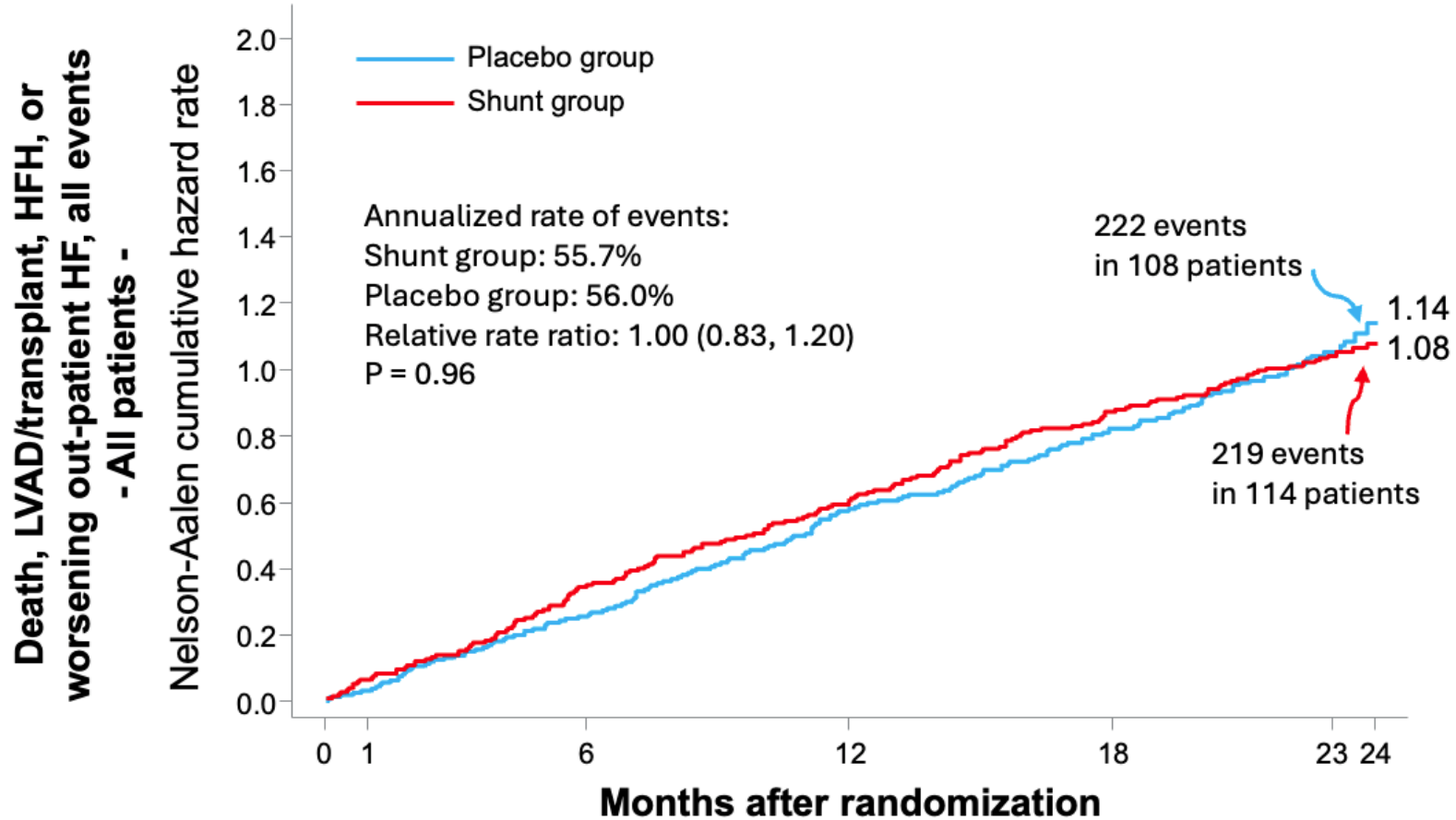
Total wins = 28,662, total losses = 32,305  
Win ratio (unweighted) = 28,662/32,305 = 0.89 (0.72, 1.09)  
Win ratio (phase weighted for interim analysis) = 0.86 (0.61, 1.22); **p=0.20**





# Risk of all Cardiovascular Events

- All-cause death, LVAD/HT, all HFHs, and all out-patient worsening HF events -



Number at Risk:

Placebo	258	257	251	222	144	109	50
Shunt	250	249	236	211	162	123	58



# Risk of all Cardiovascular Events

- All-cause death, LVAD/HT, all HFHs, and all out-patient worsening HF events -

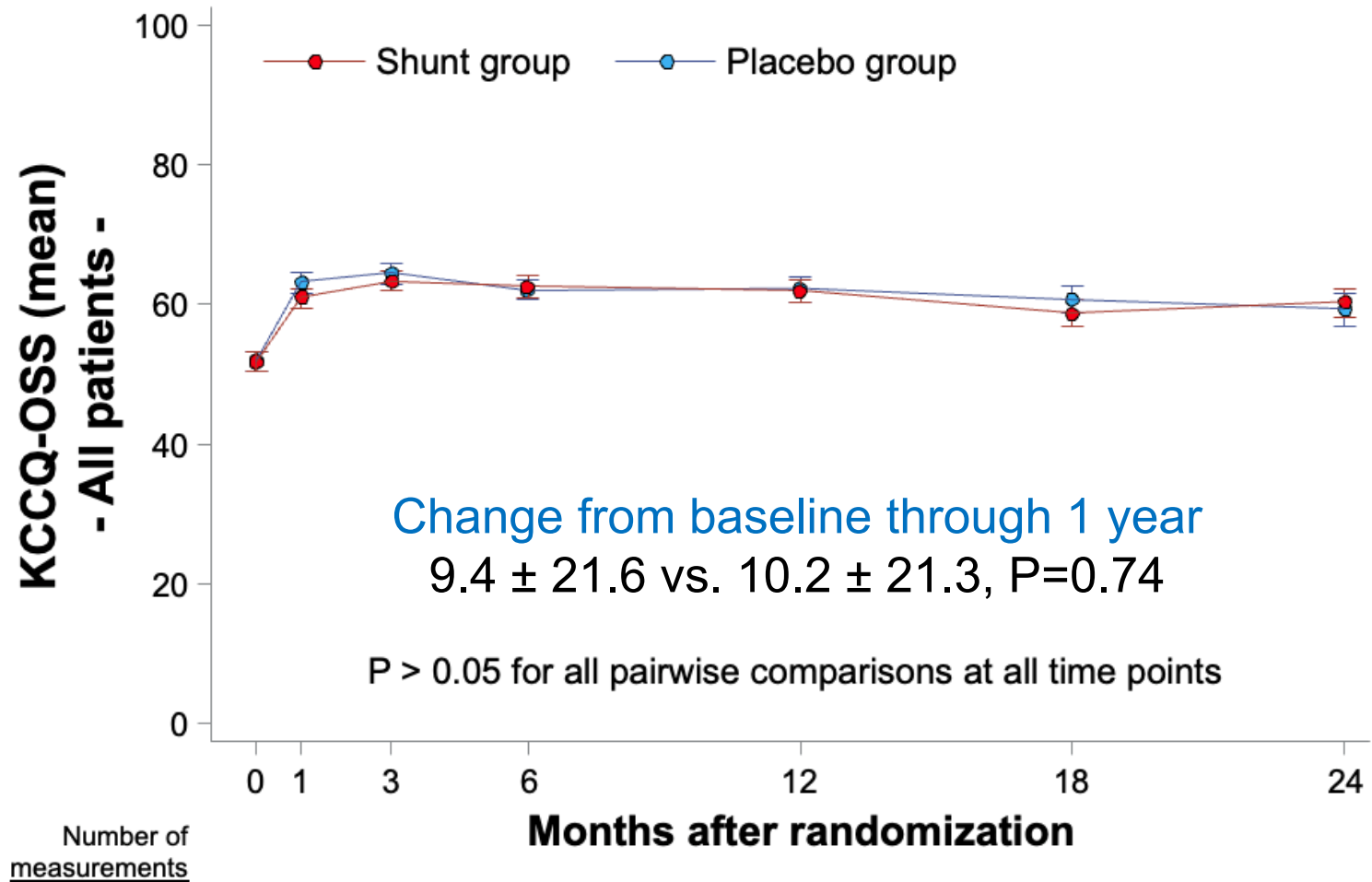
2-year rates	Shunt group (N=101)	Placebo group (N=108)	RR or HR (95% CI)	P-value
<b>All events<sup>1</sup></b>	219/392.7 (55.7%/year)	222/396.1 (56.0%/year)	1.00 (0.83, 1.20)	0.96
<b>All-cause death<sup>2</sup></b>	35 (15.6%)	27 (13.7%)	1.31 [0.79, 2.16]	0.30
<b>LVAD/HT<sup>2</sup></b>	2 (0.8%)	2 (1.1%)	1.01 [0.14, 7.14]	1.00
<b>All HFHs<sup>1,3</sup></b>	128/392.7 (32.6%/year)	125/396.1 (31.6%/year)	1.09 [0.79, 1.50]	0.60
<b>All out-pt WHFs<sup>1,3</sup></b>	55/392.7 (14.0%/year)	64/396.1 (16.2%/year)	0.88 [0.61, 1.26]	0.48

<sup>1</sup>Total no. of events/total no. of patient-years of follow-up (annualized rate) with relative rate ratio (95% CI)

<sup>2</sup>Time-to-first event analysis – n events (Kaplan-Meier estimated rate) with HR (95% CI) from a Cox model

<sup>3</sup>HR (95% CI) from a joint frailty model accounting for the competing risk of death

# Change in KCCQ-OSS Over Time



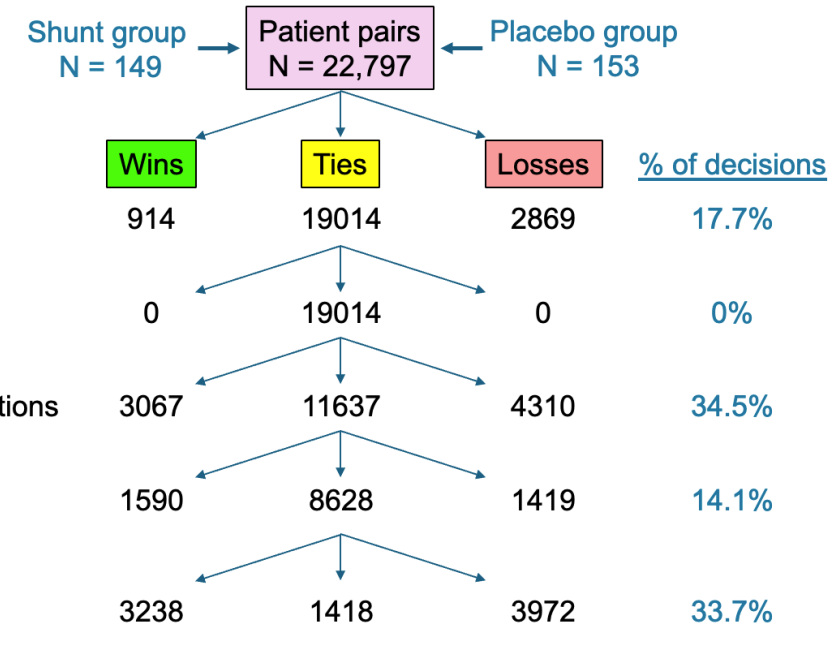
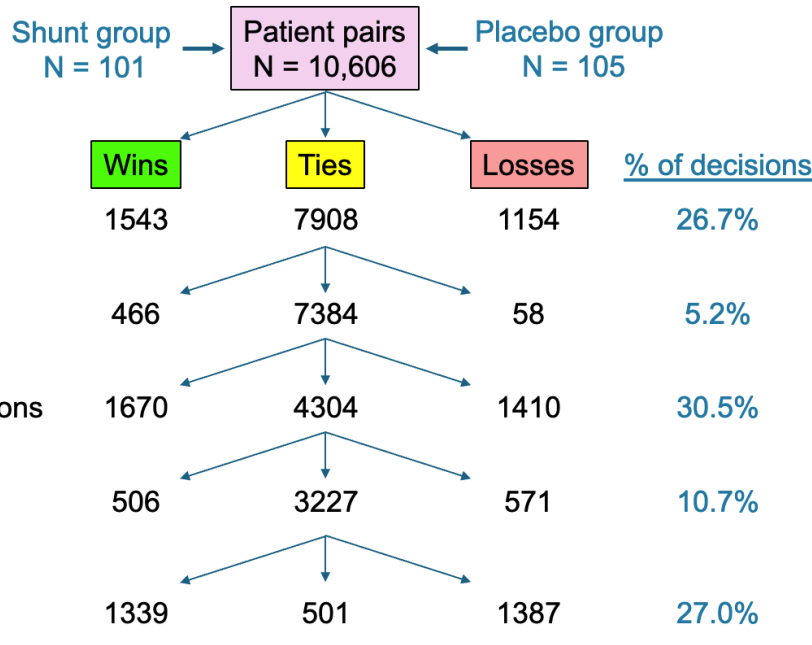
Placebo	258	252	243	238	226	143	106
Shunt	250	244	236	227	221	156	121



# Primary Effectiveness Outcome by LVEF

**LVEF ≤40% (n=206)**

**LVEF >40% (n=302)**



Total wins = 5524; Total losses = 4580  
 Win ratio (unweighted) = 5524/4580 = 1.21 (0.87, 1.67)  
 Win ratio (phase weighted for interim analysis) = 1.40 [0.80, 2.46]

Total wins = 8809; Total losses = 12,570  
 Win ratio (unweighted) = 8809/12,570 = 0.70 (0.54, 0.92)  
 Win ratio (phase weighted for interim analysis) = 0.61 [0.39, 0.98]

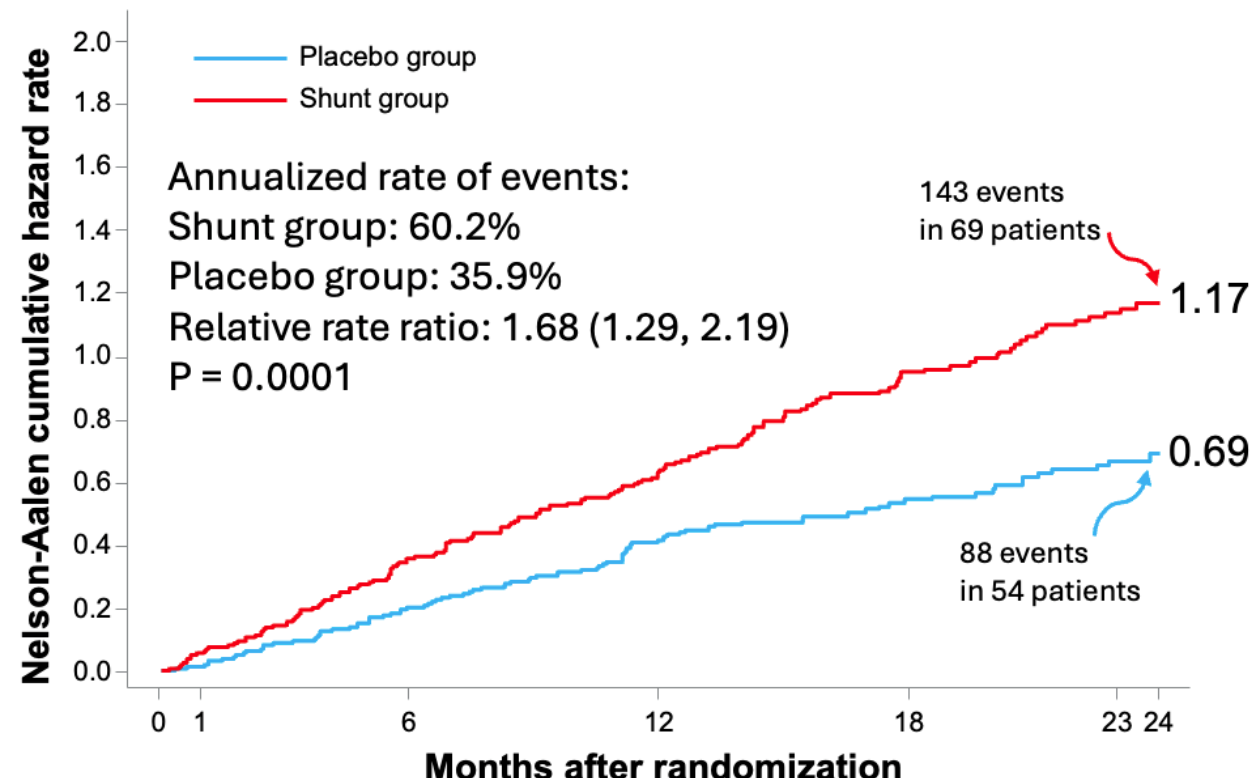
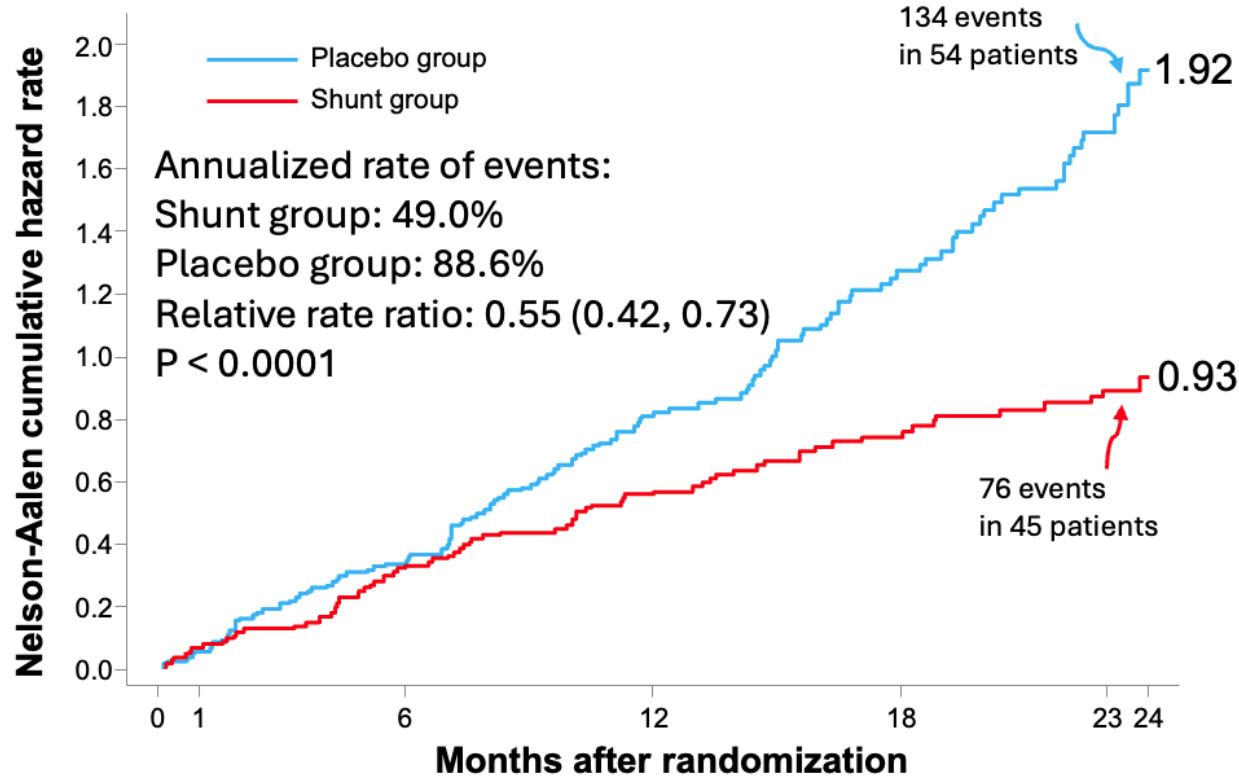


# Risk of all Cardiovascular Events by LVEF

- All-cause death, LVAD/HT, all HFHs, and all out-patient worsening HF events -

**LVEF ≤40% (n=206)**

**LVEF >40% (n=302)**



**N at Risk:**

Placebo	105	104	101	84	51	38	19
Shunt	101	101	96	84	60	46	17

**N at Risk:**

Placebo	153	153	150	138	93	72	31
Shunt	149	148	140	127	102	77	41

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**P<sub>interaction</sub> < 0.0001**

# Risk of all Cardiovascular Events by LVEF

- All-cause death, LVAD/HT, all HFHs, and all out-patient worsening HF events -

	LVEF ≤40%			LVEF >40%		
2-year rates	Shunt group (N=101)	Placebo group (N=108)	RR or HR (95% CI)	Shunt group (N=149)	Placebo group (N=153)	RR or HR (95% CI)
<b>All events<sup>1</sup></b>	76/155.2 (49.0%/year)	134/151.2 (88.6%/year)	0.55 (0.42, 0.73) <b>P&lt;0.0001</b>	143/237.5 (60.2%/year)	88/245.0 (35.9%/year)	1.68 (1.29, 2.19) <b>P=0.0001</b>
<b>All-cause death<sup>2</sup></b>	13 (14.3%)	20 (26.8%)	0.63 [0.31, 1.26] P=0.19	22 (16.4%)	7 (5.2%)	3.24 [1.38, 7.59] <b>P=0.004</b>
<b>LVAD/HT<sup>2</sup></b>	1 (1.5%)	6 (9.0%)	0.16 [0.02, 1.32] <b>P=0.051</b>	0 (0.0%)	0 (0.0%)	-
<b>All HFHs<sup>1,3</sup></b>	41/155.2 (26.0%/year)	78/151.2 (52.0%/year)	0.52 [0.31, 0.86] <b>P=0.01</b>	87/237.5 (37.0%/year)	47/245.0 (19.0%/year)	2.05 [1.35, 3.10] <b>P=0.0008</b>
<b>All out-pt WHFs<sup>1,3</sup></b>	21/155.2 (14.0%/year)	30/151.2 (20.0%/year)	0.70 [0.39, 1.23] P=0.21	34/237.5 (14.0%/year)	34/245.0 (14.0%/year)	1.04 [0.64, 1.68] P=0.88

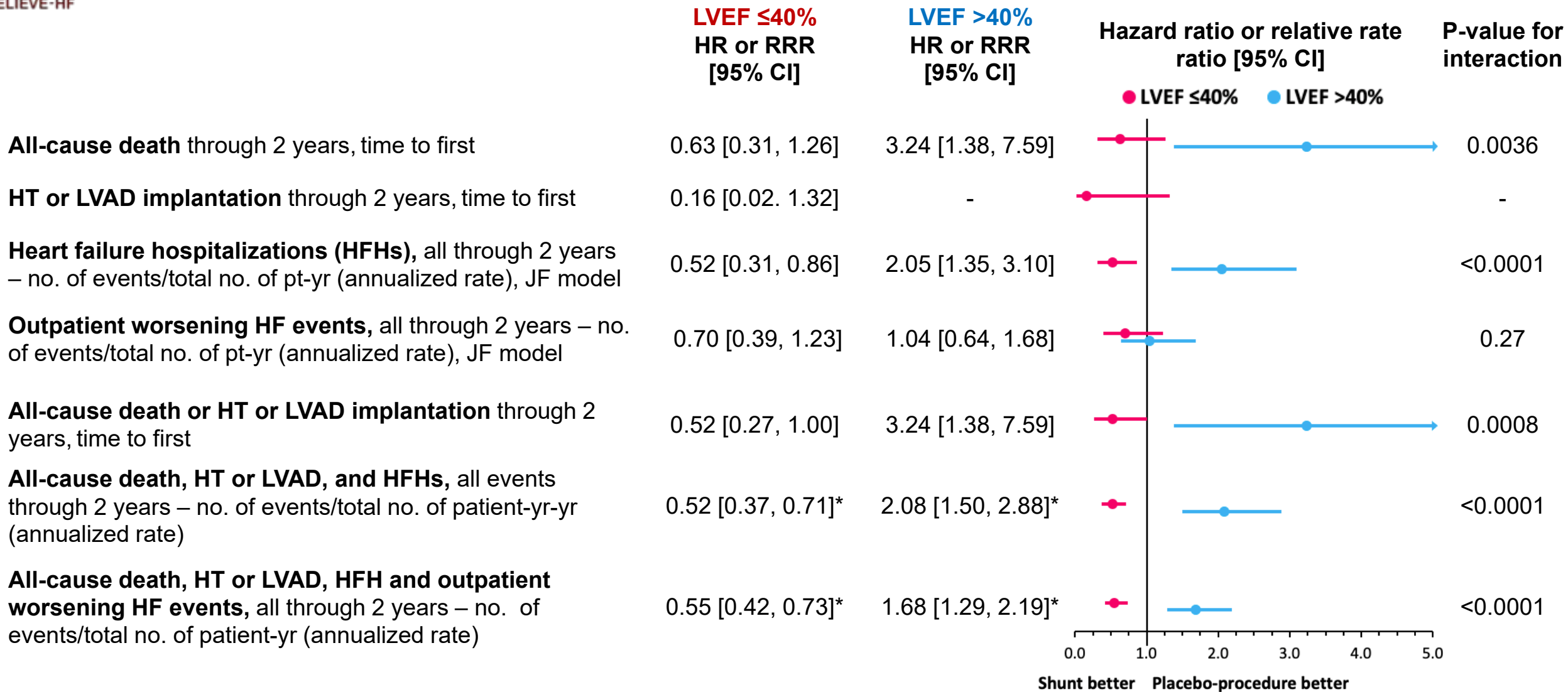
<sup>1</sup>Total no. of events/total no. of patient-years of follow-up (annualized rate) with relative rate ratio (95% CI)

<sup>2</sup>Time-to-first event analysis – n events (Kaplan-Meier estimated rate) with HR (95% CI) from a Cox model

<sup>3</sup>HR (95% CI) from a joint frailty model accounting for the competing risk of death



# Risk of Cardiovascular Events by LVEF

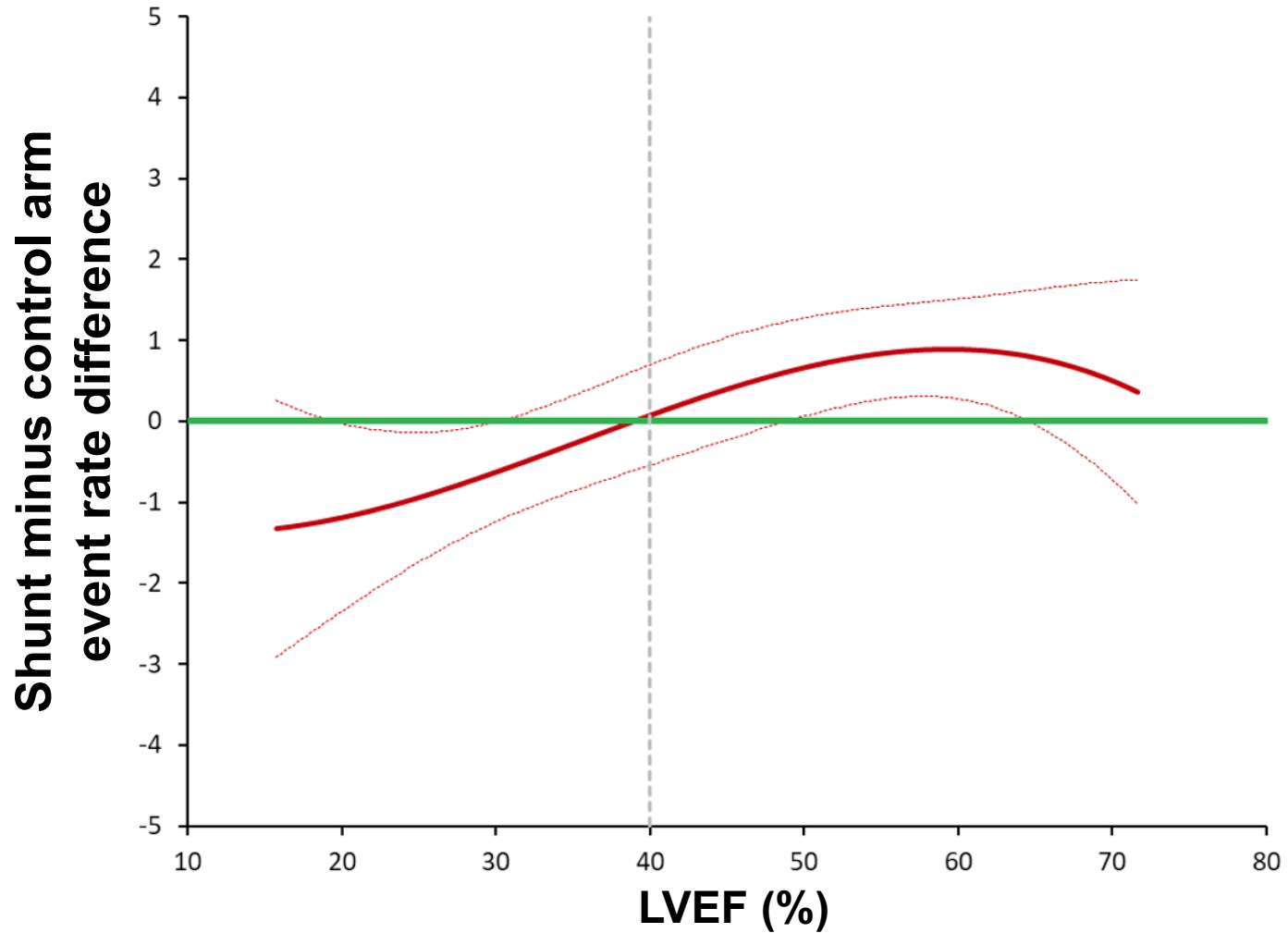






# Risk of all Cardiovascular Events by LVEF

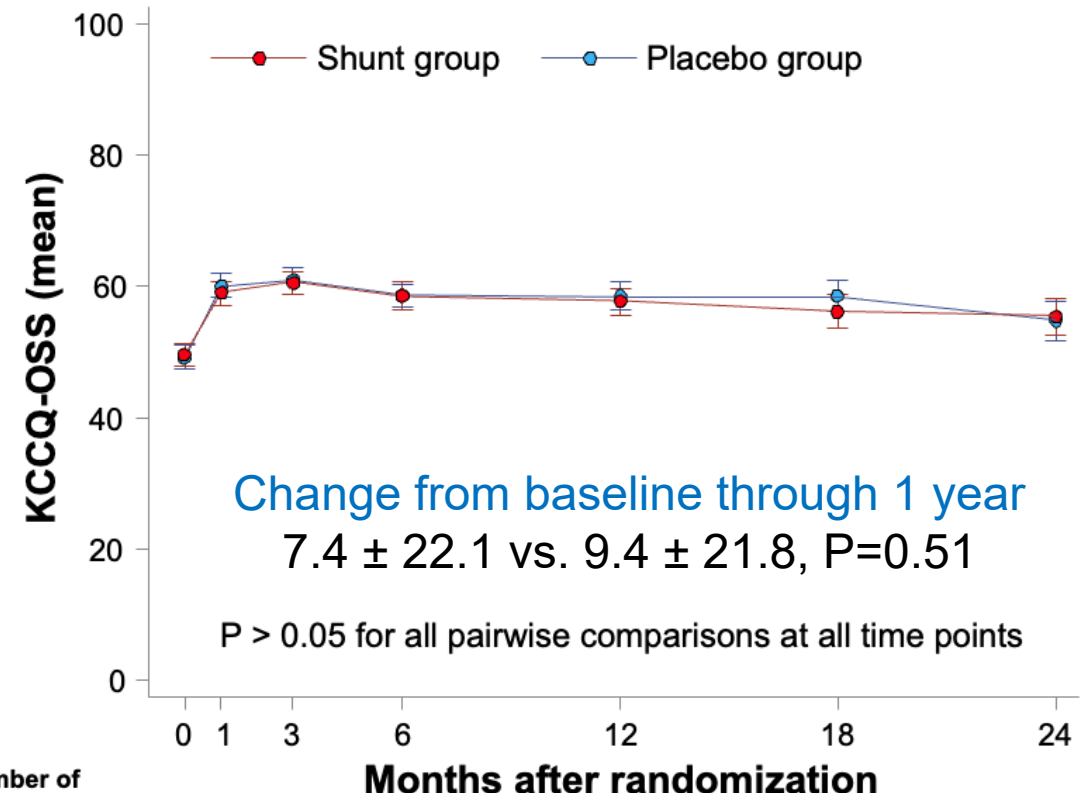
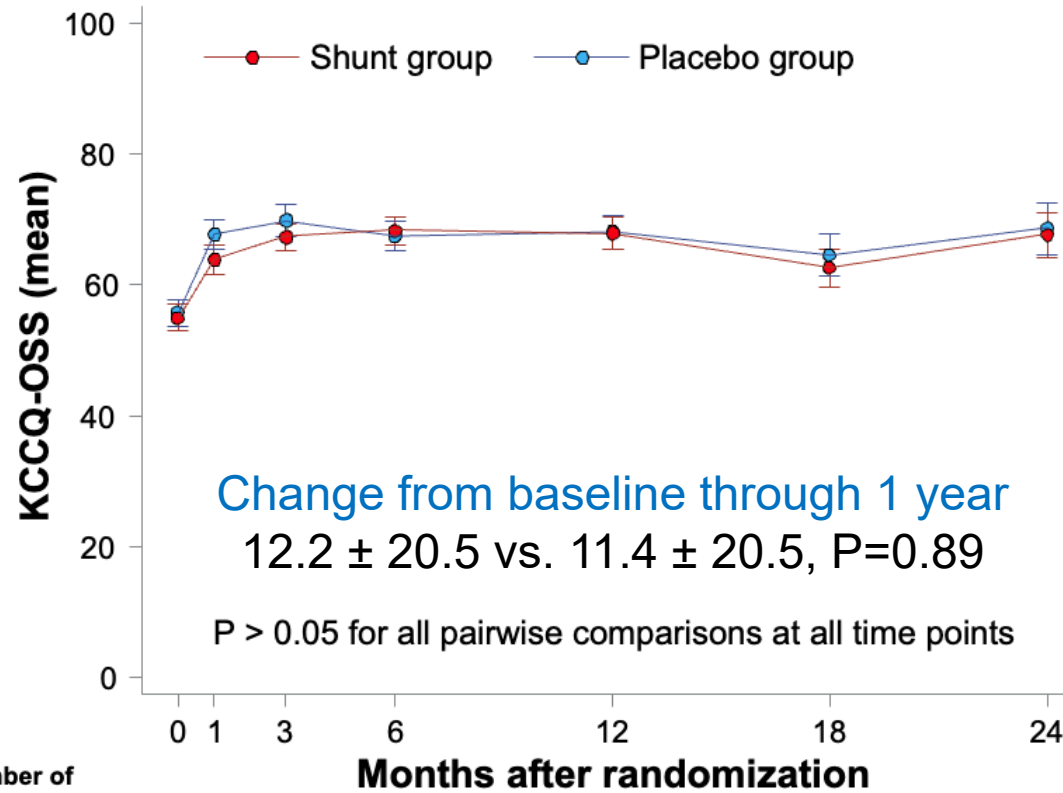
- All-cause death, LVAD/HT, all HFHs, and all out-patient worsening HF events -



# Change in KCCQ-OSS Over Time by LVEF

## LVEF ≤40% (n=206)

## LVEF >40% (n=302)



	Number of measurements						
	0	1	3	6	12	18	24
Placebo	105	100	96	95	86	52	35
Shunt	101	100	97	94	91	60	48

	Number of measurements						
	0	1	3	6	12	18	24
Placebo	153	152	147	143	140	91	71
Shunt	149	144	139	133	130	96	73

# Limitations

1. The present results apply only to the profile of the pts enrolled and treated with the Ventura inter-atrial shunt
2. The reduced and preserved LVEF groups, although pre-specified randomized strata, were not individually powered for effectiveness; the results within each strata must therefore be considered exploratory
  - However, the strong interaction ( $P < 0.0001$ ) and spline curve analysis for cardiovascular events suggests these findings are not due to play of chance
3. The large and similar increase in KCCQ-OSS in both the device and control groups emphasizes the relevance of the placebo effect and the necessity for blinded trials
  - Moreover, the similar magnitude of KCCQ-OSS improvement and the lack of between-group differences in this metric despite a large decrease in HFHs in shunt-treated pts with reduced LVEF and a large increase in HFHs and mortality in shunt-treated pts with preserved LVEF confounds its interpretation in blinded (and open-label) trials

# Conclusions

- Transcatheter implantation of the Ventura inter-atrial shunt was safe but did not reduce symptoms or improve prognosis through 2 years in patients with HF across the full range of all LVEF
- The results from a pre-specified stratified analysis suggest that inter-atrial shunt implantation is beneficial in patients with reduced LVEF and harmful in patients with preserved LVEF





# Study Leadership and Organization

- *Principal investigators:* Stefan D. Anker, JoAnn Lindenfeld, Josep Rodés-Cabau, Gregg W. Stone
- *Executive Committee:* PIs + Michael Zile, Saibal Kar, John Gorcsan, Rich Holcomb, William T. Abraham
- *Steering Committee:* EC + Maria Rosa Costanzo, Antoni Bayes-Genis, Jeroen Bax, Alan Bank, Stefan Verheye, Ariel Roguin, Gerasimos Filippatos, Stephan von Bardeleben, Raj Makkar, Tom McRae, Wayne Batchelor, Frank Ruschitzka, Berkert Pieske
- *Central Eligibility Committee:* Michael Zile (moderator), JoAnn Lindenfeld, Jeroen Bax, Alan Bank, Maria Rosa Costanzo, Gregg W. Stone, Josep Rodes-Cabau, Ariel Roguin, Stefan Verheye
- *Echocardiographic Core Laboratory:* Penn State Health-Milton S. Hershey Medical Center: Michael P. Pfeiffer (director), 1/26/21-current; Washington University: John Gorcsan (director), 2/24/18-1/26/21
- *Clinical Endpoints Committee:* Cardiovascular Research Foundation (CRF); Marrick Kukin (chair)
- *Data Safety Monitoring Board:* CRF; Bernard Gersh (chair)
- *Data management and biostatistics:* CRF; Ovidiu Dressler and Yiran Zhang
- *Site management and data monitoring:* V-Wave Ltd.
- *Sponsor and funding:* V-Wave Ltd.

# Top 12 Randomizing Sites

PI	Hospital, City, State, Country	N randomized
Julio Núñez	Hospital Clínico Universitario, INCLIVA, University of Valencia, Valencia, Spain	32
Josep Rodés-Cabau	Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval, Quebec City, Quebec, Canada	25
Elizabeth Lee	Rochester General Health System, Rochester, NY, US	23
Antoni Bayes-Genis	Hospital Universitari Germans Trias and Pujol de Badalona, Barcelona, Spain	19
Michal Laufer-Perl	Tel Aviv Sourasky Medical Center, affiliated with the Tel Aviv School of Medicine, Tel Aviv University, Tel Aviv, Israel	18
Gil Moravsky	Assaf HaRofeh Medical Center, Beer Yaakov, Israel	17
Sheldon Litwin	Medical University of South Carolina, Charleston, South Carolina, US	15
Hemal Gada	UPMC Pinnacle / Pinnacle Health Cardiovascular Institute, Harrisburg, PA, US	14
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