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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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RELIEVE-HF

Background

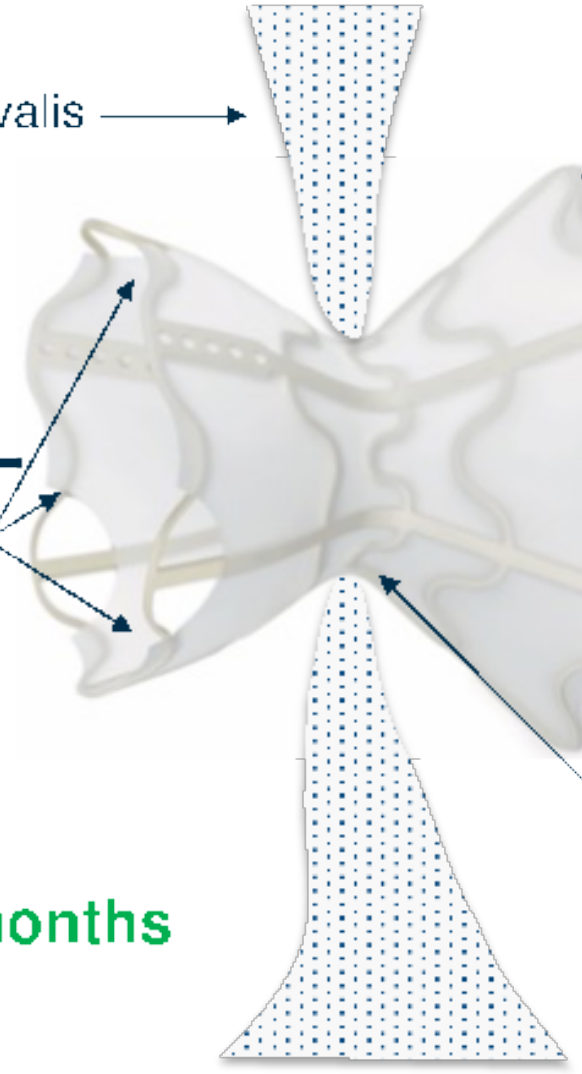
- Heart failure (HF) is characterized by increased left atrial pressure and pulmonary venous congestion
- Left atrial pressure rises with exercise and fluid overload and may be difficult to regulate pharmacologically
- An inter-atrial shunt (IAS) may provide an autoregulatory mechanism to decrease left 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 (≤40%) and preserved (>40%) LVEF

V-Wave Ventura Inter-atrial Shunt



Fossa ovalis

Nitinol frame

14F delivery system
Over-the-wire, retrievable

Full ePTFE encapsulation
- Channels flow
- Prevents late lumen loss

Right Atrium

Left Atrium

Exit hood
- Blocks route of paradoxical emboli transit in RA

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

• **DAPT 6 months**

Length: 12mm; LA diameter: 14mm; RA diameter: 11mm;
Neck diameter: 5.1mm; Qp/Qs: approximately 1.2:1

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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 ≥100 meters - ≤450 meters
5. Written, informed consent

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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 ≤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 ≥ LAP (or PCWP) when LAP (PCWP) is ≥7 mmHg; CI <1.5 L/min/m ^{2}; 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.*

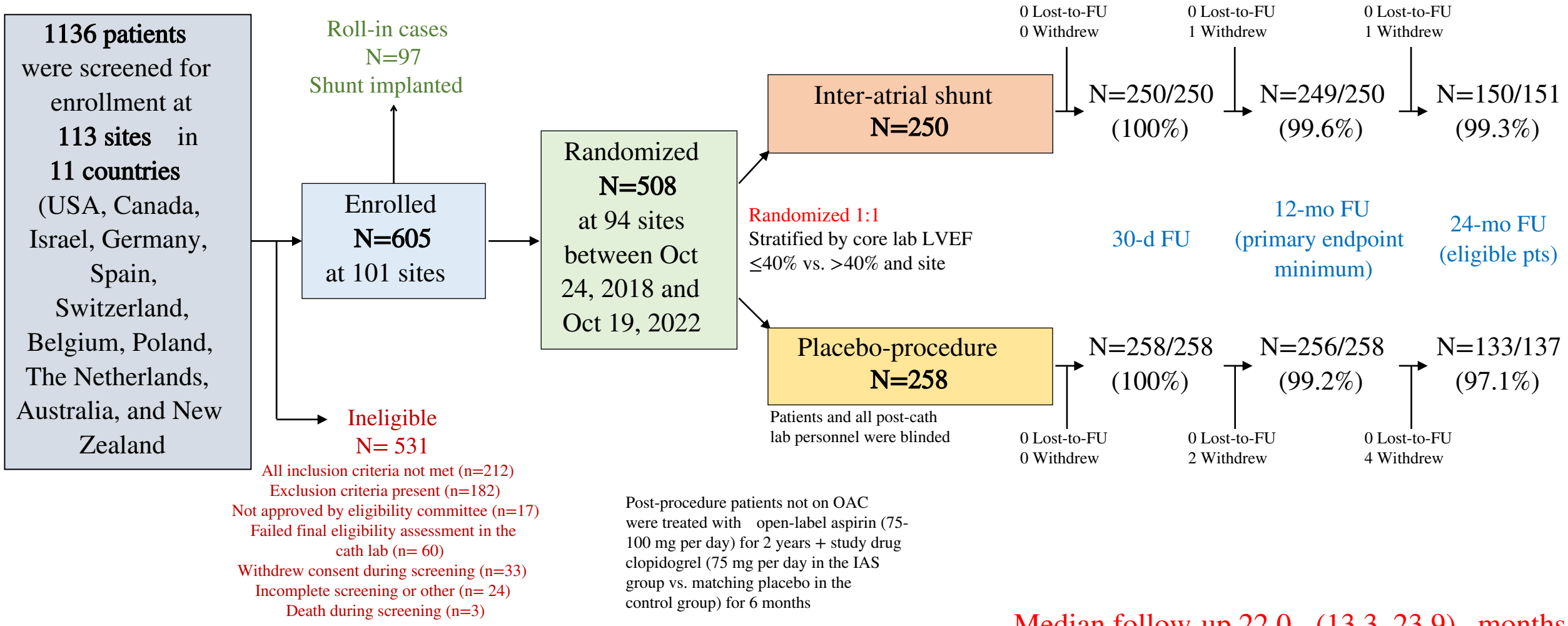
*Cui L, Hung HMJ, Wang S-J. Biometrics 1999;55:853-857

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



Baseline Characteristics (1)

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

RELIEVE-HF

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^2	45.5 (37.5, 59.8)	48.5 (37.2, 60.8)
- <60 mL/min/1.73 m^2	188 (75.2%)	188 (72.9%)

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Baseline TTE (core-lab)

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

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Baseline Right Heart Catheterization

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

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Procedural Details

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

*Site randomization error

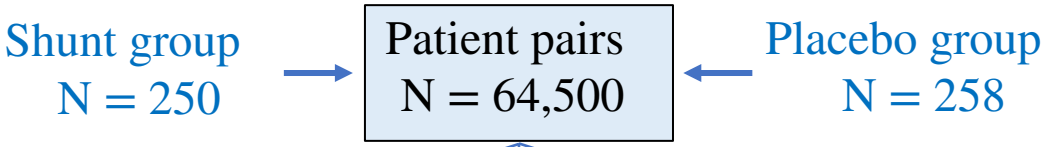
RELIEVE-HF Primary Safety Endpoint

- 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

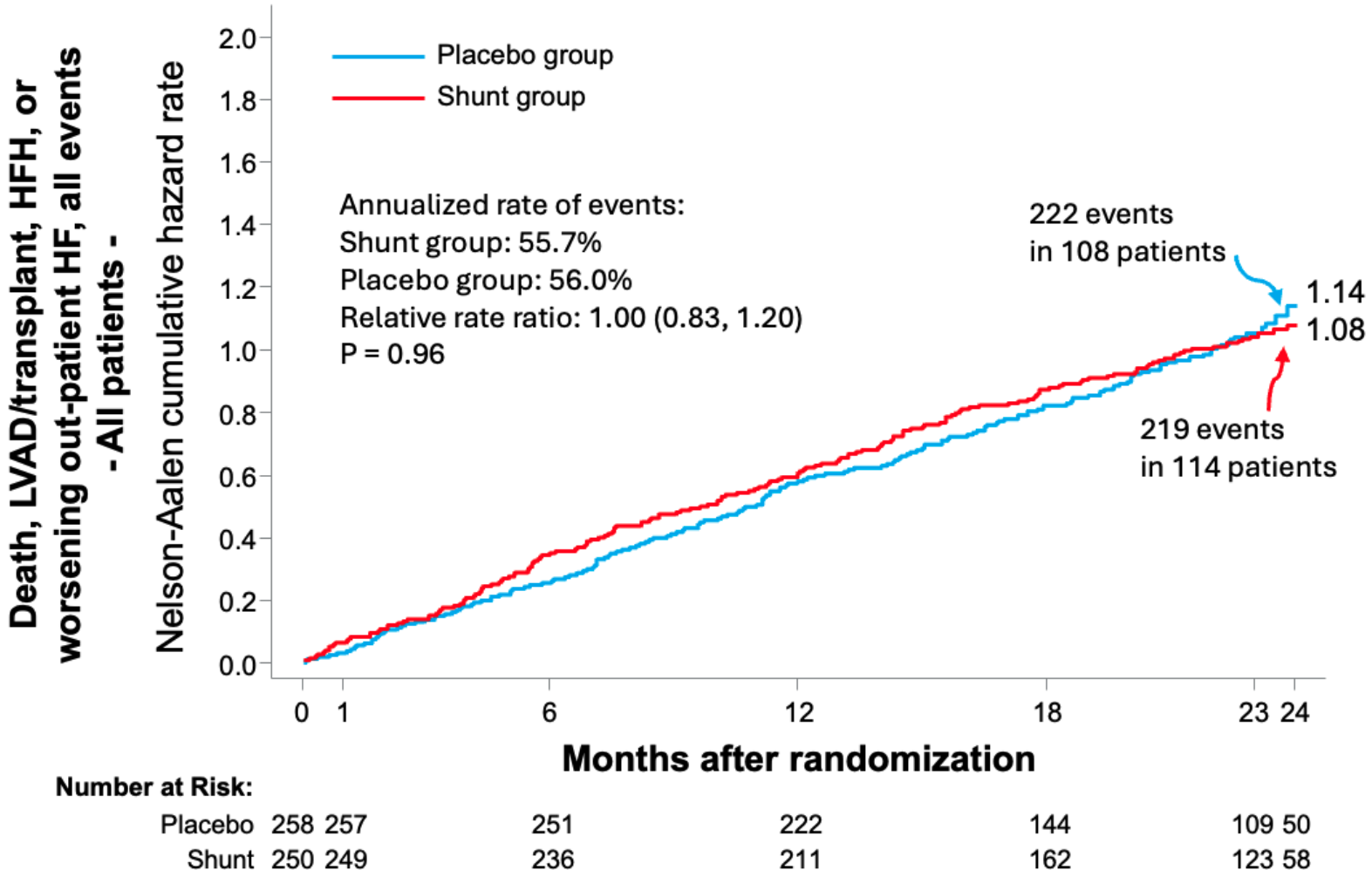


Shunt group outcomes	Wins	Ties	Losses	% of decisions
Level 1: All-cause death	5424	51,461	7615	21.4%
Level 2: Cardiac transplantation or LVAD implantation	1177	50,122	162	2.2%
Level 3: Heart failure hospitalizations	9264	30,271	10,587	32.5%
Level 4: Out-patient worsening heart failure events	3921	22,488	3862	12.8%
Level 5: Change in KCCQ from baseline by at least 5 points	8876	3533	10,079	31.1%

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 -



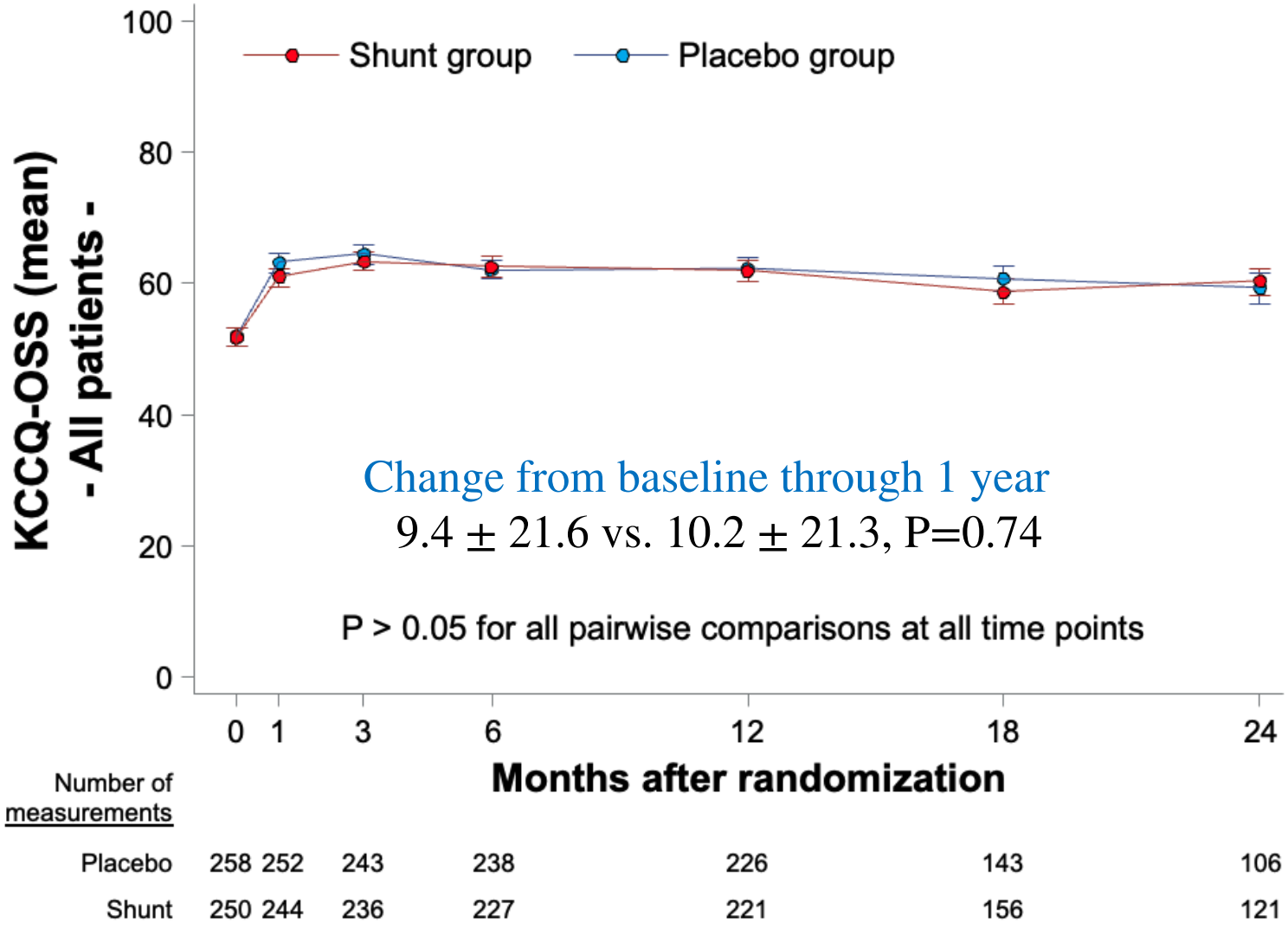
Risk of all Cardiovascular Events

- 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
All events [1]	219/392.7 (55.7%/year)	222/396.1 (56.0%/year)	1.00 (0.83, 1.20)	0.96
All-cause death [2]	35 (15.6%)	27 (13.7%)	1.31 [0.79, 2.16]	0.30
LVAD/HT[2]	2 (0.8%)	2 (1.1%)	1.01 [0.14, 7.14]	1.00
All HFHs [1,3]	128/392.7 (32.6%/year)	125/396.1 (31.6%/year)	1.09 [0.79, 1.50]	0.60
All out-pt WHFs [1,3]	55/392.7 (14.0%/year)	64/396.1 (16.2%/year)	0.88 [0.61, 1.26]	0.48

[1]Total no. of events/total no. of patient-years of follow-up (annualized rate) with relative rate ratio (95% CI)
[2]Time-to-first event analysis – n events (Kaplan-Meier estimated rate) with HR (95% CI) from a Cox model
[3]HR (95% CI) from a joint frailty model accounting for the competing risk of death

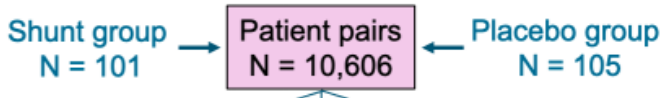
Change in KCCQ-OSS Over Time



RELIEVE-HF

Primary Effectiveness Outcome by LVEF

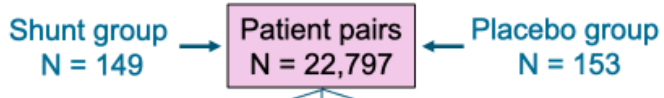
LVEF ≤40% (n=206)



Shunt group outcomes	Wins	Ties	Losses	% of decisions
Level 1: All-cause death	1543	7908	1154	26.7%
Level 2: Cardiac transplantation or LVAD implantation	466	7384	58	5.2%
Level 3: Heart failure hospitalizations	1670	4304	1410	30.5%
Level 4: Outpatient worsening heart failure events	506	3227	571	10.7%
Level 5: Change in KCCQ from baseline by at least 5 points	1339	501	1387	27.0%

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]

LVEF >40% (n=302)



Shunt group outcomes	Wins	Ties	Losses	% of decisions
Level 1: All-cause death	914	19014	2869	17.7%
Level 2: Cardiac transplantation or LVAD implantation	0	19014	0	0%
Level 3: Heart failure hospitalizations	3067	11637	4310	34.5%
Level 4: Outpatient worsening heart failure events	1590	8628	1419	14.1%
Level 5: Change in KCCQ from baseline by at least 5 points	3238	1418	3972	33.7%

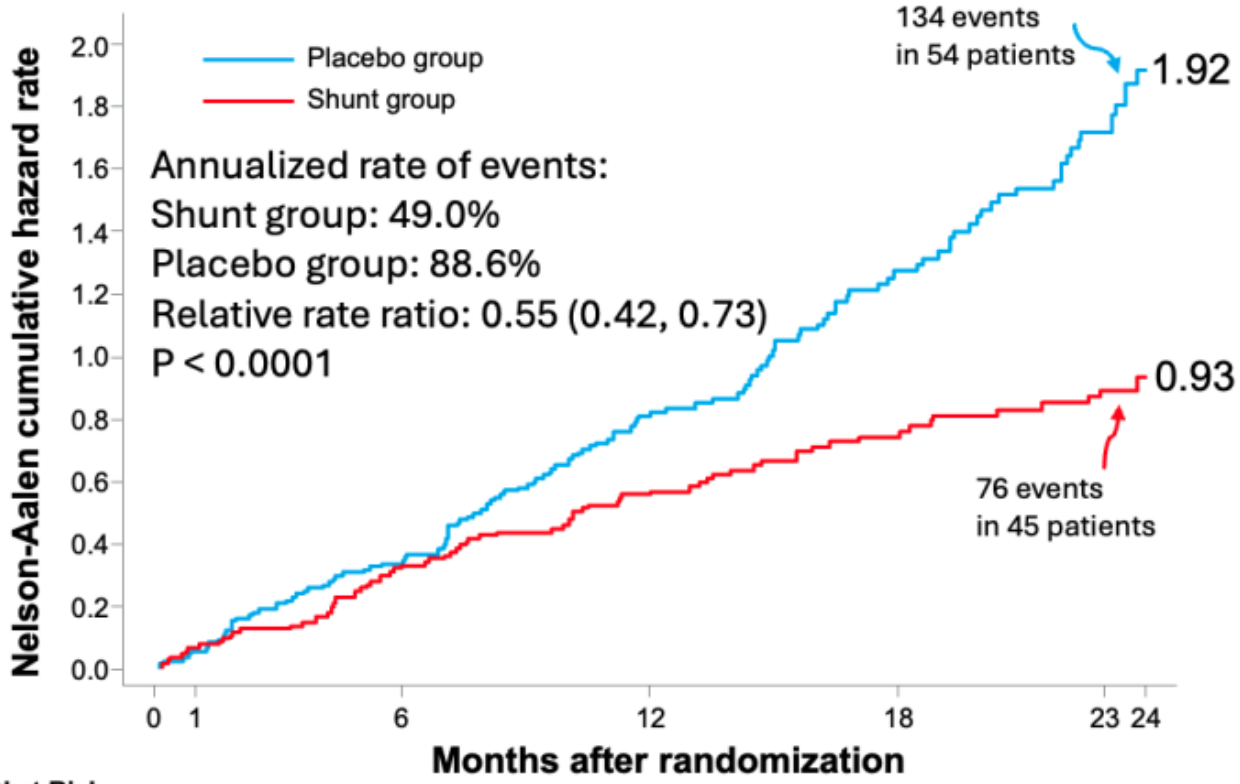
Total wins = 8809; Total losses = 12,570
Win ratio (unweighted) = 8809/12,570 = 0.70 (0.54, 0.92)
Win ratio (phase weighted for interim analysis) = 0.61 [0.39, 0.98]

$P_{interaction}$ =0.0275

Risk of all Cardiovascular Events by LVEF

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

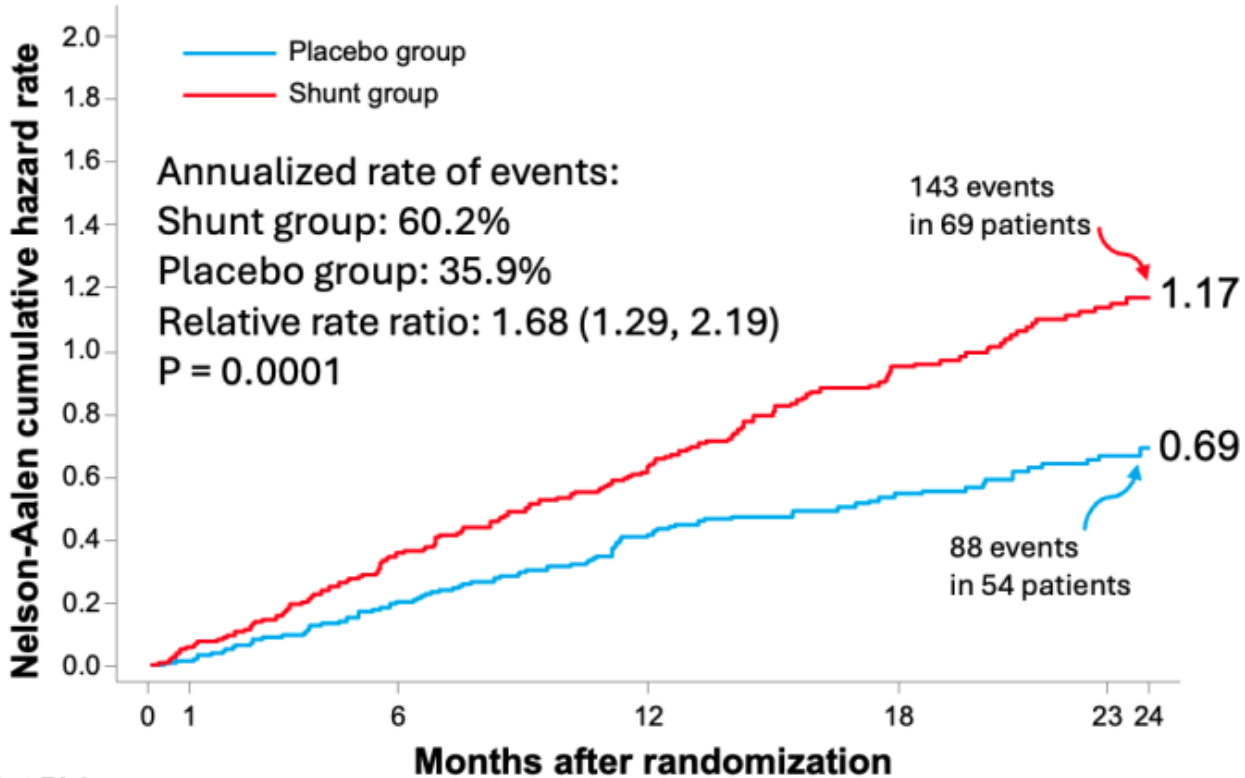
LVEF ≤40% (n=206)



N at Risk:

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

LVEF >40% (n=302)



N at Risk:

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

$P_{interaction}$ <0.0001

Risk of all Cardiovascular Events by LVEF

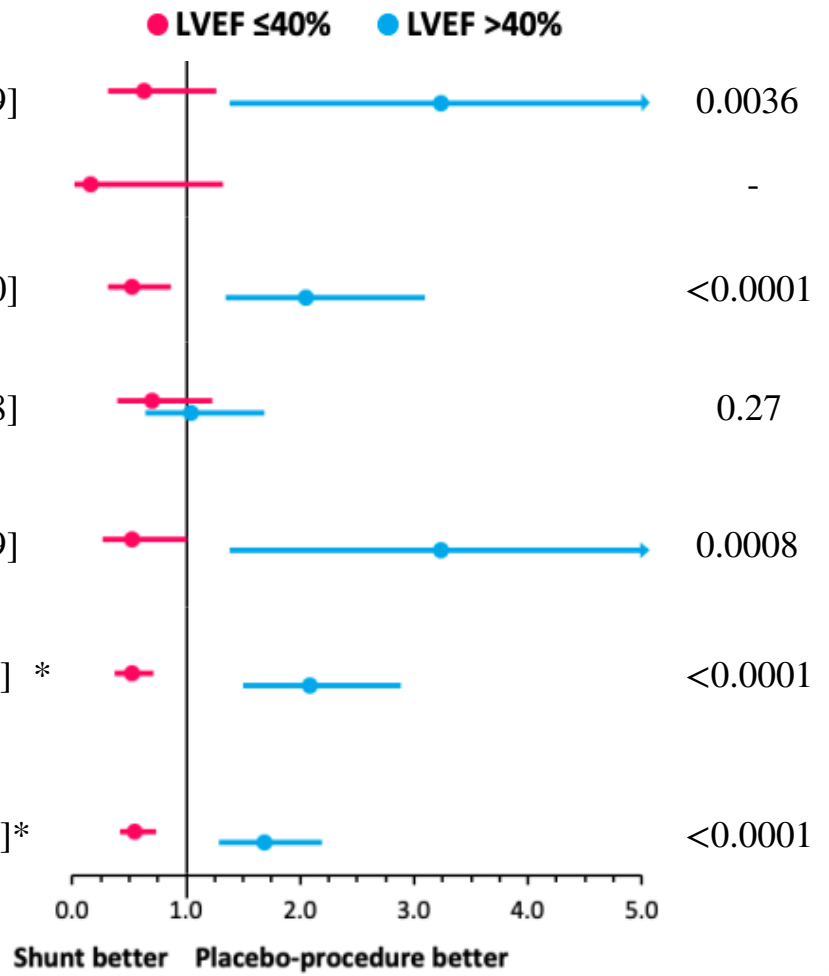
- All-cause death, LVAD/HT, all HFHs, and all out-patient worsening HF events -

	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)
All events [1]	76/155.2 (49.0%/year)	134/151.2 (88.6%/year)	0.55 (0.42, 0.73) **P<0.0001**	143/237.5 (60.2%/year)	88/2450 (35.9%/year)	1.68 (1.29, 2.19) **P=0.0001**
All-cause death [2]	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] **P=0.004**
LVAD/HT[2]	1 (1.5%)	6 (9.0%)	0.16 [0.02, 1.32] P=0.051	0 (0.0%)	0 (0.0%)	-
All HFHs [1,3]	41/155.2 (26.0%/year)	78/151.2 (52.0%/year)	0.52 [0.31, 0.86] **P=0.01**	87/237.5 (37.0%/year)	47/245.0 (19.0%/year)	2.05 [1.35, 3.10] **P=0.0008**
All out-pt WHFs [1,3]	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

[1]Total no. of events/total no. of patient-years of follow-up (annualized rate) with relative rate ratio (95% CI)
[2]Time-to-first event analysis – n events (Kaplan-Meier estimated rate) with HR (95% CI) from a Cox model
[3]HR (95% CI) from a joint frailty model accounting for the competing risk of death

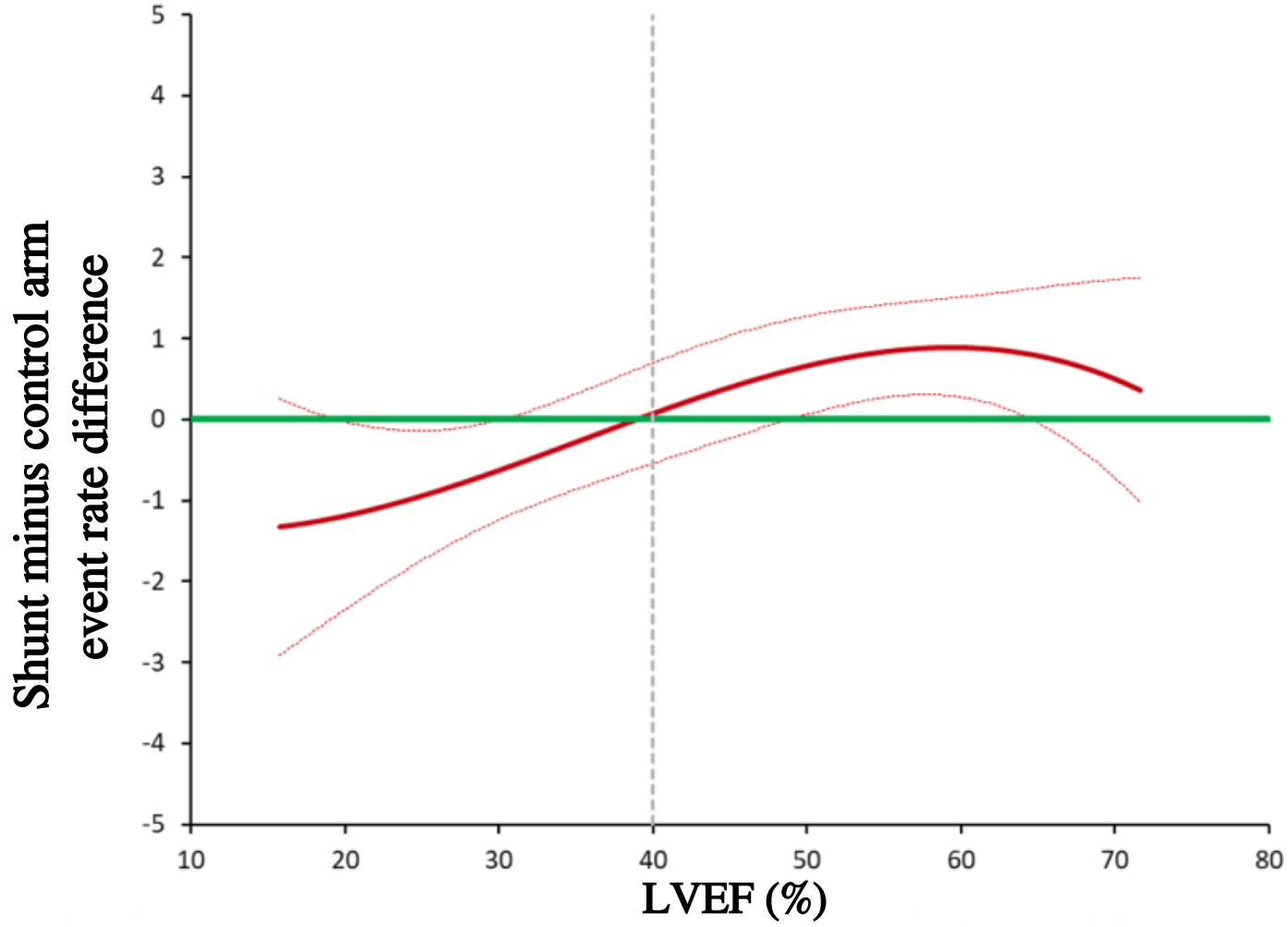
Risk of Cardiovascular Events by LVEF

	LVEF ≤40% HR or RRR [95% CI]	LVEF >40% HR or RRR [95% CI]	P-value for interaction
All-cause death through 2 years, time to first	0.63 [0.31, 1.26]	3.24 [1.38, 7.59]	0.0036
HT or LVAD implantation through 2 years, time to first	0.16 [0.02. 1.32]	-	-
Heart failure hospitalizations (HFHs), all through 2 years – no. of events/total no. of pt-yr (annualized rate), JF model	0.52 [0.31, 0.86]	2.05 [1.35, 3.10]	<0.0001
Outpatient worsening HF events, all through 2 years – no. of events/total no. of pt-yr (annualized rate), JF model	0.70 [0.39, 1.23]	1.04 [0.64, 1.68]	0.27
All-cause death or HT or LVAD implantation through 2 years, time to first	0.52 [0.27, 1.00]	3.24 [1.38, 7.59]	0.0008
All-cause death, HT or LVAD, and HFHs, all events through 2 years – no. of events/total no. of patient-yr-yr (annualized rate)	0.52 [0.37, 0.71]*	2.08 [1.50, 2.88] *	<0.0001
All-cause death, HT or LVAD, HFH and outpatient worsening HF events, all through 2 years – no. of events/total no. of patient-yr (annualized rate)	0.55 [0.42, 0.73]*	1.68 [1.29, 2.19]*	<0.0001



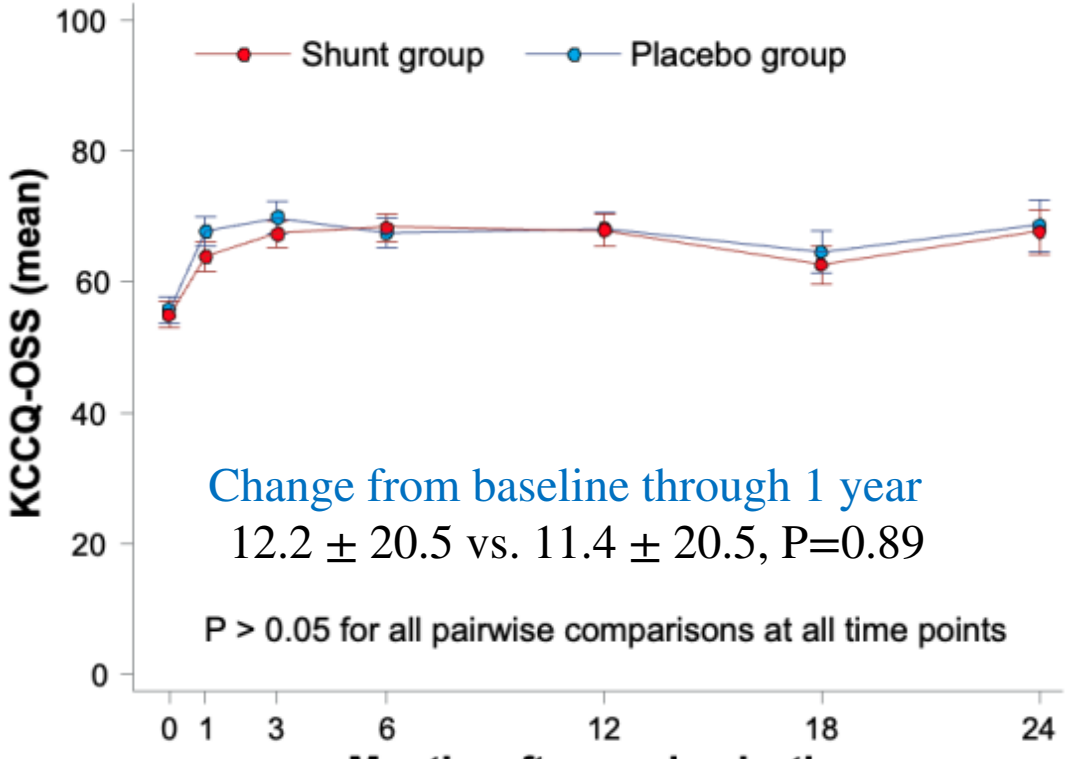
Risk of all Cardiovascular Events by LVEF

- 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)

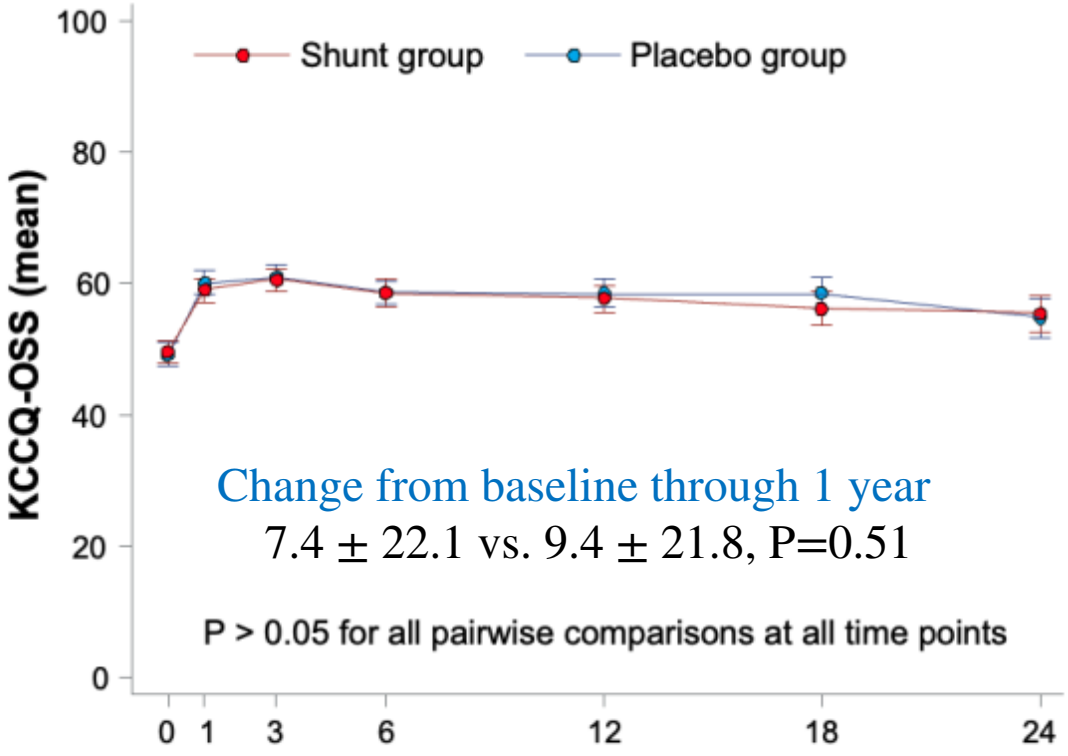


Change from baseline through 1 year
12.2 ± 20.5 vs. 11.4 ± 20.5, P=0.89

P > 0.05 for all pairwise comparisons at all time points

Number of measurements							
Placebo	105	100	96	95	86	52	35
Shunt	101	100	97	94	91	60	48

LVEF >40% (n=302)



Change from baseline through 1 year
7.4 ± 22.1 vs. 9.4 ± 21.8, P=0.51

P > 0.05 for all pairwise comparisons at all time points

Number of measurements							
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

RELIEVE-HF

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.

RELIEVE-HF

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
Edgard Prihadi	Antwerp Cardiovascular Center, ZNA Middelheim Hospital, Antwerpen, Belgium	13
Dimitry Schewel	Marienkrankrankenhas, Hamburg, Germany	12
Eugene Chung	Lindner Center for Research and Education at The Christ Hospital, Cincinnati, OH, US	12
Matthew Price	Scripps Clinic, La Jolla, CA, US	12