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Premarket Approval Application (PMA) for V-Wave's Ventura Interatrial Shunt System

Circulatory System Devices Advisory Committee Meeting

December 3, 2025

Introduction, Background, Clinical Study Design

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Review Team

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Outline

- Background
- Clinical Study Design
- Statistical Analysis
- Clinical Study Results
- Post-approval Study
- Conclusions

Heart Failure (HF)

- HF results from impairment of cardiac filling or ejection of blood
- Characterized by high mortality and hospitalization rates with reduced quality of life
- 6.7 million Americans – lifetime risk of 24%[1,2,3]
- HF management requires high levels of health care resources

1. Ambrosy P, Fonarow GC, Butler J, et al. The Global Health and Economic Burden of Hospitalizations for Heart Failure. Lessons Learned from Hospitalized Heart Failure Registries. J Am Coll Cardiol. 2014;63:1123–1133.
2. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics-2014 Update. A Report from the American Heart Association. Circulation 2014,128: DOI: 10.1161/01.cir.0000441139.02102.80.
3. Butler J, Braunwald E, Gheorghiade M. Recognizing worsening chronic heart failure as an entity and an end point in clinical trials. JAMA. 2014;312(8):789-90.

Left Ventricular Ejection Fraction (LVEF)

- LVEF is calculated by dividing the amount of blood pumped out during a heartbeat (stroke volume) by the total amount of blood that filled the chamber before the beat (end-diastolic volume)
  - LVEF is expressed as a percent
- LVEF describes phenotypes:
  - Heart failure with reduced ejection fraction (HFrEF): LVEF ≤40%
  - Heart failure with preserved ejection fraction (HFpEF): LVEF >40%

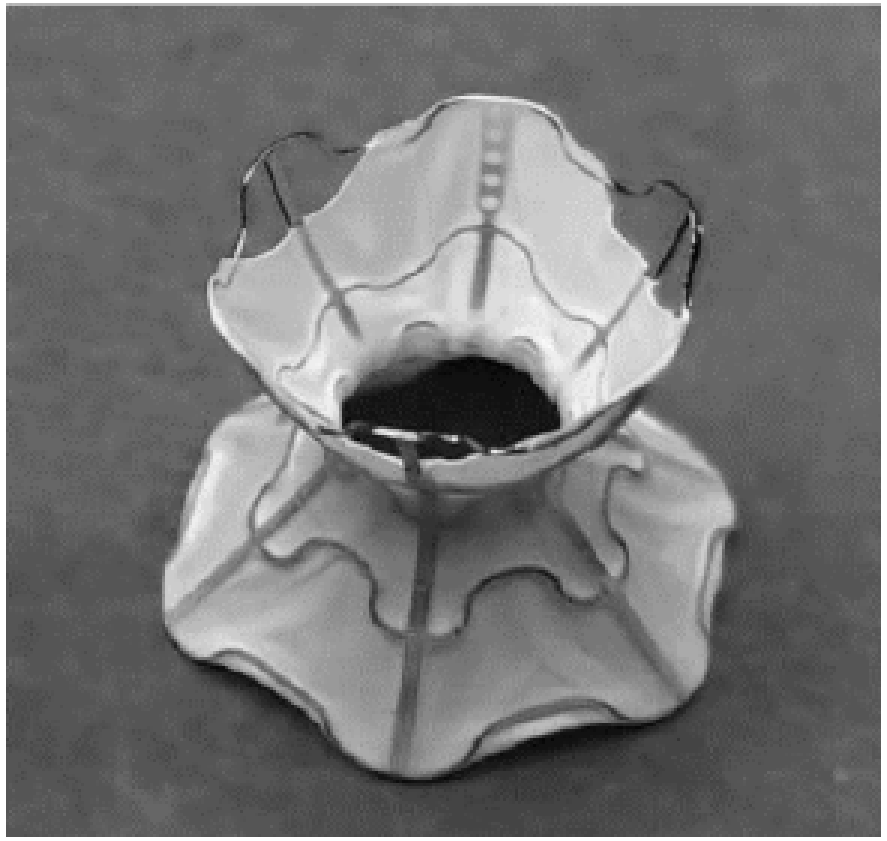
Current HF Treatment

- HFrEF patients:
  1. Lifestyle and comorbidity management
  2. Sodium-glucose cotransporter-2 (SGLT2) inhibitor
  3. Loop diuretics for symptom management
  4. Neurohormonal modulators
  5. Implantable cardioverter defibrillator (ICD)/cardiac resynchronization therapy (CRT) in eligible patients
- HFpEF patients:
  1. Numbers 1, 2, and 3 from above
  2. Hypertension management
  3. Atrial fibrillation management (if applicable)

Pathophysiological Rational for Interatrial Shunting

- HF patients have increased left atrial to right atrial pressure difference, irrespective of LVEF
- Interatrial shunting permits left-to-right blood flow and could lower left atrial pressure and lead to symptom improvement
- Still many unknowns with this procedure (e.g., optimal shunt size, optimal flow rates, optimal patient population)

Ventura Interatrial Shunt System



Proposed Indications for Use

The Ventura Shunt is indicated for NYHA Class III heart failure patients who remain symptomatic despite guideline-directed medical therapy, have a **LVEF of ≤40%,** and who are judged by a Heart Team to be appropriate for Shunt therapy, to reduce the risk of hospitalization for heart failure.

New York Heart Association (NYHA) Functional Classification

NYHA functional class categorizes heart failure patients based on symptoms

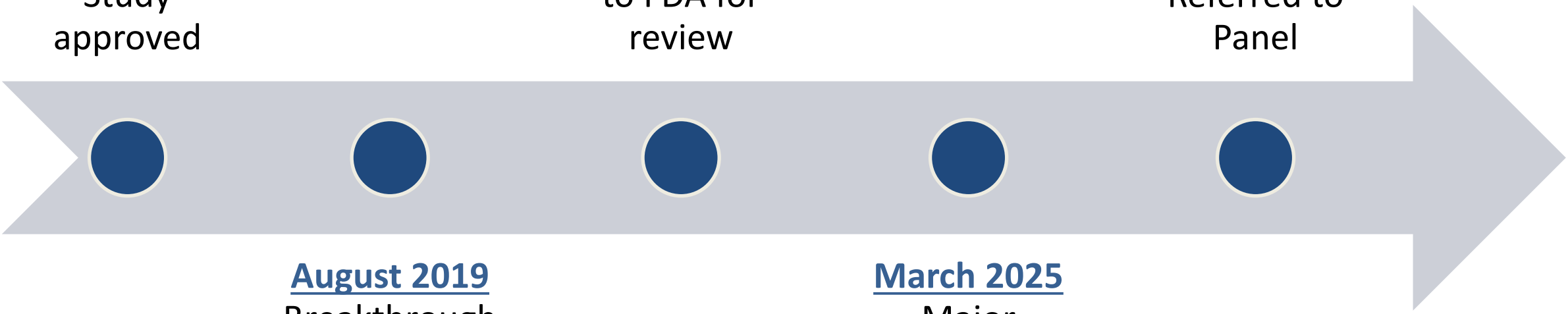
- Class I - no symptoms during normal activity
- Class II - mild limitations of physical activity
- Class III - marked limitations of physical activity
- Class IV - severe limitations and symptoms, even at rest

Non-Clinical Testing

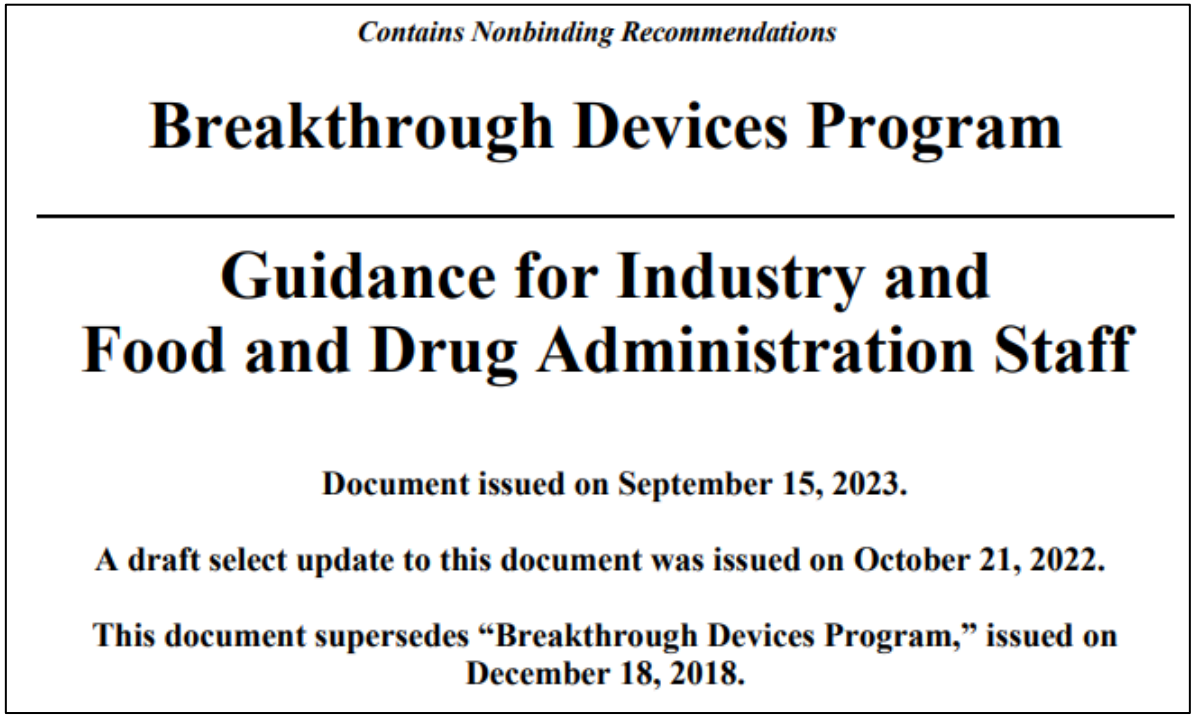
- Design verification & validation (including delivery system testing)
- Stability (shelf life, corrosion, FEA, fatigue, and particulate testing)
- MRI
- Packaging & sterilization
- GLP animal studies
- Biocompatibility

Non-clinical testing is complete and acceptable

Regulatory Timeline



Breakthrough Devices Program



Contains Nonbinding Recommendations

Breakthrough Devices Program

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 15, 2023.

A draft select update to this document was issued on October 21, 2022.

This document supersedes "Breakthrough Devices Program," issued on December 18, 2018.

- A breakthrough device has the potential to provide more effective treatment or diagnosis of a life-threatening or irreversibly debilitating disease vs. current available options
- The program is intended to provide patients with timely access to selected devices by expediting their development, assessment and review
- The Ventura Shunt was granted breakthrough status in August 2019 for NYHA Class III and ambulatory Class IV HF patients (HFrEF and HFpEF)

Breakthrough Devices Program

- Allows for:
  - Increased FDA review team support
  - Enhanced timely interactions with FDA
  - Efficient and flexible clinical study design
  - Balanced pre/postmarket data collection
  - Priority review
- Does not alter or reduce the statutory requirement for premarket approval (a reasonable assurance of safety and effectiveness)

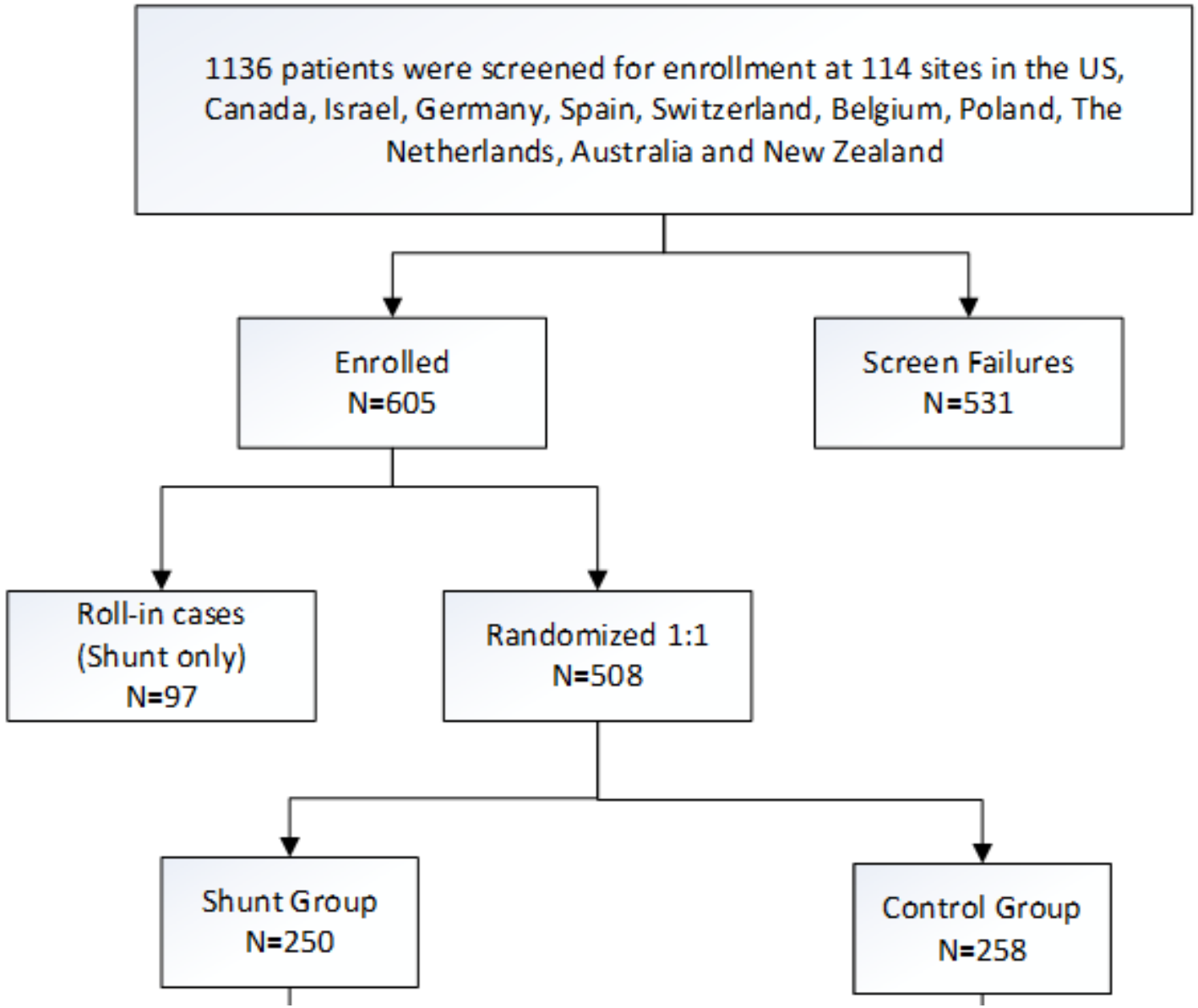
Pre/Postmarket Balance of Data Collection

- FDA may accept greater uncertainty for a premarket submission along with timely postmarket data collection if the uncertainty is sufficiently balanced and addressed
- Benefit/Risk considerations include:
  - Probable benefits from earlier access, vs.
  - Probable risk of harm should postmarket data show that the device is ineffective or unsafe

RELIEVE-HF Pivotal Trial Overview

- Enrolled symptomatic HF patients treated with guideline-directed medical therapy (GDMT)
- Two phases:
  - Roll-in phase (97 patients) treated with shunt
  - A 1:1 randomized, blinded, sham-controlled trial of Shunt treatment vs a sham procedure with 508 randomized patients
    - Study subjects and personnel involved in endpoint collection were blinded

Cohort Assignment



Key Inclusion Criteria

- Ischemic or non-ischemic cardiomyopathy with HFrEF or HFpEF and documented HF for ≥6 months prior to baseline
- NYHA Class II, Class III, or ambulatory Class IV
- Treated with GDMT for HF consisting of HF drugs with a Class I indication
- Treated with Class I guideline-recommended cardiac rhythm management device therapy (if indicated)
- Able to perform a 6-minute walk test for ≥100 meters and ≤450 meters

Key Exclusion Criteria

- Severe pulmonary hypertension
- Right ventricular (RV) dysfunction
- Left ventricular end-diastolic diameter (LVEDD) >8 cm by baseline transthoracic echocardiogram (TTE)
- Untreated moderately severe or severe aortic or mitral stenosis
- Mitral valve repair device implanted ≤3 months prior to the baseline visit

Primary Safety Endpoint

- The proportion of Shunt group patients experiencing device- or procedure-related major adverse cardiovascular or neurological events (MACNE) during the first 30 days after randomization
  - MACNE – Composite of all-cause death, stroke, systemic embolism, need for open cardiac surgery, or major endovascular surgical repair
- The following events were not included in the primary safety endpoint event rate
  - Percutaneous drainage of a pericardial effusion
  - Percutaneous catheter snaring and removal of an embolized but uncomplicated Shunt device
  - Non-surgical treatment of access site complications.

Primary Effectiveness Endpoint

- Hierarchical composite of the following:
  - All-cause death
  - Cardiac transplantation or left ventricular assist device (LVAD) implantation
  - HF hospitalizations (HFH) that includes ER HF visits duration ≥6 hours
  - Worsening HF events treated as an outpatient
  - Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score of ≥5 points from baseline to 12 months
- Performed when last patient followed for 12 months and included all data through 24 months of follow-up

Heart Failure Endpoint Definitions

- A **heart failure hospitalization** required a non-elective in-hospital stay for worsening heart failure that was present at the time of admission and considered as the primary cause of hospitalization and that included at least one calendar date change and required intravenous or mechanical heart failure therapies or the significant augmentation of oral heart failure medications.
- A **worsening HF event** was an unscheduled outpatient medical contact associated with changes in heart failure therapy and required:
  - Documented new or worsening symptoms due to heart failure
  - Objective evidence of new or worsening heart failure
  - Treatment specifically for worsening heart failure
  - Documented response to treatment

Secondary Endpoints

Hierarchically tested secondary effectiveness endpoints included:

1. KCCQ score change from baseline to 12 months
2. Rate of HFH (adjusted for all-cause mortality)
3. Time to all-cause death, LVAD/transplant or HFH
4. Time to all-cause death or first HFH
5. Cumulative HFHs
6. Time to first HFH
7. Hierarchical composite of all-cause death, LVAD/transplant, HFH, and worsening HF treated as an outpatient (WHF)
8. Change in 6-minute walk test (6MWT) from baseline to 12 months

Key Subgroups

- Age
- Sex
- BMI
- Diabetes
- Hypertension
- Ischemic vs non-ischemic cardiomyopathy
- LVEF (stratified by HFrEF and HFpEF)
- Baseline NYHA class (III vs. IV)
- Baseline 6MWT
- Baseline KCCQ score

Statistical Analysis

Chuan Bi, PhD
Statistician
Office of Clinical Evidence and Analysis

Primary Safety Endpoint

- **Definition:**
  - Percentage of Treatment Group patients experiencing device- or procedure-related Major Adverse Cardiovascular and Neurological Events (MACNE) during the first 30 days after randomization
- **Hypothesis**
  - H_0: R ≥ 11%, H_1: R < 11%, where R = true device-related MACNE rate
- **Statistical Method**
  - Exact binomial test (one-sided)
  - One-sided $\alpha = 0.025$
  - Performance Goal: 11%
  - Power: 87% to detect difference between 5% expected rate and 11% performance goal
  - Sample Size: N = 200 evaluable treatment group patients.

Primary Effectiveness Endpoint

- **Definition** (composite endpoint with ranked components)**:**
  1. All-cause death
  2. Cardiac transplant or LVAD implantation
  3. HF hospitalization (HFH), including ER visits ≥6 hours
  4. Worsening HF treated as an outpatient
  5. KCCQ improvement ≥5 points at 12 months
- **Hypothesis**
  - H_0: No treatment effect on composite components
  - H_1: ≥1 component favors intervention
- **Statistical Method**
  - Test Statistic: Finkelstein-Schoenfeld (F-S) statistic
  - $\alpha = 0.025$ (one-sided)
  - Effect Size Measure: Win-ratio with 95% confidence interval
  - Power: 90% with 400 patients (200 per arm)

Design Assumptions Used for Study Powering

Type of Event	HFrEF Control	HFrEF Shunt	**HFrEF Improvement**	HFpEF Control	HFpEF Shunt	**HFpEF Improvement**
Loss to Follow-up	1.7%	1.7%	0	1.7%	1.7%	0
Death	5.1%	4.2%	0.9	3.6%	2.9%	0.7
LVAD/ Transplant	1.6%	1.2%	0.4	0	0	0
HFH1	27.5%	20.7%	**6.8%**	21.4%	11.5%	**9.9%**
HFH2	30.1%	22.8%	**7.3%**	23.5%	12.7%	**10.8%**
HFH3+	32.9%	24.9%	**8%**	25.7%	13.8%	**11.9%**
KCCQ	8	16	**8**	11	22	**11**

Note: Assumptions shown are from the SAP and were used for powering the study; they do not represent observed outcomes.

1. **Both LVEF strata were assumed to benefit from shunting**
2. **HFpEF assumed to have greater benefit**

Control of Type I Error Rate

- Type I Error: concluding a device works when it actually does not.
- Pre-specification of Type I error rate control (in the protocol or statistical analysis plan) ensures findings are statistically reliable and scientifically credible.
- Statistical significance cannot be attributed to findings in post-hoc analyses.
- Performing unplanned post-hoc analyses and deviations from pre-specified analysis plan should not be viewed as a conclusive statistical evidence. They are generally used for hypothesis generation.

Source:
Design Considerations for Pivotal Clinical Investigations for Medical Devices
ICH E9 statistical principles for clinical trials - Scientific guideline

Type I Error Control Strategy for RELIEVE-HF Study

- Primary Endpoints
  - Independent testing at alpha = 0.025 each (safety and effectiveness tested separately)
- Secondary Endpoints
  - Fixed-order of testing (gatekeeping): each endpoint tested only if all previous endpoints were significant
- Planned Adaptive Design and Interim Analysis
  - Initial design: 400 patients; pre-specified re-estimation plan at interim analysis allowed adjustment with Type I error control*
  - DSMB: continue as planned; sample size increased to 508 per plan.

* Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics. 1999

Proposed Additional Tests

- A COVID-19 impact analysis was also proposed to assess potential external influences.
- Secondary Endpoints were only to be tested if primary effectiveness endpoint was significant, using same alpha = 0.025 (one-sided) in strict hierarchical order.
- Fifteen (15) pre-specified subgroup analyses of the primary safety and effectiveness endpoints were analyzed for descriptive purposes only.
- Seventeen (17) additional effectiveness endpoints and nine (9) additional safety endpoints would be explored descriptively.

Because the primary effectiveness endpoint was not met, all and any subsequent analyses should be considered exploratory

Interaction Tests for Subgroup Analyses

- The treatment effect may vary with subgroups.
  - Some interactions are expected in advance and are planned in confirmatory analyses. Most subgroup or interaction analyses are exploratory.
  - Nominally significant Interaction test results may represent true heterogeneity or chance finding
  - Purpose: assess consistency of overall treatment effects (if any) across subgroups.
- Per RELIEVE-HF SAP, interaction tests were to be explored in subgroups for descriptive purposes only.

Any observed differences across subgroups should be viewed as exploratory and hypothesis generating

Source:
Design Considerations for Pivotal Clinical Investigations for Medical Devices
ICH E9 statistical principles for clinical trials - Scientific guideline

Post-Hoc Analyses and Statistical Concerns

Sponsor's Assertion/Post-hoc Analysis	Concerns
There was a statistically significant difference in the treatment effect between the HFrEF and HFpEF patients (nominal P = 0.0146). Each LVEF stratum was separately analyzed, which demonstrated contrasting directionally opposite outcomes. Permutation testing was conducted, and the Type I error inflation was minimal. Multiple changes to endpoints and analytic methods were made to support Shunt effectiveness for HFrEF patients	**Interaction P-value only reflects difference In treatment effect between the groups.** **P-values arising from post-hoc analyses (e.g., unplanned within-stratum hypothesis test, exploration of alternative endpoints such as cumulative hospitalizations) may not be interpreted as demonstrations of statistical significance, as no Type I error rate control can be attributed to post-hoc observations.**

Source:
Design Considerations for Pivotal Clinical Investigations for Medical Devices
ICH E9 statistical principles for clinical trials - Scientific guideline

RELIEVE-HF Pivotal Clinical Trial Results

Andrew Farb, MD
Chief Medical Officer
FDA Office of Cardiovascular Devices

Outline

- RELIEVE-HF Results – All Randomized Subjects
- RELIEVE-HF HFrEF Subgroup Results
- RELIEVE-HF HFpEF Subgroup Results
- Pathophysiologic Insights
- RELIEVE-HF Strengths, Limitations, and Benefit-Risk considerations

Outline

- RELIEVE-HF Results – All Randomized Subjects
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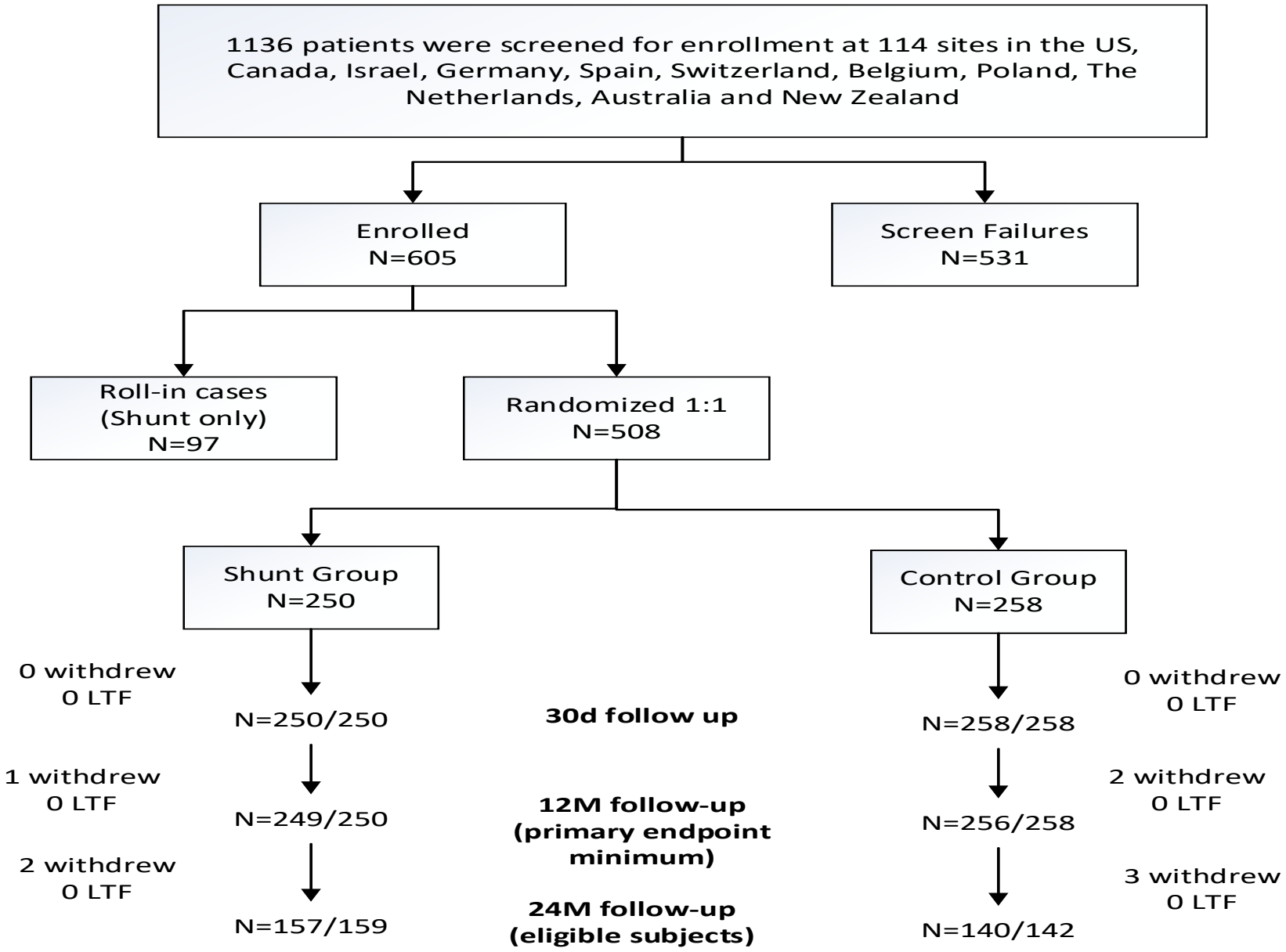
RELIEVE-HF Subject Assignment & Accountability



ITT Population Baseline Demographic & Clinical Characteristics, All RCT Subjects

	Shunt group, (N=250)	Control group, (N=258)
Age, years	72.6 ± 10.0	70.4 ± 10.5
Male	162 (64.8%)	157 (60.9%)
Caucasian	227 (90.8%)	232 (89.9%)
Body mass index, kg/m^2	30.5 ± 6.2	31.2 ± 6.1
Duration of heart failure, months	70.5 ± 66.3	75.1 ± 71.9
HFHs during prior 1 yr	0.76 ± 0.97	0.68 ± 0.88
Diabetes mellitus	124 (49.6%)	125 (48.4%)
Hypertension	209 (83.6%)	216 (83.7%)
Hyperlipidemia	201 (80.4%)	195 (75.6%)
CAD	169 (67.6%)	160 (62.0%)
Current or previous smoker	133 (53.2%)	137(53.1%)
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%)
Prior MI	104 (41.6%)	103 (39.9%)
Baseline rhythm atrial fibrillation or flutter	76 (30.4%)	64 (24.8%)
NYHA Class III	239 (95.6%)	251 (97.3%)
KCCQ summary score	52.1 (35.4, 66.9)	50.8 (34.6, 66.4)
Six-minute walk distance, m	265 (196, 325)	2701 (198, 330)
BNP, pg/ml	238 (117,413)	221 (101, 518)
NT ProBNP, pg/ml	1939 (1066, 3259)	1597 (852, 2868)
eGFR <60 ml/min/1.73 m^2	188 (75.2%)	188 (72.9%)

ITT Population Baseline HF Medical and Electronic Rhythm Therapies, all RCT Subjects

	Shunt group, N=250	Control group, N=258
Beta-blockers	224 (89.6%)	222 (86.0%)
RAS inhibitors	176 (70.4%)	185 (71.7%)
-ACEi	32 (12.8%)	38 (14.7%)
-ARB	39 (15.6%)	38 (14.7%)
-ARNi	105 (42.0%)	109 (42.2%)
MRAs	145 (58.0%)	174 (67.4%)
SGLT-2 inhibitors	93 (37.2%)	113 (43.8%)
Vasodilators	33 (13.2%)	34 (13.2%)
- Long-acting nitrates	29 (11.6%)	25 (9.7%)
- Hydralazine	10(4.0%)	20 (7.8%)
Diuretics	230 (92.0%)	239 (92.6%)
Antiplatelet agents	106 (42.4%)	111 (43.0%)
Chronic oral anticoagulation	152 (60.8%)	141 (54.7%)
ICD or CRT-D	115 (46.0%)	123 (47.7%)
CRT-D or CRT-P	70 (28.0%)	59 (22.9%)

ITT Population Baseline Transthoracic Echocardiography Parameters, all RCT Subjects

	Shunt group, N=250	Control 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)
LVEF (biplane),%	45.4 (33.4, 58.9)	45.3 (33.3, 57.4)
LVEF ≤40% (HFrEF)	101/250 (40.4%)	105/258 (40.7%)
LVEF >40% (HFpEF)	149/250 (59.6%)	153/258 (59.3%)
LA volume (biplane), ml	78.5 (63.5, 103.0)	76.0 (59.5, 101.0)
Stroke volume, ml	54.0 (41.0, 67.0)	54.0 (44.0, 67.0)
Stroke volume index, ml/m^2	26.7 (21.7, 31.9)	27.5 (21.8, 33.0)
Cardiac output, L/min	3.7 (2.9, 4.6)	3.8 (3.1, 4.7)
Cardiac index, L/min/m^2	1.8 (1.5, 2.2)	1.9 (1.5, 2.3)
RV fractional area change, %	37.7 (33.3, 42.9)	37.5 (33.3, 42.9)
Tricuspid annular plane systolic excursion, mm	16.5 (14.0, 20.0)	17.0 (14.0, 19.0)
PA systolic pressure, mmHg	32.0 (24.0, 41.0)	32.0 (25.0, 40.0)
RV end-diastolic area index, 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%)

ITT Population Baseline Right Heart Catheterization Data , all RCT Subjects

	Shunt group, N=250	Control group, N=258
Heart rate, bpm	68.4 ± 13.6	68.3 ± 13.3
SBP, mmHg	118.4 ± 18.7	118.8 ± 19.8
DBP, mmHg	65.4 ± 12.2	65.5±11.2
Mean RA pressure, mmHg	9.6 ± 4.3	9.1 ± 4.1
PA systolic, mmHg	38.7 ± 10.9	38.2 ± 10.7
Mean PAP, mmHg	26.1 ± 7.2	25.7 ± 7.2
PVR, Wood units	2.3 ± 1.1	2.2 ± 1.3
PCWP, mmHg	16.5 ± 6.0	16.5 ± 6.1
Cardiac output, L/min	4.5 ± 1.5	4.6 ± 1.5
Cardiac index, L/min/m²	2.3 ± 0.7	2.3 ± 0.7

Procedural Outcomes in Randomized Shunt Subjects

- Successful device implant in all subjects (n=250)
- Shunt flow 1010 ± 321 ml/min
- Shunt flow direction
  - –96% continuous LA to RA
  - –4% intermittent bi-directional
- Estimated Qp/Qs 1.25 ± 0.11

No cases of Shunt migration, embolization, or thrombosis

RELIEVE-HF Blinding

Blinded	Not Blinded
• Study subjects • Clinical Events Committee • Research staff administering KCCQ • Research staff collecting study endpoints	• Shunt implanters • Sonographers • Echo readers

2% to 8% of randomized patients correctly guessed their group assignment beyond the play of chance

Blinding appears to have been adequately maintained through one year

Primary Safety Endpoint

- Rate of device or procedure related major adverse cardiovascular or neurological events (MACNE) at 30 days post-randomization
- Evaluated in the 250 Shunt group patients
- Performance goal (PG) 11%

Safety events in 250 Shunt group patients	Event rate
MACNE at 30-days post-randomization, % (n/N)	0.0% (0/250)
All-cause death, % (n/N)	0.0% (0/250)
Stroke, % (n/N)	0.0% (0/250)
Systemic embolism, % (n/N)	0.0% (0/250)
Need for open cardiac surgery, % (n/N)	0.0% (0/250)
Need for major endovascular surgical repair, % (n/N)	0.0% (0/250)

- No MACNE events through 30 days in Shunt subjects
- Upper 97.5% confidence limit = 1.5%, lower than the 11% PG, $p < 0.0001$

Primary safety endpoint met

Secondary Safety Endpoint events

	Shunt group, N=250	Control group, N=258
Cerebrovascular events at 2 years	11 (5.1%)	6 (2.5%)
CNS infarct, stroke	7 (3.3%)	5 (2.1%)
CNS hemorrhage, intracerebral or subarachnoid	0 (0.0%)	1 (0.5%)
Transient ischemic attack	4 (1.9%)	1 (0.4%)
Pulmonary embolization events at 2 years	2 (1.0%)	0 (0.0%)
MI at 2 years	8 (3.8%)	13 (6.6%)
Shunt embolization at 2 years	0 (0.0%)	-
Systemic embolization events at 2 years	0 (0.0%)	0 (0.0%)
BARC type 3 bleeding at 30 days	2 (0.8%)	-

- **Cerebrovascular & PE event rates numerically higher in the Shunt group**
- **MI rate numerically higher in the Control group**

RELIEVE-HF Primary Effectiveness Endpoint

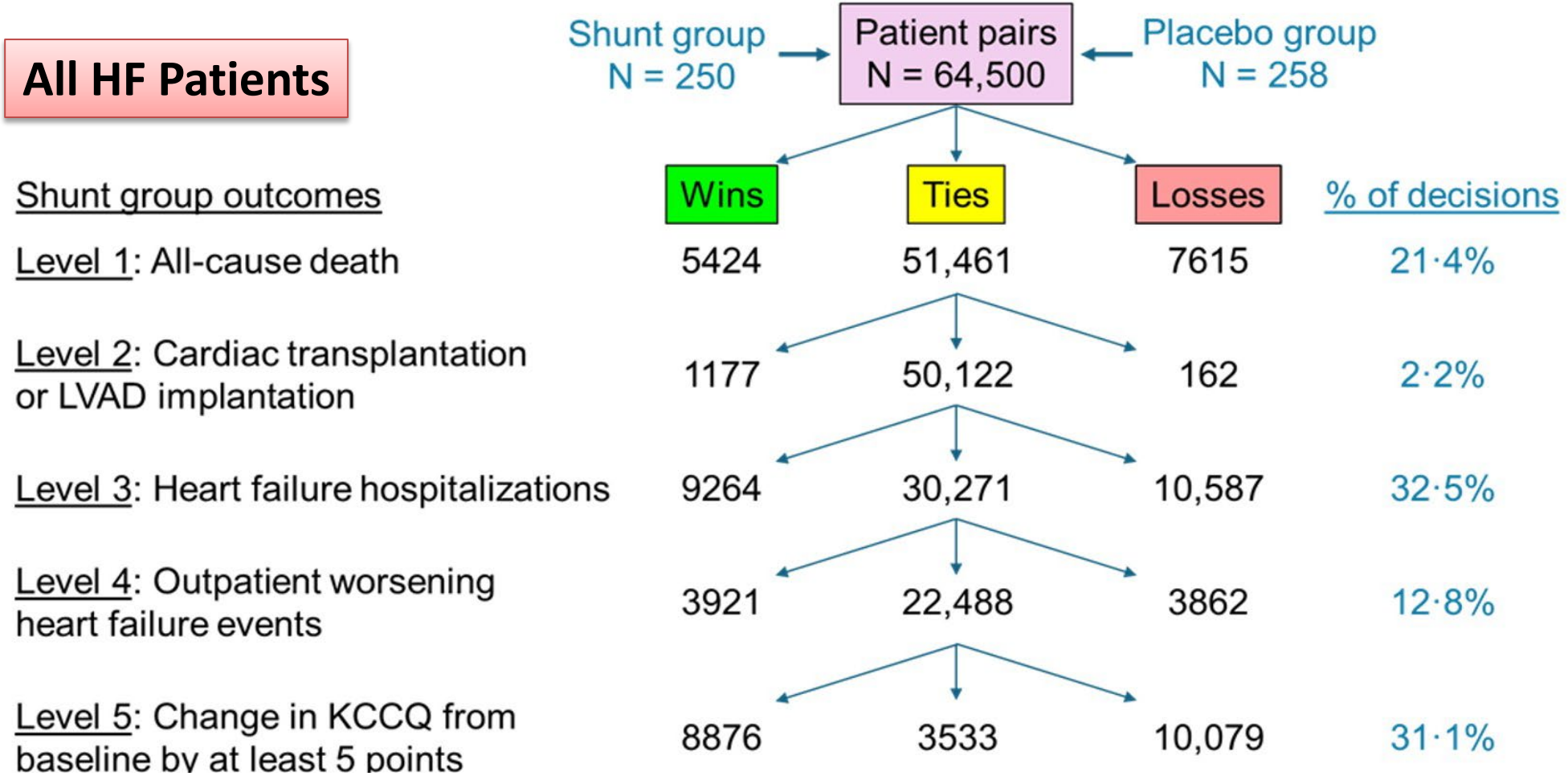
Hierarchical composite of:

1. All-cause death
2. Cardiac transplant or LVAD implantation
3. All heart failure hospitalizations (HFH)
4. All outpatient worsening HF (WHF) events; and
5. KCCQ score change

Hierarchical composite analyzed by the Finkelstein-Schoenfeld method and calculating a win ratio

Primary Effectiveness Endpoint Win Ratio, All Randomized Subjects

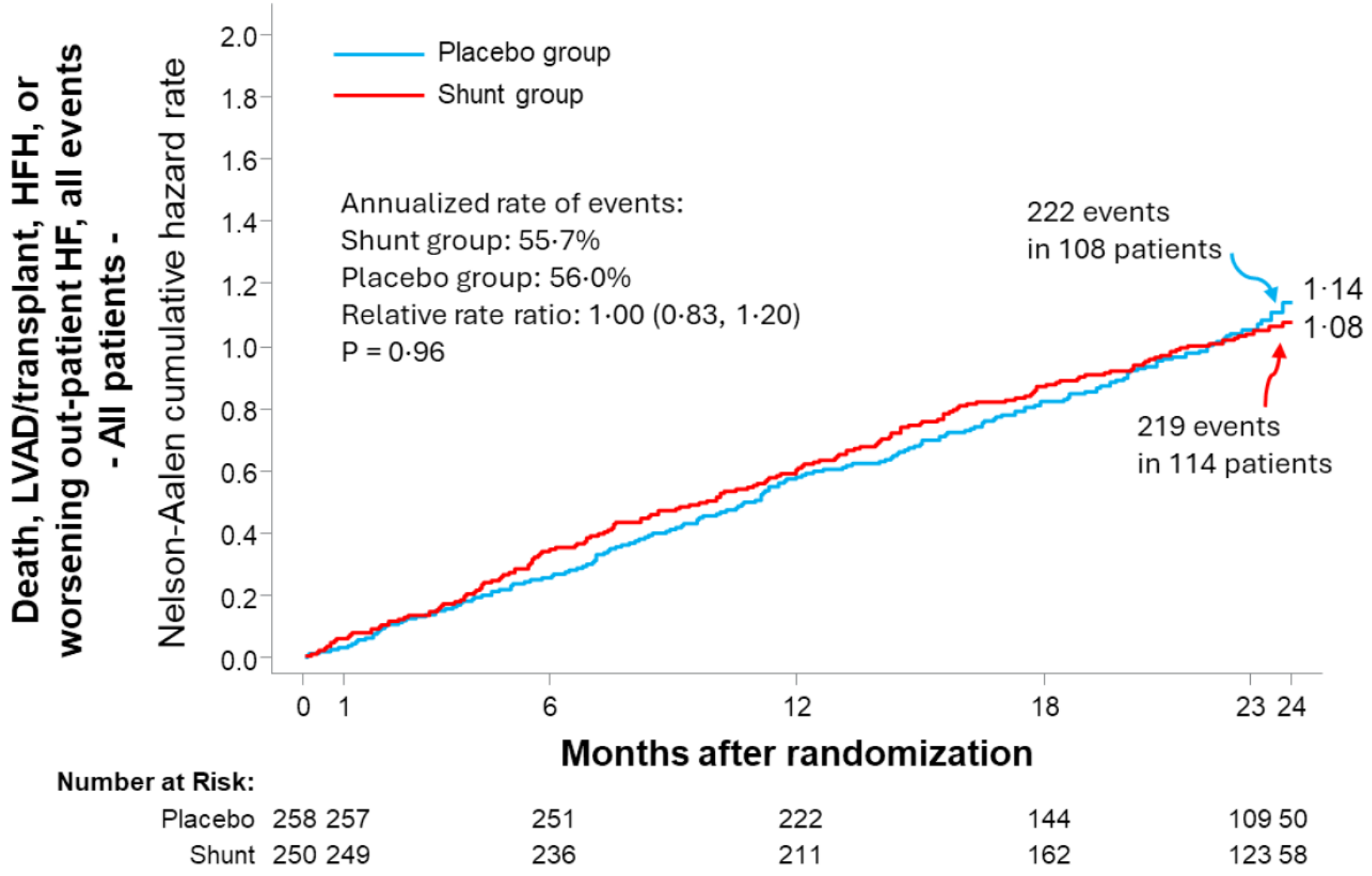
All HF Patients



Win ratio 0.86, 95% CI 0.61 to 1.22, p = 0.20

The primary effectiveness endpoint was not met

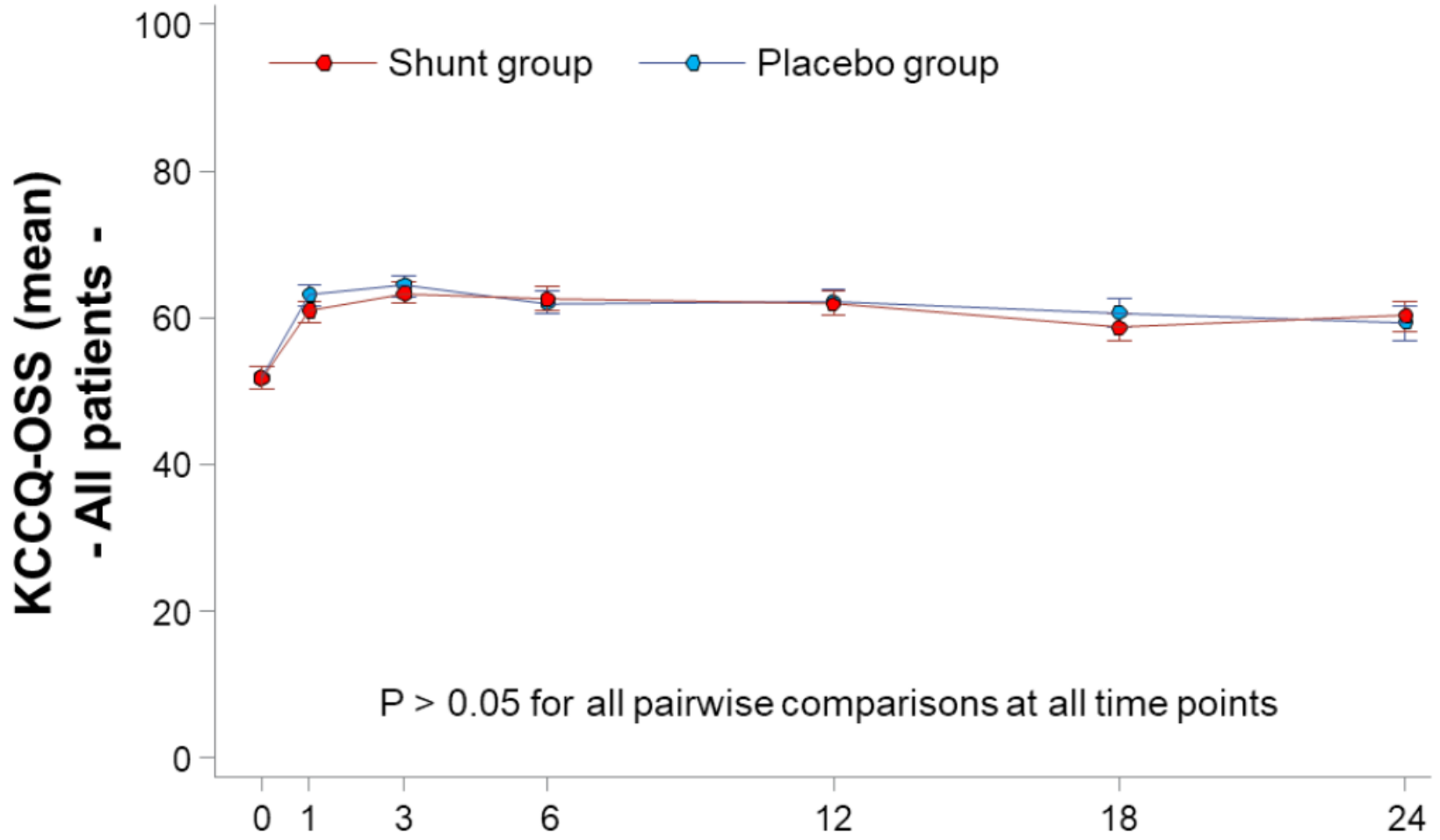
Post Hoc Cumulative Event Analysis Through 2 Years, All Randomized Subjects



Individual Component Rates of the Primary Effectiveness Endpoint
All Randomized Subjects at Longest Follow-up

	Shunt group	Control group	Relative risk
All-cause death	35 (15.6%)	27 (13.7%)	1.31 [0.79, 2.16]
Cardiac transplantation or LVAD	1 (0.6%)	6 (3.4%)	0.17 [0.02, 1.38]
All HFHs, no. of events/total no. of patient-yrs (annualized rate)	128/392.7 (32.6%)	125/396.1 (31.6%)	1.09 [0.79, 1.50]
All worsening outpatient HF events, no. of events/total no. of patient-yrs (annualized rate)	55/392.7 (14.0%)	64/396.1 (16.2%)	0.88 [0.61, 1.26]

KCCQ Score Change Through 2 Years, All Randomized Subjects



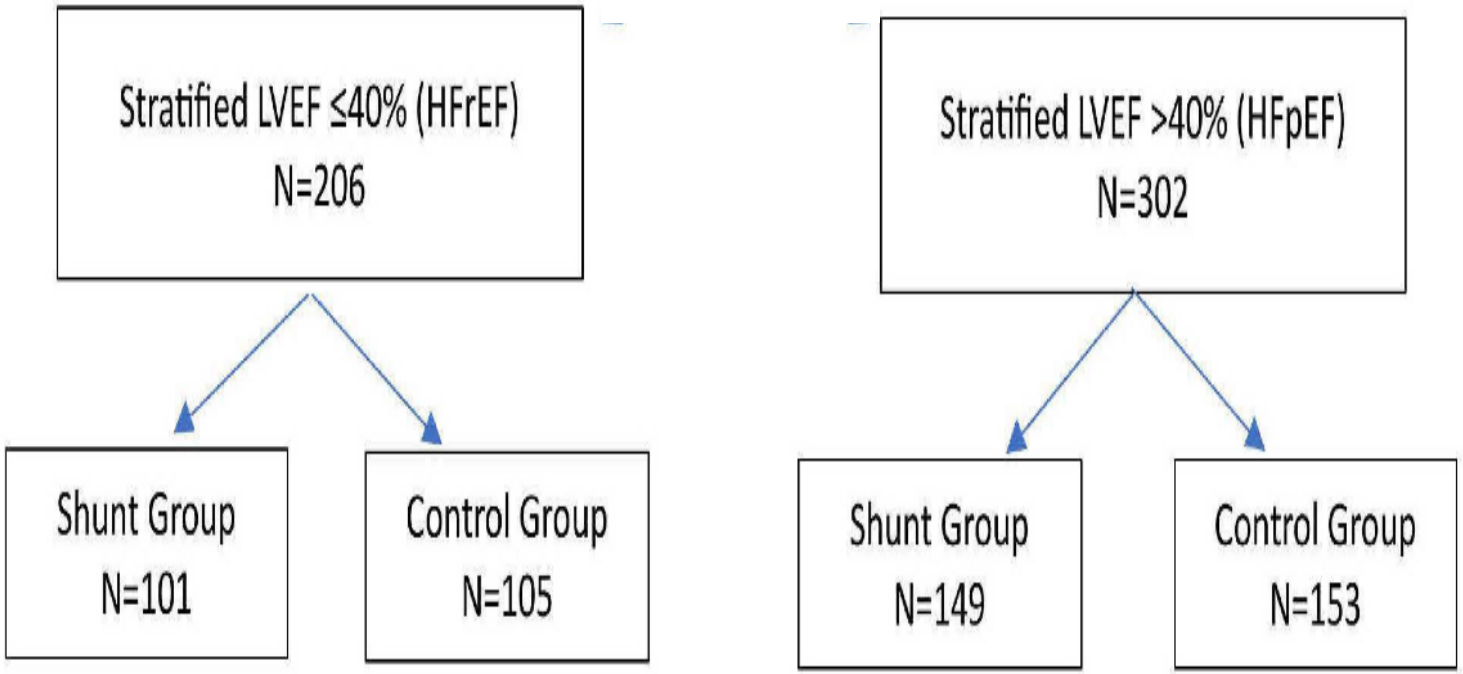
Number of measurements							
Placebo	258	252	243	238	226	143	106
Shunt	250	244	236	227	221	156	121

Primary Effectiveness Endpoint Summary
All Randomized Subjects

- Primary effectiveness endpoint was not met and no signal of Shunt benefit in the primary effectiveness endpoint results.
- Rates for the composite endpoint components of death, cardiac transplantation/LVAD, all HFHs, and all worsening outpatient HF event rates generally similar between treatment groups and at all timepoints through 2 years
  - Between group differences groups were small
    - All-cause death and HFH rates numerically favored the Control group, while cardiac transplantation/LVAD and worsening outpatient HF event rates favored the Shunt group
- Changes in KCCQ score similar between the Shunt and Control groups

HF Phenotype Subgroup Analyses
HFrEF (LVEF ≤40%) vs. HFpEF (LVEF >40%)

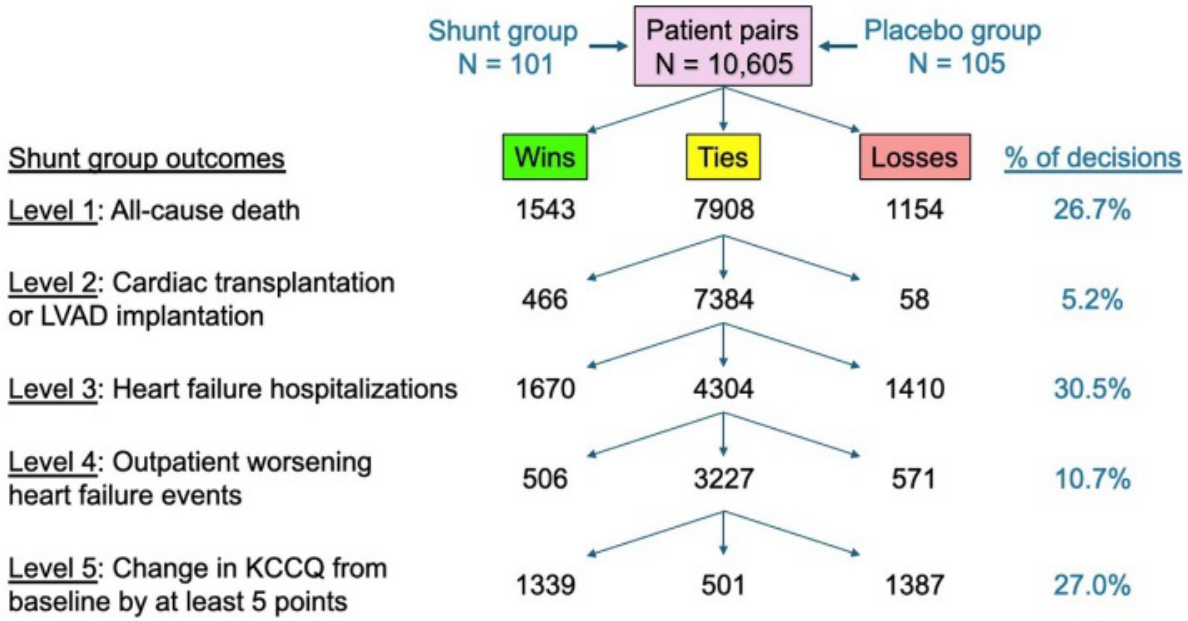
Randomization stratified by site and baseline TTE LVEF (determined by Echo Core Lab)



Primary Effectiveness Endpoint Stratified by HF Phenotype

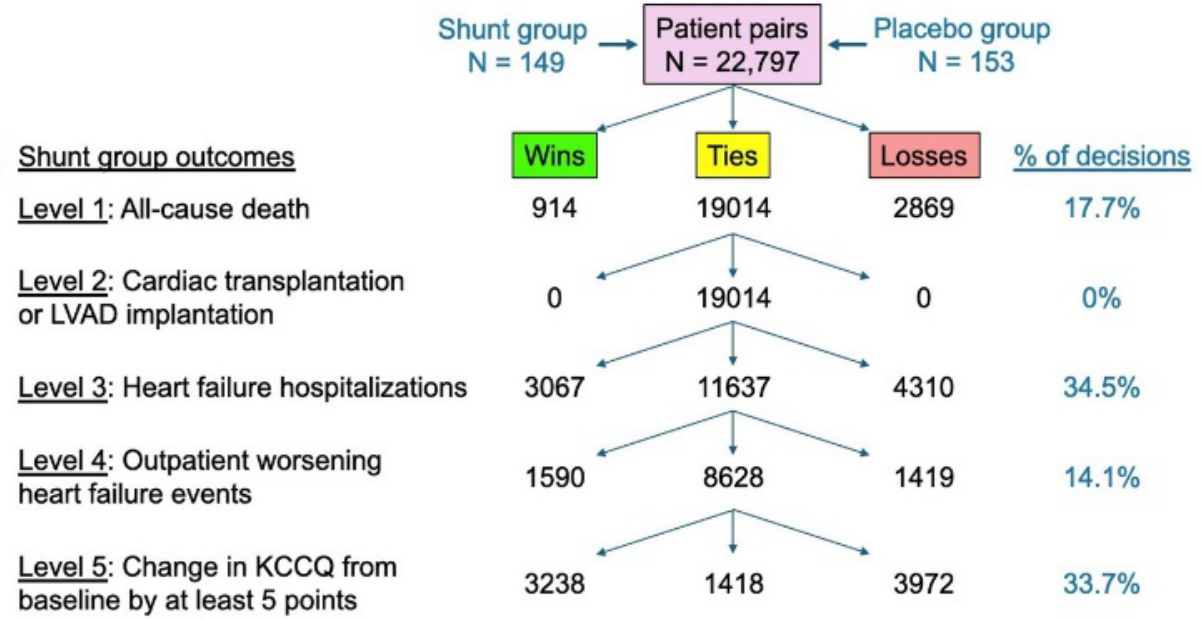
HF Phenotype Win Ratio Analysis Interaction

HFrEF, LVEF ≤40% (N = 206)



Win ratio = 1.40 (95% CI 0.80 to 2.46)

HFpEF, LVEF >40% (N = 302)



Win ratio = 0.61 (95% CI 0.39 to 0.98)

Interaction p-value = 0.0146

Other Subgroup Analyses and Interaction Test Results

Subgroup		Win Ratio	P
Age	≤median, 266	1.02 [0.77-1.37]	0.14
	>median, 242	0.74 [0.55-1.01]	
Sex	Male, 319	0.94 [0.72-1.21]	0.50
	Female, 189	0.81 [0.58-1.13]	
BMI	≤median, 256	0.82 [0.61-1.09]	0.44
	>median, 252	0.96 [0.72-1.28]	
Diabetes	Present, 249	0.96 [0.72-1.28]	0.47
	Absent, 259	0.82 [0.62-1.10]	
HTN	Present, 425	0.86 [0.69-1.08]	0.59
	Absent, 83	1.01 [0.60-1.69]	

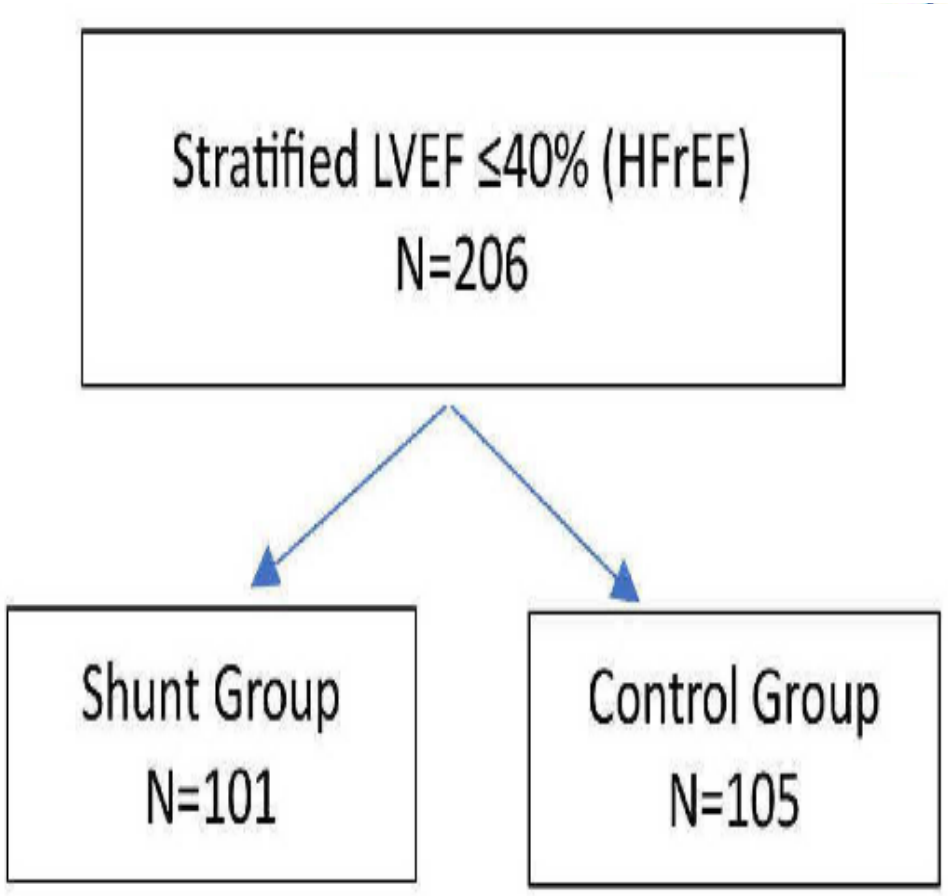
Subgroup		Win Ratio	P
CMP	Ischemic, 234	1.10 [0.82-1.49]	0.14
	Non-ischemic, 274	0.73 [0.55-0.97]	
Geo	US, 250	0.96 [0.72-1.29]	0.46
	OUS, 258	0.83 [0.62-1.10]	
NYHA	Class II/III, 506	0.88 [0.72-1.08]	NA
	Class IV, 2	NA	
BNP/NT-proBNP	≤median, 254	0.88 [0.66-1.19]	0.85
	>median, 253	0.92 [0.69-1.23]	
Prior COVID-19	Yes, 128	1.04 [0.69-1.56]	0.36
	No, 380	0.84 [0.66-1.06]	

Subgroup		Win Ratio	P
Baseline 6MWT	≤median, 254	0.84 [0.63-1.11]	0.58
	>median, 254	0.94 [0.70-1.26]	
Baseline KCCQ	≤median, 254	0.78 [0.58-1.04]	0.15
	>median, 254	1.05 [0.79-1.41]	
LVEF	HFrEF, 206	1.21 [0.87-1.67]	0.0146
	HFpEF, 302	0.70 [0.54-0.92]	
Baseline eGFR	≤median, 254	0.67 [0.50-0.89]	0.006
	>median, 254	1.20 [0.89-1.60]	

Outline

- RELIEVE-HF Results – All Randomized Subjects
- RELIEVE-HF HFrEF Subgroup Results
- RELIEVE-HF HFpEF Subgroup Results
- Pathophysiologic Insights
- RELIEVE-HF Strengths, Limitations, and Benefit-Risk considerations

HFrEF (LVEF ≤40%) Subgroup Analyses



HFrEF Subgroup Baseline Demographic & Clinical Characteristics

	Shunt group, N = 101	Control group, N = 105
Age, years	69.8±11.1	66.5 ± 10.6
Male	84 (83.2%)	84 (80.0%)
Caucasian	91 (90.1%)	93 (88.6%)
Body mass index, kg/m^2	29.1 ± 5.4	30.4.2 ± 5.7
Duration of heart failure, months	97.4 ± 80.5	98.0 ± 82.9
Diabetes mellitus	50 (49.5%)	55 (52.4%)
Hypertension	81 (80.2%)	80 (76.2%)
Hyperlipidemia	80 (79.2%)	75 (71.4%)
CAD	77 (76.2%)	76 (72.4%)
Ischemic cardiomyopathy	65 (64.4%)	64 (61.0%)
Non-ischemic cardiomyopathy	36 (35.5%)	41 (39.0%)
Current or previous smoker	61 (60.4%)	60 (57.1%)
COPD	18 (17.8%)	20 (19.0%)
At least one HFH in the prior year	55 (54.5%)	53 (50.5%)
Baseline rhythm AFib or flutter	27 (26.7%)	19 (18.1%)
NYHA class III	97 (96.0%)	99 (94.3%)
KCCQ summary score	56.0 (35.9, 72.1)	54.2 (39.1, 69.8)
Six-minute walk distance, m	295 (216, 355)	263 (204, 345)
BNP (pg/ml)	301 (203, 751)	319 (155,651)
NT-ProBNP (pg/ml)	2231 (1300, 3944)	1867(954, 3772)
eGFR <60 ml/min/1.73 m2	76 (75.2%)	74 (70.5%)

HFrEF Subgroup Baseline HF Medical and Electronic Rhythm Therapies

	Shunt group, N = 101	Control group, N = 105
Beta-blockers	99 (98.0%)	101 (96.2%)
RAS inhibitors	95 (94.1%)	93 (88.6%)
-ACEi	7 (6.9%)	7 (6.7%)
-ARB	8 (7.9%)	7 (6.7%)
-ARNi	80 (79.2%)	79 (75.2%)
MRAs	74 (73.3%)	77 (73.3%)
Diuretics	93 (92.1%)	98 (93.3%)
SGLT-2 inhibitors	48 (47.5%)	56 (53.3%)
Vasodilators	8 (7.9%)	13 (12.4%)
- Long-acting nitrates	7 (6.9%)	11 (10.5%)
- Hydralazine	2 (2.0%)	8 (7.6%)
Antiplatelet agents	51 (50.5%)	52 (49.5%)
Chronic oral anticoagulation	63 (62.4%)	54 (51.4%)
ICD or CRT-D	89 (88.1%)	95 (90.5%)
CRT-D or CRT-P	49 (48.5%)	43(41.0%)

HFrEF Subgroup Medications at Baseline and 12 months

	Baseline		12 months	
	Shunt group (N = 101)	Control group (N = 105)	Shunt group (N = 101)	Control group (N = 105)
Beta-blockers	99 (98.0%)	101 (96.2%)	92 (100%)	91 (96.8%)
RAS inhibitors	95 (94.1%)	93 (88.6%)	87 (94.6)	84 (89.4%)
MRAs	74 (73.3%)	77 (73.3%)	66 (71.7%)	65 (69.1%)
SGLT-2 inhibitors	48 (47.5%)	56 (53.3%)	59 (64.1%)	56 (59.6%)
Vasodilators	8 (7.9%)	13 (12.4%)	10 (10.9%)	12 (12.8%)
-Long-acting nitrates	7 (6.9%)	11 (10.5%)	9 (9.8%)	8 (8.5%)
-Hydralazine	2 (2.0%)	8 (7.6%)	3 (3.3%)	8 (8.5%)
Diuretics	93 (92.1%)	98 (93.3%)	85 (92.4%)	83 (88.3%)
Antiplatelet agents	51 (50.5%)	52 (49.5%)	49 (53.3%)	49 (52.1%)
Oral anticoagulants	63 (62.4%)	54 (51.4%)	59 (64.1%)	56 (59.6%)

HFrEF Subgroup Baseline Transthoracic Echocardiography Parameters

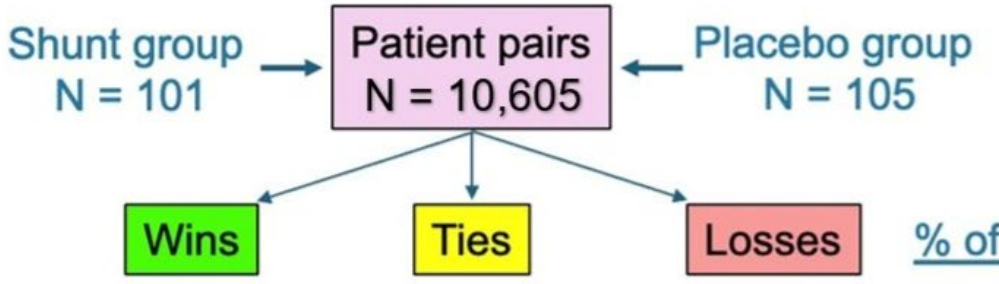
	HFrEF Shunt subgroup, N = 101	HFrEF Control subgroup, N = 105
LVEDV, ml	188.5 (155.5, 238.0)	187.5 (140.0, 249.5)
LVEDV, ml	131.0 (103.5, 167.5)	128.5 (92.5, 184.0)
LVEF, %	31.1 (24.9, 35.4)	30.2 (23.8, 34.8)
LA volume, ml	84.5 (65.5, 109.5)	77.5 (61.5, 104.0)
Stroke volume, ml	54.0 (42.0, 67.0)	51.0 (45.0, 62.0)
Stroke volume index, mUm^2	26.9 (21.4, 33.3)	24.7 (21.0, 31.5)
Cardiac output, L/min	3.76 (2.95, 4.66)	3.76 (3.05, 4.66)
Cardiac index, L/min/m^2	1.89 (1.56, 2.30)	1.77 (1.46, 2.28)
RV fractional area change,%	36.8 (32.0, 41.7)	35.0 (31.6, 40.0)
Tricuspid annular plane systolic excursion, mm	16.0 (13.0, 19.0)	15.0 (14.0, 18.0)
PA systolic pressure, mmHg	29.5 (22.0, 39.0)	32.0 (25.0, 41.0)
TR moderate or greater	12/98 (12.2%)	17 (16.2%)
RV end-diastolic area index, cm^2/m^2	10.4 (8.7, 12.4)	10.9 (9.0, 13.5)
IVC diameter max, cm	1.6 (1.2, 1.9)	1.6 (1.2, 2.0)
MR moderate or greater	**24 (23.8%)**	19 (18.1%)

HFrEF Subgroup Baseline Right Heart Catheterization Data

	HFrEF Shunt subgroup, N = 101	HFrEF Control subgroup, N = 105
Heart rate, bpm	69.9 ± 12.4	69±10.2
SBP, mmHg	112.9 ± 17.4	111.1 ± 17.1
DBP, mmHg	65.5 ± 12.3	65.8 ± 10.0
Mean RA pressure, mmHg	8.9 ± 4.2	9.3 ± 4.4
PA systolic pressure, mmHg	37.0 ± 10.8	39.6 ± 12.3
Mean PAP, mmHg	25.6 ± 7.7	27.1 ±8.6
PVR, Wood units	2.3 ± 1.3	2.4 ± 1.4
PCWP, mmHg	16.4 ± 6.6	17.2 ± 6.9
Cardiac output, L/min	4.5 ± 1.4	4.6 ± 1.6
Cardiac index, L/min/m2	2.2 ± 0.6	2.3 ± 0.7

HFrEF Subgroup Primary Effectiveness Endpoint

LVEF ≤40%

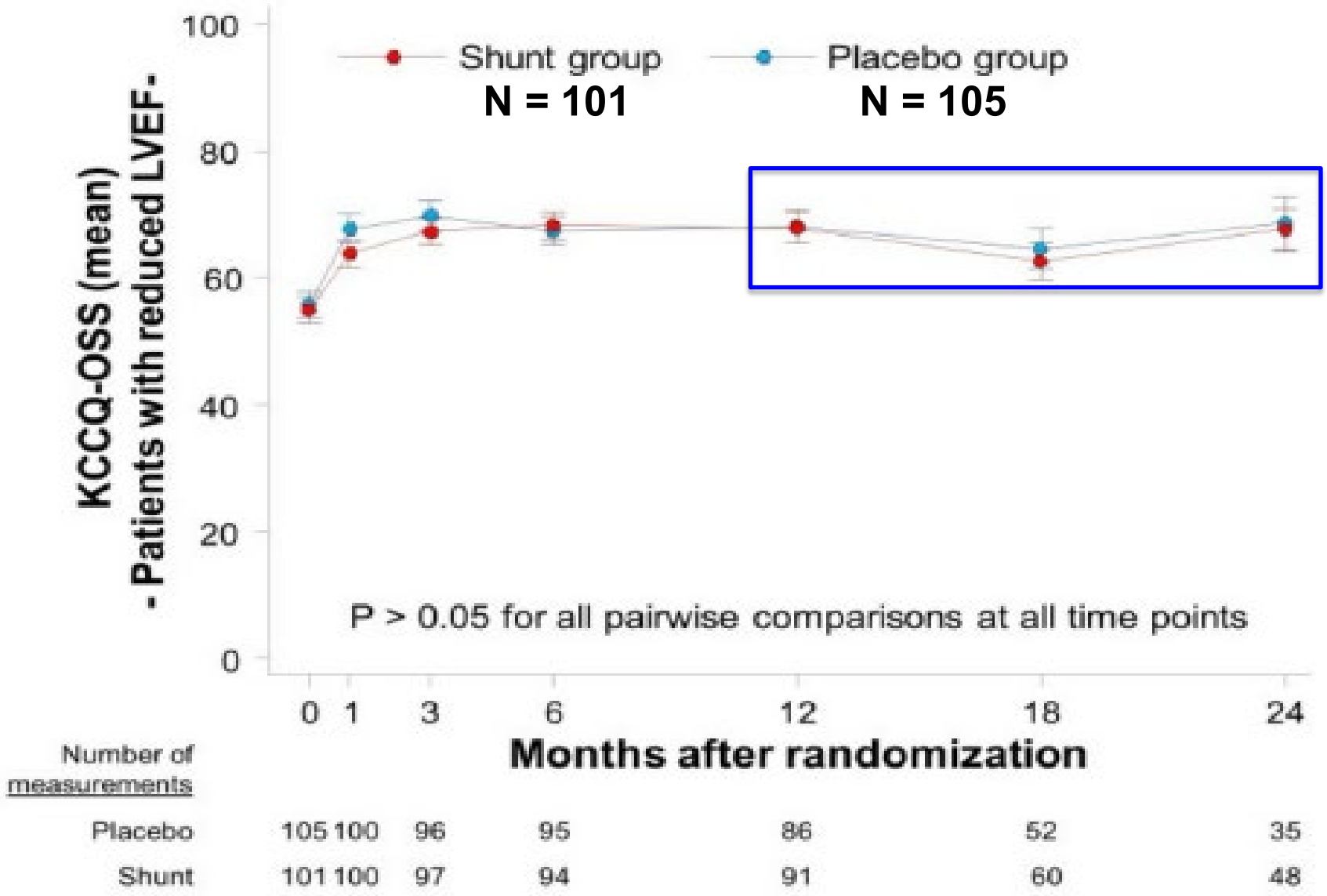


Shunt group outcomes	Wins	Ties	Losses	% of decisions
Level 1: All-cause death	1543	7908	1154	26.7%
Level 2: Cardiac transplantation or LVAD implantation	466	7384	58	5.2%
Level 3: Heart failure hospitalizations	1670	4304	1410	30.5%
Level 4: Outpatient worsening heart failure events	506	3227	571	10.7%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

Win ratio 1.40, 95% CI 0.80 to 2.46

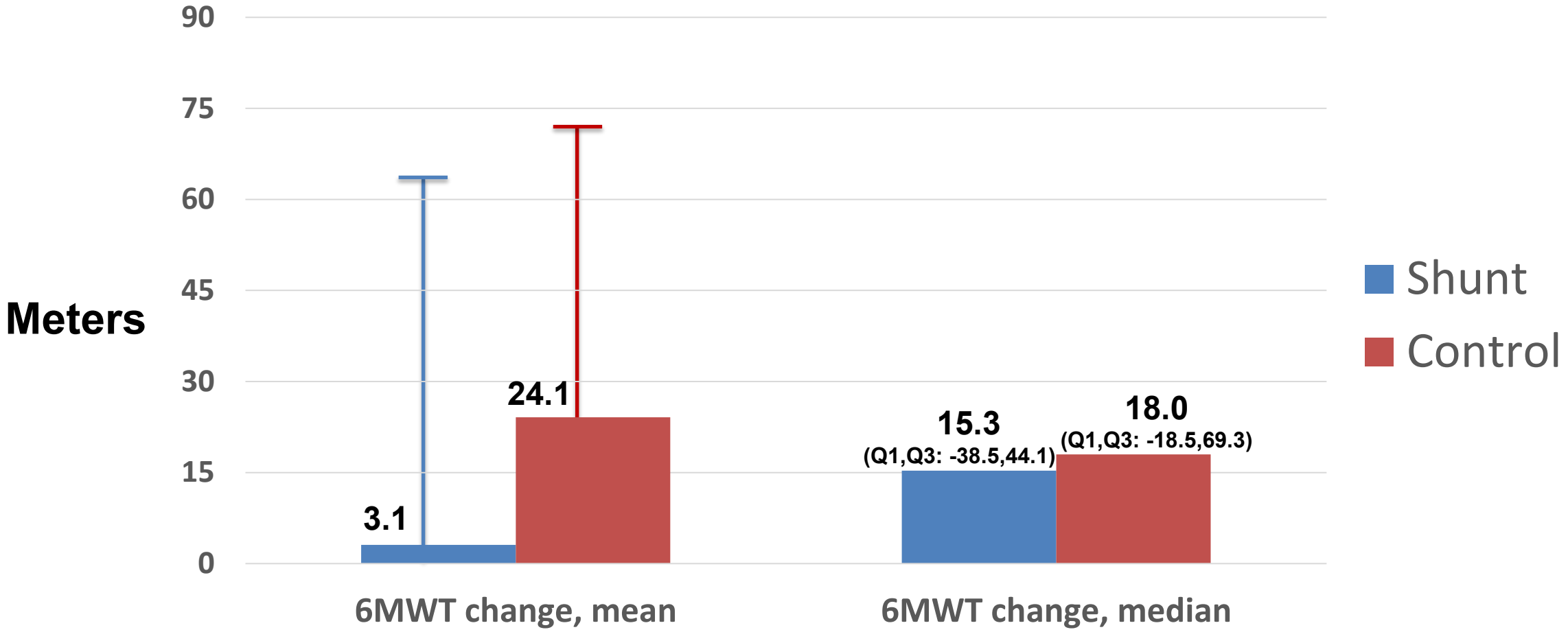
95% CI: Indeterminate conclusion regarding the Shunt's benefit-risk in HFrEF patients

HFrEF Subgroup KCCQ Score Analysis



KCCQ Change to 1-year	
Shunt	Control
12.2 ± 20.5	11.4 ± 20.5

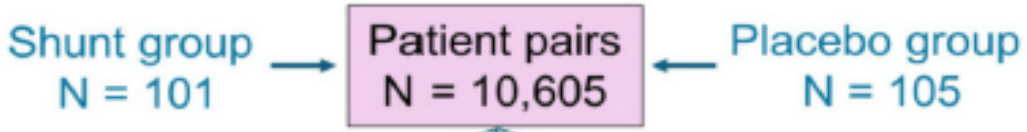
HFrEF Subgroup 6-Minute Walk Test
Changes from Baseline to 12-Months



>25% of the 12-month FU data was missing due to COVID

HFrEF Subgroup Primary Effectiveness Endpoint Excluding KCCQ

LVEF ≤40%



Shunt group outcomes	Wins	Ties	Losses	% of comparisons
Level 1: All-cause death	1543	7908	1154	25.4%
Level 2: Cardiac transplantation or LVAD implantation	466	7384	58	4.9%
Level 3: Heart failure hospitalizations	1670	4304	1410	29.0%
Level 4: Outpatient worsening heart failure events	506	3227	571	10.2%
			Ties	30.4%

Win ratio 1.31, 95% CI 0.87 to 1.97

95% CI: Indeterminate conclusion regarding the Shunt's benefit-risk in the HFrEF subgroup when KCCQ score change removed from the primary effectiveness endpoint

HFrEF Subgroup Mortality Analysis

- 13 deaths (14.3%) in the Shunt group vs. 20 deaths (26.8%) in the Control group (unadjusted p-value 0.19).
- CEC adjudication
  - 11 cardiovascular (CV) deaths in the Shunt group vs. 12 CV deaths in the Control group
  - 1 non-CV death in the Shunt group (neurologic death) and 6 non-CV deaths in the Control group (malignancy 2, infection 2, trauma 1 and pulmonary 1).

Cause of death	Shunt group	Control group
All cause	13	20
Cardiovascular	11	12
Non-Cardiovascular	1	6
Unknown	1	2

HFrEF Subgroup Event Rates of Individual Components of the Primary Effectiveness Endpoint

	Shunt group (N=101)	Control group (N=108)	RR or HR [95% CI]
All events	76/155.2 (49.0%/year)	134/151.2 (88.6%/year)	0.55 [0.42,0.73]
All-cause Death	13 (14.3%)	20 (26.8%)	0.63 [0.31,1.26]
LVAD/HT	1 (1.5%)	6 (9.0%)	0.16 [0.02,1.32]
All HFHs	41/155.2 (26.4%/year)	78/151.2 (51.6%/year)	0.52 [0.31,0.86]
All out-pt WHFs	21/155.2 (13.5%/year)	30/151.2 (19.8%/year)	0.70 [0.39,1.23]

HFrEF Subgroup Recurrent HF Event Analysis

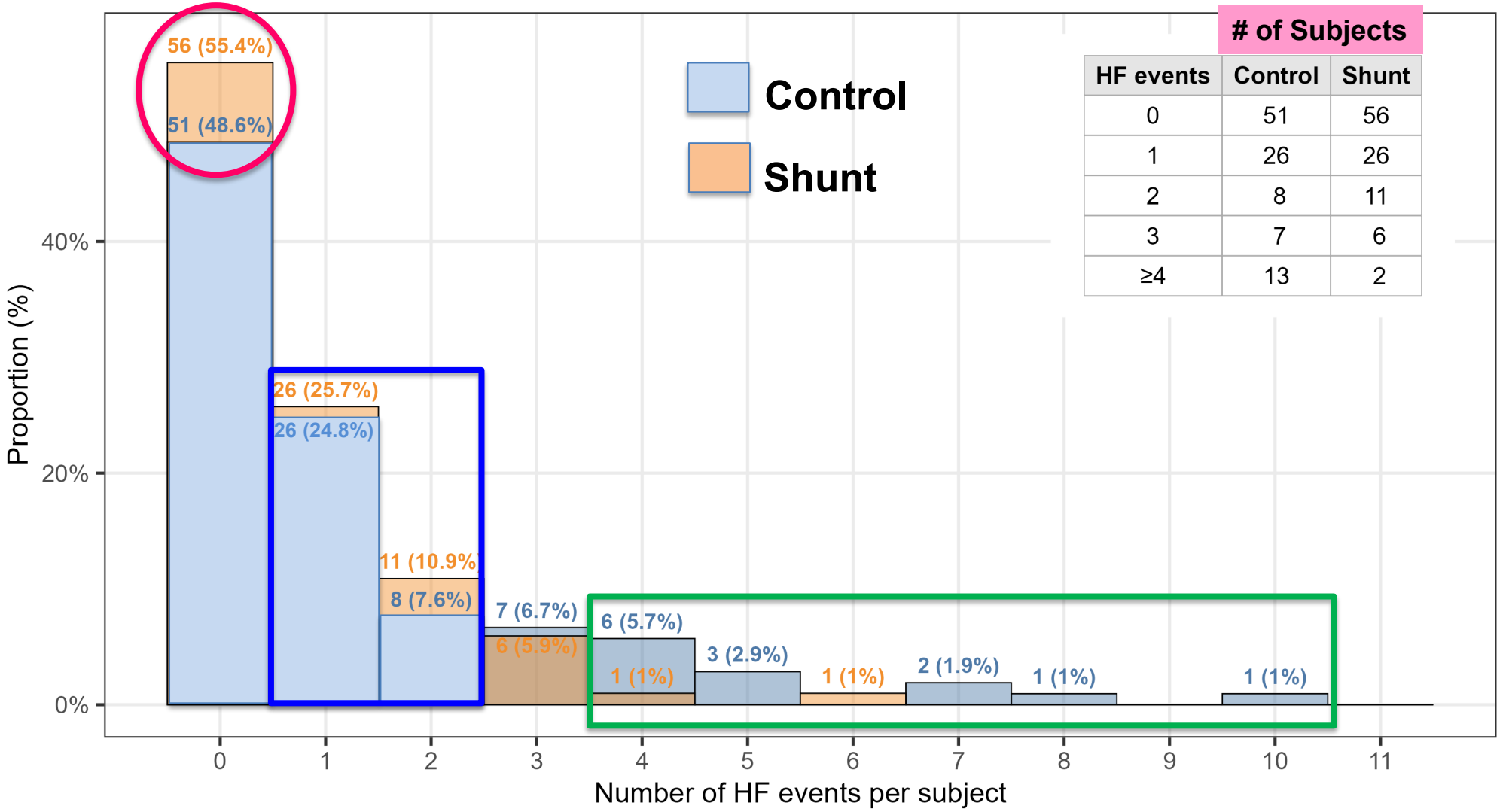
- The sponsor noted that for HF Events (HFH and worsening out-patient HF events), Shunt patients had generally fewer first events vs. Controls (54 vs. 69 first HF events, respectively)
- However, the frequency of recurrent HF events was disproportionally greater in Control subjects vs. Shunt subjects (74 vs. 34 recurrent HF events, respectively)
- In an additional post-hoc analysis, the Sponsor noted a trend favoring the Shunt for time-to-first event methods and a nominally significant difference for two recurrent event assessments of HFH (joint frailty model and Nelson-Aalen estimator)

	Shunt, N = 101	Control, N = 105	Difference, HR, HRR, RR, or Win Ratio [95% CI]
Time-to-first heart failure hospitalization, K-M estimate	28.7%	41.7%	HR 0.68 [0.41, 1.12]
HFH adjusted for all-cause mortality, joint frailty model	0.29	0.56	HR 0.52 [0.31, 0.86]
Cumulative HFHs at study duration, Nelson-Aalen estimator	0.52	1.13	HRR 0.46 [0.29, 0.69]

HFrEF Subgroup Recurrent HF Events: FDA Analysis

Distribution of HF-Event Counts per Subject (HFrEF only)

Overlapping histograms by arm; includes subjects with 0 HF events



# of Subjects

HF events	Control	Shunt
0	51	56
1	26	26
2	8	11
3	7	6
≥4	13	2

HFrEF Subgroup Recurrent HF Events: FDA Sensitivity Analysis

We compared original analyses of the hierarchically-tested secondary effectiveness endpoints with results obtained after removing 4 HFrEF control group subjects with the most HF events

Hierarchically Tested Secondary Effectiveness Endpoints	Difference, HR, HRR, RR, or Win Ratio (95% CI)	
	Original	4 Subjects Removed
1. KCCQ changes from Baseline to 12 months	Difference 0.4 (-5.3, 6.1)	Difference -5.3 (-14.5, 3.8)
2. HFH adjusted for all-cause mortality	**HR 0.52 (0.31, 0.86)**	**HR 0.68 (0.42, 1.10)**
3. All-cause death, LVAD/Transplant, or HFH	HR 0.71 (0.45, 1.11)	HR 0.76 (0.48, 1.19)
4. All-cause death or first HFH	HR 0.72 (0.46, 1.13)	HR 0.77 (0.49, 1.22)
5. Cumulative heart failure hospitalizations	**HRR 0.46 (0.29, 0.69)**	**HRR 0.70 (0.44, 1.09)**
6. HFH	HR 0.68 (0.41, 1.12)	HR 0.74 (0.44, 1.24)
7. Modified Primary Effectiveness Endpoint	WR 1.31 (0.87, 1.97)	WR 1.24 (0.82, 1.88)

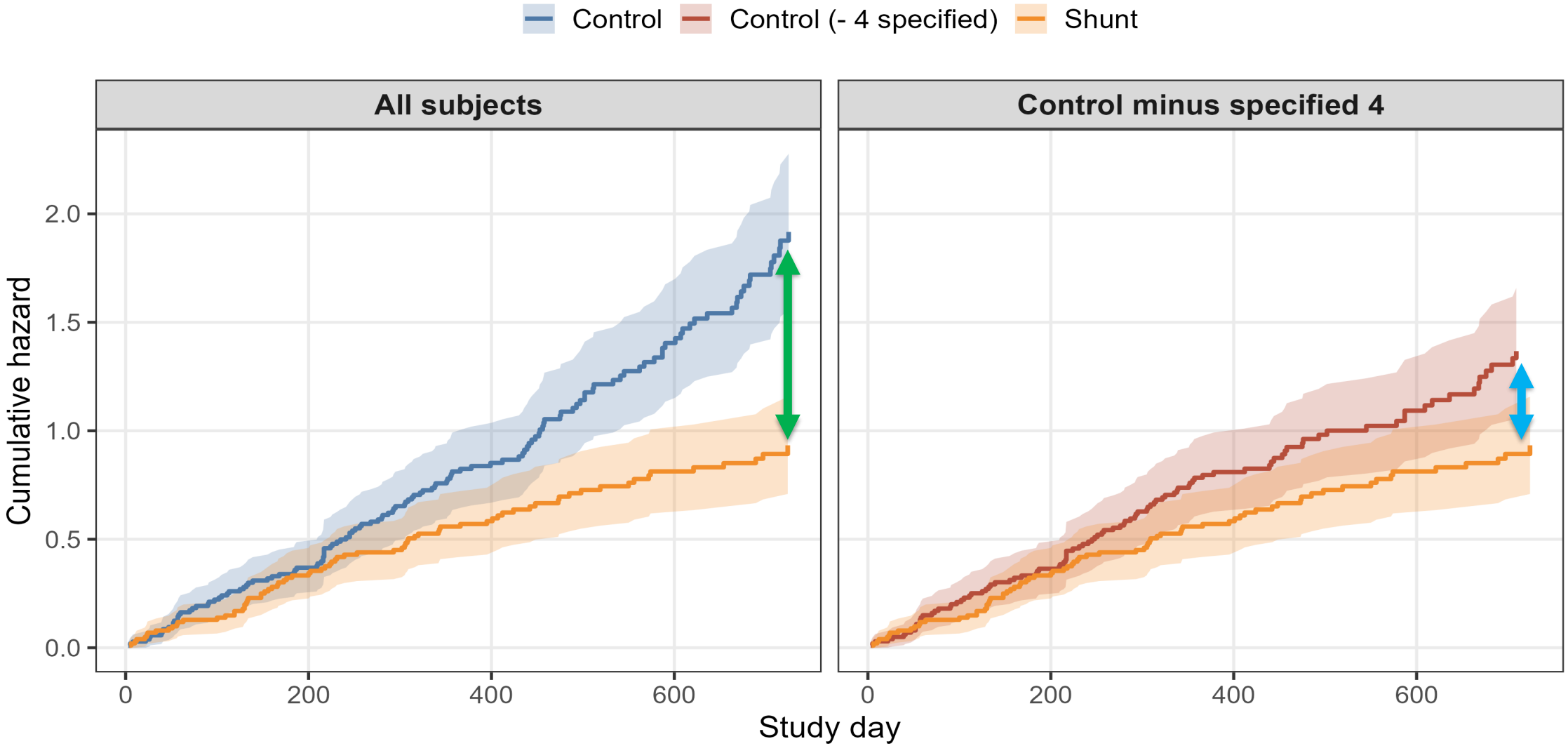
- Originally, HFH adjusted for all-cause mortality and cumulative HFHs had nominally significant HRs favoring the Shunt group
- After removing the 4 control subjects, Shunt benefit no longer statistically significant; HRs shift toward unity

Pattern suggests that a small number of influential control subjects may have disproportionately affected the observed analysis results

HFrEF Subgroup Recurrent HF Events: FDA Sensitivity Analysis

Cumulative Hazard (Nelson–Aalen) with 95% CI — HFrEF

Left: Shunt vs Control (all) | Right: Shunt vs Control (Control minus 4 specified subjects)



HFrEF Subgroup Recurrent HF Events: FDA Sensitivity Analysis

Outcome		Nelson Aalen Hazard Rate (95% CI)	
		Original	4 Subjects Removed
Single Event Types	All-Cause Death	0.48 (0.20, 1.07)	0.63 (0.25, 1.42)
	Heart Transplant/LVAD (HT/LV)	0.15 (0.00, 0.98)	0.15 (0.00, 0.97)
	Hospitalization for HF (HFH)	0.46 (0.29, 0.68)	0.70 (0.44, 1.09)
	Hospitalization not for HF (NHFH)	0.76 (0.54, 1.07)	0.83 (0.58, 1.19)
	All-Cause Hospitalization (ACH)	0.61 (0.47, 0.79)	0.78 (0.59, 1.02)
	Worsening HF Outpatient (WHF)	0.64 (0.33, 1.17)	0.85 (0.43, 1.67)
Composite Event Types	Terminal Events (All-cause Death, HT/LV)	0.42 (0.18, 0.84)	0.50 (0.21, 1.02)
	WHF and HFH	0.51 (0.35, 0.70)	0.74 (0.51, 1.06)
	All-cause Death, HT/LV, HFH	0.45 (0.31, 0.63)	0.64 (0.43, 0.92)
	All-cause Death, HT/LV, ACH	0.58 (0.45, 0.74)	0.73 (0.57, 0.95)
	HF Events (All-cause Death, HT/LV, HFH, WHF)	0.49 (0.35, 0.65)	0.68 (0.49, 0.94)
	All Events (All-cause Death, HT/LV, ACH, WHF)	0.59 (0.47, 0.73)	0.75 (0.59, 0.95)

HFrEF Subgroup Recurrent HF Events Sensitivity Analysis

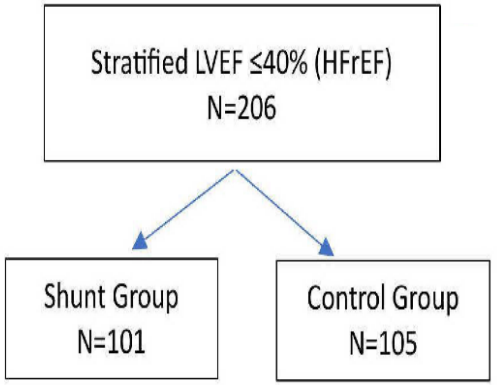
- The sponsor's argument for symmetric study subject trimming as a more "fair" approach misinterprets the intent of FDA's sensitivity analysis
- The FDA approach is asymmetric and biased in favor of the control group
- Results show that nominal statistical significance can be impacted by as few as 4 extreme patients with the most heart-failure events

Post-Hoc Subgroup Analyses Between LVEF Subgroup Phenotypes

		Hazard Rate (95% CI)		Nominal Interaction P-value
		HFrEF	HRpEF	
Single Event Types	All-Cause Death	0.49 (0.20, 1.11)	3.37 (1.47, 13.0)	0.005
	Heart Transplant/LVAD (HT/LV)	0.16 (0.00, 1.10)	–	-
	Hospitalization for HF (HFH)	0.46 (0.29, 0.69)	2.05 (1.41, 3.15)	<0.001
	Hospitalization not for HF (NHFH)	0.76 (0.53, 1.07)	1.61 (1.26, 2.06)	<0.001
	All-Cause Hospitalization (ACH)	0.61 (0.47, 0.79)	1.71 (1.41, 2.10)	<0.001
	Worsening HF Outpatient (WHF)	0.64 (0.33, 1.18)	1.14 (0.65, 1.96)	0.25
Composite Event Types	Terminal Events (All-cause Death, HT/LV)	0.42 (0.18, 0.86)	3.37 (1.47, 13.0)	0.002
	WHF and HFH	0.51 (0.35, 0.70)	1.66 (1.23, 2.27)	<0.001
	All-cause Death, HT/LV, HFH	0.45 (0.30, 0.63)	2.22 (1.58, 3.23)	<0.001
	All-cause Death, HT/LV, ACH	0.58 (0.46, 0.74)	1.78 (1.46, 2.18)	<0.001
	HF Events (All-cause Death, HT/LV, HFH, WHF)	0.49 (0.36, 0.65)	1.79 (1.36, 2.40)	<0.001
	All Events (All-cause Death, HT/LV, ACH, WHF)	0.59 (0.47, 0.74)	1.64 (1.38, 1.99)	<0.001

- Analyses not prespecified and are post-hoc
- Most endpoints incorporated recurrent events
- Interaction findings not confirmed by alternative test methodology

HFrEF (LVEF ≤40%) Subgroup Analyses Summary



- No significant Shunt benefit in the 5-level win ratio or 4-level win ratio
- No reduced CV mortality associated with the Shunt
- No Shunt-associated KCCQ score positive effect size versus the control group
- Additional analyses suggest that the shunt was associated with a reduced HF event rate

Analyses showing statistically significant Shunt benefits in the HFrEF subgroup:

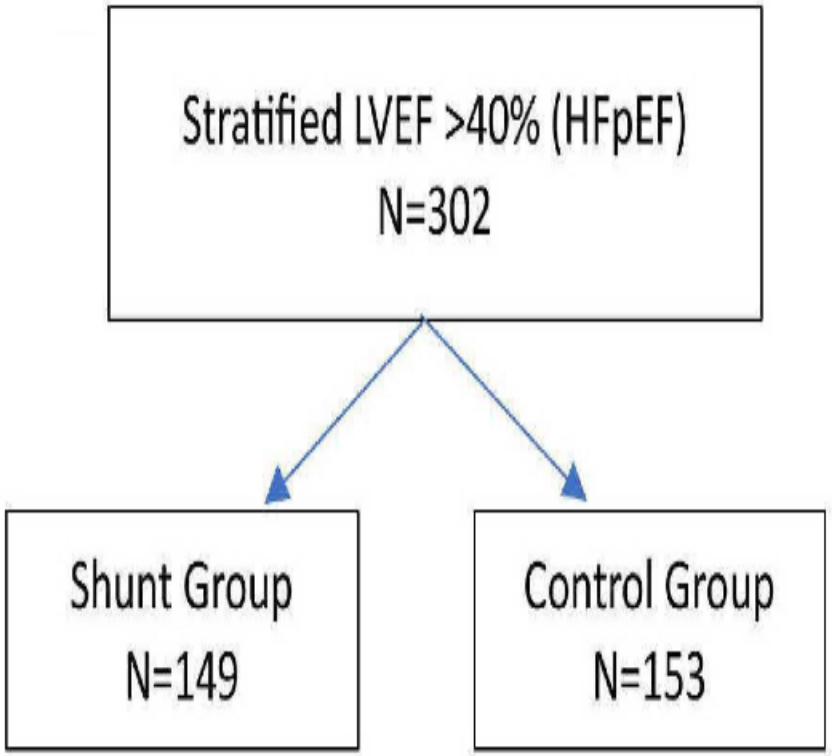
- Unplanned and post hoc
- Deviated from the prespecified plan to control type I error & have an unquantifiable type I error rate
- Apparent HF outcome differences favoring the Shunt in the HFrEF subgroup may have been driven by a few high-event Control subjects

Results may be considered hypothesis-generating and interpreted with caution

Outline

- RELIEVE-HF Results – All Randomized Subjects
- RELIEVE-HF HFrEF Subgroup Results
- RELIEVE-HF HFpEF Subgroup Results
- Pathophysiologic Insights
- RELIEVE-HF Strengths, Limitations, and Benefit-Risk considerations

HFpEF (LVEF >40%) Subgroup Analyses



HFpEF Subgroup Baseline Demographic & Clinical Characteristics

	Shunt group, N = 149	Control group, N = 153
Age, years	74.6 ± 8.6	73.0 ± 9.5
Female	71 (47.7%)	80 (52.3%)
Caucasian	139 (93.3%)	142 (92.8%)
Body mass index, kg/m^2	31.4±6.6	31.8 ± 6.3
Duration of heart failure, months	52.3 ±46.8	59.3 ± 58.5
Diabetes mellitus	74 (49.7%)	70 (45.8%)
Hypertension	128 (85.9%)	136 (88.9%)
Hyperlipidemia	121 (81.2%)	120 (78.4%)
CAD	92(61.7%)	84 (54.9%)
Current or previous smoker	72 (48.3%)	77 (50.3%)
COPD	25 (16.8%)	32 (20.9%)
lschemic cardiomyopathy	49 (32.9%)	56 (36.6%)
Non-ischemic cardiomyopathy	100 (67.1%)	97 (63.4%)
At least one HFH in the prior year	73 (49.0%)	74 (48.4%)
Prior myocardial infarction	46 (30.9%)	43 (28.1%)
Baseline rhythm AFib or flutter	49 (32.9%)	45 (29.4%)
NYHA class III	142 (95.3%)	152 (99.3%)
KCCQ summary score	49.0 (34.8, 64.3)	47.4 (32.3, 62.8)
Six-minute walk distance, m	240 (186,316)	275 (193, 321)
BNP, pg/ml	178 (105, 325)	177.5 (79,391)
NT-ProBNP, (pg/ml)	1654 (873, 2766)	1454 (779, 2544)
eGFR <60 ml/min/1.73 m^2	**112 (75.2%)**	114 (74.5%)

HFpEF Subgroup Baseline HF Medical and Electronic Rhythm Therapies

	Shunt group, N = 149	Control group, N = 153
Beta-blockers	125 (83.9%)	121 (79.1%)
RAS inhibitors	81 (54.4%)	92 (60.1%)
-ACEi	25 (16.8%)	31 (20.3%)
-ARB	31 (20.8%)	31 (20.3%)
-ARNi	25 (16.8%)	30 (19.6%)
MRAs	71 (47.7%)	97 (63.4%)
SGLT-2 inhibitors	45 (30.2%)	57 (37.3%)
Vasodilators	25 (16.8%)	21 (13.7%)
- Long-acting nitrates	22 (14.8%)	14 (9.2%)
- Hydralazine	8 (5.4%)	12 (7.8%)
Diuretics	137 (91.9%)	141 (92.2%)
Antiplatelet agents	55 (36.9%)	59 (38.6%)
Chronic oral anticoagulation	89 (59.7%)	87 (56.9%)
ICD or CRT-D	26 (17.4%)	28 (18.3%)
CRT-D or CRT-P	21 (14.1%)	16 (10.5%)

HFpEF Subgroup Baseline Transthoracic Echocardiography Parameters

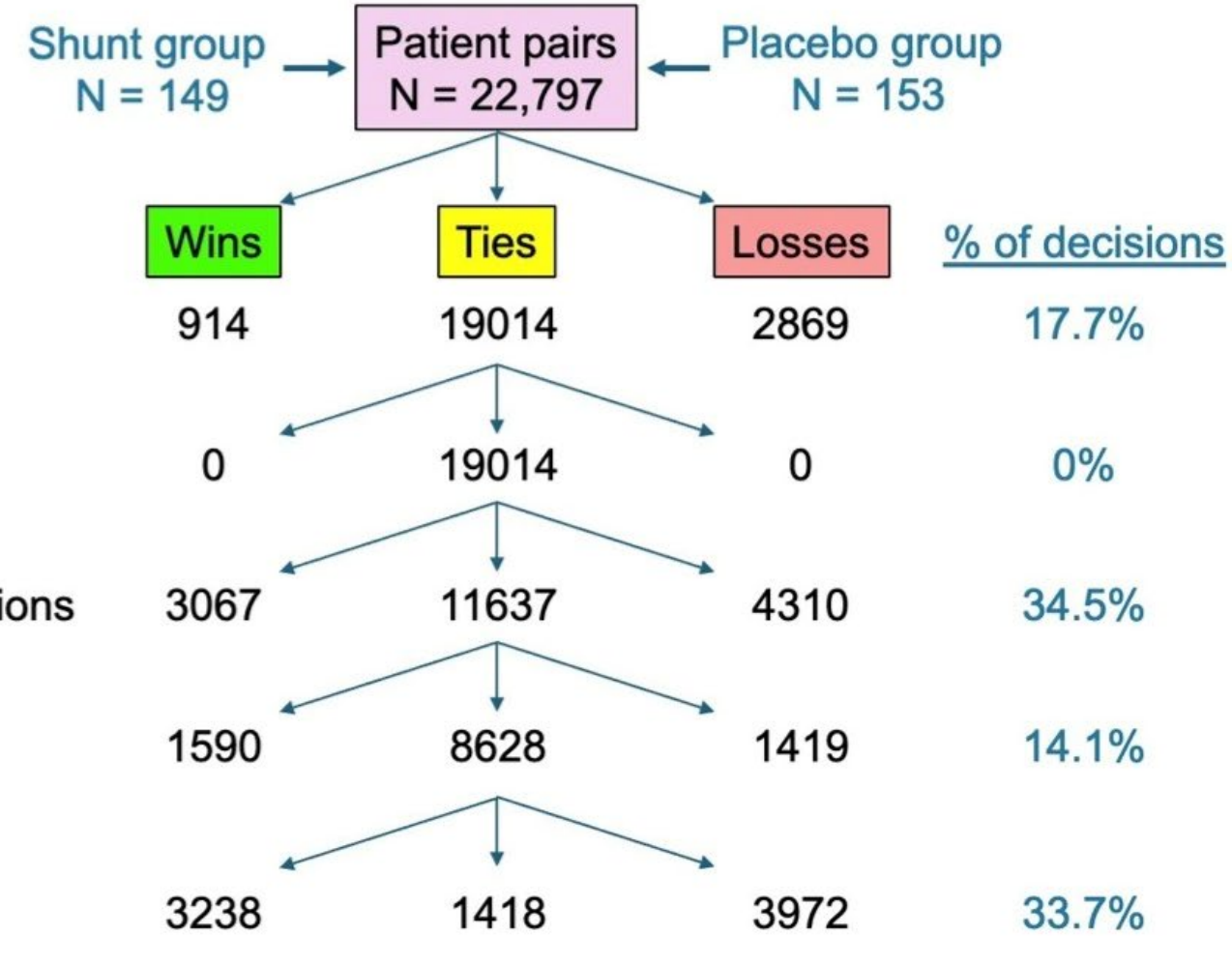
	Shunt group, N = 149	Control group, N = 153
LVEDV, ml	97.5 (73.0, 122.0)	106.0 (80.5, 128.5)
LVESV, ml	42.0 (28.0, 61.5)	47.0 (33.0, 64.5)
LVEF, %	56.3 (49.4, 62.6)	54.3 (47.6, 62.2)
LA volume, ml	75.3 (62.0, 97.3)	74.3 (58.5, 101.0)
Stroke volume, ml	54.0 (41.0, 66.0)	56.0 (44.0, 69.0)
Stroke volume index, mUm^2	26.5 (22.2, 31.6)	28.6 (22.6, 34.5)
Cardiac output, L/min	3.60 (2.79, 4.48)	3.92 (3.11, 4.73)
Cardiac index, L/min/m^2	1.79 (1.49, 2.10)	1.95 (1.57, 2.32)
RV fractional area change,%	38.1 (33.3, 42.9)	38.9 (34.8, 45.0)
Tricuspid annular plane systolic excursion, mm	17.0 (15.0, 20.0)	17.0 (15.0, 20.0)
Pulmonary artery systolic pressure, mmHg	34.0 (26.0, 41.0)	32.0 (26.0, 40.0)
Right ventricular end-diastolic area index, cm^2/m^2	9.3 (8.0, 11.3)	9.9 (8.3, 11.3)
Inferior vena cava diameter max, cm	0.7 (0.4, 1.0)	0.7 (0.4, 1.0)
MR moderate or greater	25 (16.8%)	19 (12.4%)
TR moderate or greater	38 (25.5%)	28/152 (18.4%)

HFpEF Subgroup Baseline Right Heart Cath Data

	Shunt group, N = 149	Control group, N = 153
Heart rate, bpm	67.4 ± 14.4	67.1 ± 15.0
Systolic blood pressure, mmHg	122.1 ± 18.7	123.9 ± 19.8
Diastolic blood pressure, mmHg	65.3 ± 12.1	65.3 ± 11.9
Mean right atrial pressure, mmHg	10.0 ± 4.4	9.1 ± 4.0
Systolic pulmonary artery pressure, mmHg	39.8 ± 10.9	37.3 ± 9.5
Mean pulmonary artery pressure, mmHg	26.3 ± 6.8	24.8 ± 5.9
Pulmonary vascular resistance, Wood units	2.4 ± 1.0	2.0 ± 1.1
Pulmonary capillary wedge pressure, mmHg	16.5 ± 5.7	16.0 ± 5.4
Cardiac output, L/min	4.5 ± 1.6	4.6 ± 1.4
Cardiac index, L/min/m2	2.3 ± 0.7	2.3 ± 0.7

HFpEF Subgroup Primary Effectiveness Endpoint Outcome

LVEF >40%



Win ratio 0.61
95% CI 0.39 to 0.98

HFpEF Subgroup Rates of Individual Components of the Primary Effectiveness Endpoint (Except KCCQ) Through 2 Years

	Shunt group (N=149)	Control group (N=153)	RR or HR [95% CI]
All events	143/237.5 (60.2%/year)	88/245.0 (35.9%/year)	1.68 [1.29, 2.19]
All-cause Death	22 (16.4%)	7 (5.2%)	3.24 [1.38, 7.59]
LVAD/HT	0 (0.0%)	0 (0.0%)	
All HFHs	87/237.5 (36.6%/year)	47/245.0 (19.2%/year)	2.05 [1.35, 3.10]
All out-pt WHFs	34/237.5 (14.3%/year)	34/245.0 (13.9%/year)	1.04 [0.64, 1.68]

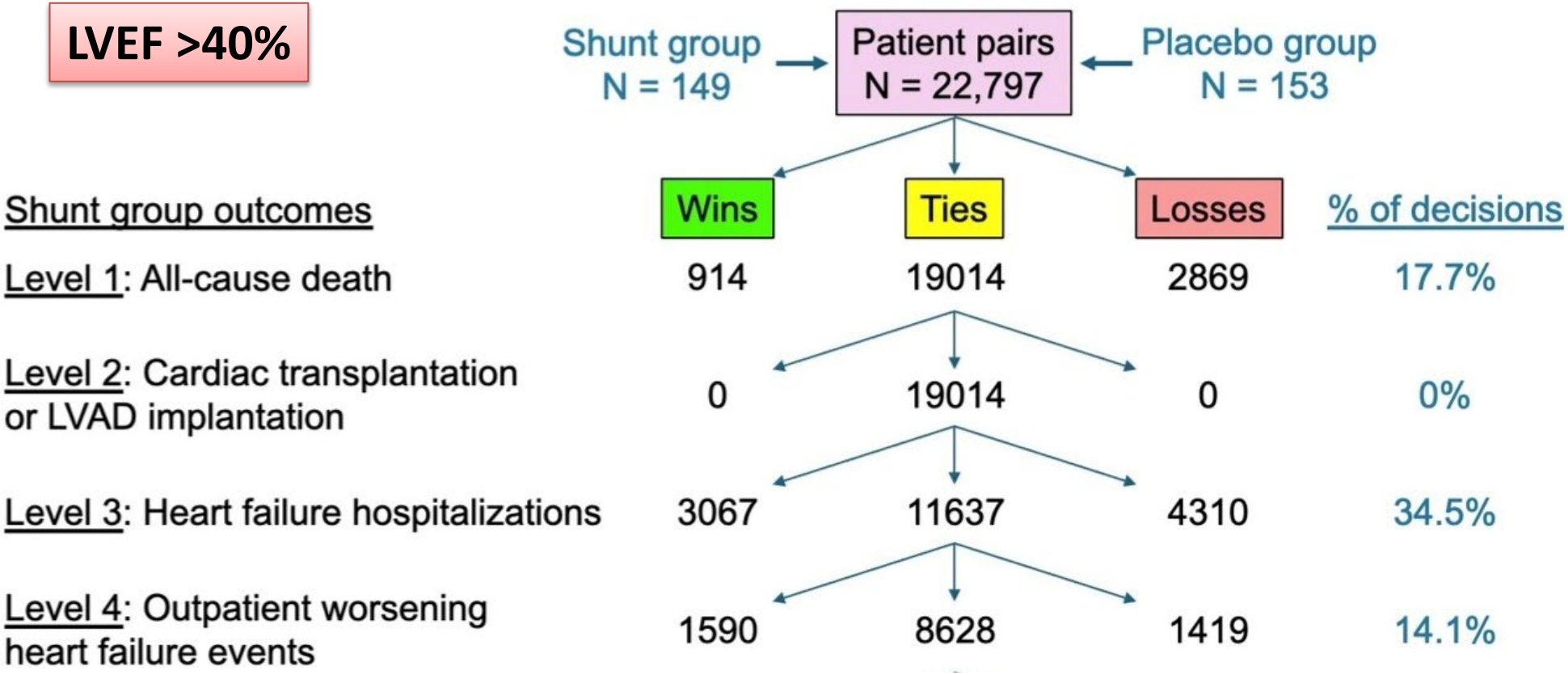
HFpEF Subgroup Mortality Analysis

- At the time of the primary analysis, there were 22 deaths (16.4%) in the Shunt group vs. 7 deaths (5.2%) in the Control group (unadjusted p-value = 0.004)
- CEC adjudication
  - 12 cardiovascular (CV) deaths in the Shunt group vs. 4 CV deaths in the Control group (unadjusted p-value = 0.037)
  - 9 non-CV deaths in the Shunt group and 3 non-CV deaths in the Control group

Cause of death	Shunt group (N=149)	Control group (N=153)
All cause	22 (16.4%)	7 (5.2%)
Cardiovascular	12	4
Non-Cardiovascular	9	3
Unknown	1	0

HFpEF Subgroup Effectiveness Endpoint Outcome Excluding KCCQ

LVEF >40%



Win ratio (excluding KCCQ) 0.65
95% CI 0.45 to 0.93

Outline

- RELIEVE-HF Results – All Randomized Subjects
- RELIEVE-HF HFrEF Subgroup Results
- RELIEVE-HF HFpEF Subgroup Results
- Pathophysiologic Insights
- RELIEVE-HF Strengths, Limitations, and Benefit-Risk considerations

Pathophysiologic Insights From TTEs

- 508 RELIEVE-HF randomized patients underwent a baseline TTE at a median of 1.1 months prior to randomization.
  - Of these, 428 patients underwent a 12-month TTE
  - 80 studies at 12 months not performed
  - 18 patients died or had a heart transplant or LVAD before the 12-month TTE
  - 62 patient echos (12.2%) assumed to be missing at random
- 17,272 total TTE measurements (17 measurements/study/patient)
  - 15,495 parameters (89.7%) analyzed by the echo core lab
  - 1777 parameters (10.3%) imputed

16 Selected Longitudinal TTE Parameters Evaluated

LV end-diastolic volume index, ml/m2
LV end-systolic volume index, ml/m2
LV stroke volume index, ml/m2
LV cardiac index, L/min/m2
LV ejection fraction, %
LV global longitudinal strain, %
LA volume index, ml/m2
E/e’
RV end-diastolic area index, cm2/m2
RV stroke area index, cm2/m2
RV fractional area change, %
TAPSE, mm
RA area index, cm2/m2
IVC diameter max, cm
PA systolic pressure, mmHg
TAPSE/PA systolic pressure, mm/mmHg

Summary of within HF phenotype TTE findings

- HFrEF subgroup
  - Reverse LV remodeling in Shunt subjects.
  - Smaller increase in estimated PASP in Shunt vs. Control subjects
- HFpEF subgroup
  - Increased right ventricular, right atrial and inferior vena cava size and pulmonary artery systolic pressure in Shunt vs. Control subjects

Considerations

- Post-hoc exploratory analyses
- Missing data & TTE assessment test-to-test variability
- Unclear clinical significance of numerical differences (considering sample sizes and 95% CIs) in selected cardiac morphologic and hemodynamic parameters between Shunt and respective Control subjects within HF phenotypes

Outline

- RELIEVE-HF Results – All Randomized Subjects
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RELIEVE-HF Strengths

- RELIEVE-HF was a well-executed RCT
- Enrollment included predominately NYHA Class III HF patients that were symptomatic despite a reasonable regimen of guideline-directed medical therapy and cardiac rhythm device therapies (if indicated)
- Primary safety endpoint met

RELIEVE-HF Limitations (1)

- Primary prespecified effectiveness 5-level win ratio composite endpoint (selected by the Sponsor) *not* met for the total enrolled cohort (both HFrEF and HFpEF subjects)
- Uncertainty regarding analyses suggesting clinical benefit in the HFrEF subgroup of N = 206 randomized subjects
  - 5-level win ratio composite effectiveness endpoint was *not* met
  - Excluding KCCQ, 4-level win ratio composite effectiveness endpoint was *not* met
  - No CV mortality benefit associated with Shunt use
  - No KCCQ score improvement in Shunt subjects vs. Controls
    - Improved health status anticipated based on expectation that LA decompression would reduce pulmonary vascular congestion symptoms

RELIEVE-HF Limitations (2)

Although comparing results between HF phenotype subgroups was prespecified, RELIEVE-HF neither powered nor pre-specified to test Shunt effectiveness in HFrEF vs. HFpEF

- Potential Shunt benefit in HFrEF subgroup based on post hoc analyses
- FDA contends that it's not possible to estimate subgroup analysis Type I error
- Observed HF outcome differences favoring the Shunt in the HFrEF subgroup may have been driven by a few Control subjects with a high rate of recurrent events

Limitations of Subgroup Analyses: Cautionary Tales

- Caution needed in drawing conclusions from post hoc subgroup analyses without a prespecified statistical analysis plan to control type 1 error
- PRAISE (amlodipine in chronic HF) & TACT (chelation in prior MI patients) trials
  - PRAISE
    - PRAISE 1: Stratified enrollment by ischemic vs. nonischemic cardiomyopathy (CMP)
      - Overall results: Negative for amlodipine benefit, but markedly positive for amlodipine in nonischemic CMP
    - PRAISE 2: Enrollment limited to nonischemic CMP subjects: No amlodipine benefit
  - TACT
    - TACT 1: Large chelation benefit observed in the diabetic subgroup
    - TACT 2: Limited to diabetic subjects: No chelation benefit

Praise 1 & TACT 1 authors provided mechanistic postulates to support subgroup results but concluded they were hypothesis-generating that required confirmatory studies

RELIEVE-HF Limitations (3)

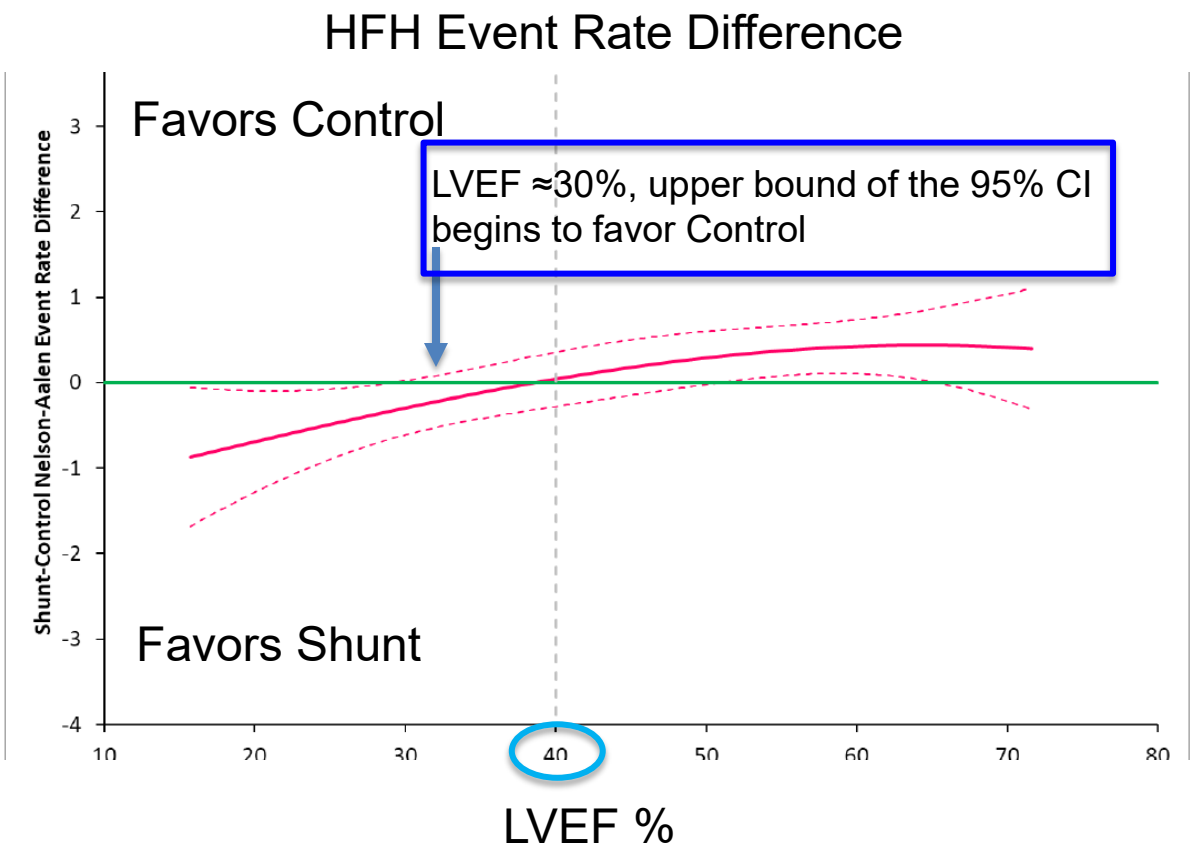
- Possible increased mortality and heart failure event risks in HFpEF patients
- Limited understanding of relationships among anatomic and hemodynamic changes associated with implanting an interatrial shunt, shunt flow metrics, and clinical outcomes in heart failure patients

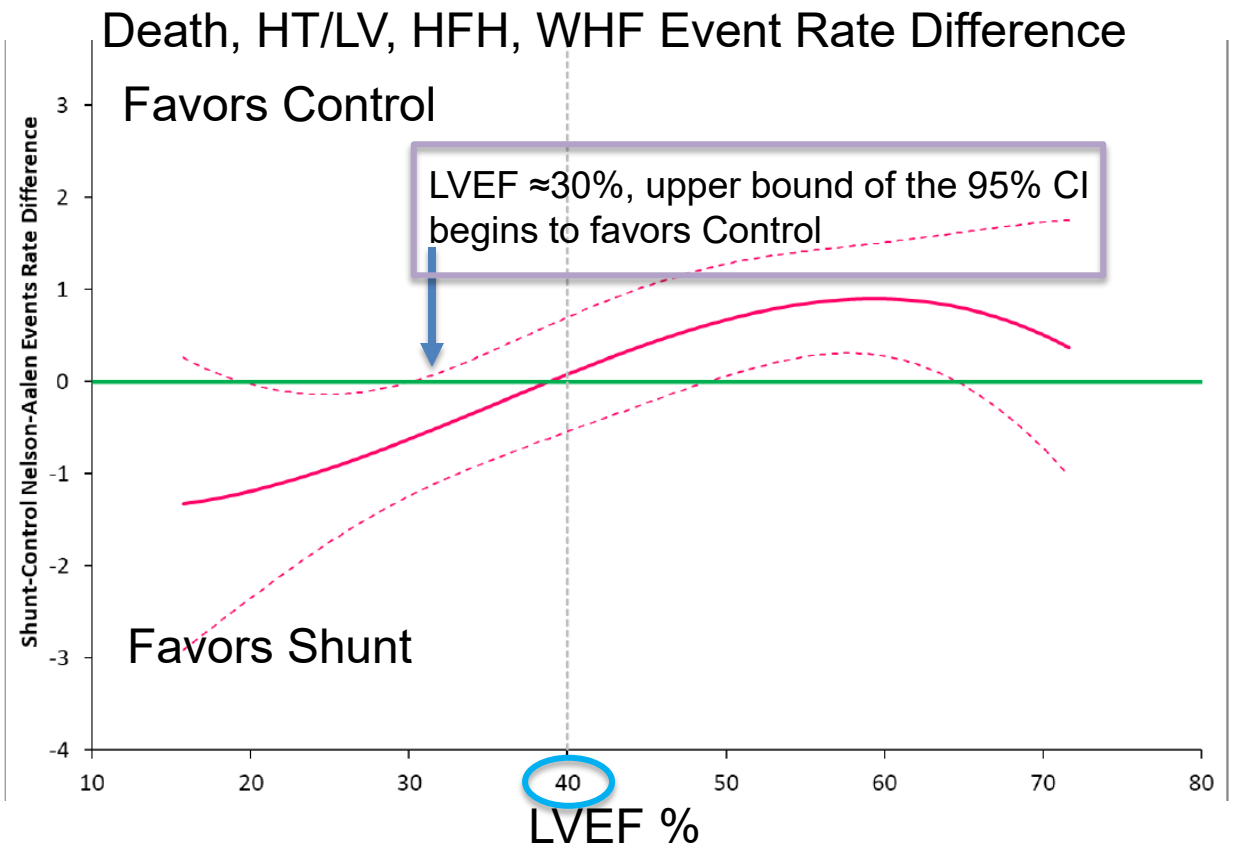
Clinical Decision-Making
LVEF Benefit-Risk Determination Challenges

- Data suggest potential benefit in one HF phenotype (HFrEF, LVEF ≤40%) and possible harm in another cohort (HFpEF, LVEF >40%)
- Clinical decision-making challenges
  - LVEF is a continuous variable
  - LVEF changes over time in response to therapeutic interventions or disease progression
  - LVEF is associated with error in the measurement and variability than can result in changes that cross the 40% EF threshold
    - Absolute intra-patient repeat LVEF measurement variability using the same method within short periods is >7% (in either direction)[1]
  - LVEF measurement accuracy is operator-dependent, relies on image quality, and is affected by heart rate and rhythm (e.g., atrial fibrillation)

[1]Christersson M. J Am Heart Assoc. 2024;13:e032257. DOI: 10.1161/JAHA.123.032257

LVEF Benefit-Risk Profile Challenges in HFrEF





Rate difference: Shunt - Control

95% Confidence intervals

Challenges in determining a favorable benefit-risk profile in clinical decision making for individual patients

LVEF Benefit-Risk HFrEF Sensitivity Analysis

Poisson HF event rates for HFrEF subjects for LVEF >40% to ≤47%

	Sample Size	Event Count	Event Rate (% per Patient-Year)	Rate Ratio (95% CI)
Baseline LVEF >40% and ≤43%				
Shunt Group	17	8	30.1	0.34 (0.14, 0.76)
Control Group	15	20	88.7	
Baseline LVEF >40% and ≤44%				
Shunt Group	20	12	39.3	0.52 (0.25, 1.06)
Control Group	18	20	75.2	
Baseline LVEF >40% and ≤45%				
Shunt Group	23	19	53.2	0.83 (0.44, 1.53)
Control Group	23	23	64.2	
Baseline LVEF >40% and ≤47%				
Shunt Group	28	22	50.2	0.97 (0.55, 1.70)
Control Group	35	28	51.9	

Limitations

- **Small sample sizes & few events**
- **95% CI upper bound crosses 1.0 for LVEF >43% such that Shunt-associated increased HF events cannot be excluded in HFrEF**

Shunt benefit-risk profile uncertainty

LVEF Benefit-Risk Determination Summary

LVEF 40% threshold directs clinical decision-making in favor of or against Shunt use

LVEF measurement factors create challenges in determining a favorable benefit-risk profile in clinical decision making for individual patients

Post Approval Study and Conclusions

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Biomedical Engineer
Office of Cardiovascular Devices

Proposed Post-Approval Study (PAS)

- Continued follow-up of RELIEVE-HF for 5 years
- New single-arm PAS
  - Prespecified performance goal
- Registry to gather real-world data

Post market data cannot be used as a substitute for necessary premarket data that establishes safety and effectiveness

Conclusions (1)

- RELIEVE-HF study was well-executed sham-controlled randomized trial
- Primary safety of MACNE within 30 days met performance goal
- Primary effectiveness composite endpoint of all cause death, LVAD/transplant, heart failure hospitalization, worsening heart failure treated as an out-patient, and KCCQ score was **not** met with a win ratio of 0.86

Conclusions (2)

- Post hoc analysis results in the HFrEF subgroup raise uncertainty due to small sample size & absent type 1 error control, and HF Event rates may have been driven by a small group of control subjects
- No observed cardiovascular mortality benefit associated with Shunt use in HFrEF patients
  - Possible mortality risk in HFpEF patients
- No observed health status/quality of life improvements in Shunt patients vs Controls

Conclusions (3)

Uncertainty remains as to whether the totality of the data establishes a favorable benefit-risk profile for the Shunt for its proposed indications for use

PANEL QUESTIONS

QUESTION 1

#1. Safety Profile

- Primary safety endpoint results
  - Rate of device or procedure related MACNE at 30 days
  - No patient experienced a primary safety endpoint event
  - 30-day safety endpoint was met
- Additional safety events through two years (shunt vs control)
  - Numerically more cerebrovascular and pulmonary embolism events
  - Numerically fewer myocardial infarction events

#1. Safety Profile

	Shunt group (N=250)	Control Placebo Procedure group (N=258)	Relative risk or difference	P value
Secondary safety endpoints:				
MACNE* or BARC types 3 or 5 bleeding at 30 days[1]	2 (0.8%)	-	-	-
BARC types 3 or 5 bleeding at 30 days[1]	2 (0.8%)	1 (0.4%)	2.07 [0.19, 22.85][2]	0.54
MACNE* at 1 year[1]	0 (0.0%)	-	-	-
MACNE* at 2 years[1]	0 (0.0%)	-	-	-
Cerebrovascular events at 2 years, any[1]	11 (5.1%)	6 (2.5%)	1.92 [0.71, 5.18][2]	0.19
CNS infarction (stroke)[1,**]	7 (3.3%)	5 (2.1%)	1.46 [0.46, 4.60][2]	0.52
CNS hemorrhage (intracerebral or subarachnoid)[1,†]	0 (0.0%)	1 (0.5%)	-	0.33
Transient ischemic attack[1]	4 (1.9%)	1 (0.4%)	4.12 [0.46, 36.91][2]	0.17
Myocardial infarction at 2 years[1]	8 (3.8%)	13 (6.6%)	0.63 [0.26, 1.52][2]	0.30
Systemic embolization events at 2 years[1]	0 (0.0%)	0 (0.0%)	-	-
Pulmonary embolization events at 2 years[1]	2 (1.0%)	0 (0.0%)	-	0.16
Shunt implant embolization at 2 years[1]	0 (0.0%)	-	-	-

#1. Safety Profile

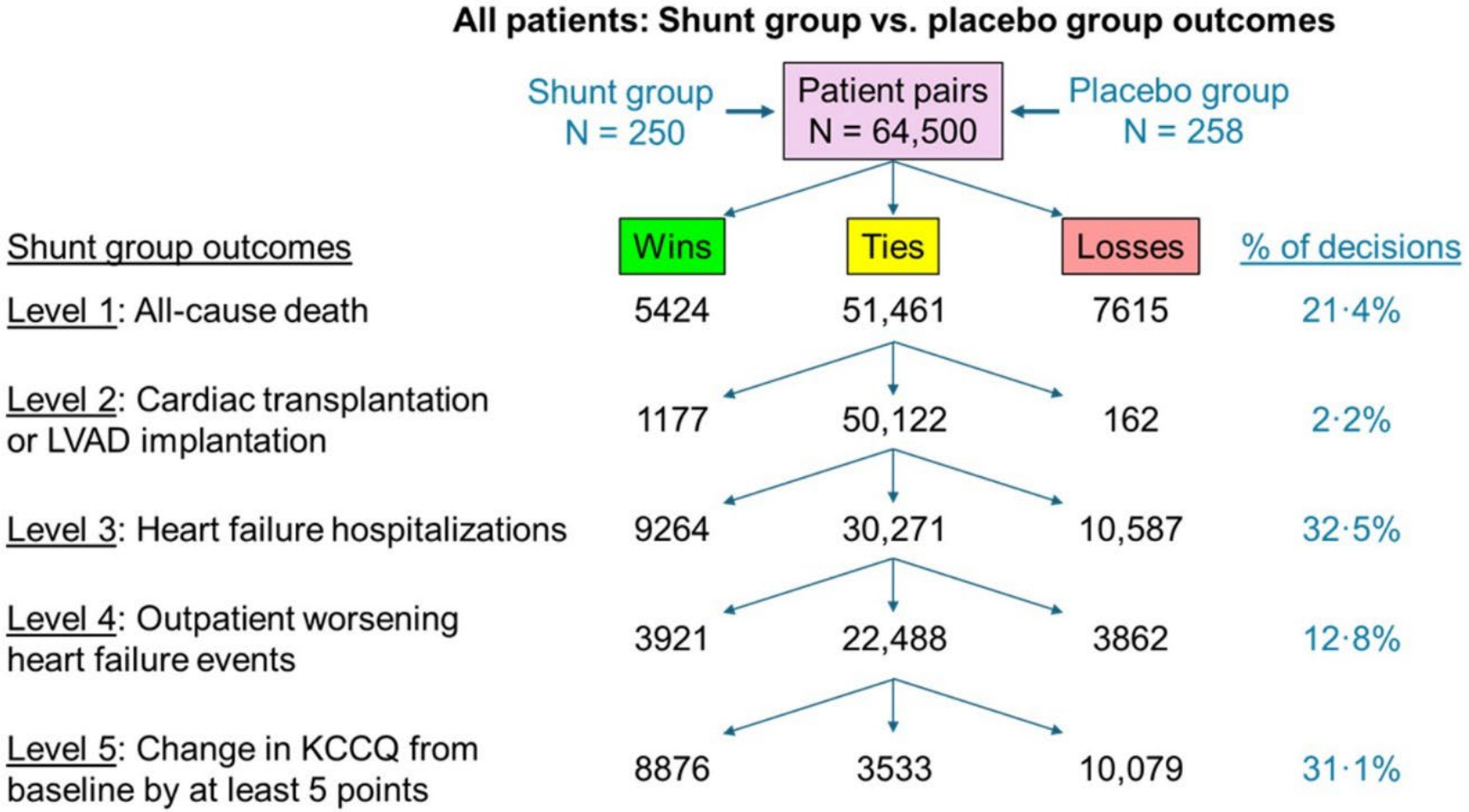
Please discuss on the clinical significance of the safety events observed in the study.

QUESTION 2

#2. Effectiveness – Primary Endpoint

- Primary effectiveness endpoint results
  - Hierarchical composite of all-cause death, cardiac transplantation or LVAD implantation, HFH, Outpatient worsening HF events, and KCCQ score change

#2. Effectiveness – Primary Endpoint



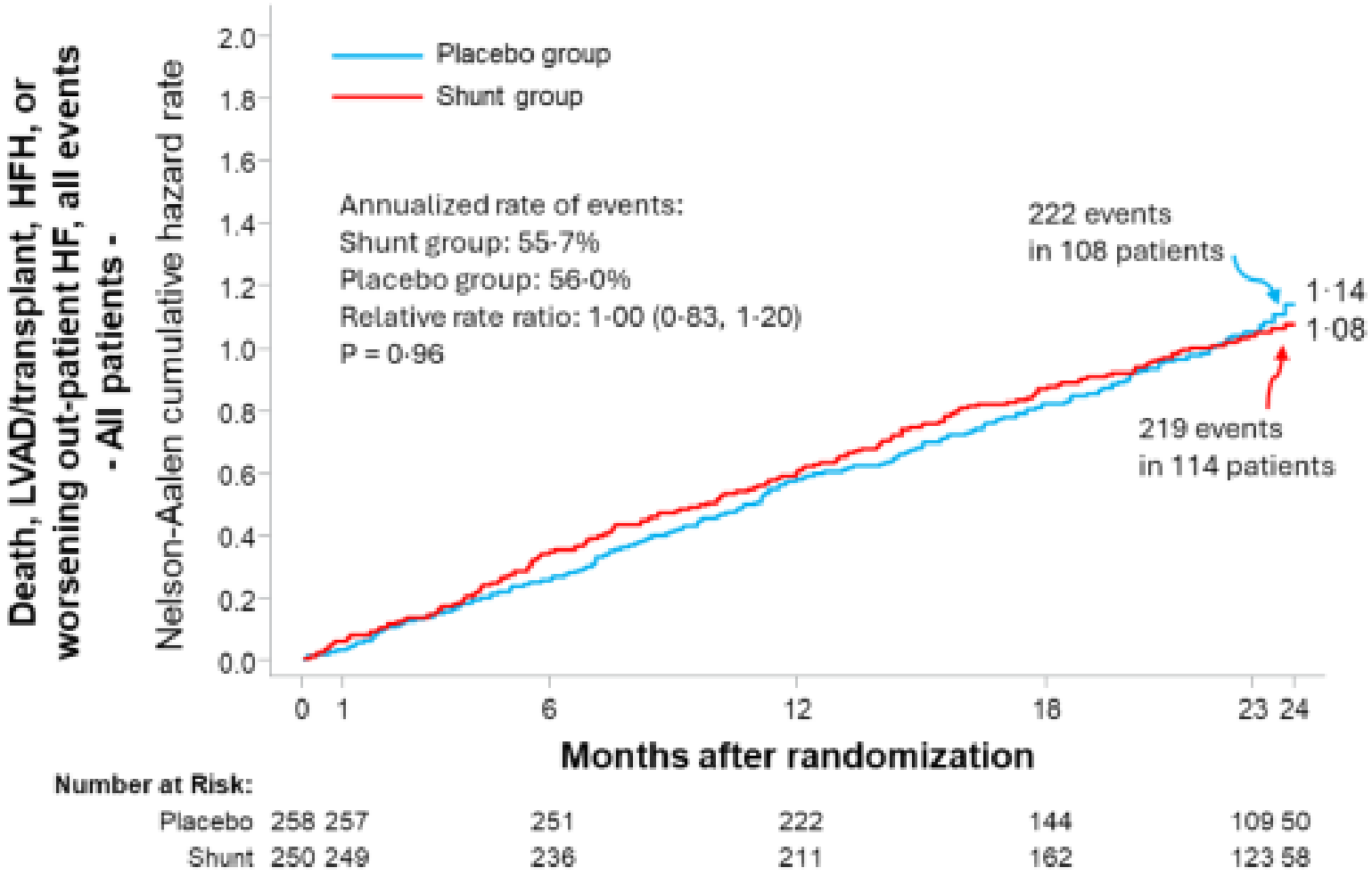
Total wins = 28,662, total losses = 32,305
Win ratio (unweighted) = 28,662/32,305 = 0·89 (0·72, 1·09)
Win ratio (phase weighted for interim analysis) = 0·86 (0·61, 1·22); p=0·20

#2. Effectiveness – Primary Endpoint

- Primary effectiveness endpoint results
  - Endpoint not met
  - Win ratio of 0.86, 95% CI 0.62 to 1.22, p = 0.20

#2. Effectiveness – Primary Endpoint

- Post-Hoc cumulative event analysis (excluding KCCQ)



#2. Effectiveness – Primary Endpoint

- Individual component rates of the primary effectiveness endpoint

Table 2: Rates of Individual Components of the Primary Effeetiveness Endpoint (Except KCCQ)

	Shunt group	Control group	Relative risk
All-cause death	35 (15.6%)	27 (13.7%)	1.31 [0.79, 2.16]
Cardiac transplantation or LVAD	1 (0.6%)	6 (3.4%)	0.17 [0.02, 1.38]
HFHs (no. of events/total no. of patient-yrs, (annualized rate)	128/392.7 (32.6%)	125/396.1 (31.6%)	1.09 [0.79, 1.50]
Worsening outpatient HF events (no. of events/total no. of patient-yrs (annualized rate)*	55/392.7 (14.0%)	64/396.1 (16.2%)	0.88 [0.61, 1.26]

#2. Effectiveness – Primary Endpoint

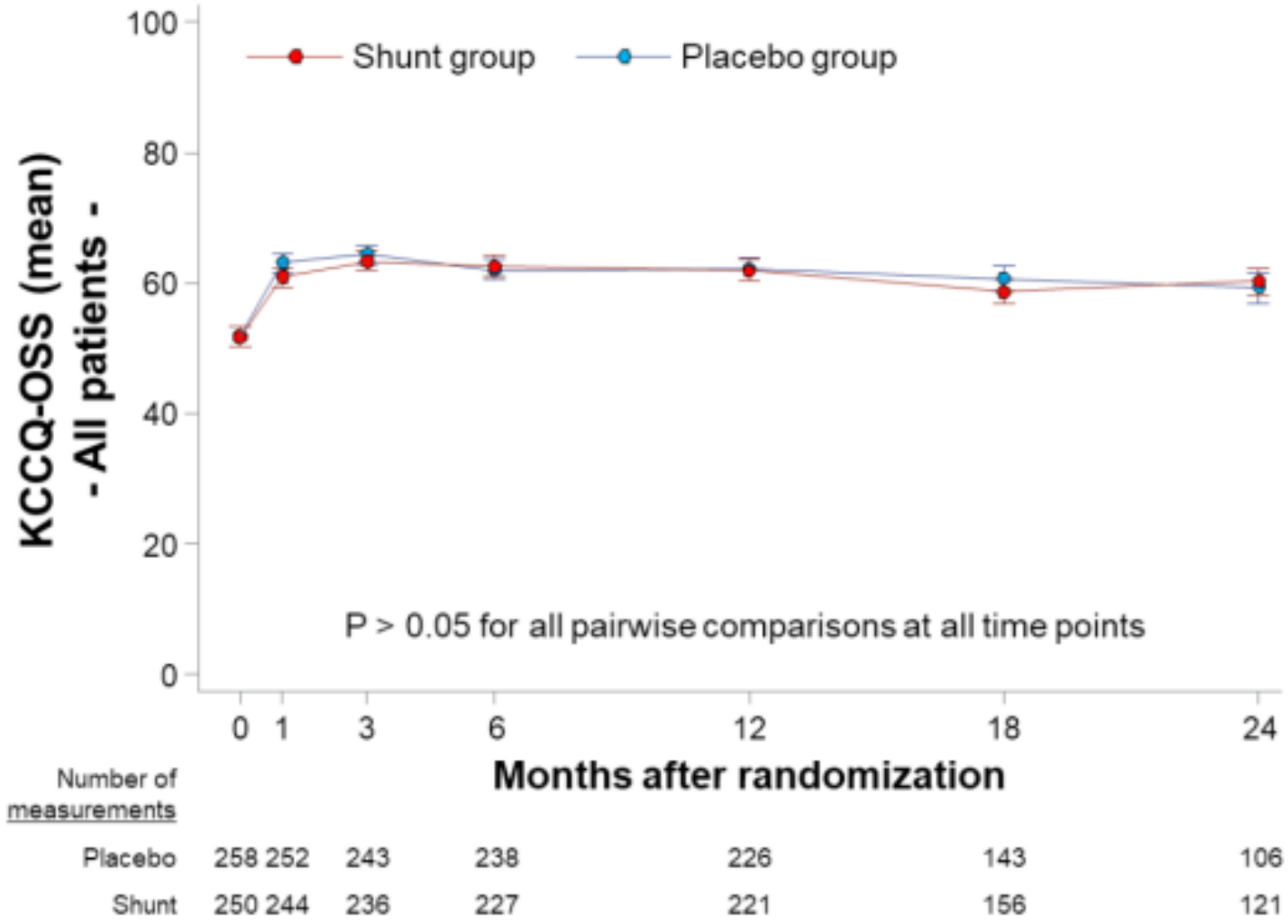


Figure 3: KCCQ outcomes over 2 years (ITT population)

#2. Effectiveness – Primary Endpoint

Please discuss the clinical significance of the primary effectiveness endpoint results.

QUESTION 3

#3. Effectiveness – HFrEF vs HFpEF

- Shunt benefit expected to be more pronounced in HFpEF vs HFrEF
- HF phenotype subgroup analysis results were discordant suggesting Shunt benefit in HFrEF (win ratio 1.4) and harm in HFpEF (win ratio 0.61)
- Interaction test analysis showed nominally significant p-value of 0.0146
- Study designed to evaluate the effect in the total population, not in each LVEF subgroup separately
- No pre-specified plan to control Type I error in subgroup analysis

#3. Effectiveness – HFrEF vs HFpEF

- HFrEF (LVEF ≤40%) subgroup (n = 206 randomized subjects) post hoc analyses
  - 5-level (all-cause death, cardiac transplant/LVAD, HFH, outpatient WHF, and KCCQ change) win ratio analysis: No statistically significant difference between Shunt and Control groups
  - 4-level (excluding KCCQ change) win ratio analysis: No statistically significant difference between Shunt and Control groups
  - HF events (along with HF event in combination components of the primary effectiveness composite endpoint, excluding KCCQ) utilizing multiple analytic models favored the Shunt group
  - All-cause death and transplant/LVAD rates favored the Shunt group
  - Cardiovascular death rates similar between Shunt and Control groups
  - Similar KCCQ scores in Shunt and Control groups

#3. Effectiveness – HFrEF vs HFpEF

- HFpEF (LVEF >40%) subgroup (n = 302 randomized subjects) post hoc analyses
  - 5-level (all-cause death, cardiac transplant/LVAD, HFH, outpatient WHF, and KCCQ change) win ratio analysis: Favored the Control group
  - Death and HF event rates favored the Control group

#3. Effectiveness – HFrEF vs HFpEF

- Pathophysiologic insights:
  - The Sponsor conducted post-hoc, exploratory analyses of between group differences in transthoracic echocardiographic (TTE) changes at baseline and 12 months
  - N=508 randomized patients; 12.2% missing 12-month follow-up TTEs
  - Among the 16 TTE parameters assessed, follow-up TTEs showed:
    - Reverse left ventricular remodeling in HFrEF subgroup Shunt subjects.
    - A smaller increase in estimated pulmonary artery systolic pressure in the HFrEF Shunt group vs. the Control group
    - Increased right ventricular, right atrial and inferior vena cava size and pulmonary artery systolic pressure in HFpEF Shunt subjects vs. Controls

#3. Effectiveness – HFrEF vs HFpEF

a. Please discuss the strengths and limitations of the evidence (and your level of uncertainty) that the Shunt is beneficial in HFrEF patients.
b. Please discuss the strengths and limitations of the evidence (and your level of uncertainty) that this Shunt is harmful in HFpEF patients.

QUESTION 4

#4. Benefit/Risk

Given the totality of the evidence presented regarding the safety and effectiveness of the device, please comment on the benefit-risk profile of the device.

QUESTION 5

#5. Labeling

The sponsor has proposed the following indications for use statement:

The Ventura Shunt is indicated for NYHA Class III heart failure patients who remain symptomatic despite guideline-directed medical therapy, have a LVEF of ≤ 40%, and who are judged by a Heart Team to be appropriate for Shunt therapy, to reduce the risk of hospitalization for heart failure.

a. **Please discuss whether the available clinical data support the proposed indications for use.**
b. **The Shunt proposed indications for use is limited to patients with LVEF ≤40%. Please discuss the clinical implications of using LVEF as a patient selection criterion considering the variability and measurement error in LVEF assessments, the potential for LVEF to change over time with therapy or disease progression, and the challenges this presents for clinical decision making for individual patients.**

QUESTION 6

#6. Post-market Study

The sponsor has proposed the following approach to post-market clinical data collection:

- Continued follow-up of implanted subjects from the RELIEVE-HF study for 5 years
- A single-arm new enrollment post-approval study (PAS) with a performance goal
- A post-approval registry for all commercial US patients not included in the post-approval study

#6. Post-market Study

Please discuss the strengths and limitations of the proposed approach to post-market data collection. Please also comment on whether any additional study objectives, design features, or surveillance are recommended.