Ventura® Interatrial Shunt for Reduction of Heart Failure Hospitalizations in Patients with Heart Failure with Reduced Ejection Fraction (HFrEF)

December 3, 2025

Circulatory Systems Device Panel

V-Wave, a Johnson & Johnson Company

Johnson&Johnson MedTech

Introduction & Trial Design

William T. Abraham, MD

College of Medicine Distinguished Professor

The Ohio State University

Chief Medical Officer

V-Wave, a Johnson & Johnson Company

Proposed Indication Limited to HFrEF Patients With Focus on Reduced Risk of HF Hospitalization

The Ventura Shunt is indicated for NYHA Class III HF 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.

NYHA = New York Heart Association
LVEF = left ventricular ejection fraction

Agenda

Introductory Remarks and RELIEVE-HF Trial Design	**William T. Abraham, MD** College of Medicine Distinguished Professor, The Ohio State University Chief Medical Officer, V-Wave, a Johnson & Johnson Company
Safety and Effectiveness Results	**Gregg Stone, MD** Director of Academic Affairs Professor of Medicine (Cardiology) Professor of Population Health Sciences and Policy Icahn School of Medicine at Mount Sinai, New York
Mechanistic Basis for Differential Effects of Shunt Treatment in HFrEF vs HFpEF	**Michael R. Zile, MD** Charles Ezra Daniel Professor of Medicine, Cardiology Division Medical University of South Carolina
Benefit-Risk Summary and Clinical Perspective	**JoAnn Lindenfeld, MD** Professor of Medicine, Division of Cardiovascular Medicine Vanderbilt University Medical Center

Significant Unmet Need for Therapies that Improve Prognosis in HFrEF Patients

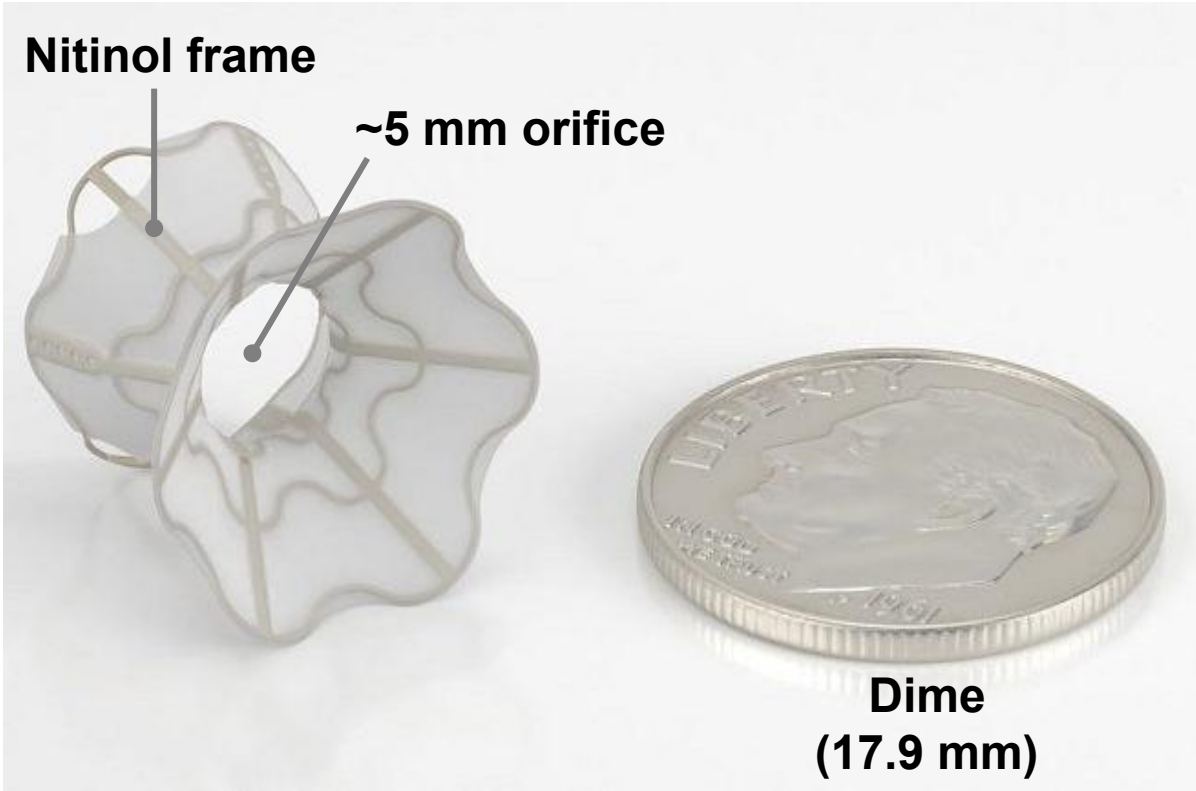
- Significant residual risk of HF hospitalization and mortality despite guideline-directed medical therapy (GDMT)
- Elevated left atrial pressure is the primary cause of these poor clinical outcomes
- Lowering left atrial pressure improves clinical outcomes in HF but is difficult to achieve with medical therapy[1]
- No alternative therapies to improve clinical outcomes in NYHA Class III HFrEF patients who are treated with optimal GDMT

1. Lindenfeld et al., 2024

V-Wave Ventura Interatrial Shunt

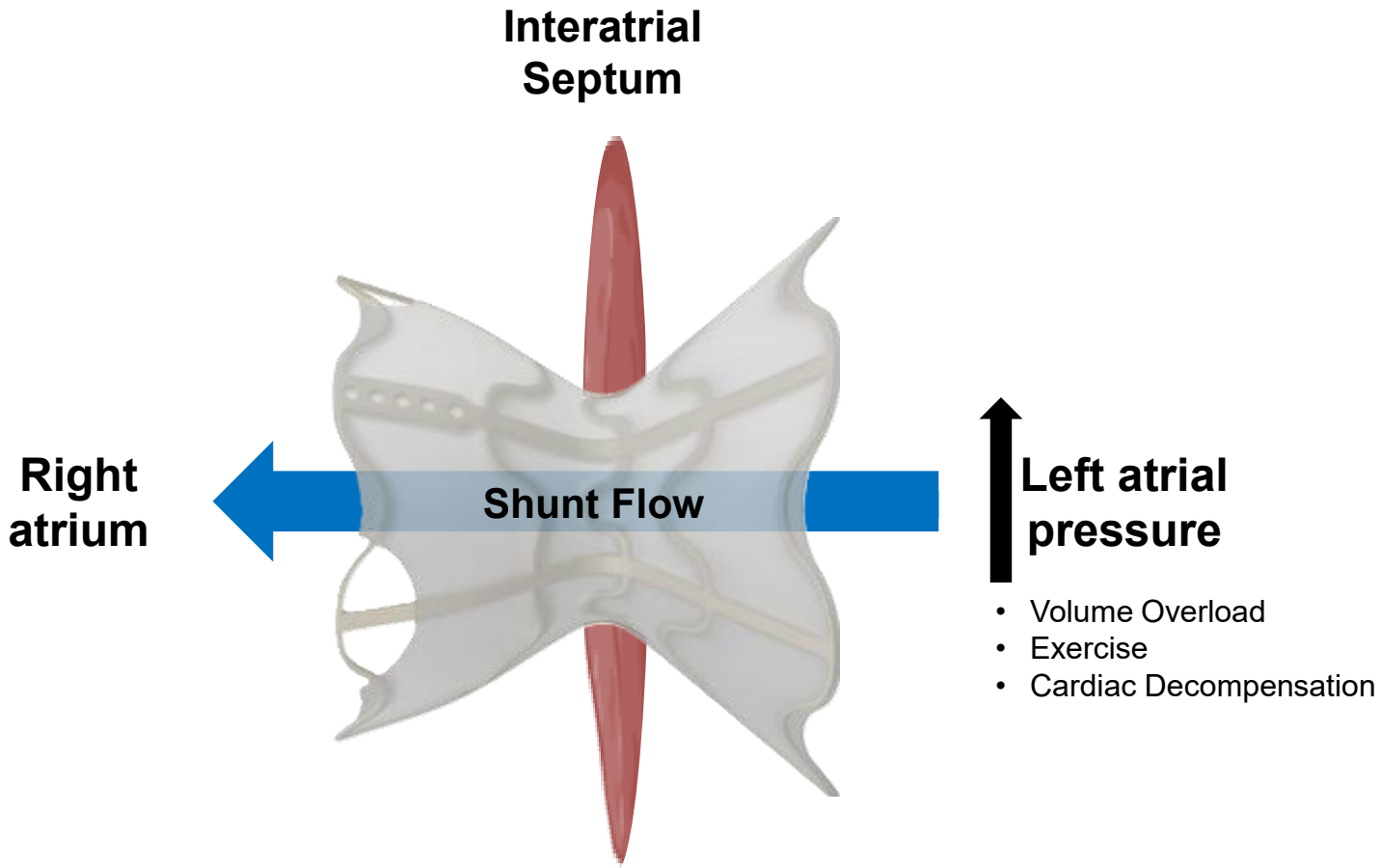
**Addresses primary cause of HF hospitalizations -
Elevated left atrial pressure resulting in pulmonary congestion**

- Permanently implanted across fossa ovalis
- 5 mm opening
- 14 Fr delivery system
- Performed in cardiac catheterization lab
- Procedure time ~1 hr



Encapsulated with expanded polytetrafluoroethylene

Ventura Interatrial Shunt Mechanism of Action



Shunt flow increases “automatically” when left atrial pressure rises

Ventura Interatrial Shunt Granted Breakthrough Device Designation

Criteria	Description (Statute and Guidance)	Ventura Shunt
First Criterion	Device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or condition	☑
Second Criterion	Device also meets <u>at least one</u> of the following:	
	a) Represents Breakthrough Technology	☑
	b) No approved or cleared alternatives exist *– OR –* b) Offers significant advantages over existing approved or cleared alternatives	☑
	c) Device availability is in best interest of patients	☑

Breakthrough Device Designation Granted in 2019

21 U.S.C. § 360e-3(b); Breakthrough Devices Program – Guidance for Industry and Food and Drug Administration Staff. Document issued on December 18, 2018.

Approval Under Breakthrough Device Designation

"As part of the benefit-risk determination for Breakthrough Devices subject to a PMA, FDA may accept a greater extent of uncertainty of the benefit-risk profile for these devices if appropriate under the circumstances, including that the uncertainty is sufficiently balanced by other factors, such as the probable benefits for patients to have earlier access to the device…and adequate postmarket controls to support premarket approval…"

Breakthrough Devices Program – Guidance for Industry and Food and Drug Administration Staff. Document updated on September 15, 2023.

Well-Executed, Robust, Double-Blind Study

- Multicenter, randomized, double-blind, sham-controlled
  - 114 sites
- Symptomatic HF on optimal (i.e., maximally tolerated) GDMT
  - Assessed by Central Eligibility Committee
- Randomized 508 patients
  - > 95% NYHA Class III
  - Median follow-up 22 months
  - 98.4% follow-up at primary analysis
- Few major protocol deviations
- No confounding interventions

Pre-Study Expectations, Considerations, and Planning

- Anticipated potential treatment benefit for HFrEF and HFpEF
- Included patients across the full spectrum of LVEF
- Acknowledged functional differences between HFrEF and HFpEF phenotypes could affect response
- Randomization stratified by LVEF group
- Prespecified interaction testing between strata

Device and Procedure Safety Clearly Demonstrated

- Primary Safety Endpoint was met
- No device- or procedure-related major adverse cardiovascular or neurologic events (MACNE) through 2 years
- Stroke, MI, and thromboembolic events occurred infrequently and at similar rates in HFrEF Shunt and Control groups

Summary of Effectiveness Findings

- Primary effectiveness endpoint (win ratio) not met
- Interaction observed between LVEF strata for primary endpoint and therefore could not be pooled for analysis of effectiveness
- LVEF stratum separately analyzed → directionally opposite outcomes
- Benefit in HFrEF patients - Harm in HFpEF patients

Totality of Data Support Probable Benefit in HFrEF

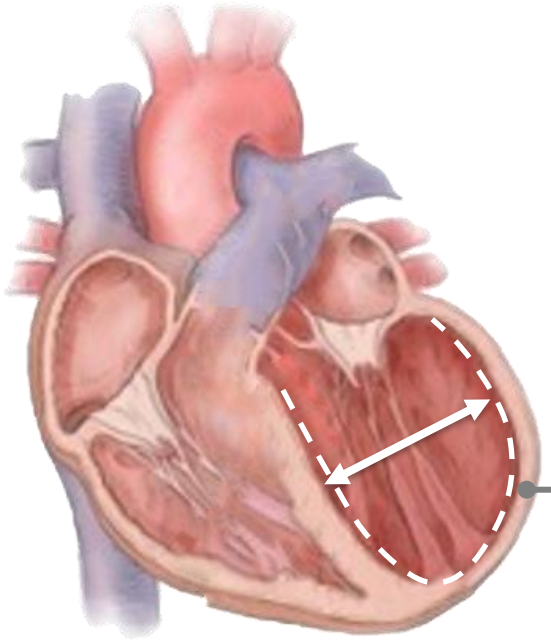
	HFrEF Shunt N = 101 pts *[Events]*	HFrEF Control N = 105 pts *[Events]*	2yr Nelson-Aalen Hazard Rate Ratio *(95% CI)*	Reduction (%)	NNT*
Primary Endpoint HF Events *[2yr]*	**76**	**134**	**0.49** *(0.35, 0.65)*	**51%**	**1.0**
All-cause death	**13**	**20**	**0.48** *(0.20, 1.06)*	**52%**	**6.4**
LVAD/HT	**1**	**6**	**0.15** *(0.00, 0.98)*	**85%**	**12.7**
All HFHs	**41**	**78**	**0.46** *(0.29, 0.68)*	**54%**	**1.6**
All outpatient WHFs	**21**	**30**	**0.64** *(0.33, 1.17)*	**36%**	**7.3**

LVAD = Left ventricular assist device
HT = Heart transplant
HFH = Heart failure hospitalization
WHF = Worsening heart failure
NNT = Number needed to treat
* Number of patients needed to treat with the shunt to prevent on average 1 event during 2-year follow-up

Biologic Plausibility: Echo Core Lab Analyses Show Differences in Cardiac Structure and Function

Differences in Left Ventricular Structure and Function Affect Responses to Interatrial Shunt

HFrEF

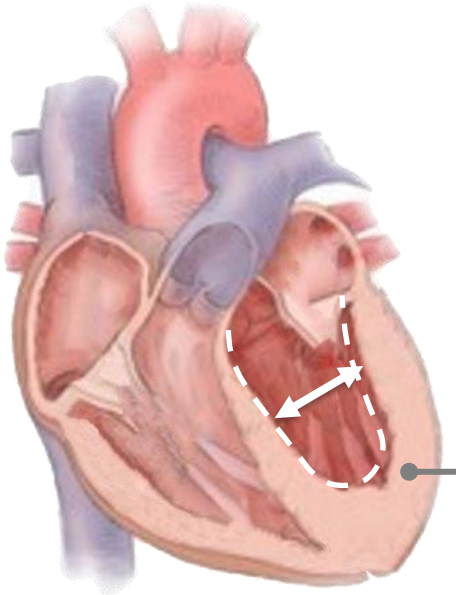


Enlarged LV size

Compliant LV

LEFT VENTRICLE **undergoes REVERSE REMODELING** (↓ LVEDV) in response to Shunt placement

HFpEF



Normal LV size

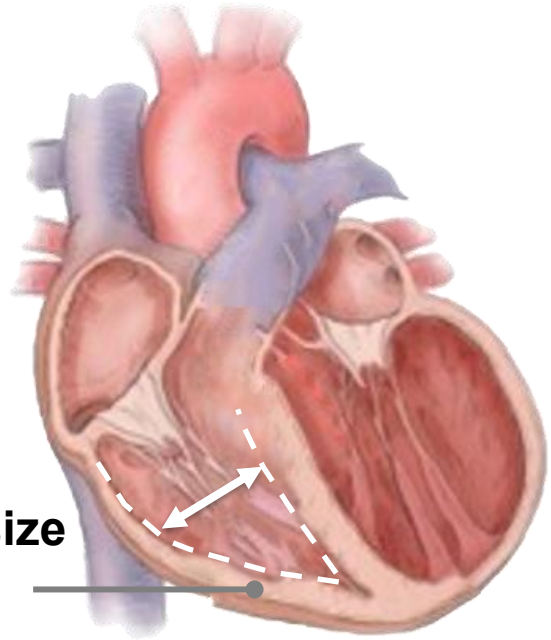
Non-compliant LV

LEFT VENTRICLE **unable to undergo REVERSE REMODELING** in response to Shunt placement

Zile et al., JACC CV Imaging Published Online Aug 29, 2025

Differences in Right Ventricular Structure and Function Affect Responses to Interatrial Shunt

HFrEF

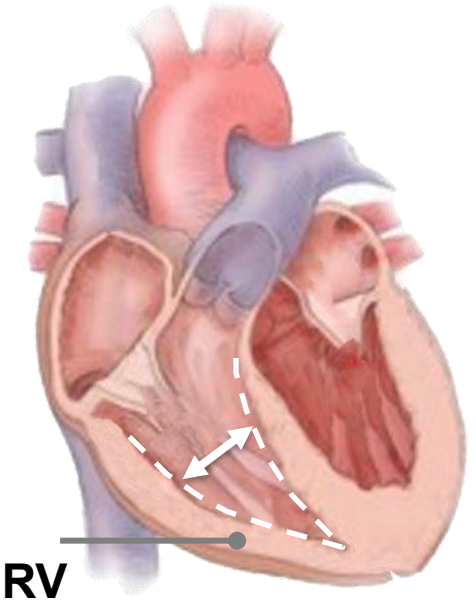


Enlarged RV size

Compliant RV

RIGHT VENTRICLE **able to accept** an increase in redistributed blood volume without resulting in changes in right heart size or increased PA pressure

HFpEF



Normal RV size

Non-compliant RV

RIGHT VENTRICLE **NOT able to accept** an increase in redistributed blood volume, resulting in increased right heart size and increased PA pressure

Zile et al., JACC CV Imaging Published Online Aug 29, 2025

Access to Ventura Shunt Will Benefit HFrEF Patients

Clinical Burden

HFrEF high rates of HF hospitalization and mortality despite GDMT[1]
HF hospitalization and mortality rates increasing since 2012[1,2]

Dire Outcomes

RELIEVE-HF Control Group →

- 15% annualized mortality rate
- 89% annualized rate of HF Events[3]
- 52% annualized rate of HF hospitalization

No Alternatives

No alternative therapies to reduce risk of HF hospitalization in HFrEF patients

Breakthrough

Ventura Interatrial Shunt is needed for HFrEF patients

1. Bozkurt B, et al. J Cardiac Fail 2025; 31:66-116; 2. Sayed A, et al. JAMA Cardiol 2024; 9:585-589; 3. Stone GW, et al. Circulation 2024; 150:1931-1943.

Conditions of Approval Will Support Safe and Responsible Use and Data Collection*

"As part of the benefit-risk determination for Breakthrough Devices subject to a PMA, FDA may accept a greater extent of uncertainty of the benefit-risk profile for these devices if appropriate under the circumstances, including that the uncertainty is sufficiently balanced by other factors, such as the probable benefits for patients to have earlier access to the device … and adequate postmarket controls to support premarket approval…

…FDA intends to weigh the device's impact on patient health, including the probable benefit of earlier access to the device, against the probable risk of harm to patients from the device should subsequent data collection demonstrate that the device is ineffective or unsafe."

- Limited indication
- Requirement for local heart team for patient selection
- Extensive physician training plan
- Gradual and controlled commercial roll-out
- Robust post-approval study
- Registry enrolling all U.S. patients treated with a commercial device

*Similar to those required for structural heart devices

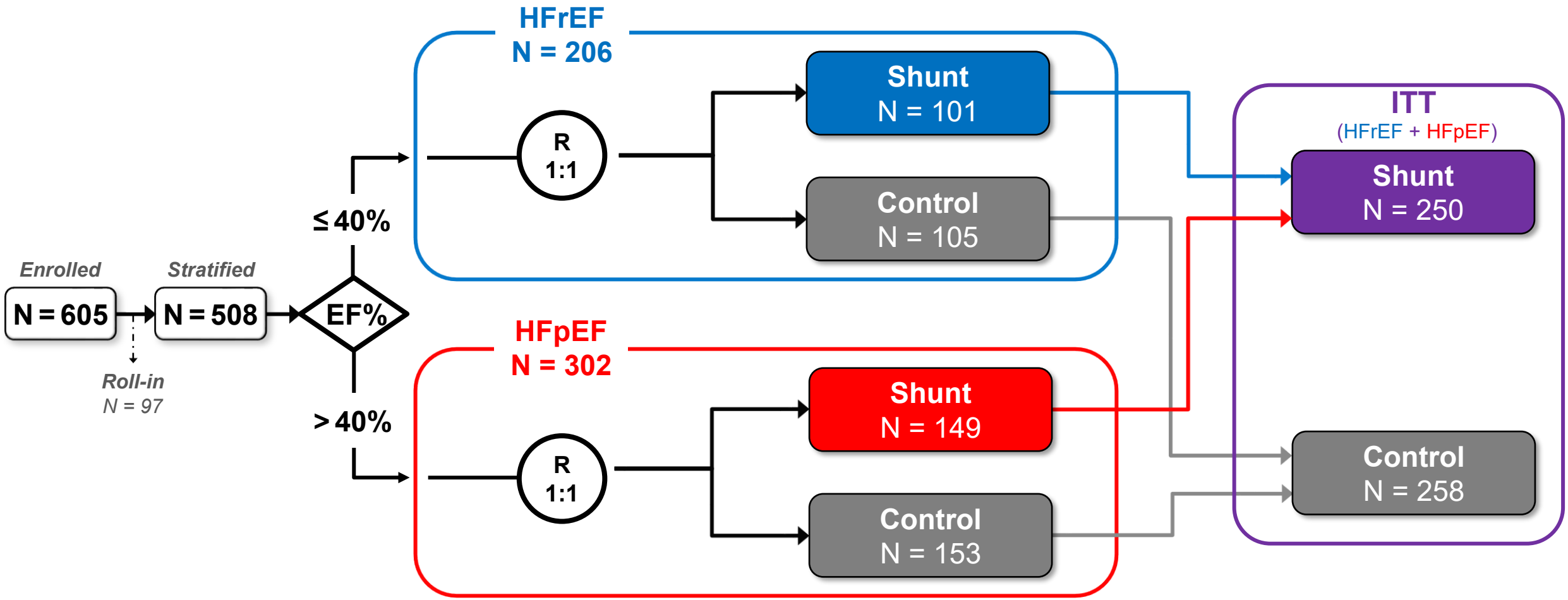
Benefit of Therapy Outweighs the Risk in HFrEF

- ✓ Safety
- ✓ Effectiveness
- ✓ Biological Plausibility
- ✓ Unmet Need / Breakthrough
- ✓ Post-Approval Commitments

RELIEVE-HF Trial Design

Robust, Prespecified Randomization by LVEF

RELIEVE-HF – A Randomized, Double-Blind, Sham-Controlled Trial



Roll-in cohort = unblinded cases used to train sites on the procedure as well as to develop more safety data

Quality Control Assured Throughout the Trial

- Sponsor-independent processes
  - Eligibility committee confirmed patients met eligibility criteria, received maximally-tolerated GDMT, and remained symptomatic
  - Clinical Events Committee (CEC) adjudicated all outcomes
  - Data and Safety Monitoring Board (DSMB) provided trial oversight
  - Echocardiography core laboratory evaluated imaging
  - Data management and biostatistics
- Strict blinding procedures and blinding assessments at 2 timepoints

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 device therapy for HF as assessed by a Central Eligibility Committee
3. HF hospitalization within the prior 12 months and/or elevated (BMI-adjusted) BNP/NT-proBNP – both required for NYHA class II patients
4. 6-minute walk test (6MWT) ≥ 100 meters to ≤ 450 meters

NYHA = New York Heart Association; GDMT = guideline-directed medical therapy; BMI = body mass index;
BNP/NT-proBNP = B-type natriuretic peptide/N-terminal pro-B-type natriuretic peptide

Key Exclusion Criteria

1. Resting SBP < 90 or > 160 mmHg or intractable heart failure
2. Severe pulmonary hypertension defined as PA systolic pressure > 70 mmHg (or pulmonary vascular resistance > 4.0 WU on right heart catheterization 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. Atrial septal defect, patent foramen ovale, anomalous pulmonary venous return, corrected congenital heart defect, severe valve lesions

LVEDD = left ventricular end-diastolic diameter; PA = Pulmonary artery; RVFAC = RV fractional area change;
SBP = systolic blood pressure; TAPSE = Tricuspid annular plane systolic excursion; TTE = transthoracic echocardiography; WU = Wood Units

Final Key Exclusion Criteria After Right Heart Catheterization and Transesophageal or Intracardiac Echocardiography Performed

Hemodynamic, heart rhythm, or respiratory instability

- Need for IV vasopressor or inotrope medication
- Malignant arrhythmias
- Acute respiratory distress or hypoxemia
- SBP < 90 or > 160 mmHg
- Cardiac index < 1.5 L/min/m^2
- Mean PCWP < 7 mmHg or > 35 mmHg
- Severe pulmonary hypertension*
- RA pressure ≥ LA pressure (or PCWP) when left atrial pressure (PCWP) is ≥ 7 mmHg

Anatomical anomaly that precludes implanting shunt

- Minimal fossa ovalis thickness > 6 mm or lengths < 10 mm
- Atrial septal defect or patent foramen ovale with > trace shunting
- Atrial septal aneurysm
- Intracardiac thrombus

* PA systolic pressure > 70 mmHg with pulmonary vascular resistance > 4.0 WU on right heart catheterization that cannot be reduced by vasodilator therapy

SBP = systolic blood pressure; PCWP = pulmonary capillary wedge pressure; RA = right atrial; LA = left atrial

Primary Safety Endpoint

- Composite of device- or procedure-related major adverse cardiovascular or neurologic events (MACNE) in shunt arm within 30 days
  - All-cause death, stroke, systemic embolism, need for open cardiac surgery or major endovascular surgical repair
- **Performance goal 11%, analyzed with an exact binomial test**

Primary Effectiveness Endpoint

- Win ratio hierarchical composite of
  1. All-cause death
  2. Heart transplantation or left ventricular assist device (LVAD) implantation (HTLV)
  3. All HF hospitalizations (HFH)
  4. All outpatient worsening HF Events (WHF)
  5. Change in health status through longest blinded follow-up measured by KCCQ-OSS
- **Analyzed by win ratio when last enrolled patient reached 12 months with longest follow-up through 24 months**

KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire overall summary score

Prespecified Secondary Endpoints

1. KCCQ change from baseline to 12 months (ANCOVA)
2. All HFHs adjusted for all-cause mortality through 24 months (joint frailty)
3. Composite death, HTLV, or HFH through 24 months (time-to-first event)
4. Composite death or HFH through 24 months (time-to-first event)
5. Cumulative HFHs through 24 months (Nelson-Aalen estimate)
6. HFH through 24 months (time-to-first event)
7. Primary Effectiveness Endpoint including mortality, LVAD/Transplant, HFH, and WHF treated as an outpatient, but without KCCQ (win ratio)
8. 6MWT change from baseline to 12 months (ANCOVA)

Statistical Considerations for ITT Analysis

- Effectiveness powered for all randomized patients
- Randomization stratified by baseline LVEF (HFrEF vs HFpEF), to assess "poolability" (i.e., consistent treatment effects) using an interaction test
- Study protocol
  - *"The safety and effectiveness of the shunt according to pre-specified LVEF subgroups will be assessed by interaction testing."*[1]
  - *"Primary effectiveness endpoint analysis will be performed on a combined HFrEF and HFpEF population. The homogeneity of the treatment effect will be examined in an analysis of the interaction between treatment effect and the HFrEF/HFpEF subpopulation…"*[1]

1. RELIEVE-HF Protocol (CL7018) versions (numbered 0.0-7.0)

Safety and Effectiveness Results

Gregg Stone, MD

Director of Academic Affairs

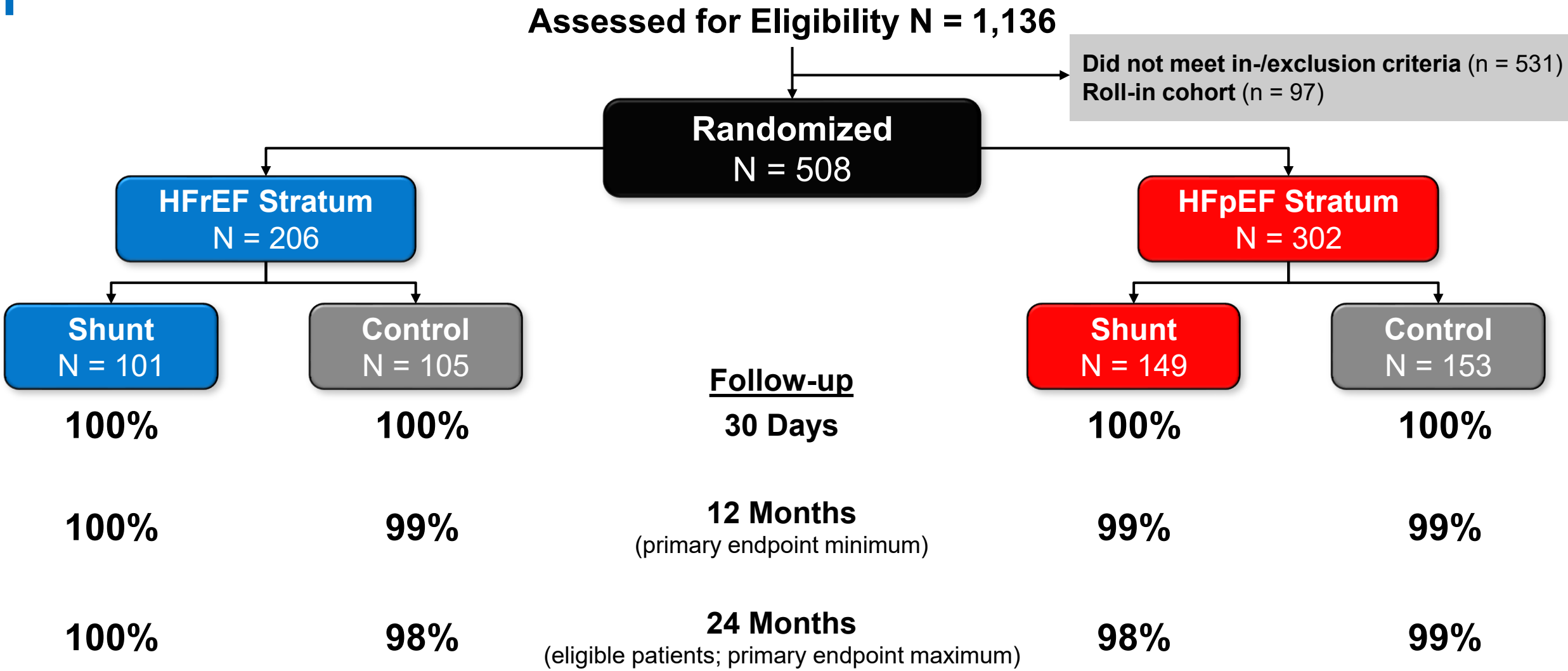
Professor of Medicine (Cardiology)

Professor of Population Health Sciences and Policy

Icahn School of Medicine at Mount Sinai, New York

Results: Patient Disposition and Baseline Characteristics

RELIEVE-HF: Patient Disposition



Median follow-up = 22.0 mos (13.3, 23.9)

Selected Baseline Characteristics

	HFrEF Total N = 206		HFpEF Total N = 302		p-value*
	n	%	n	%	
Age, years	70 (62, 76)		75 (68, 80)		< 0.0001
Male	168	81.6%	151	50.0%	< 0.0001
Diabetes mellitus	105	51.0%	144	47.7%	0.47
LVEF (core lab)	30.5% (24.4, 35.3)		55.5% (48.5, 62.3)		< 0.0001
Ischemic cardiomyopathy	129	62.6%	105	34.8%	< 0.0001
NYHA Class III	196	95.1%	294	97.4%	0.19
KCCQ Summary Score	55 (39, 72)		48 (33, 64)		0.002
eGFR < 60 mL/min/1.73m^2	150	72.8%	226	74.8%	0.61
NTproBNP, pg/mL	2162 (1069, 3840)		1547 (816, 2700)		0.0003

Nearly all patients were NYHA class III and had multiple comorbidities

Continuous data measurements are median and IQR; * p-value between HFrEF vs HFpEF (not reviewed by FDA)

Baseline Medications and Electrical Therapies

	HFrEF Total N = 206		HFpEF Total N = 302		
	n	%	n	%	p-value*
Beta-blockers	200	97.1%	247	81.8%	< 0.0001
Renin-angiotensin system inhibitors	188	91.3%	173	57.3%	< 0.0001
ACEi	14	6.8%	56	18.5%	< 0.0001
ARB	15	7.3%	62	20.5%	< 0.0001
ARNi	159	77.2%	55	18.2%	< 0.0001
Mineralocorticoid receptor antagonists	151	73.3%	168	55.6%	< 0.0001
SGLT2 inhibitors	104	50.5%	102	33.8%	0.0002
ICD or CRT-D	184	89.3%	54	17.8%	< 0.0001
CRT-D or CRT-P	92	44.7%	37	12.3%	< 0.0001

Use of GDMT and CRT was high, especially in HFrEF

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor
* p-value between HFrEF vs HFpEF (not reviewed by FDA)

Results: Implant Procedure Metrics

Procedure Metrics (ITT)

	Shunt N = 250		Control N = 258	
	n	%	n	%
Shunt implant attempt	250	100%	1	0.4%
Shunt implanted successfully	250	100%	1	0.4%
Procedure duration, mins	80 (59, 100)		43 (30, 55)	
Fluoroscopy time, mins	14 (10, 20)		4 (2, 7)	
Heparin administered, units	9000 (7000, 12000)		-	
Activated clotting time, secs	291 (246, 342)		-	
Contrast administered, mL	0 (0, 0)		0 (0, 0)	
Hospital duration post procedure, days	1 (1, 1)		1 (1, 1)	

Shunt implant success was 100%
Procedures were brief and most patients were discharged the next day

Continuous data measurements are median and IQR

Results: Safety

Primary Safety Endpoint at 30 Days was Met (ITT)

	Shunt Through 30 Days N = 250	
	Total n	Rate*
Any device/procedure-related MACNE	0	0%
All-cause death	0	0%
Stroke	0	0%
Systemic embolism	0	0%
Need for open cardiac surgery	0	0%
Need for major endovascular surgical repair	0	0%

30-day Device- or Procedure-Related MACNE = 0% (upper 97.5% CI 1.5%), < performance goal of 11% (p < 0.0001)

* Event rates are Kaplan-Meier estimates

Analysis of All Shunt-Treated Patients: Primary Safety Endpoint at 30 Days and 2 Years

Shunt-treated patients (250 ITT Shunt + 1 ITT Control + 97 Roll-in)	Shunt Through 30 Days N = 348		Shunt Through 2 Years N = 348	
	Total n	Rate*	Total n	Rate*
Any device/procedure-related MACNE	0	0%	0	0%
All-cause death	0	0%	0	0%
Stroke	0	0%	0	0%
Systemic embolism	0	0%	0	0%
Need for open cardiac surgery	0	0%	0	0%
Need for major endovascular surgical repair	0	0%	0	0%

- 30-day Device- or Procedure-Related MACNE = 0%
- 2-year Device- or Procedure-Related MACNE = 0%

* Event rates are Kaplan-Meier estimates

All MACNE Through 2 Years: HFrEF Population

Whether or not device- or procedure-related

	Shunt N = 101		Control N = 105		Hazard Ratio (95% CI)
	Total n	Rate*	Total n	Rate*	
Any MACNE during first 2 years (first event)	16	16.6%	28	32.7%	0.56 (0.30, 1.07)
All-cause death	13	14.3%	20	26.8%	0.63 (0.31, 1.26)
Stroke	3	1.1%	2	2.2%	1.54 (0.26, 9.23)
Systemic embolism	0	0%	0	0%	-
Need for open cardiac surgery	1	1.5%	6	9.0%	0.16 (0.02, 1.32)
Need for major endovascular surgical repair	0	0%	0	0%	-

No differences in all MACNE or its component safety events between Shunt and Control

* Event rates are Kaplan-Meier estimates

Additional Safety Endpoints Through 2 Years: HFrEF

Whether or not device- or procedure-related

	Shunt N = 101		Control N = 105		
	Total n	Rate*	Total n	Rate*	p-value
Shunt implant embolization/thrombosis	0	0%	-	-	-
Pericardial effusion/cardiac tamponade	0	0%	0	0%	-
BARC types 3 or 5 bleeding	1	1.0%	3	3.1%	0.33
Cerebrovascular events	4	4.1%	3	3.2%	0.67
CNS infarction (stroke)	3	3.1%	2	2.2%	0.63
CNS hemorrhage (intracerebral or subarachnoid)	0	0%	1	1.2%	0.31
Transient ischemic attack	1	1.0%	1	1.0%	0.98
Myocardial infarction	1	1.1%	3	3.5%	0.32
Systemic embolization	0	0%	0	0%	-
Pulmonary emboli	1	1.7%	0	0%	0.36

No safety issues were identified in Shunt-treated patients with HFrEF

* Event rates are Kaplan-Meier estimates

Site-Reported (Blinded) SAEs and Adverse Device Effects: HFrEF Population

	Shunt N = 101	Control N = 105	RR (95% CI)	p-value
All SAE	**172**	**282**	0.59 (0.50, 0.69)	< 0.0001
Cardiovascular	**102**	**160**	0.62 (0.49, 0.79)	0.0001
Non-cardiovascular	**70**	**122**	0.56 (0.42, 0.76)	0.0002
Respiratory	14	22		
Renal urinary	11	19		
Infection	7	17		
Injury	3	11		
Gastrointestinal	13	10		
Neoplasm	2	10		
Other	20	33		
Unexpected adverse device effect	**0**	**0**		

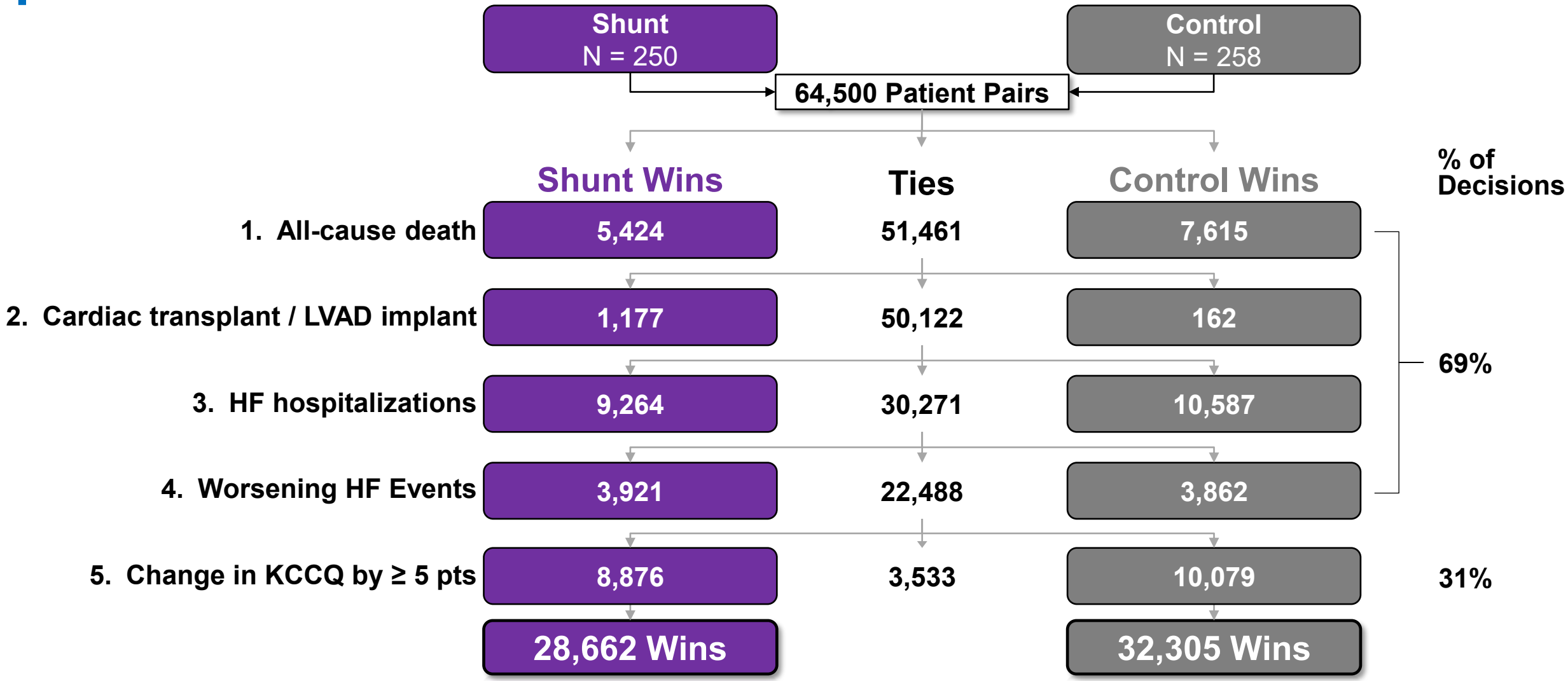
MedDRA coded events

Summary: Ventura Shunt has Strong Safety Profile

- Primary 30-day safety endpoint of device- or procedure-related MACNE met: $p < 0.0001$
- No device- or procedure-related MACNE during 2-year follow-up
- Shunt implant success: 100%
- Peri-procedural complications rare and not increased in Shunt group; and no Shunt embolization nor adherent thrombus during 2-year follow-up
- Stroke, MI, or thromboembolic events occurred infrequently and at similar rates in Shunt and blinded Control groups

Results: Effectiveness

Win Ratio Analysis for the Primary Hierarchical Composite Effectiveness Endpoint (ITT)



Win Ratio* = 0.86 (95% CI: 0.61, 1.22); p-value = 0.20

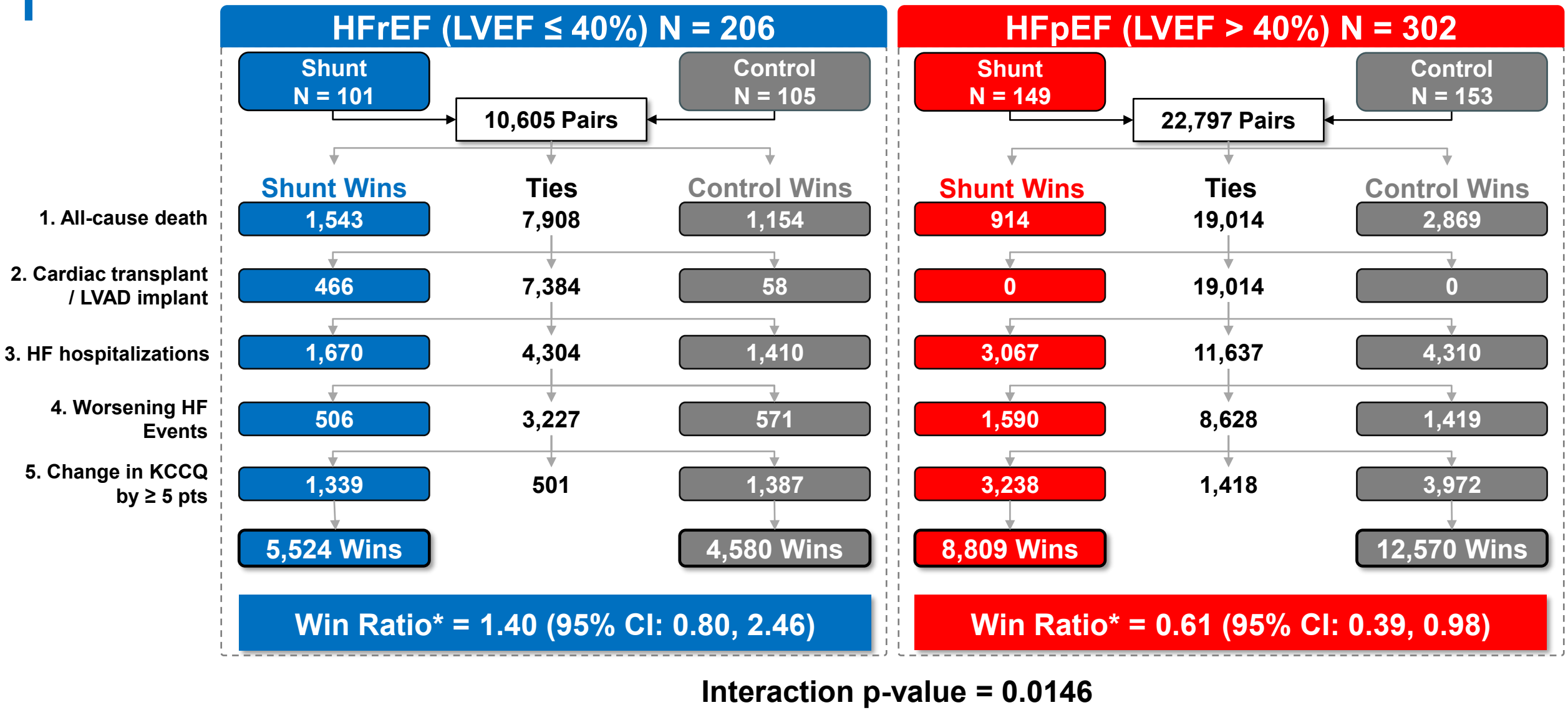
* Weighted for interim analysis

LVEF Strata versus 14 Exploratory Subgroups

Characteristic	LVEF Strata (HFrEF and HFpEF)	All Other Subgroups* (Age, Sex, BMI, Diabetes, Hypertension, Ischemic/Non, BL NYHA class, BL 6MWT, BL KCCQ, Shunt encapsulation process, US vs Non, Prior COVID-19 Y/N, patent/non-patent)
Stratification variable (at randomization)	YES	NO
Included in "Scientific Rationale for Study Design" section of protocol	YES	NO
Separate sample size calculation based on these groups in protocol	YES	NO
Included in "Topline Analysis" prior to unblinding for primary and secondary endpoints	YES	NO
Included in "Primary Effectiveness Endpoint" section of SAP (section 4.1.2) with an interaction analysis	YES	NO

*Site was also a stratification variable

Primary Effectiveness Outcome by LVEF



Interaction p-value = 0.0146

* Weighted for interim analysis. Confidence intervals are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference

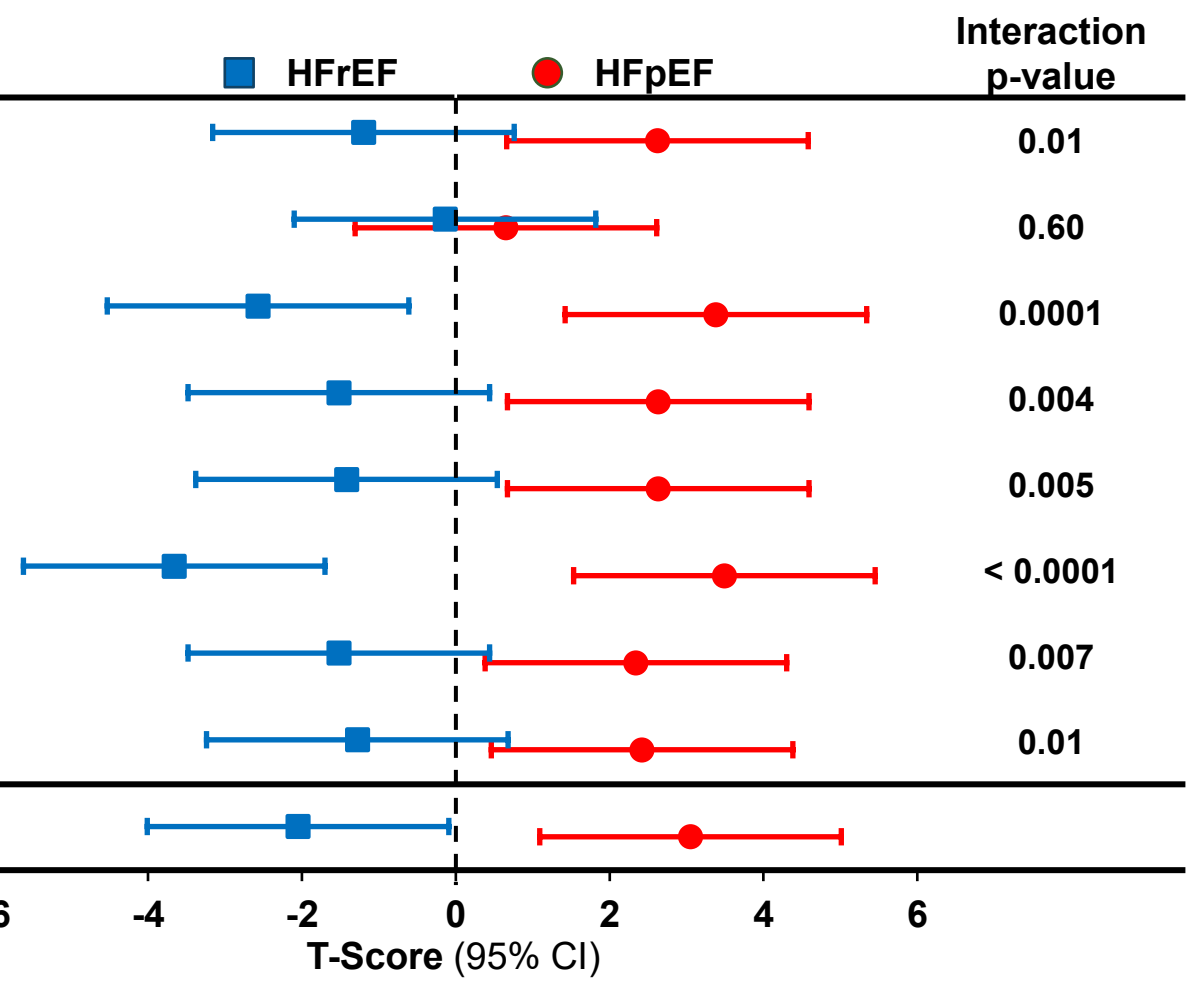
Analyses of the Totality of Effectiveness Data from RELIEVE-HF

Global Statistical Test (GST) Evaluates Totality of Evidence

- Integrates treatment effects from prespecified primary & secondary outcomes
  - HF Events and KCCQ (components of primary endpoint)
  - First and recurrent events
- “Null Hypothesis” = Shunt Treatment does not affect HF outcomes
- “Alternative Hypothesis” = Shunt Treatment affects HF outcomes
- GST accounts only for unique contribution of endpoints & avoids double counting

Totality of Evidence Supports Effectiveness of Ventura Interatrial Shunt in HFrEF

	T-Score (95% CI) HFrEF	T-Score (95% CI) HFpEF	Interaction p-value
Primary Endpoint (Win Ratio)	-1.20 (-3.16, 0.76)	2.62 (0.66, 4.58)	0.01
S1: KCCQ change from Baseline	-0.14 (-2.10, 1.82)	0.65 (-1.31, 2.61)	0.60
S2: Recurrent HFH (Joint Frailty)	-2.57 (-4.53, -0.61)	3.38 (1.42, 5.34)	0.0001
S3: Time to first death, LVAD / transplant, or HFH	-1.52 (-3.48, 0.44)	2.63 (0.67, 4.59)	0.004
S4: Time to first death or HFH	-1.42 (-3.38, 0.54)	2.63 (0.67, 4.59)	0.005
S5: Cumulative HFH (Nelson-Aalen)	-3.66 (-5.62, -1.70)	3.49 (1.53, 5.45)	< 0.0001
S6: Time to first HFH	-1.52 (-3.48, 0.44)	2.34 (0.38, 4.30)	0.007
S7: Primary Endpoint without KCCQ (Win Ratio)	-1.28 (-3.24, 0.68)	2.42 (0.46, 4.38)	0.01
Global Statistical Test (GST)	-2.05 (-4.01, -0.09)	3.05 (1.09, 5.01)	
	p = 0.04		



Low likelihood that the positive GST outcome is a chance finding (i.e. Type-I error)

(See figure 24 of the briefing document)

Confidence intervals and nominal P-values are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

Limitations of Win Ratio Analysis

Win Ratio

- Only counts one win, loss, or tie per patient pair
- Does not reflect all events patients are experiencing
- Underestimates the total burden of disease

Recurrent Events Analysis

- Cumulative hazard rates for both first and recurrent events over time
- Represents risk of all adverse outcomes
- Appropriately reflects overall burden of disease

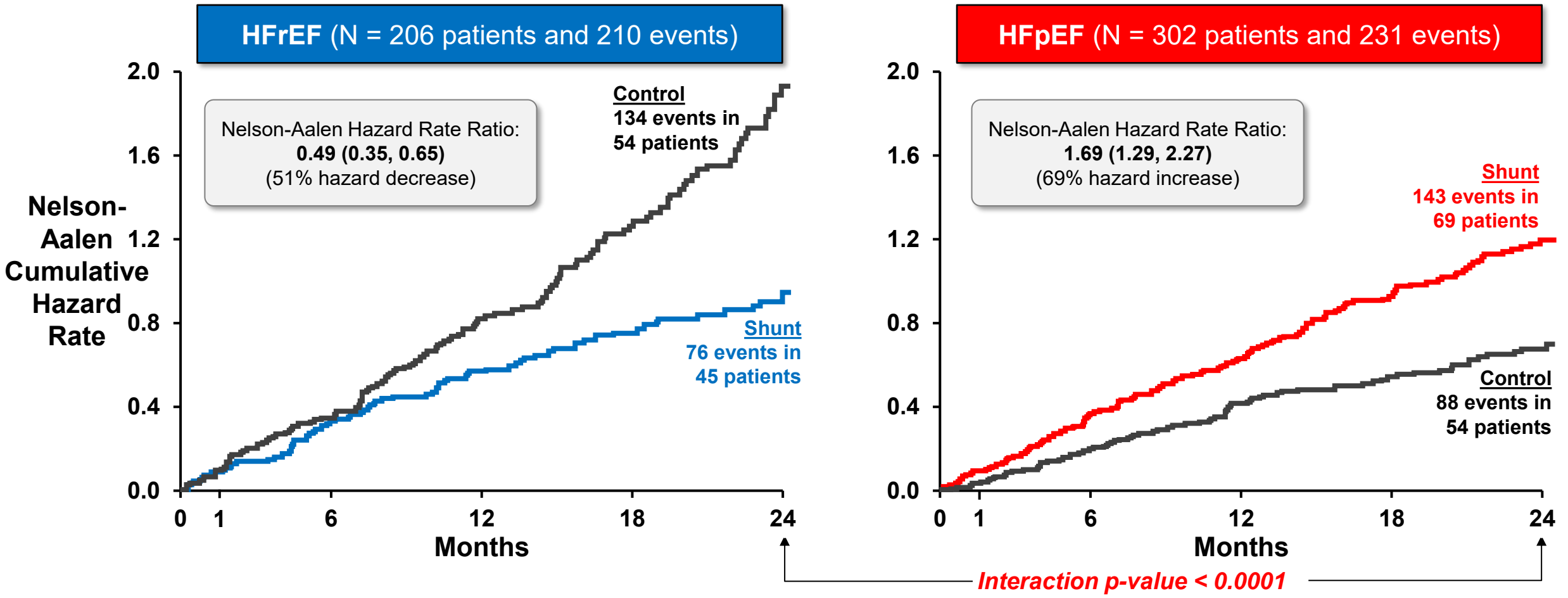
Number of HFH and WHF Events Excluded from the Win Ratio Analysis in HFrEF Patients

		Shunt N = 101	Control N = 105
Win Ratio Tier 3 HFH Events	All HFHs	41	78
	HFHs excluded due to death or HT/LVAD	10	40
	% HFHs excluded	24.4%	51.3%
	HFHs remaining	31	38
Win Ratio Tier 4 WHF Events	All WHFs	21	30
	WHFs excluded due to death or HT/LVAD or HFH	5	10
	% WHFs excluded	24.0%	33.3%
	WHFs remaining	16	20

The win ratio analysis concealed 38% of all HF-related events, including nearly twice as many events that occurred in the control group compared with the shunt group

HFrEF Benefit: Reduction of All HF Events

(All-Cause Mortality, Cardiac Transplant or LVAD, Heart Failure Hospitalization, Worsening HF Events)

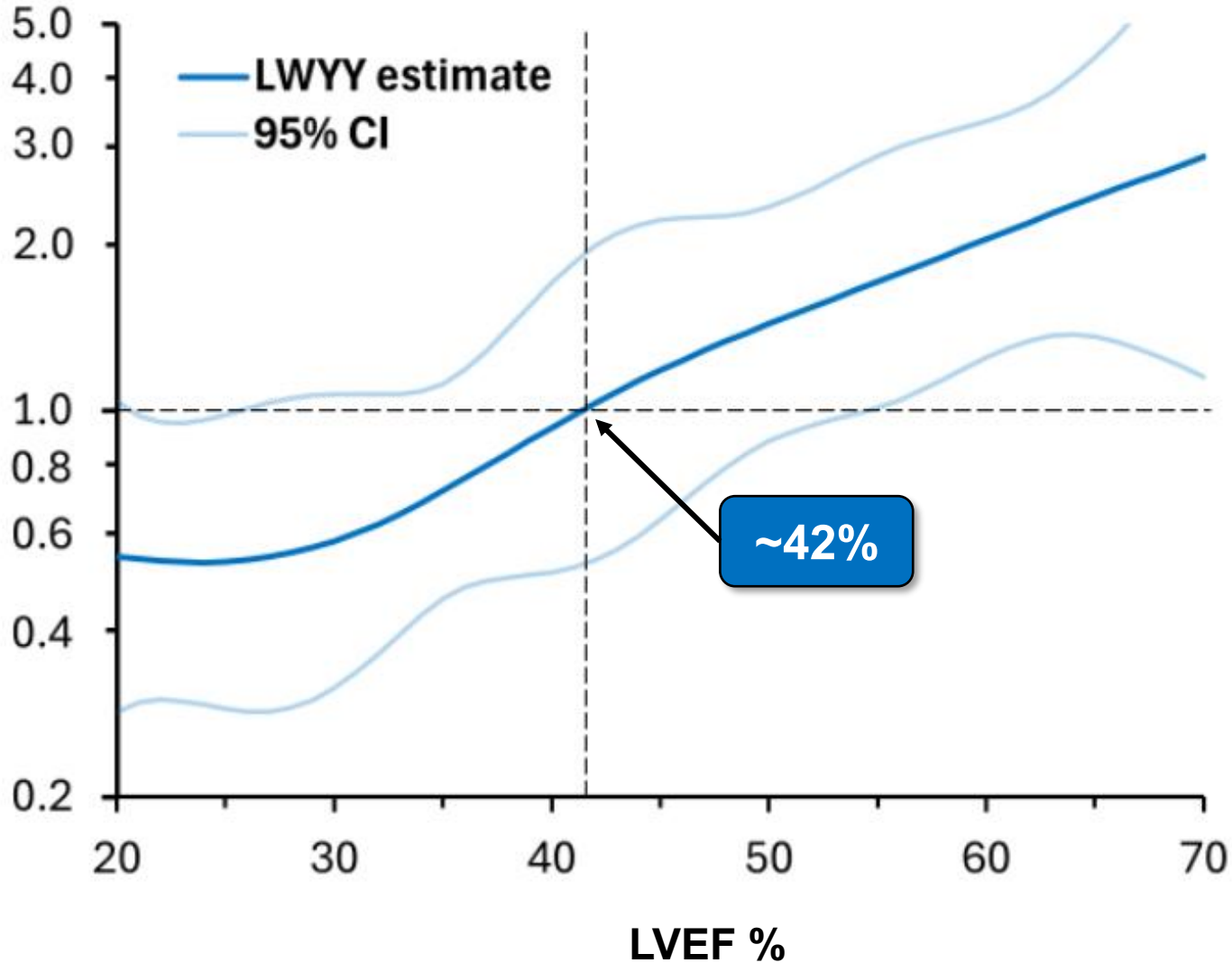


HFrEF patients ⇨ Greatest risk of HF Events & greater unmet clinical need
HFrEF patients with shunt-treatment ⇨ Pronounced reduction in HF Events

Confidence intervals are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

Continuous Relationship Between Baseline LVEF and All HF Events

All HF Events
(Shunt vs Control)
LWYY HR



Sensitivity Analysis of Baseline LVEF Ranges > 40% to ≤ 45%

	LVEF > 40% to ≤ 43% N = 32		LVEF > 40% and ≤ 44% N = 38		LVEF > 40% and ≤ 45% N = 46	
	Shunt N = 17	Control N = 15	**Shunt** N = 20	Control N = 18	**Shunt** N = 23	Control N = 23
Patient-years of follow-up	**26.61**	**22.54**	**30.54**	**26.58**	**35.73**	**35.79**
Death, HT/LVAD, HFH, WHF, n **(%/y)**	8 **(30.1%)**	20 **(88.7%)**	12 **(39.3%)**	20 **(75.2%)**	19 **(53.2%)**	23 **(64.3%)**
RR (95% CI)	**0.34** (0.14, 0.76)		**0.52** (0.25, 1.06)		**0.83** (0.44, 1.53)	

HF event rates were reduced by Shunt treatment up to an LVEF of 43%. The effect was attenuated when including higher LVEFs but were not worse even when patients with LVEF up to 45% were included.

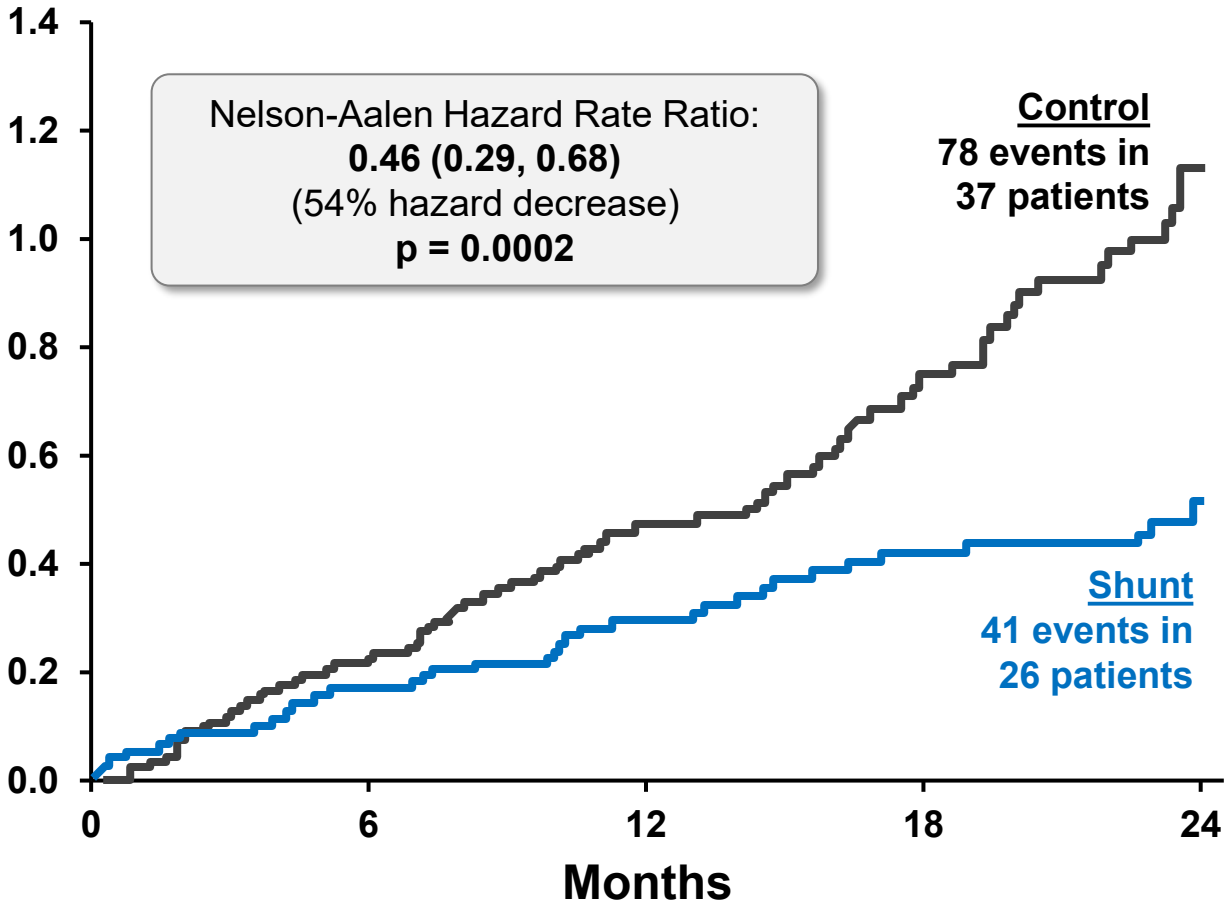
Probable HFrEF Benefit: Reduction of All HF Events

	HFrEF Shunt N = 101 pts *[Events]*	HFrEF Control N = 105 pts *[Events]*	2yr Nelson-Aalen Hazard Rate Ratio *(95% CI)*	Reduction (%)	NNT*
Primary Endpoint HF Events *[2yr]*	**76**	**134**	**0.49** *(0.35, 0.65)*	**51%**	**1.0**
All-cause death	**13**	**20**	**0.48** *(0.20, 1.06)*	**52%**	**6.4**
LVAD/HT	**1**	**6**	**0.15** *(0.00, 0.98)*	**85%**	**12.7**
All HFHs	**41**	**78**	**0.46** *(0.29, 0.68)*	**54%**	**1.6**
All outpatient WHFs	**21**	**30**	**0.64** *(0.33, 1.17)*	**36%**	**7.3**

Shunt-treated HFrEF ⇨ Consistent relative risk reductions for all primary HF Event components

*Number of patients needed to treat with the shunt to prevent on average 1 event during 2-year follow-up. Confidence intervals are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

HFrEF Benefit: Heart Failure Hospitalization



Heart Failure Hospitalization 24-Month Cumulative Hazard:

Control: *1.13 events per patient*

Treated: *0.52 events per patient*

Shunt-treated HFrEF ⇨ Marked reduction in HF hospitalization with ongoing benefit at 2 years

Confidence intervals and nominal P-values are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

HFrEF Benefit: Adjudicated Causes of Death

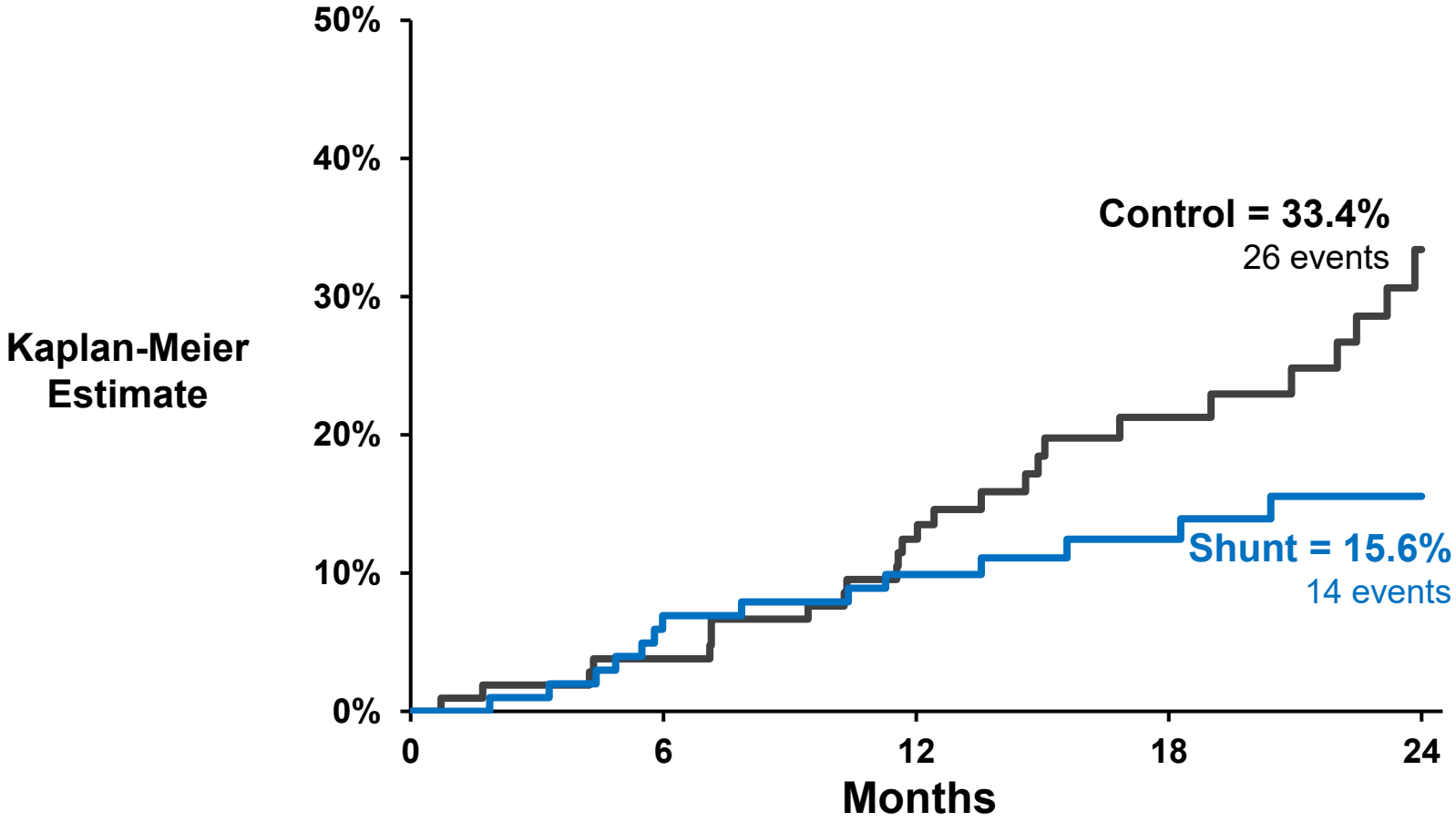
	Shunt N = 101 pts	Control N = 105 pts
All-cause	**13**	**20**
Cardiovascular or unknown	12	14
Cardiovascular	11	12
Unknown	1	2
Non-cardiovascular	1	6

- There were 2 fewer “CV or other” deaths with Shunt treatment, and 5 fewer non-CV deaths with Shunt treatment
- Non-cardiac diseases trigger/worsen heart failure, and mortality rates are increased in HF patients with non-cardiac disorders (especially cancer and infections)*

Numerically fewer deaths in the HFrEF cohort treated with the Shunt

*Drozd M et al. Circ HF 2024; Bruhn J et al. EHJ 2023; Ameri P et al. EHJ 2023; Jaiswal V et al. EHJ Open 2023; Arfaras-Melainis A et al. HF Rev 2020

Risk of All-Cause Death or Cardiac Transplant / LVAD Implant in HFrEF (Terminal Events)



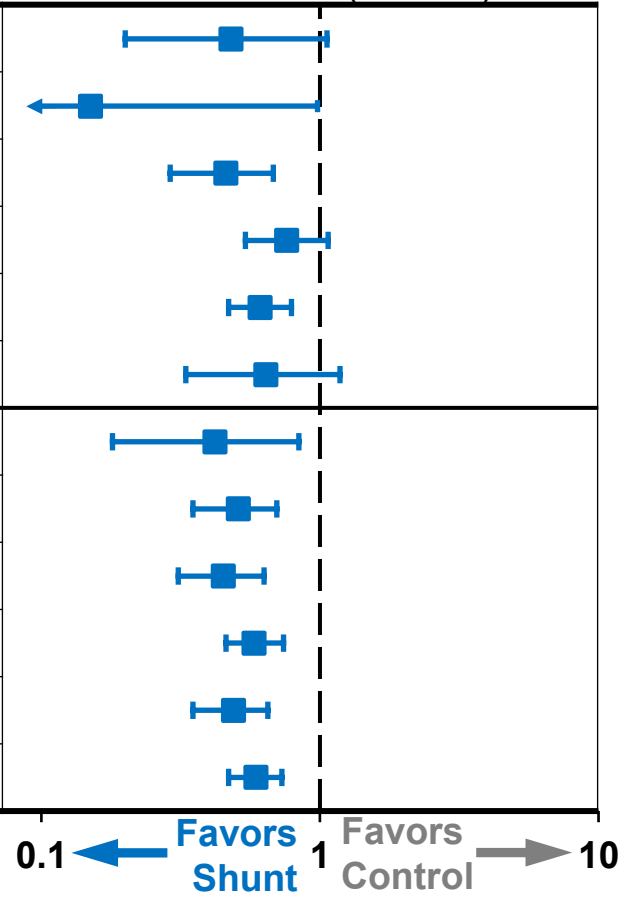
	Shunt N = 101	Control N = 105
Hazard ratio	**0.52** (0.27, 1.00)	
P-value	**0.04**	

Shunt-treated patients had a 48% reduction in death, heart transplant, or LVAD treatment

Confidence intervals and nominal P-values are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

Nelson-Aalen Cumulative Hazard Rates at 24 Months (HFrEF)

		Events (#) Shunt (N = 101) / Control (N = 105)	Hazard rate (95% CI)
Single Event Types	All-Cause Death	13 / 20	**0.48** (0.20, 1.06)
	Heart Transplant/LVAD (HT/LV)	1 / 6	**0.15** (0.00, 0.98)
	Hospitalization for HF (HFH)	41 / 78	**0.46** (0.29, 0.68)
	Hospitalization not for HF (NHFH)	68 / 85	**0.76** (0.54, 1.07)
	All-Cause Hospitalization (ACH)	109 / 163	**0.61** (0.47, 0.79)
	Worsening HF Outpatient (WHF)	21 / 30	**0.64** (0.33, 1.17)
Composite Event Types	Terminal Events (All-cause Death, HT/LV)	14 / 26	**0.42** (0.18, 0.84)
	WHF and HFH	62 / 108	**0.51** (0.35, 0.70)
	All-cause Death, HT/LV, HFH	55 / 104	**0.45** (0.31, 0.63)
	All-cause Death, HT/LV, ACH	123 / 189	**0.58** (0.46, 0.74)
	HF Events (All-cause Death, HT/LV, HFH, WHF)	76 / 134	**0.49** (0.35, 0.65)
	All Events (All-cause Death, HT/LV, ACH, WHF)	144 / 219	**0.59** (0.47, 0.73)

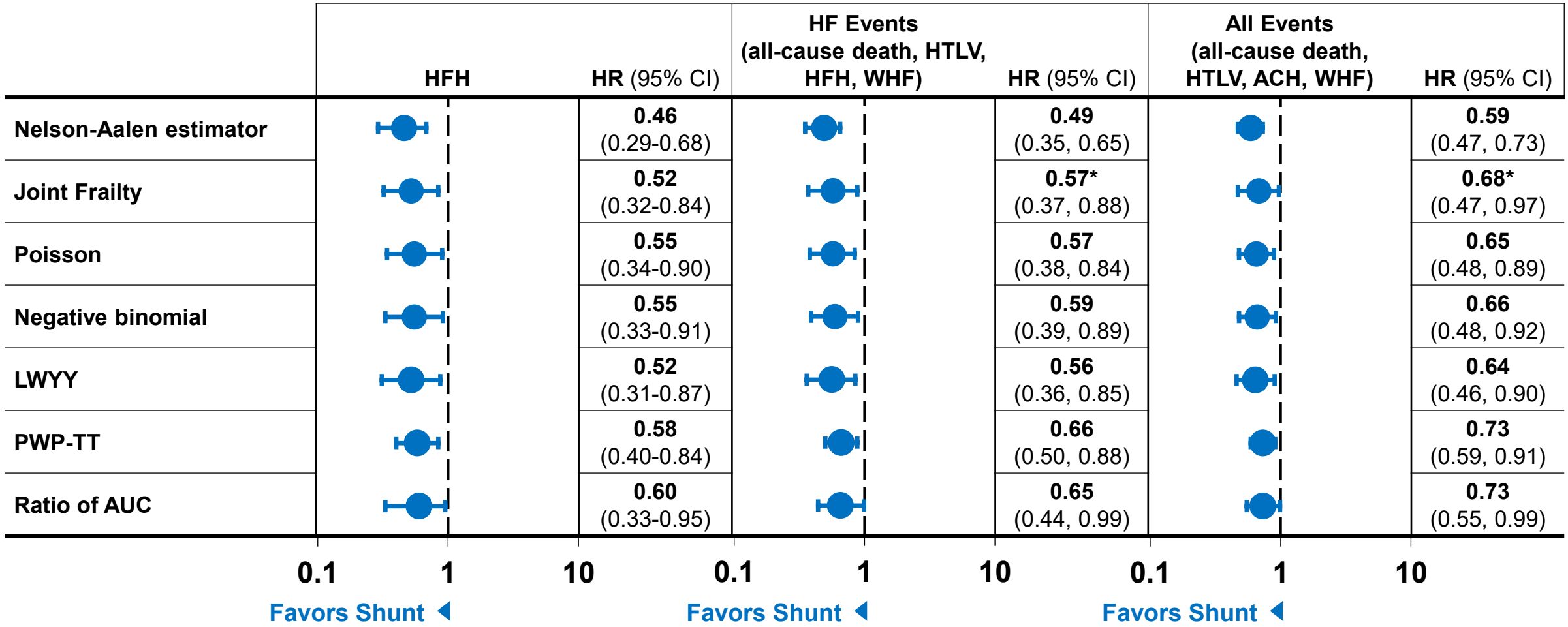


In HFrEF, Shunt treatment was associated with consistent, robust reductions in all event types

(Including hospitalizations, outpatient worsening episodes, and terminal outcomes)

Confidence intervals are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

Recurrent Event Outcomes by 24 Months in Reduced LVEF ≤ 40% (HFrEF) Stratum



*Non-fatal events, adjusted for competing risk of terminal events

Confidence intervals are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

HFrEF Sample Size and Number of Events Were Large Enough to Provide Robust Results

Event Type	HFrEF Total events in 206 pts
Single Events	
Death	33
Heart transplant/LVAD (HT/LV)	7
Hospitalizations for HF (HFH)	119
All-cause hospitalizations (ACH)	272
Worsening HF out-patient events (WHF)	51
Composite Events	
Terminal events (Death, HT/LV)	40
Primary endpoint HF events (Death, HT/LV, HFH, WHF)	210
All events (Death, HT/LV, ACH, WHF)	363

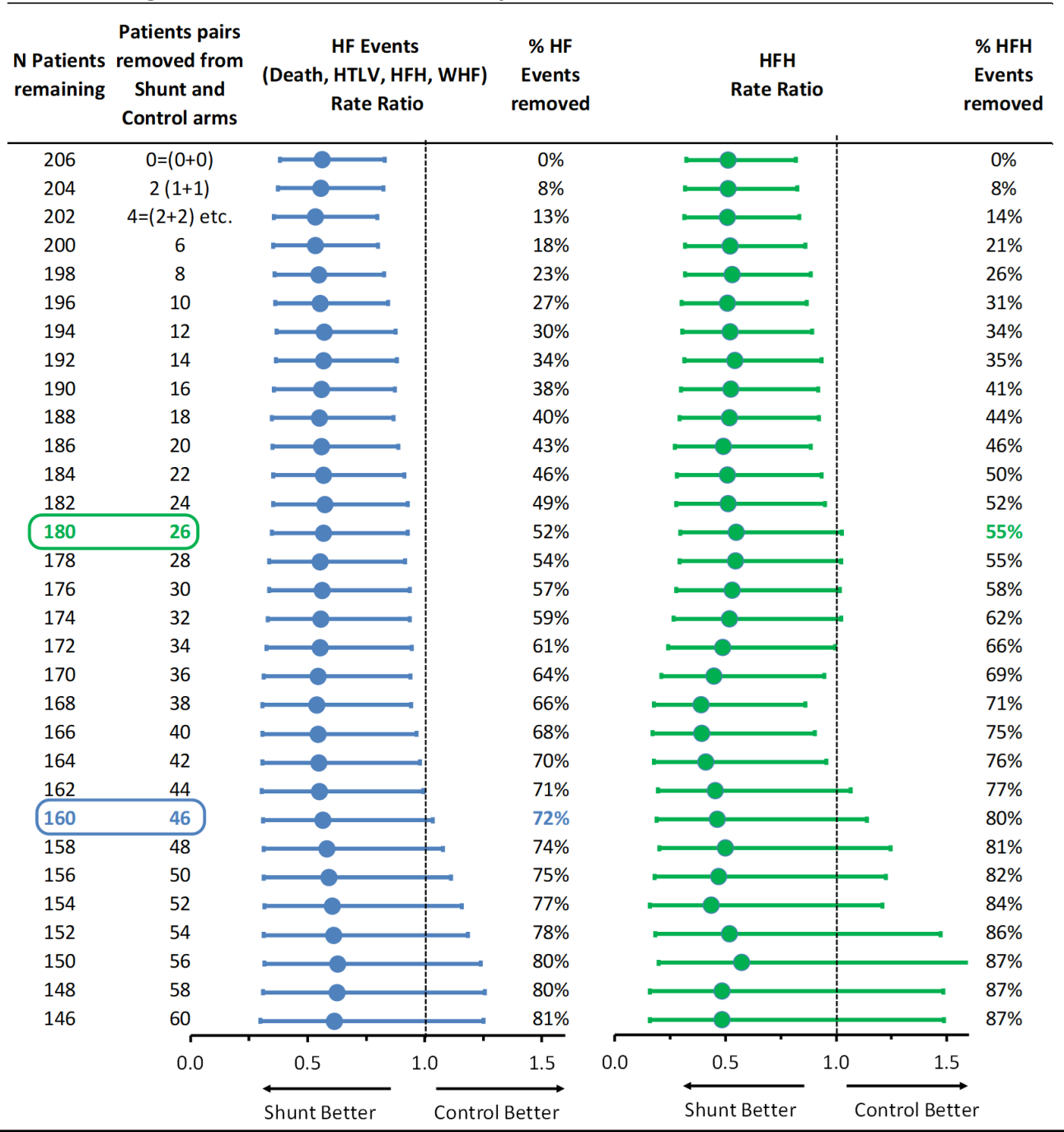
Symmetric Trimming Analysis* for HF Events and HFHs in HFrEF Patients

- Equal numbers of patients were sequentially removed from both groups, starting with those with the highest number of HF events
- For **all HF Events**, the 95% UCB of < 1 was preserved until 23 pairs of Shunt and Control patients were removed, representing 72% of all events
- For **all HFHs**, the 95% UCB of < 1 was preserved until 13 pairs of Shunt and Control patients were removed, representing 55% of all events

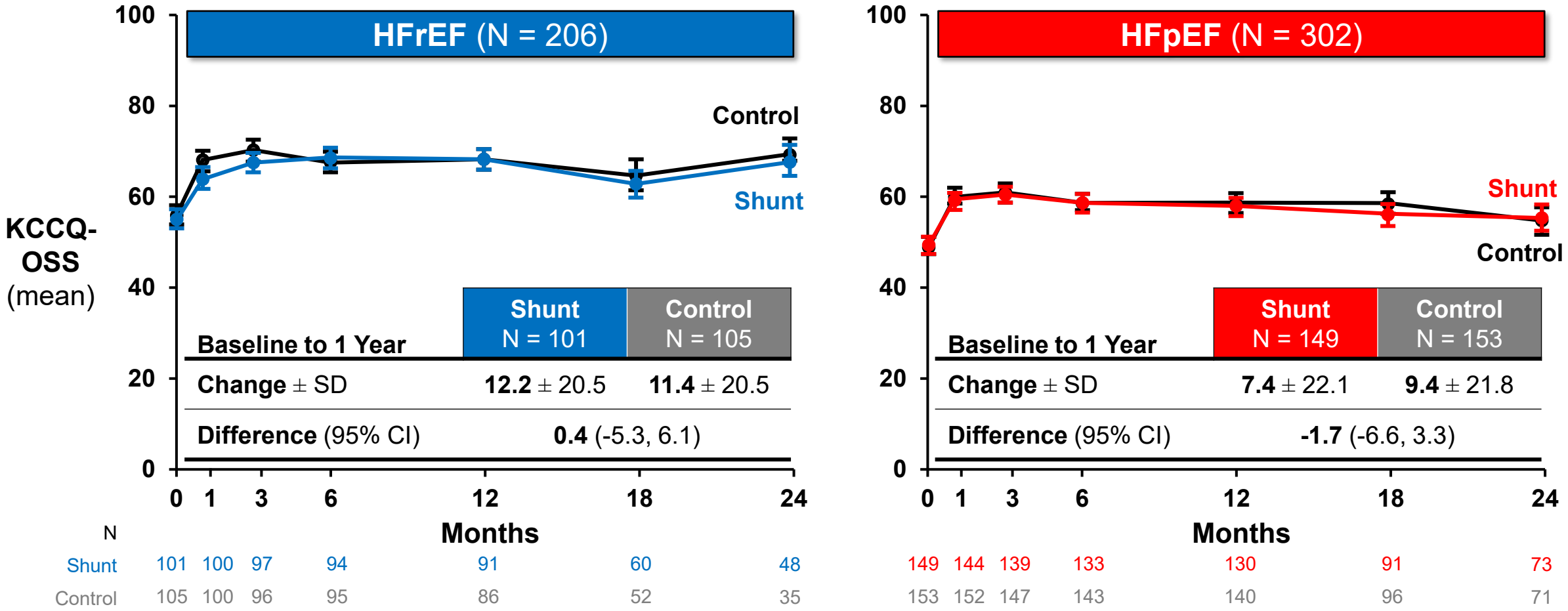
These results show that the treatment effect of the atrial shunt in HFrEF is robust and distributed across the full spectrum of patients experiencing the majority of events—not just restricted to a few outliers

*FDA has reviewed the event data but has not reviewed this analysis, which was performed after Sponsor saw FDA's slide presentation.

Negative Binomial Analysis of Recurrent Events



Change in KCCQ-OSS During 2-Year Follow-up



All patient groups felt better, with no differences in KCCQ between Shunt and Control, despite marked differences in HF Events

Confidence intervals are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

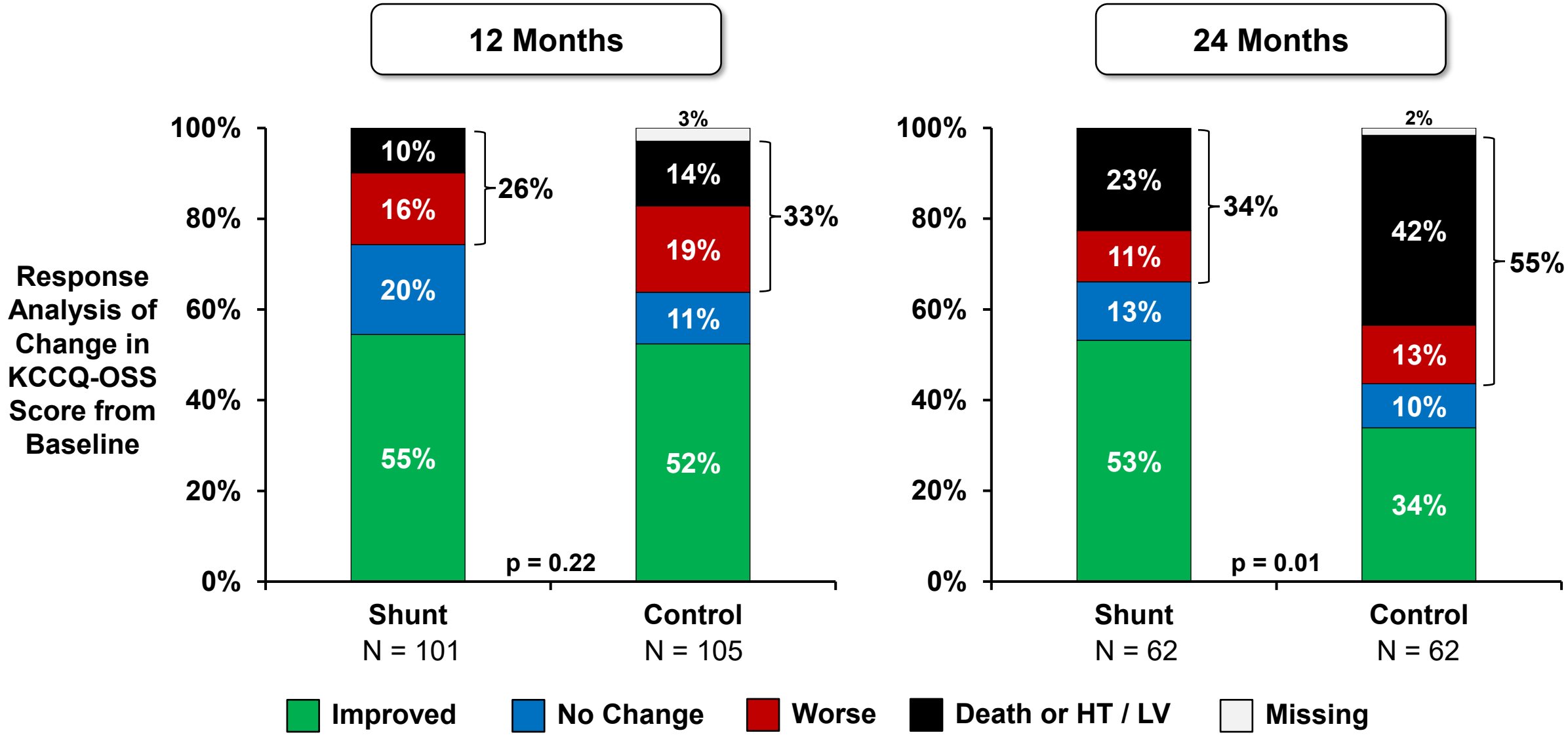
Recent Blinded, Randomized Trials Showing Reduced Death and/or HFH with Minimal Between-Group Change in KCCQ

Study	N	Disease	Intervention	Primary Endpoint: Clinical Event(s)	Primary Endpoint: HR or RRR	Between-group Change in KCCQ (MCID = 5 pts)
EMPEROR-Reduced[1]	3,730	HFrEF	Empagliflozin	CV death or HF hospitalization	0.75	**+1.7**
EMPEROR-Preserved[2]	5,988	HFpEF	Empagliflozin	CV death or HF hospitalization	0.79	**+1.3**
DAPA-HF[3]	4,744	HFrEF	Dapagliflozin	Worsening HF or CV death	0.74	**+2.8**
PARADIGM-HF[4]	8,399	HFrEF	Sacubitril/ Valsartan	CV death or HF hospitalization	0.80	**+1.6**
FINEARTS-HF[5]	6,001	HFpEF	Finerenone	CV death or worsening HF	0.79	**+1.6**
RELIEVE-HF (Reduced)[6]	206	HFrEF	Ventura Atrial Shunt	All-cause death, LVAD/HT, all HFHs, all outpatient WHFs	**0.49**	**+0.4**
RELIEVE-HF (Preserved)[6]	302	HFpEF			**1.69**	**-1.7**

MCID = minimal clinically important difference

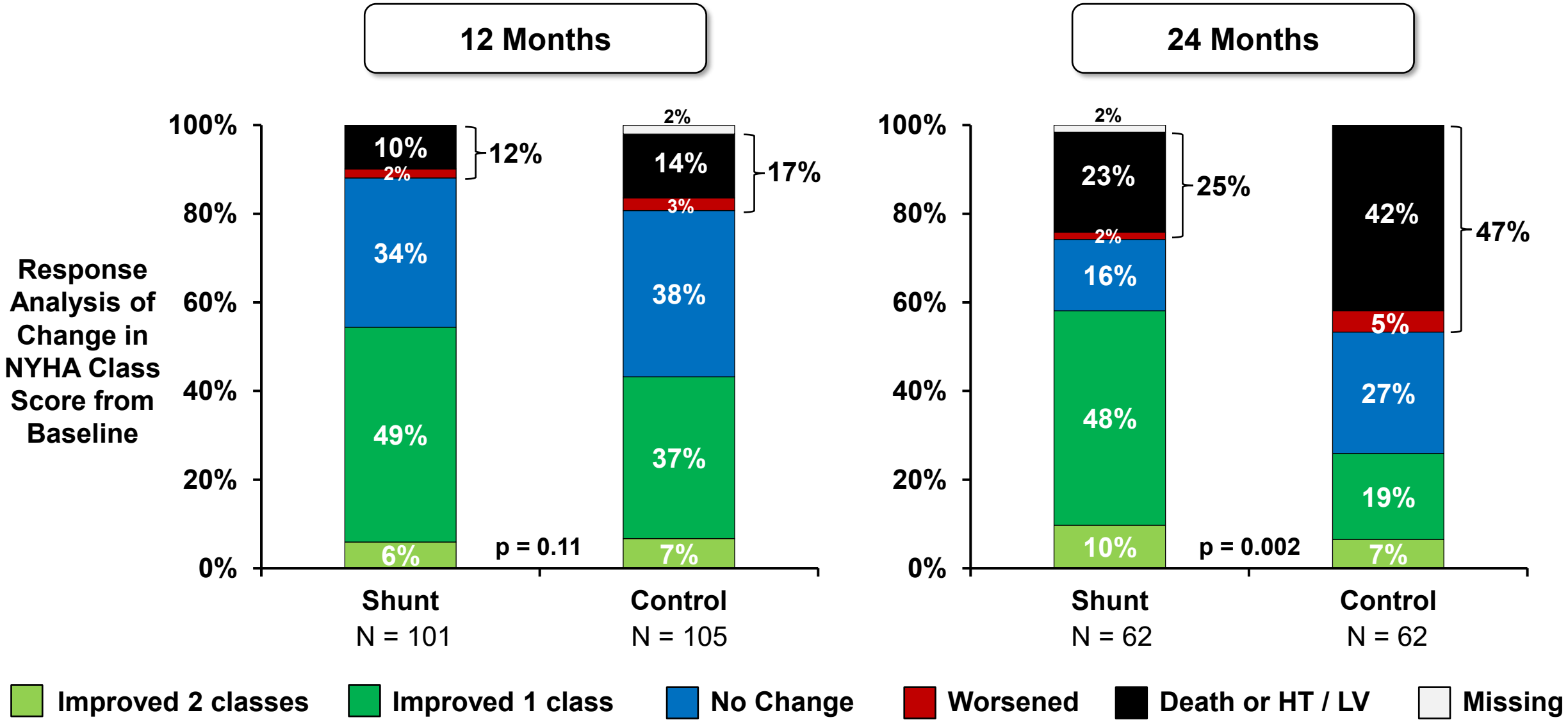
1. Packer M et al. NEJM 2020; 2. Anker SD et al. NEJM 2021; 3. McMurray JJV et al. NEJM 2019; 4. McMurray JJV et al. NEJM 2014; 5. Solomon SD et al. NEJM 2024
6. Stone GW et al. Circulation 2024.

HFrEF: KCCQ Responder Analysis



P-values are provided for descriptive purposes and should not be used to draw statistical inference.

HFrEF: NYHA Responder Analysis



P-values are provided for descriptive purposes and should not be used to draw statistical inference.

RELIEVE-HF Summary: The Ventura Atrial Shunt has Been Demonstrated to be Safe

- Primary Endpoint was met
  - 30-day MACNE = 0% (N = 250) < performance goal of 11% ($p < 0.0001$)
  - 2-year MACNE = 0% (N = 348)
- Peri-procedural complications were rare and not increased in the Shunt group; no Shunt embolizations nor adherent thrombus occurred during 2-year follow-up
- Stroke, MI, or thromboembolic events occurred infrequently and at similar rates in the Shunt and blinded Control groups
- SAEs, both CV and non-CV, were less frequent in Shunt-treated patients than in Control group patients with HFrEF

RELIEVE-HF Summary: The Totality of Data Support Ventura Atrial Shunt Effectiveness in HFrEF

	HFrEF Shunt N = 101 pts *[Events]*	HFrEF Control N = 105 pts *[Events]*	2yr Nelson-Aalen Hazard Rate Ratio *(95% CI)*	Reduction (%)	NNT*
Primary Endpoint HF Events *[2yr]*	**76**	**134**	**0.49** *(0.35, 0.65)*	**51%**	**1.0**
All-cause death	**13**	**20**	**0.48** *(0.20, 1.06)*	**52%**	**6.4**
LVAD/HT	**1**	**6**	**0.15** *(0.00, 0.98)*	**85%**	**12.7**
All HFHs	**41**	**78**	**0.46** *(0.29, 0.68)*	**54%**	**1.6**
All outpatient WHFs	**21**	**30**	**0.64** *(0.33, 1.17)*	**36%**	**7.3**

Given absence of safety risk, the data support a positive benefit-risk ratio in HFrEF

Mechanistic Basis for Differential Effects of Shunt Treatment in HFrEF vs HFpEF

Michael R. Zile, MD

Charles Ezra Daniel Professor of Medicine

Cardiology Division, Medical University of South Carolina

Structural and Functional Remodeling in HF

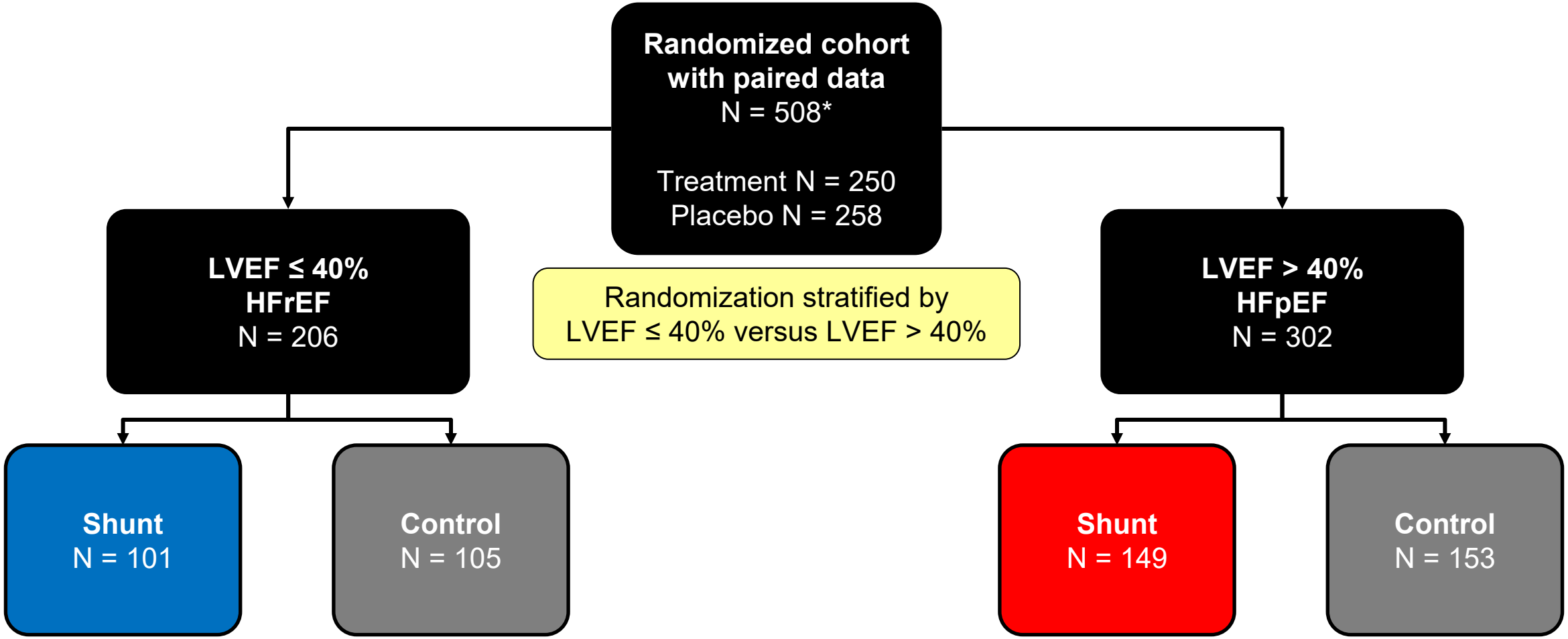
Hypothesis: Differences in cardiac structure and function between HFrEF and HFpEF provide biologically plausible explanation for differences in responses to interatrial Shunt

Structural Determinants of Mortality and Morbidity

- **LV structural remodeling: Δ End diastolic volume**
- **RV structural remodeling: RV diastolic function**
  Δ PA pressure

Zile et al, JACC CV Imaging Published Online Aug 29, 2025

RELIEVE-HF Echocardiographic Study Consort Diagram: Echo from Baseline vs 12 Months



*Number of patients with paired 12-month and baseline echocardiographic values after 2-step imputation

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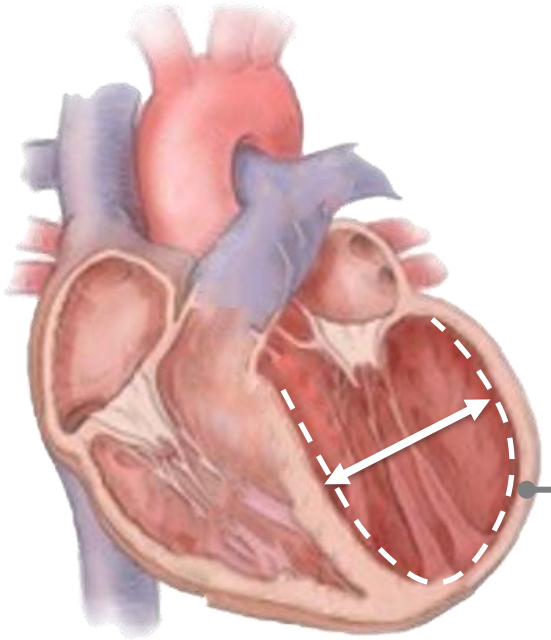
Differences in Left Ventricular Structure and Function in HFrEF vs HFpEF Affect Responses to Interatrial Shunt

HFrEF

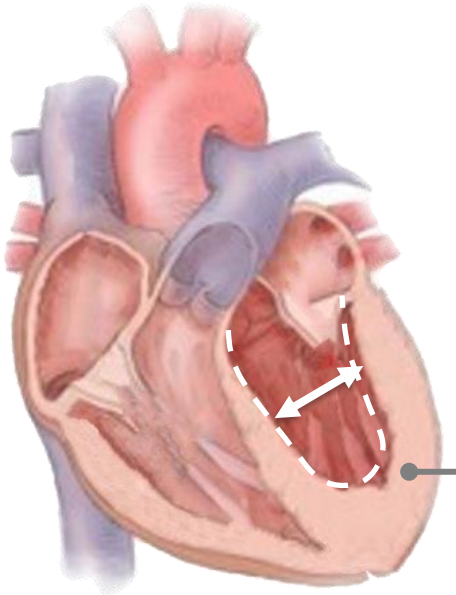


Enlarged LV size

Compliant LV

LEFT VENTRICLE **undergoes REVERSE REMODELING** (↓ LVEDV) in response to Shunt placement

HFpEF



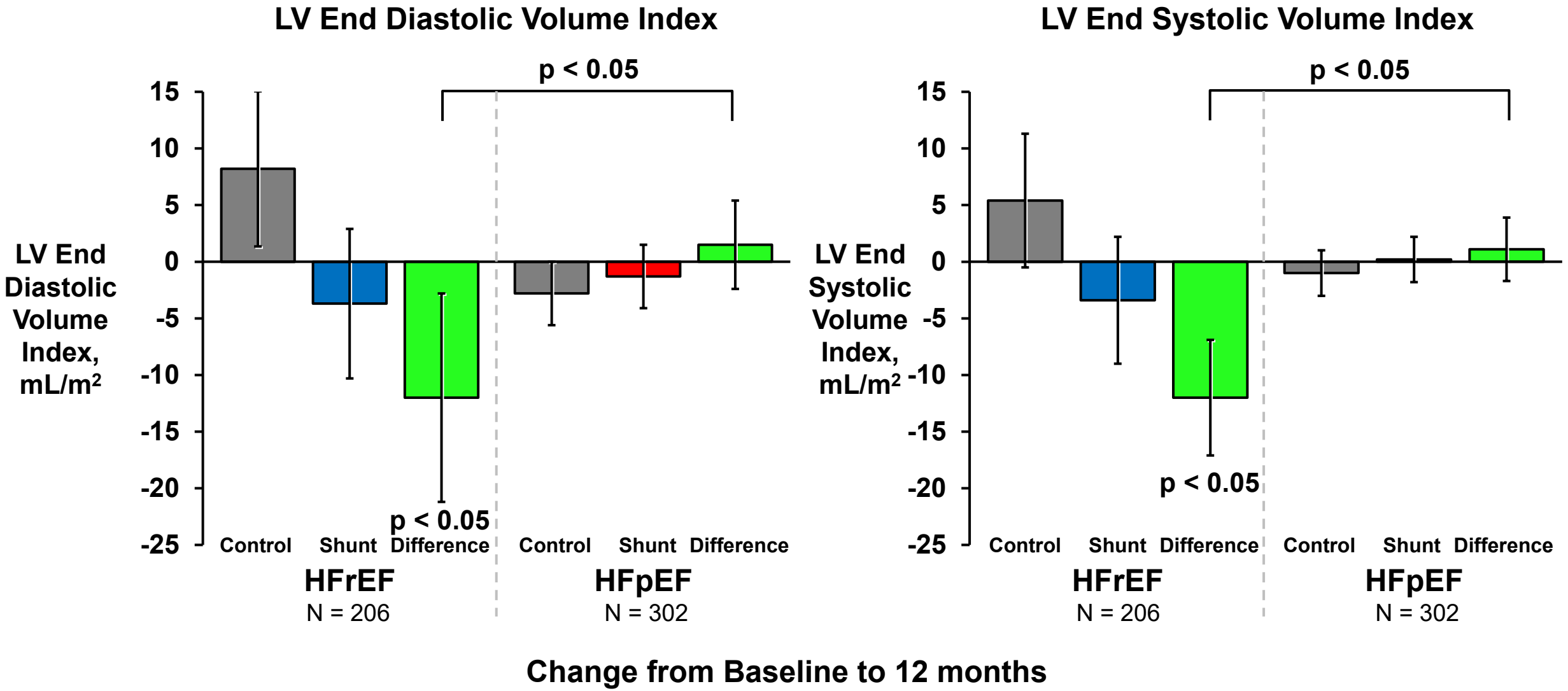
Normal LV size

Non-compliant LV

LEFT VENTRICLE **unable to undergo REVERSE REMODELING** in response to Shunt placement

Zile et al, JACC CV Imaging Published Online Aug 29, 2025

Changes in Left Heart Structure in RELIEVE-HF



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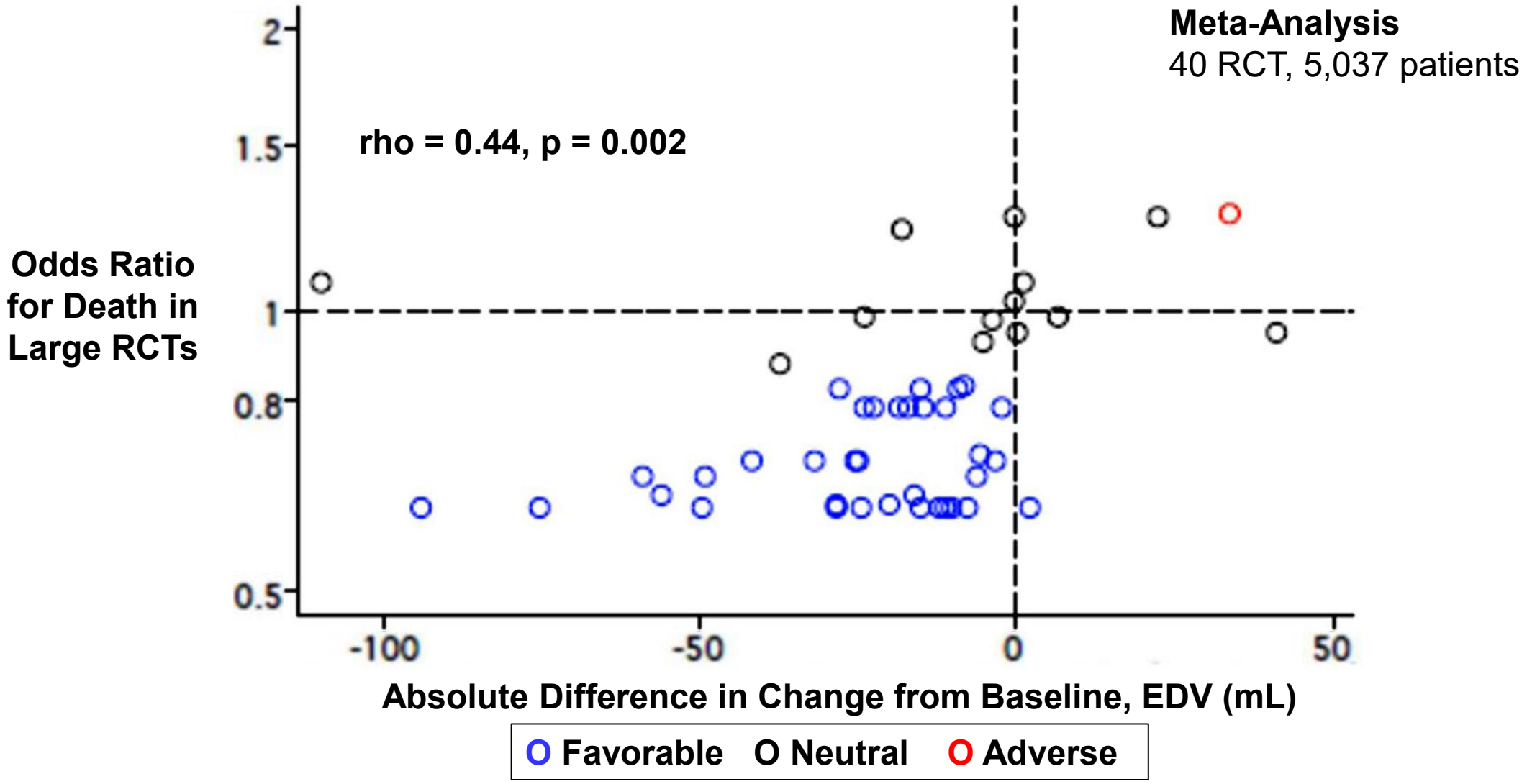
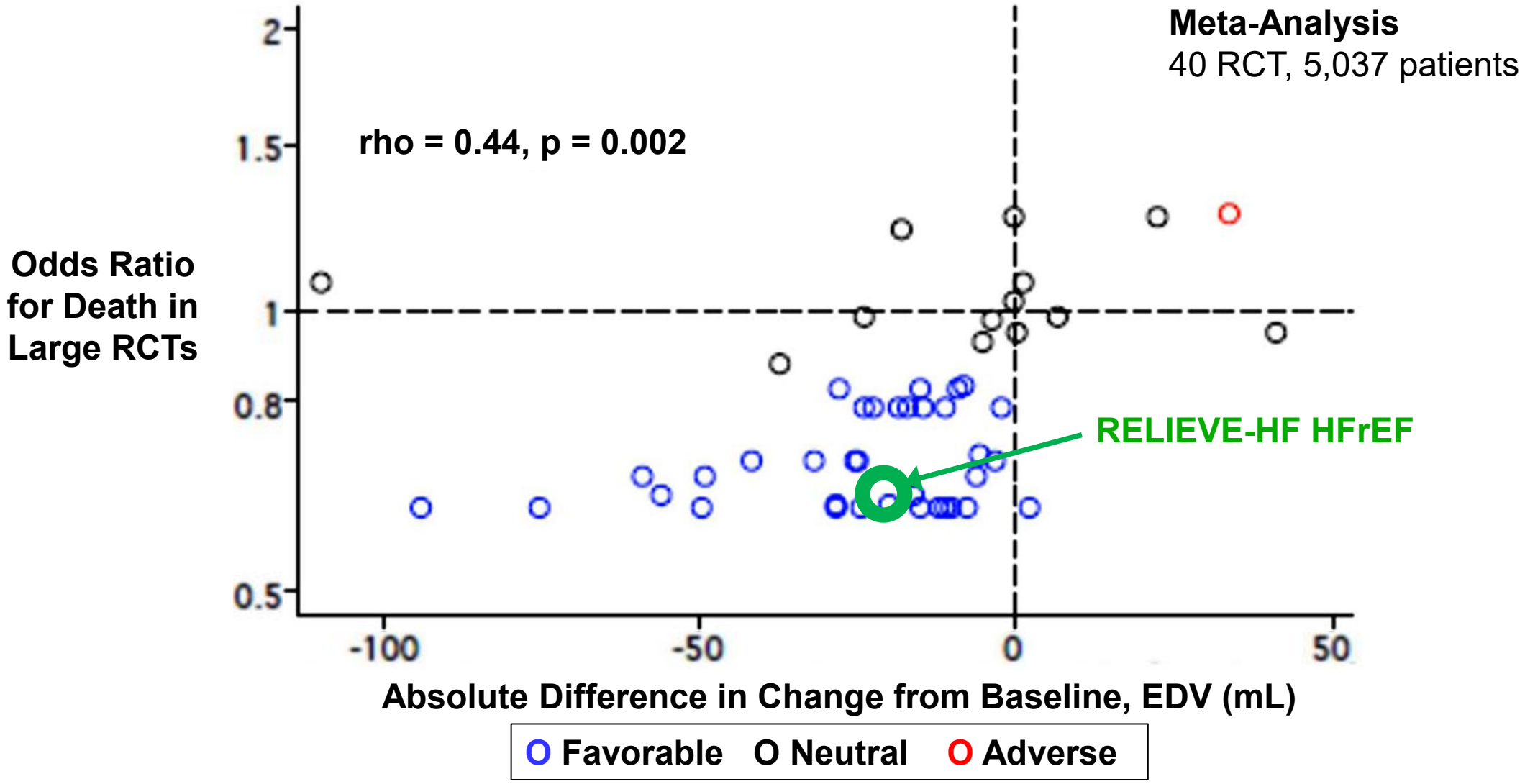
Relationship Between Change in LV End-Diastolic Volume and Mortality in HFrEF



Kramer et al., JACC 56: 392-406, 2010

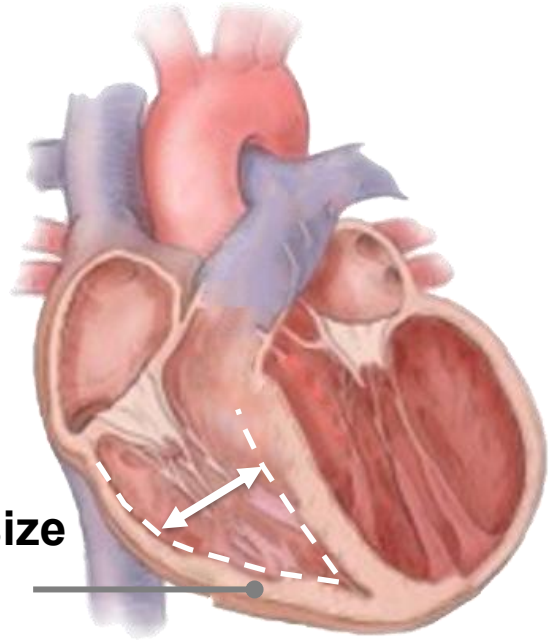
Relationship Between Change in LV End-Diastolic Volume and Mortality in HFrEF



Zile et al, JACC CV Imaging Published Online Aug 29, 2025; Kramer et al., JACC 56: 392-406, 2010

Differences in RV Structure and Function in HFrEF vs HFpEF Affect Responses to Interatrial Shunt

HFrEF

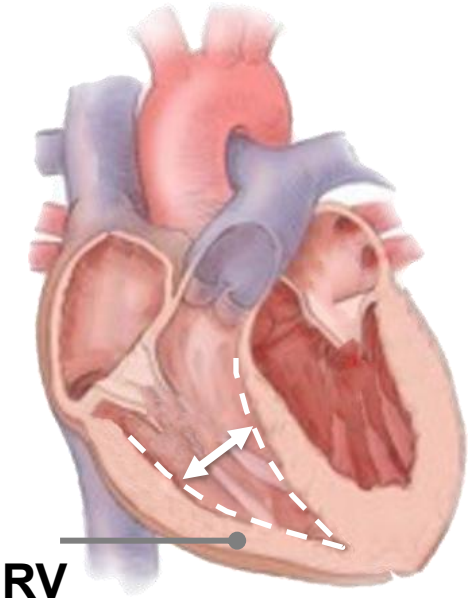


Enlarged RV size

Compliant RV

RIGHT VENTRICLE **able to accept** an increase in redistributed blood volume without resulting in changes in right heart size or increased PA pressure

HFpEF



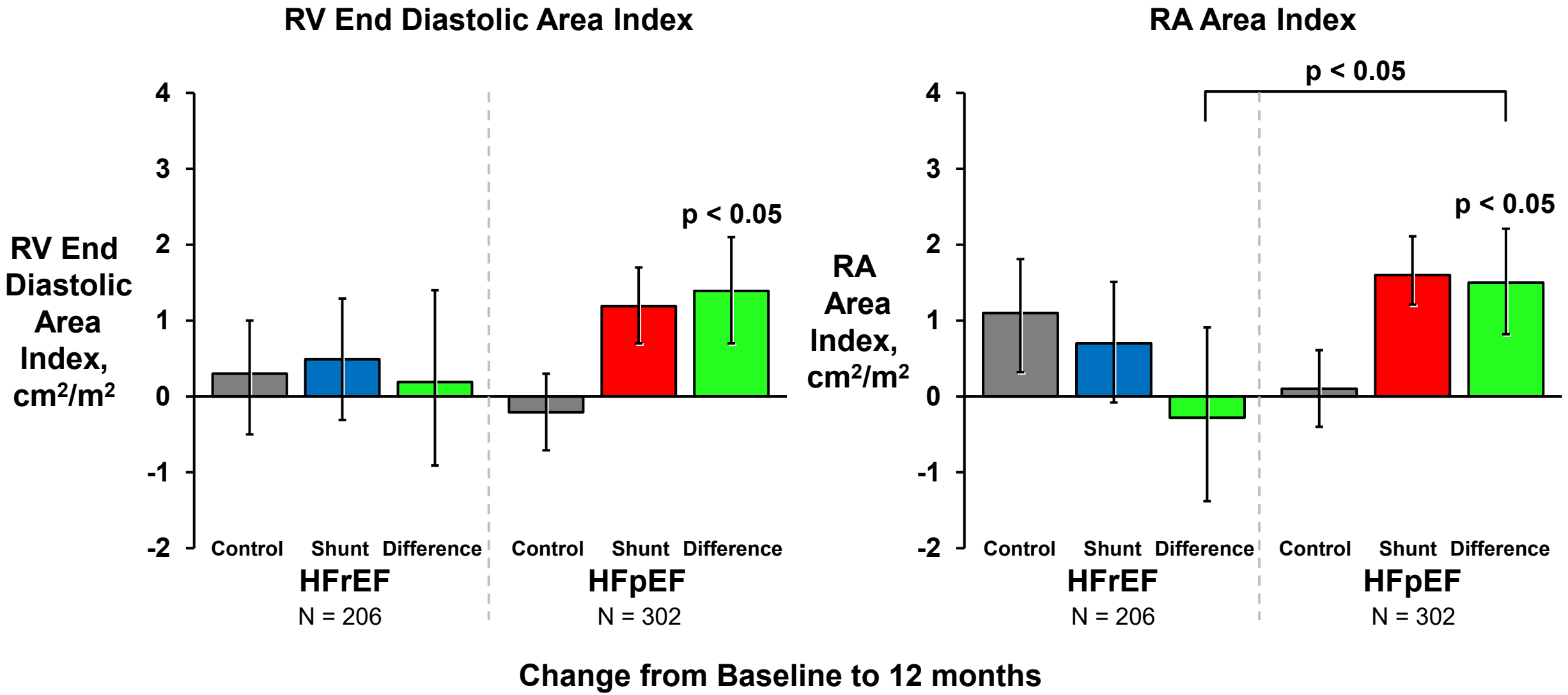
Normal RV size

Non-compliant RV

RIGHT VENTRICLE **NOT able to accept** an increase in redistributed blood volume, resulting in increased right heart size and increased PA pressure

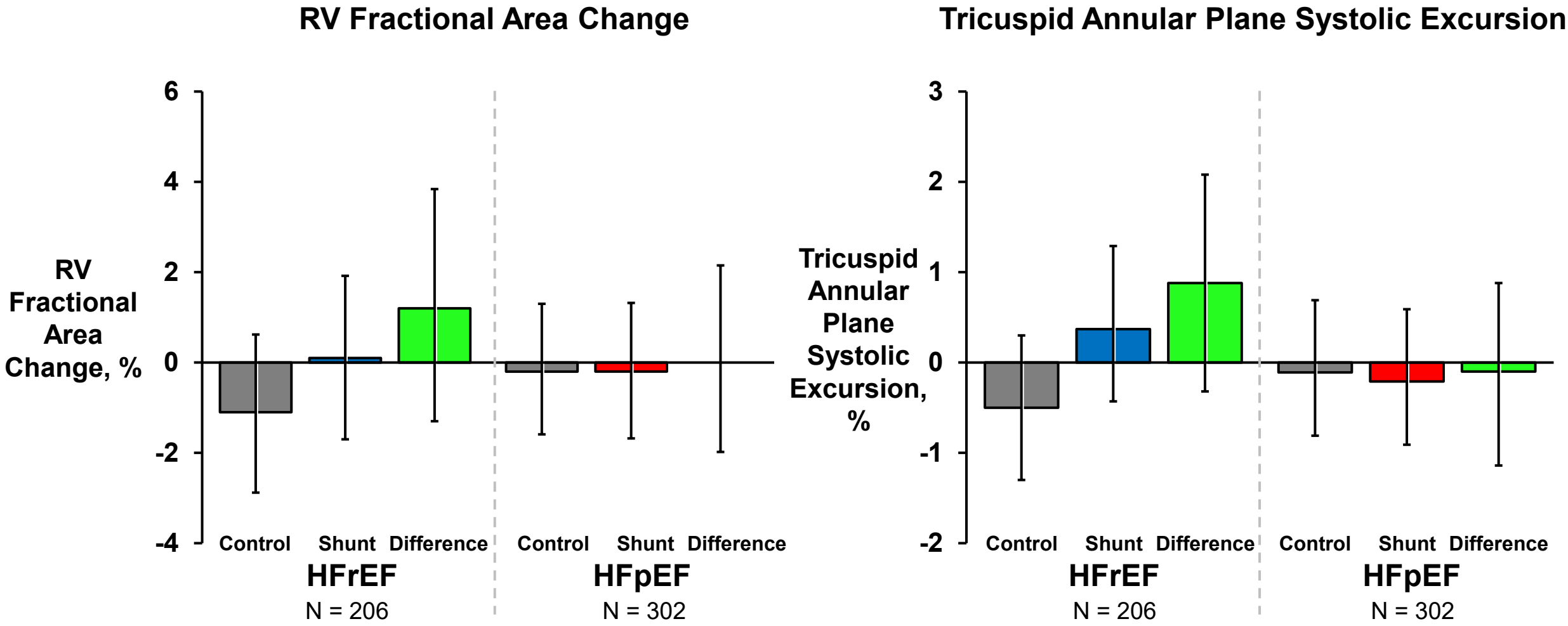
Zile et al, JACC CV Imaging Published Online Aug 29, 2025

Changes in Right Heart Structure in RELIEVE-HF



Zile et al, JACC CV Imaging Published Online Aug 29, 2025

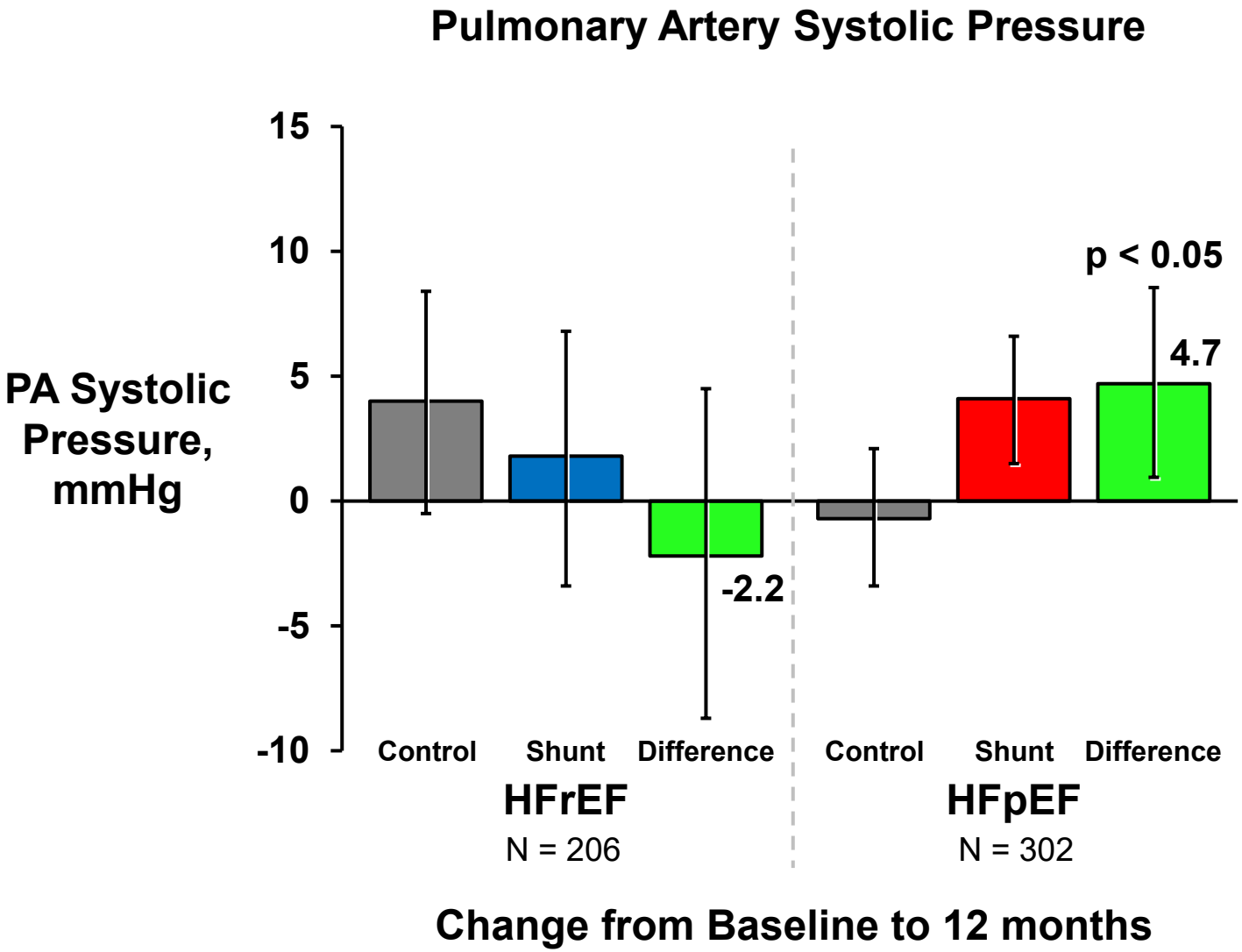
Changes in RV Systolic Function in RELIEVE-HF



Change from Baseline to 12 months

Zile et al, JACC CV Imaging Published Online Aug 29, 2025

Changes in PA Systolic Pressure in RELIEVE-HF



Zile et al, JACC CV Imaging Published Online Aug 29, 2025

Effects of Change from Baseline in PA Pressure on Subsequent All-Cause Mortality

	Analysis Method	Results	p-value
PA Diastolic	Continuous Variable	Hazard Ratio (95% CI) 1.03 (1.01, 1.05)	0.0042
	Categorical Variable	% Change in Mortality Risk	0.0237
	≤ - 2 mmHg	- 14.7%	
	≥ + 2 mmHg	+ 26.7%	
PA Systolic	Continuous Variable	Hazard Ratio (95% CI) 1.02 (1.01, 1.03)	0.0020
	Categorical Variable	% Change in Mortality Risk	0.0198
	≤ - 3 mmHg	- 14.2%	
	≥ + 3 mmHg	+ 23.8%	
PA Mean	Continuous Variable	Hazard Ratio (95% CI) 1.03 (1.01, 1.04)	0.0023
	Categorical Variable	% Change in Mortality Risk	0.0546
	≤ - 2 mmHg	- 16.7%	
	≥ + 2 mmHg	+ 13.9%	

Zile et al, Circ HF: 2025Jun;18(6):e012754

Biologically Plausible Mechanisms for Differences in Responses to Interatrial Shunt

- At baseline, there are critical differences in cardiac structure / function
- After Shunt placement, RV compliance determined the ability to accommodate the LA to RA shunted volume
- Changes in LV remodeling and PA pressures predict subsequent CV mortality and HF morbidity
- RELIEVE-HF: HFrEF patients treated with an interatrial Shunt had improved morbidity / mortality related to structure / function characteristics

Benefit-Risk Summary and Clinical Perspective

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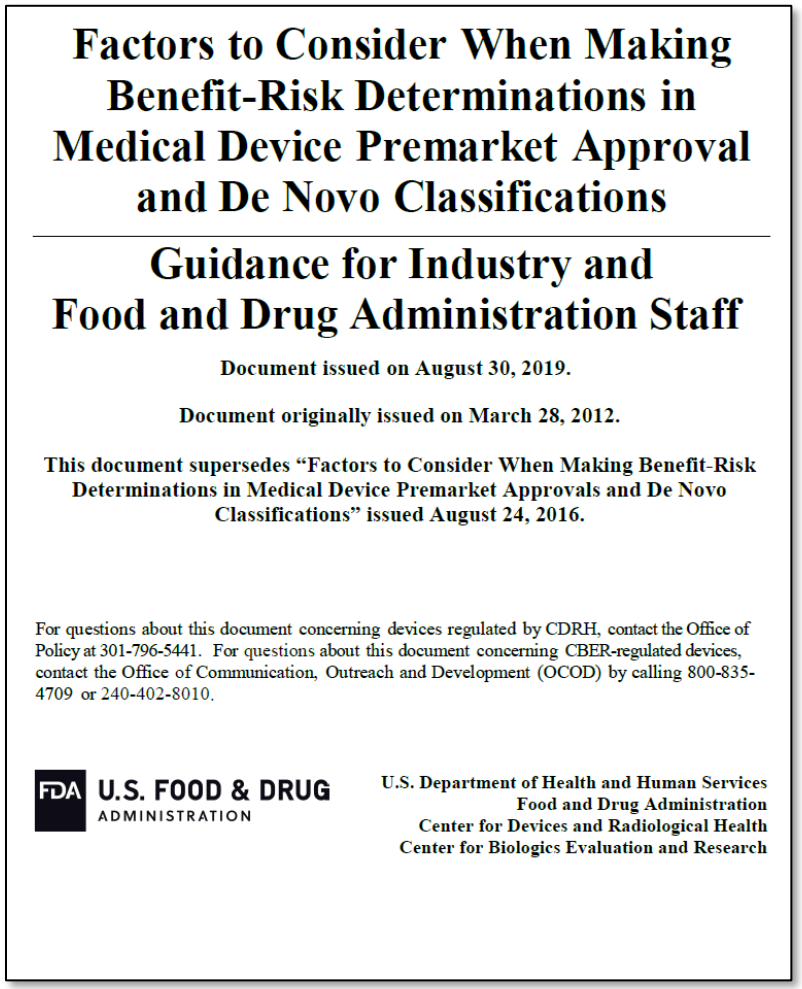
Professor of Medicine, Division of Cardiovascular Medicine

Vanderbilt University Medical Center

Benefit-Risk Determination Guidance For ANY Device



Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 30, 2019.

Document originally issued on March 28, 2012.

This document supersedes "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications" issued August 24, 2016.

For questions about this document concerning devices regulated by CDRH, contact the Office of Policy at 301-796-5441. For questions about this document concerning CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD) by calling 800-835-4709 or 240-402-8010.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

"Do the benefits of the device outweigh the risks for its intended use?"

Benefit

- ❑ *Is there any evidence of clinical benefit?*
- ❑ *What is the extent of uncertainty for the benefit?*

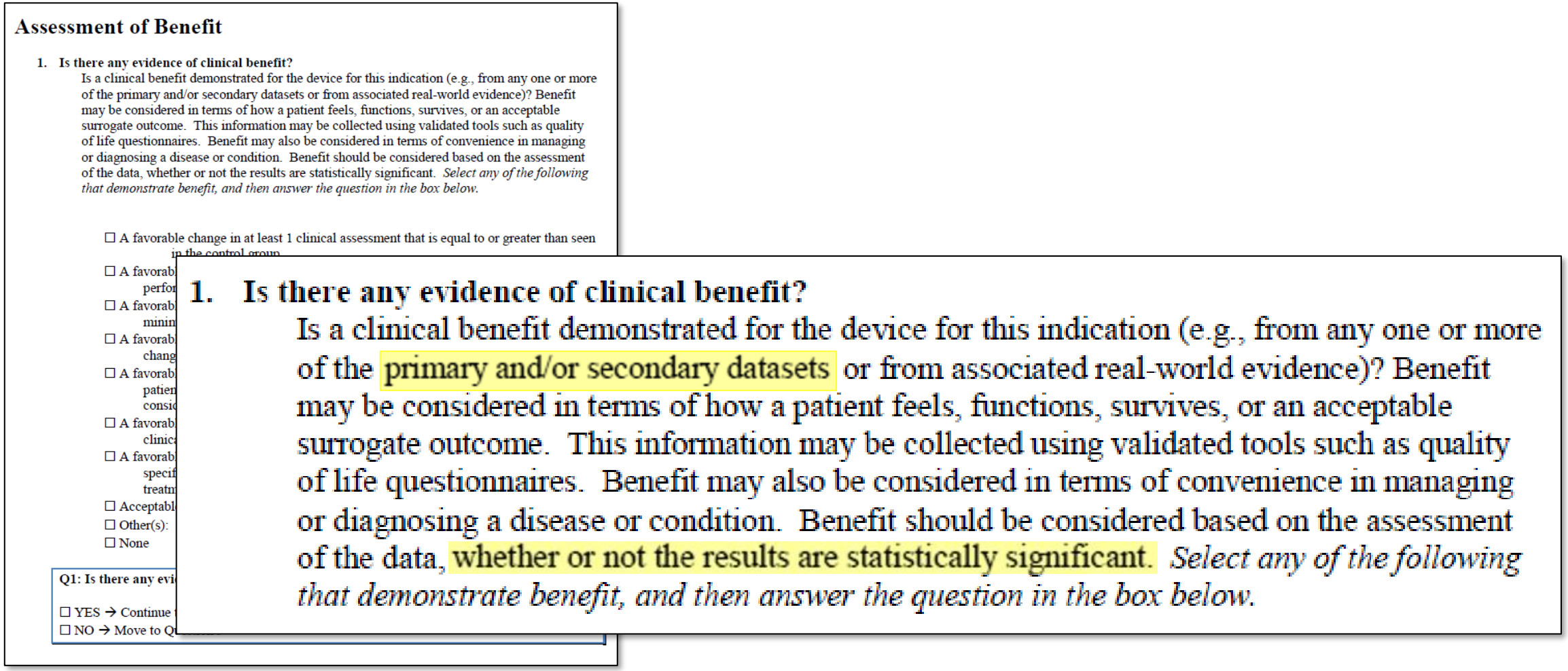
Risk

- ❑ *Are known/probable risks more than minimal?*
- ❑ *What is the extent of uncertainty for the risks?*

Benefit - Risk

- ❑ *Do the Benefits outweigh the risks?*
- ❑ *Do the Benefits outweigh the risks, considering post-market actions?*

Ability to Look Beyond Statistical Significance of Primary Datasets



Assessment of Benefit

1. **Is there any evidence of clinical benefit?**
   Is a clinical benefit demonstrated for the device for this indication (e.g., from any one or more of the primary and/or secondary datasets or from associated real-world evidence)? Benefit may be considered in terms of how a patient feels, functions, survives, or an acceptable surrogate outcome. This information may be collected using validated tools such as quality of life questionnaires. Benefit may also be considered in terms of convenience in managing or diagnosing a disease or condition. Benefit should be considered based on the assessment of the data, whether or not the results are statistically significant. *Select any of the following that demonstrate benefit, and then answer the question in the box below.*

☐ A favorable change in at least 1 clinical assessment that is equal to or greater than seen in the control group
☐ A favorab
perfor
☐ A favorab
minin
☐ A favorab
chang
☐ A favorab
patien
consi
☐ A favorab
clinic
☐ A favorab
specif
treatm
☐ Acceptabl
☐ Other(s):
☐ None

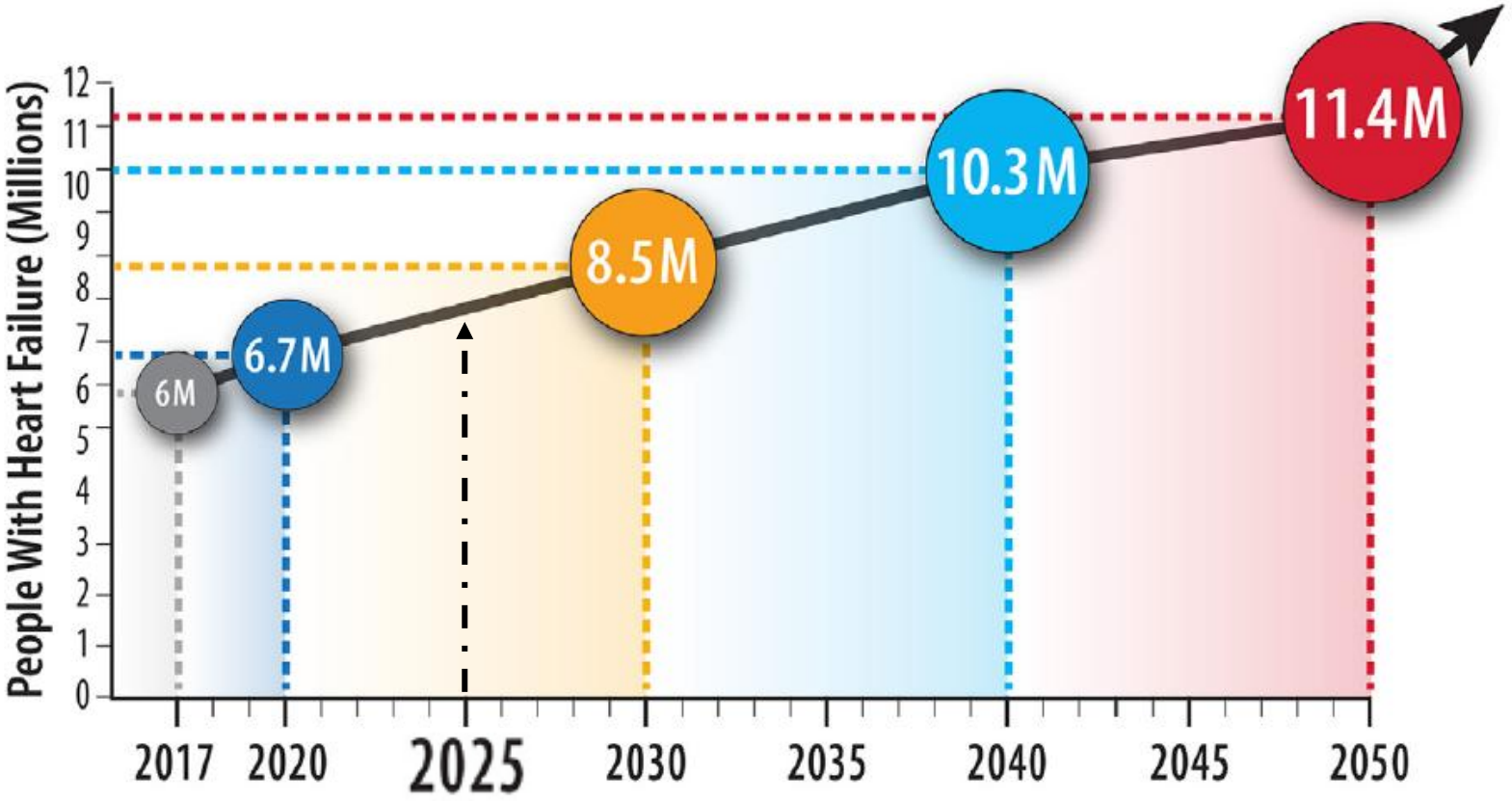
Q1: Is there any evi

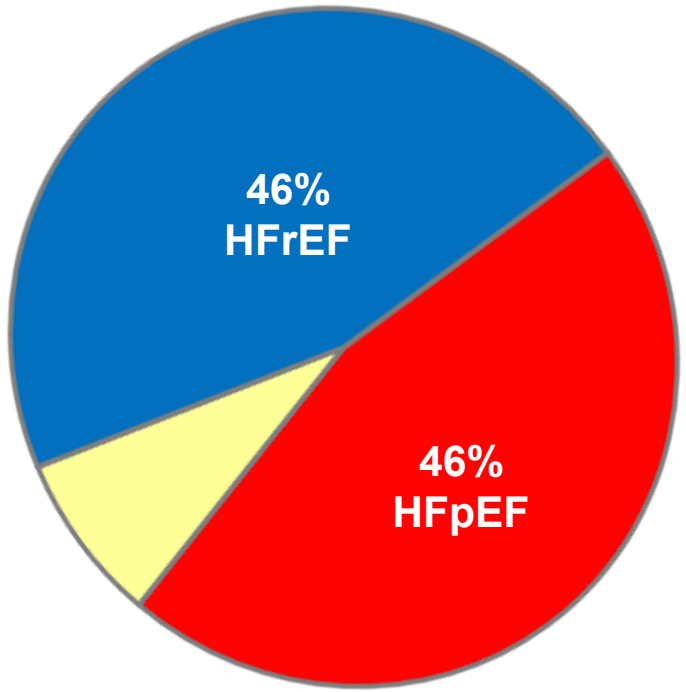
☐ YES → Continue
☐ NO → Move to Q

1. Is there any evidence of clinical benefit?

Is a clinical benefit demonstrated for the device for this indication (e.g., from any one or more of the primary and/or secondary datasets or from associated real-world evidence)? Benefit may be considered in terms of how a patient feels, functions, survives, or an acceptable surrogate outcome. This information may be collected using validated tools such as quality of life questionnaires. Benefit may also be considered in terms of convenience in managing or diagnosing a disease or condition. Benefit should be considered based on the assessment of the data, whether or not the results are statistically significant. *Select any of the following that demonstrate benefit, and then answer the question in the box below.*

Heart Failure: Is There an Unmet Need?





Joynt Maddox KE et al, Circulation. 2024 Jun 4;
Van Nuys KE et al., JACC Heart Fail. 2018; 6:401-9;
Heidenreich PA et al. Circ Heart Fail. 2013; 6:606-19

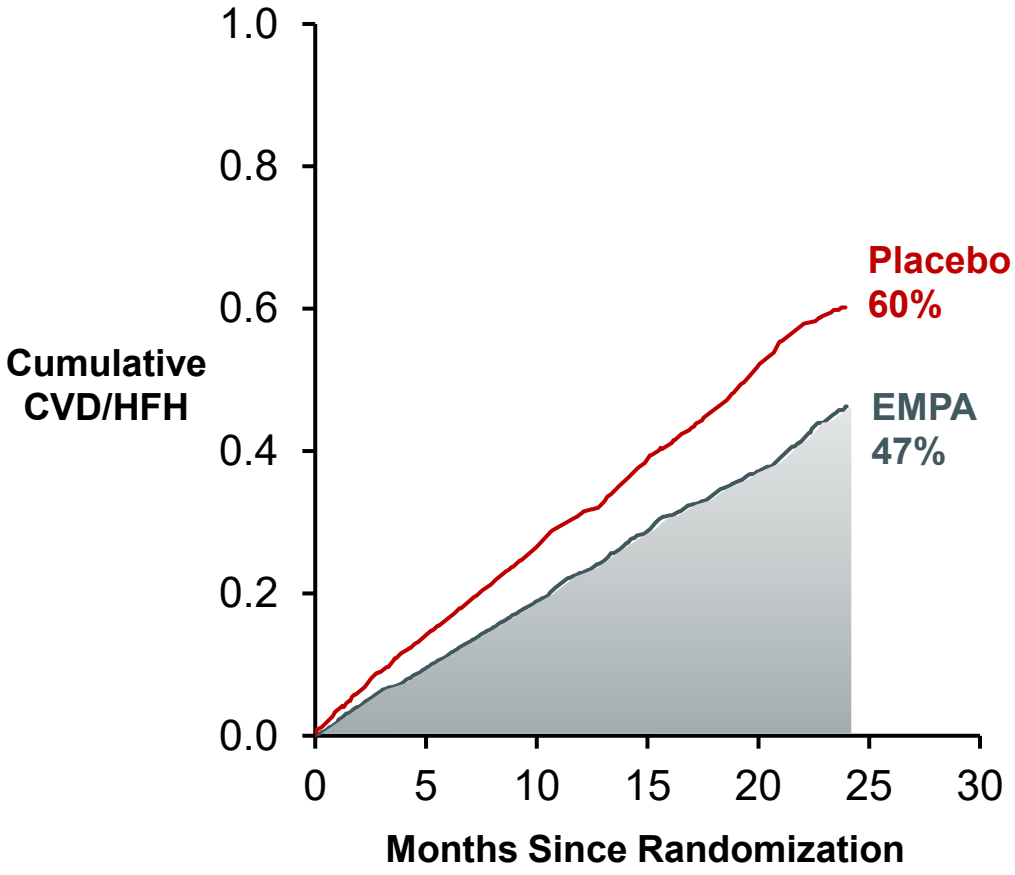
Modified from Shah KS, et al. J Am Coll Cardiol. 2017;70:2476-86.

Heart Failure is a large & growing clinical burden and HFrEF patients have very poor post-admission outcomes

HFrEF Patients Have High Risk of Recurrent HFH and CV Death Despite GDMT

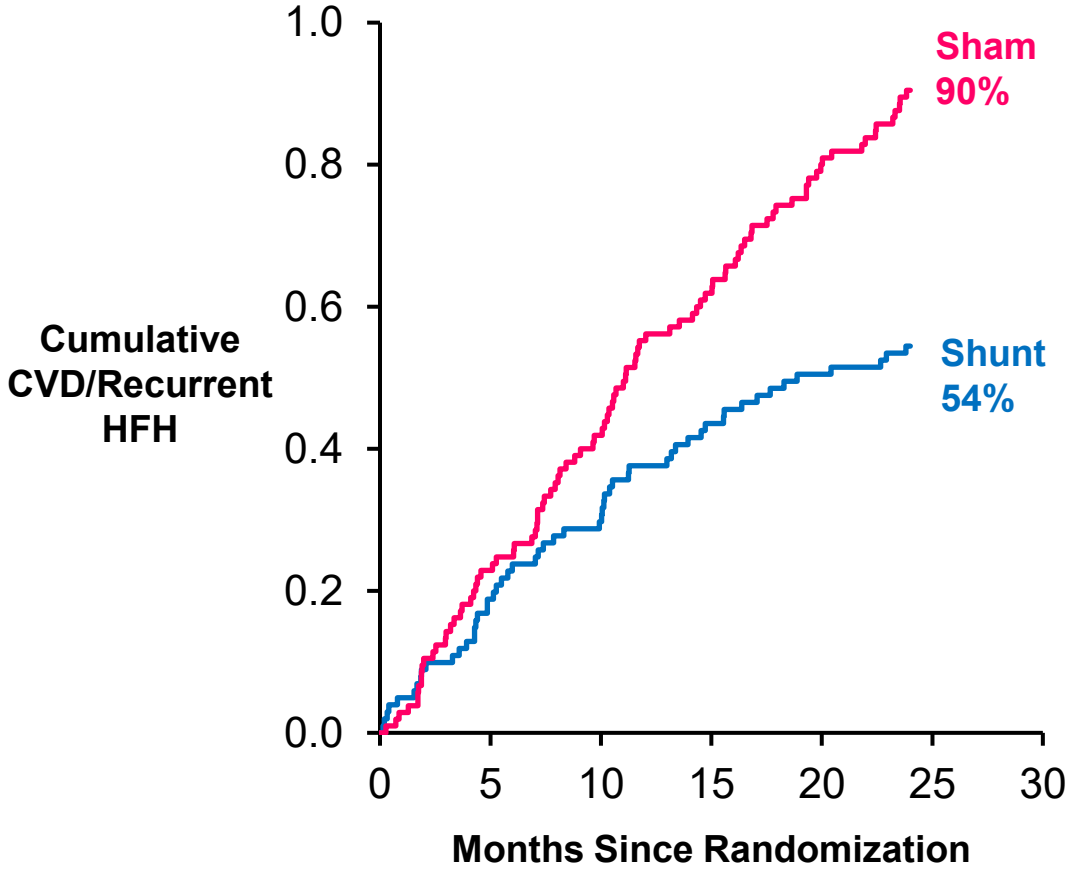
EMPEROR-Reduced

75% NYHA II



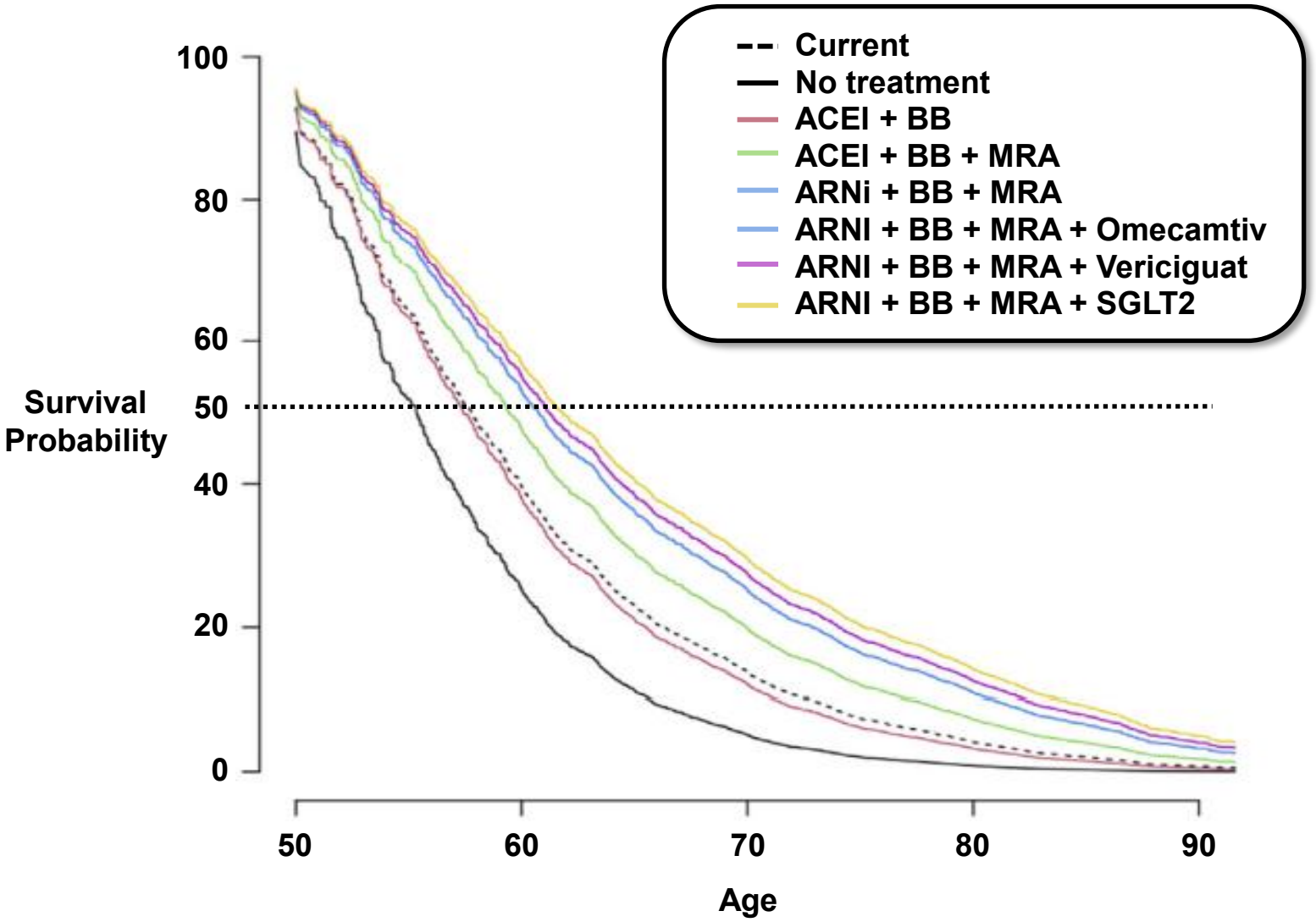
RELIEVE-HF HFrEF

96% NYHA III



Hazewinkel AD et al. JACC 2025

Half of All 50-Year-Olds on Ideal GDMT Will Die Within 12 Years



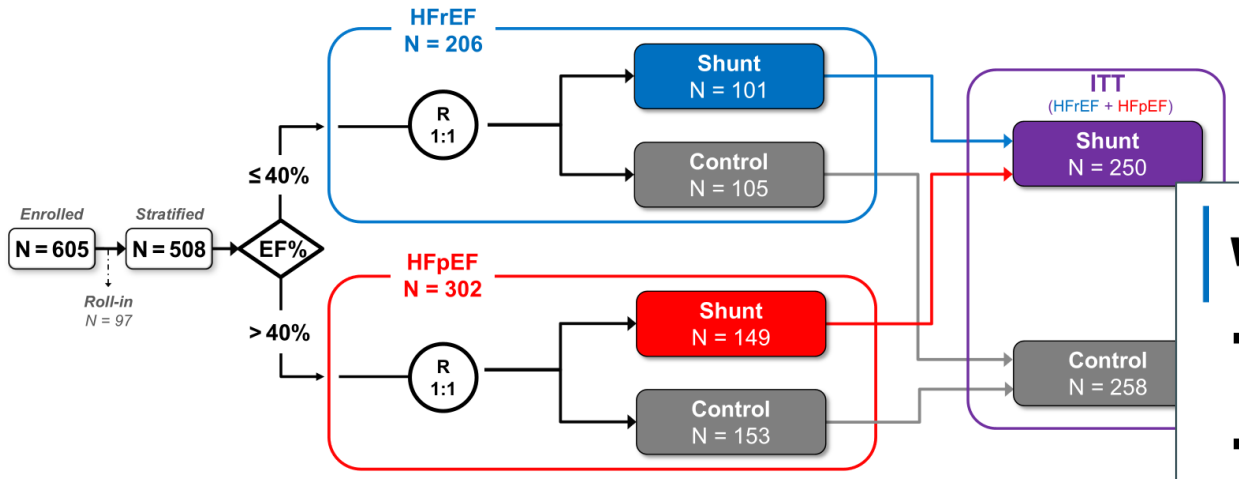
Tromp JJ et al. JACC Heart Failure 2022;10:73–84

Was the Study Well-Designed and Executed?

22

Robust, Prespecified Randomization by LVEF

RELIEVE-HF – A Randomized, Double-Blind, Sham-Controlled Trial



Roll-in cohort = unblinded cases used to train sites on the procedure as well as to develop more safety data

10

Well-Executed, Robust, Double-Blind Study

- Multicenter, randomized, double-blind, sham-controlled
  - 114 sites
- Symptomatic HF on optimal (i.e., maximally tolerated) GDMT
  - Assessed by Central Eligibility Committee
- Randomized 508 patients
  - > 95% NYHA Class III
  - Median follow-up 22 months
  - 98.4% follow-up at primary analysis
- Few major protocol deviations
- No confounding interventions

Can I Safely Treat My Patients With This Device?

40

Analysis of All Shunt-Treated Patients: Primary Safety Endpoint at 30 Days and 2 Years

Shunt-treated patients (250 ITT Shunt + 1 ITT Control + 97 Roll-in)	Shunt Through 30 Days N = 348		Shunt Through 2 Years N = 348	
	Total n	Rate*	Total n	Rate*
Any device/procedure-related MACNE	0	0%	0	0%
All-cause death	0	0%	0	0%
Stroke	0	0%	0	0%
Systemic embolism	0	0%	0	0%
Need for open cardiac surgery	0	0%	0	0%
Need for major endovascular surgical repair	0	0%	0	0%

- 30-day Device- or Procedure-Related MACNE = 0%
- 2-year Device- or Procedure-Related MACNE = 0%

* Event rates are Kaplan-Meier estimates

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Additional Safety Endpoints Through 2 Years: HFrEF

Whether or not device- or procedure-related

	Shunt N = 101		Control N = 105		
	Total n	Rate*	Total n	Rate*	p-value
Shunt implant embolization/thrombosis	0	0%	-	-	-
Pericardial effusion/cardiac tamponade	0	0%	0	0%	-
BARC types 3 or 5 bleeding	1	1.0%	3	3.1%	0.33
Cerebrovascular events	4	4.1%	3	3.2%	0.67
CNS infarction (stroke)	3	3.1%	2	2.2%	0.63
CNS hemorrhage (intracerebral or subarachnoid)	0	0%	1	1.2%	0.31
Transient ischemic attack	1	1.0%	1	1.0%	0.98
Myocardial infarction	1	1.1%	3	3.5%	0.32
Systemic embolization	0	0%	0	0%	-
Pulmonary emboli	1	1.7%	0	0%	0.36

No safety issues were identified in Shunt-treated patients with HFrEF

* Event rates are Kaplan-Meier estimates

Will My Patients Benefit From This Device?

57

Probable HFrEF Benefit: Reduction of All HF Events

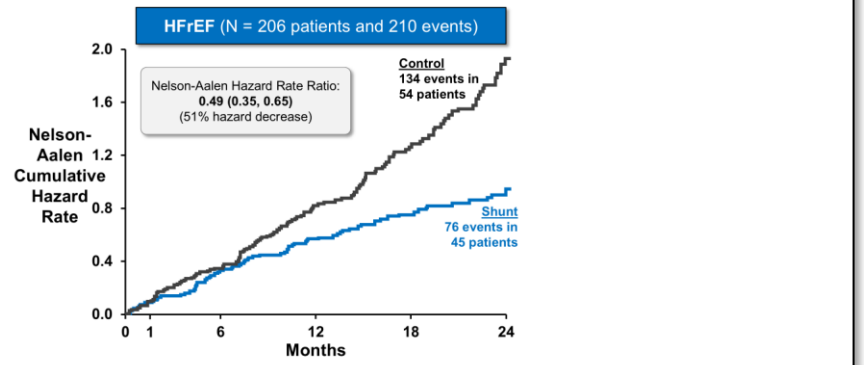
	HFrEF Shunt N = 101 pts [Events]	HFrEF Control N = 105 pts [Events]	2yr Nelson-Aalen Hazard Rate Ratio (95% CI)	Reduction (%)	NNT*
Primary Endpoint HF Events [2yr]	76	134	0.49 (0.35, 0.65)	51%	1.0
All-cause death	13	20	0.48 (0.20, 1.06)	52%	6.4
LVAD/HT	1	6	0.15 (0.00, 0.98)	85%	12.7
All HFHs	41	78	0.46 (0.29, 0.68)	54%	1.6
All outpatient WHFs	21	30	0.64 (0.33, 1.17)	36%	7.3

Shunt-treated HFrEF ⇨ Consistent relative risk reductions for all primary HF Event components

*Number of patients needed to treat with the shunt to prevent on average 1 event during 2-year follow-up. Confidence intervals are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

HFrEF Benefit: Reduction of All HF Events

(All-Cause Mortality, Cardiac Transplant or LVAD, Heart Failure Hospitalization, Worsening HF Events)



HFrEF patients ⇨ Greatest risk of HF Events & greater unmet clinical need
HFrEF patients with shunt-treatment ⇨ Pronounced reduction in HF Events

Confidence intervals are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

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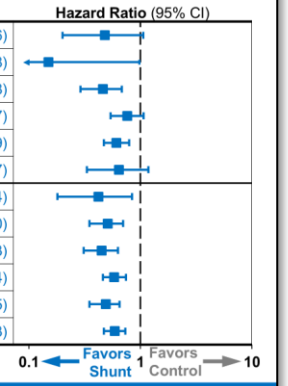
Nelson-Aalen Cumulative Hazard Rates at 24 Months (HFrEF)

		Events (#) Shunt (N = 101) / Control (N = 105)	Hazard rate (95% CI)
Single Event Types	All-Cause Death	13 / 20	0.48 (0.20, 1.06)
	Heart Transplant/LVAD (HT/LV)	1 / 6	0.15 (0.00, 0.98)
	Hospitalization for HF (HFH)	41 / 78	0.46 (0.29, 0.68)
	Hospitalization not for HF (NHFH)	68 / 85	0.76 (0.54, 1.07)
	All-Cause Hospitalization (ACH)	109 / 163	0.61 (0.47, 0.79)
	Worsening HF Outpatient (WHF)	21 / 30	0.64 (0.33, 1.17)
Composite Event Types	Terminal Events (All-cause Death, HT/LV)	14 / 26	0.42 (0.18, 0.84)
	WHF and HFH	62 / 108	0.51 (0.35, 0.70)
	All-cause Death, HT/LV, HFH	55 / 104	0.45 (0.31, 0.63)
	All-cause Death, HT/LV, ACH	123 / 189	0.58 (0.46, 0.74)
	HF Events (All-cause Death, HT/LV, HFH, WHF)	76 / 134	0.49 (0.35, 0.65)
	All Events (All-cause Death, HT/LV, ACH, WHF)	144 / 219	0.59 (0.47, 0.73)



In HFrEF, Shunt treatment was associated with consistent, robust reductions in all event types
(Including hospitalizations, outpatient worsening episodes, and terminal outcomes)

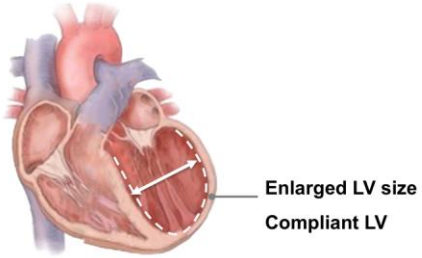
Confidence intervals are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

Is There a Plausible Biological Mechanism to Explain Differences in Treatment Effect?

74

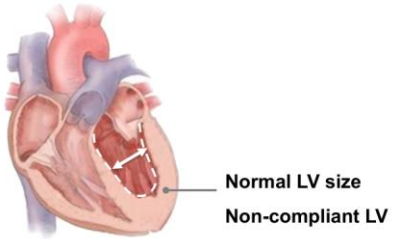
Differences in Left Ventricular Structure and Function in HFrEF vs HFpEF Affect Responses to Interatrial Shunt

HFrEF



LEFT VENTRICLE **undergoes REVERSE REMODELING** (↓ LVEDV) in response to Shunt placement

HFpEF



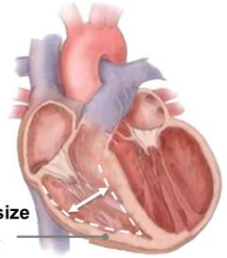
LEFT VENTRICLE **unable to undergo REVERSE REMODELING** in response to Shunt placement

Zile et al, JACC CV Imaging Published Online Aug 29, 2025

78

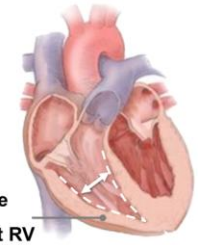
Differences in RV Structure and Function in HFrEF vs HFpEF Affect Responses to Interatrial Shunt

HFrEF



RIGHT VENTRICLE **able to accept** an increase in redistributed blood volume without resulting in changes in right heart size or increased PA pressure

HFpEF

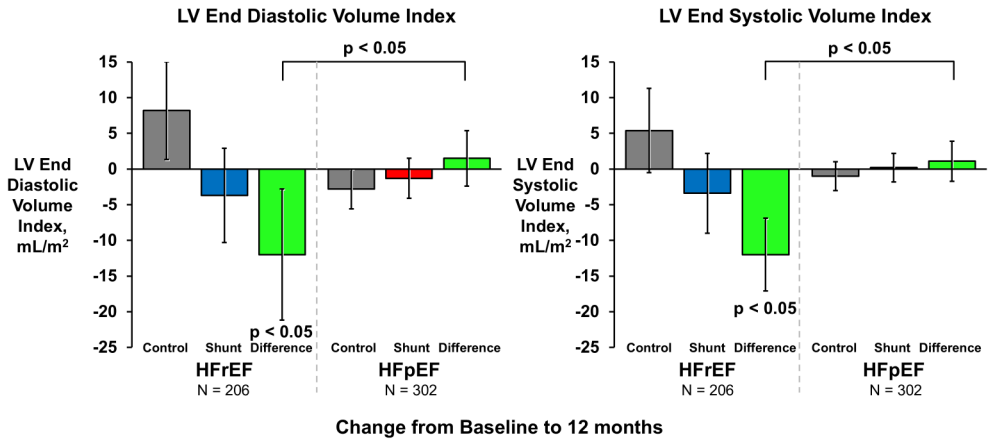


RIGHT VENTRICLE **NOT able to accept** an increase in redistributed blood volume, resulting in increased right heart size and increased PA pressure

Zile et al, JACC CV Imaging Published Online Aug 29, 2025

75

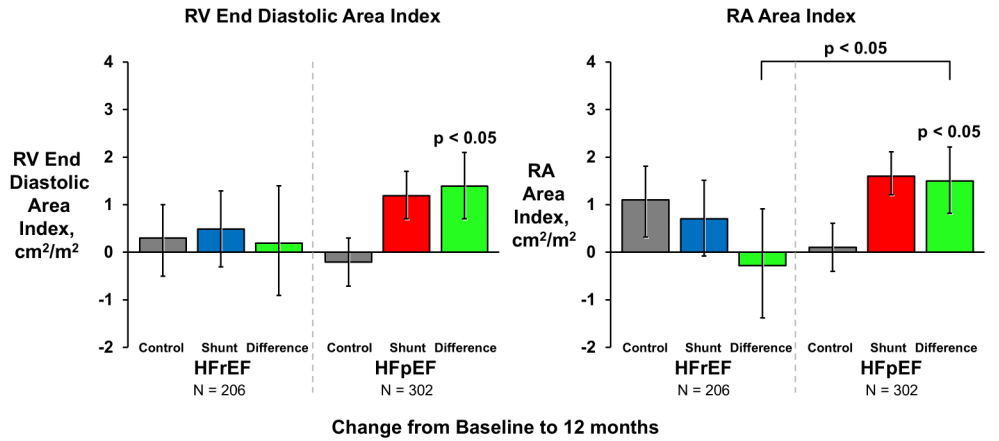
Changes in Left Heart Structure in RELIEVE-HF



Zile et al, JACC CV Imaging Published Online Aug 29, 2025

79

Changes in Right Heart Structure in RELIEVE-HF



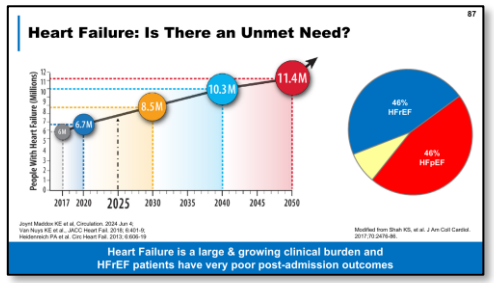
Zile et al, JACC CV Imaging Published Online Aug 29, 2025

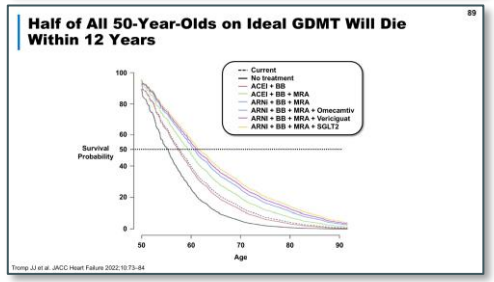
Proposed Indication: Supported by the Data & in the Best Interest of Patients in Need

The Ventura Shunt is indicated for **NYHA Class III** HF 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 heart failure hospitalization**.

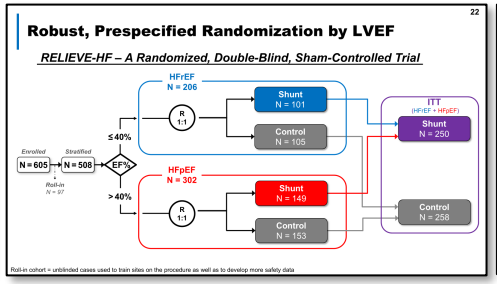
Totality of Evidence Support Approval

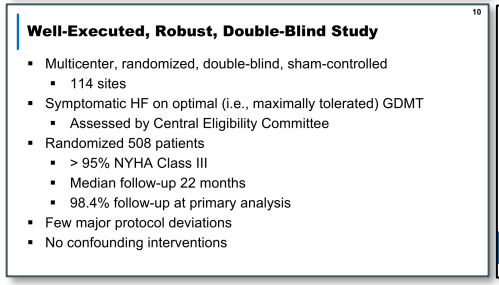
Significant Unmet Need



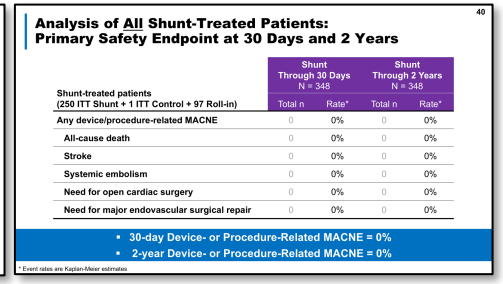


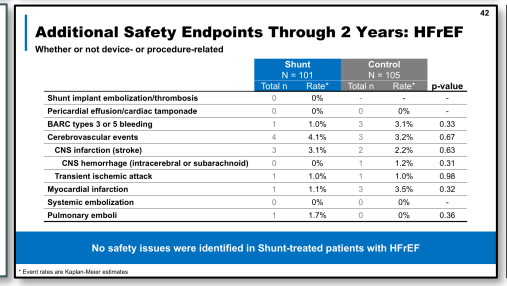
Well-Executed, Randomized, Sham-Controlled Trial



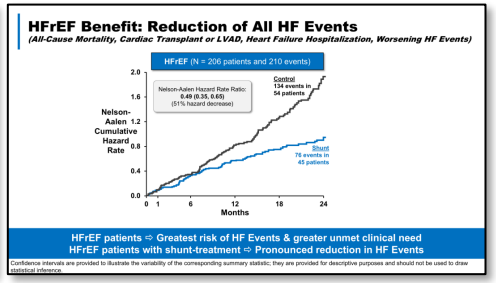


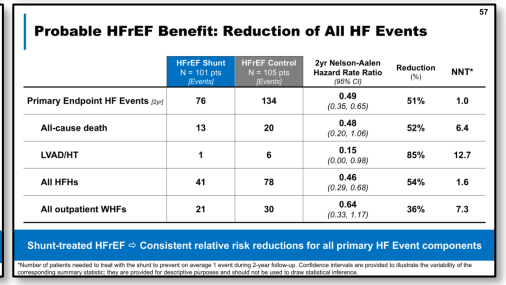
Convincing Safety Profile

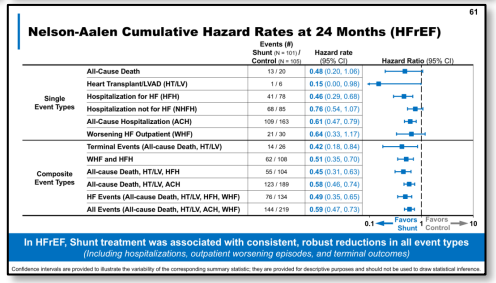




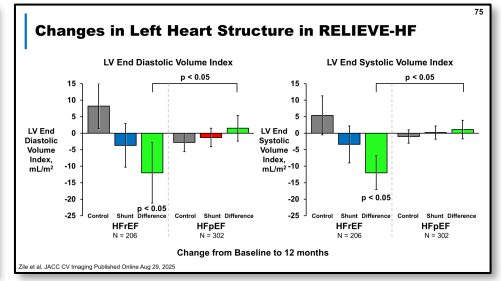
Improvements in All Clinical Measures

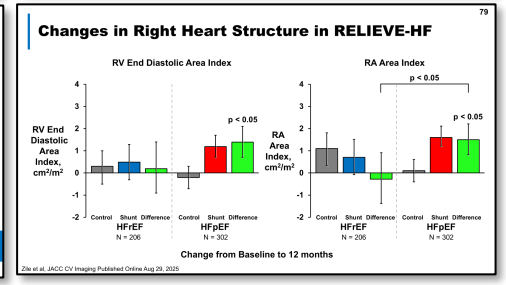






Biologically Plausible Mechanism





Favorable Benefit-Risk Profile

Ventura® Interatrial Shunt for Reduction of Heart Failure Hospitalizations in Patients with Heart Failure with Reduced Ejection Fraction (HFrEF)

December 3, 2025

Circulatory Systems Device Panel

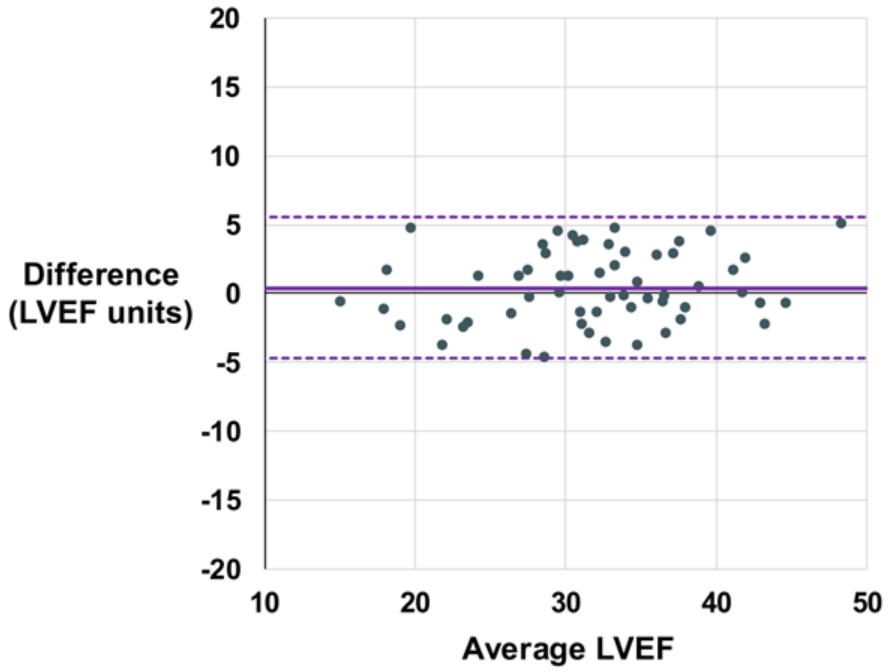
V-Wave, a Johnson & Johnson Company

Johnson&Johnson MedTech

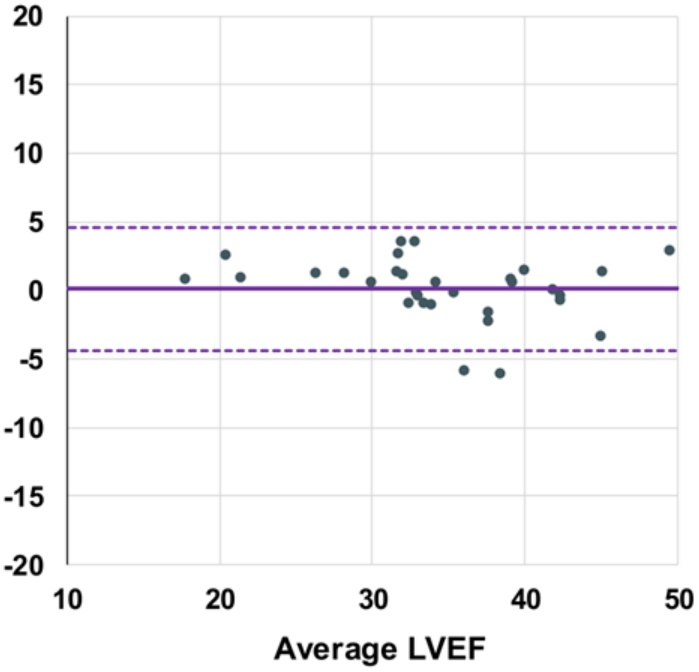
ADDITIONAL SLIDES SHOWN

Quality Assessment of Echo Core Lab - LVEF

Bland-Altman Plot: Inter-observer variability of LVEF
(Reader 1 vs Reader 2)



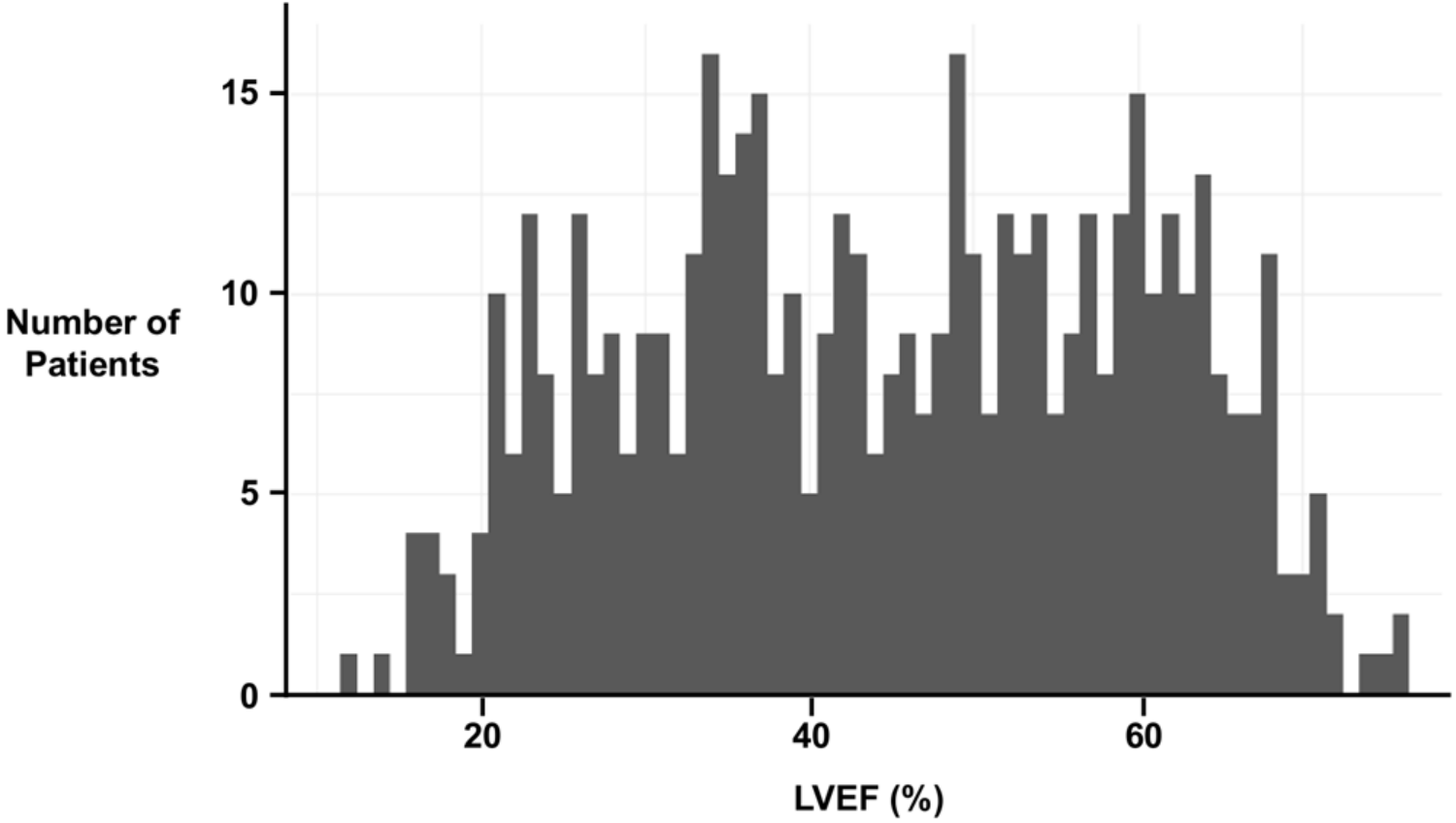
Bland-Altman Plot: Intra-observer variability
(Within Reader 1)



From Table 38: Echocardiographic Data at Baseline and 12 Months in HFrEF (LVEF ≤ 40%)

	Shunt N = 101			Control N = 105				
	Baseline	12 Months	12 Month-Baseline Difference	Baseline	12 Months	12 Month-Baseline Difference	Difference Shunt-Control	ANCOVA Nominal *P*-value
LV end-diastolic volume index, ml/m²	**98.1** (90.9, 105.3)	**94.5** (86.8, 102.1)	**-3.7** (-10.2, 2.9)	**96.9** (89.8, 103.9)	**105.0** (97.2, 112.9)	**8.2** (1.3, 15.0)	**-11.9** (-21.3, -2.5)	**0.01**
LV end-systolic volume index, ml/m²	**69.4** (63.1, 75.7)	**66.0** (59.4, 72.6)	**-3.4** (-9.0, 2.1)	**70.0** (63.9, 76.2)	**75.6** (68.7, 82.4)	**5.5** (-0.4, 11.4)	**-8.9** (-17.2, -0.7)	**0.03**
LV ejection fraction, %	**30.0** (28.4, 31.7)	**32.2** (30.4, 34.0)	**2.2** (0.4, 4.0)	**29.2** (27.6, 30.8)	**30.5** (28.8, 32.2)	**1.3** (-0.4, 3.0)	**0.9** (-1.5, 3.3)	**0.46**
LV global longitudinal strain, %	**9.6** (8.9, 10.3)	**10.3** (9.6, 11.0)	**0.7** (-0.0, 1.5)	**9.9** (9.2, 10.6)	**9.7** (9.0, 10.4)	**-0.2** (-0.9, 0.5)	**1.0** (-0.1, 2.0)	**0.06**
Left atrial volume index, ml/m²	**45.2** (41.1, 49.3)	**45.7** (41.5, 49.9)	**0.5** (-3.7, 4.8)	**40.9** (36.9, 44.9)	**47.2** (43.0, 51.3)	**6.3** (2.1, 10.5)	**-5.8** (-11.8, 0.2)	**0.06**
E/e	**18.2** (16.1, 20.3)	**17.6** (15.3, 19.9)	**-0.6** (-2.7, 1.6)	**16.3** (14.2, 18.4)	**19.5** (17.3, 21.6)	**3.2** (1.2, 5.2)	**-3.7** (-6.7, -0.7)	**0.02**

LVEF Values at Baseline Reflect Epidemiology

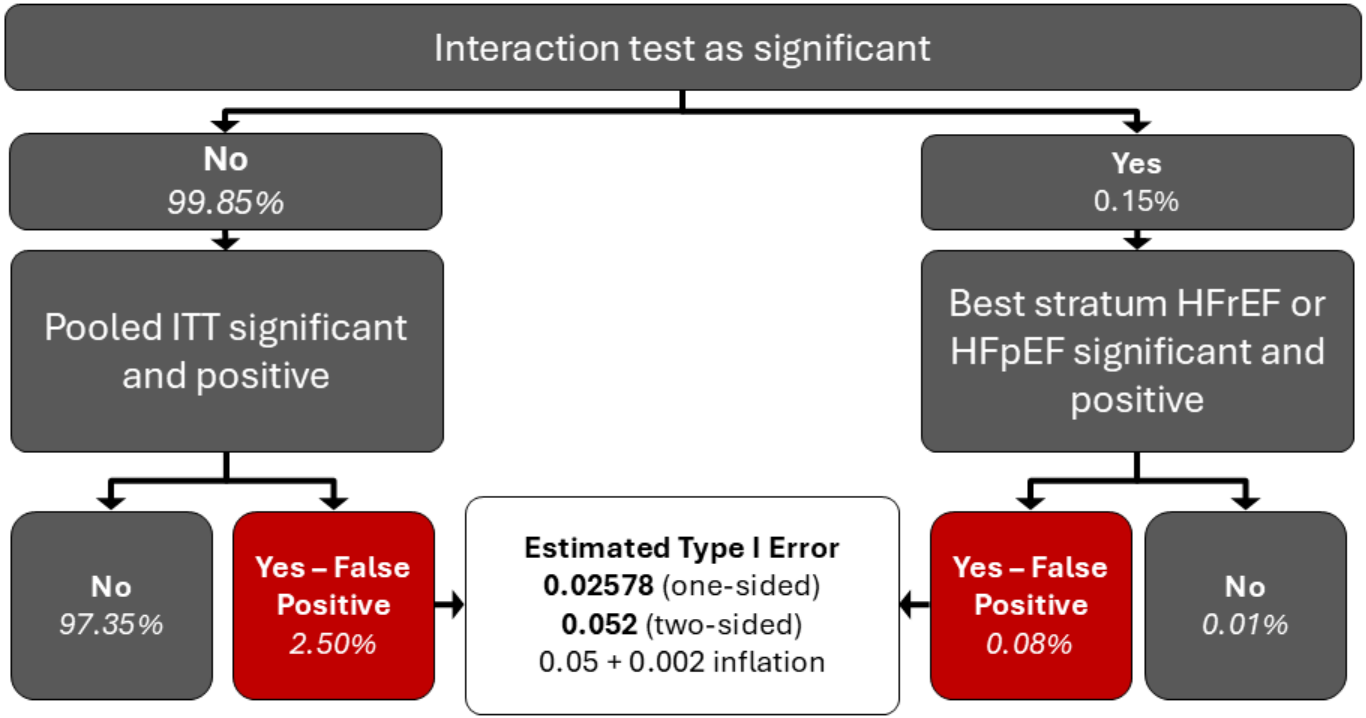


Type I Error Estimate

Three opportunities for success resulting in potential inflation of type 1 error:

1. **Overall**
2. **HFrEF**
3. **HFpEF**

Analysis includes primary and 7 secondaries

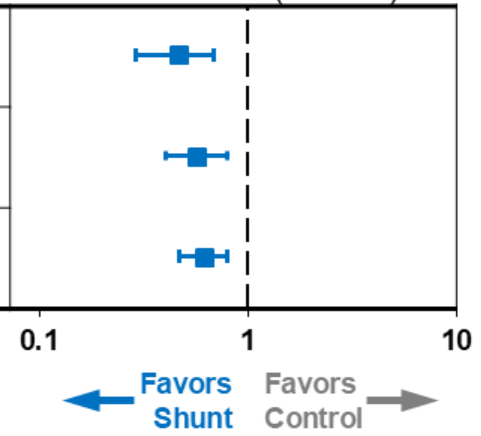


Tested 100,000 simulations

Since the null is true for these random scenarios, "Positive" indicates a false positive, or a Type I Error under the Null

Nelson-Aalen Cumulative Hazard Rates at 24 Months (HFrEF)

		Events (#) Shunt (N = 101) / Control (N = 105)	Hazard rate (95% CI)	Hazard Ratio (95% CI)
Single Event Types	Hospitalization for HF (HFH)	41 / 78	**0.46** (0.29, 0.68)	
	Hospitalization for CV (CVH)	104 / 64	**0.57** (0.40, 0.79)	
	All-Cause Hospitalization (ACH)	109 / 163	**0.61** (0.47, 0.79)	



In HFrEF, Shunt treatment was associated with consistent, robust reductions in all event types

(Including hospitalizations, outpatient worsening episodes, and terminal outcomes)

Confidence intervals are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

Table 19: 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%)
Renin-angiotensin system inhibitors	95 (94.1%)	93 (88.6%)	87 (94.6)	84 (89.4%)
-ACEi	7 (6.9%)	7 (6.7%)	7 (7.6%)	7 (7.4%)
-ARB	8 (7.9%)	7 (6.7%)	6 (6.5%)	3 (3.2%)
-ARNi	80 (79.2%)	79 (75.2%)	74 (80.4%)	74 (78.7%)
Mineralocorticoid receptor antagonists	74 (73.3%)	77 (73.3%)	66 (71.7%)	65 (69.1%)
Sodium-glucose cotransporter-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%)
Chronic oral anticoagulation	63 (62.4%)	54 (51.4%)	59 (64.1%)	56 (59.6%)

ACEi : angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNi: angiotensin receptor neprilysin inhibitor

Table 13: Post-Procedure Antiplatelet/Anticoagulation Treatment at Implant Procedure Discharge – ITT Population

	Shunt Group (N=250) n (%)	Control Group (N=258) n (%)
Antiplatelet agents, open-label (clinical)	121 (48.4)	132 (51.2)
Antiplatelet agents, study medications [a]	55 (22.0)	63 (24.4)
Chronic oral anticoagulation	158 (63.2)	150 (58.1)

a. Aspirin and clopidogrel (one or both) unless the patient was otherwise taking open-label aspirin and a platelet P2Y12 receptor inhibitor or on anticoagulation due to a clinical indication.

Roll-In TEE (Patency)

	Shunt N = 97	6 Months N = 90	12 Months N = 82	p-value
Studies analyzed				
TEE or TTE	97 (100%)	87 (97%)	75 (91%)	
TEE	86 (89%)	69 (77%)	56 (68%)	
Time to TEE, months	0 [0-0]	6.2 [5.7-6.6]	12.3 [11.9-12.9]	
Results				
Shunt patent	97 (100%)	87 (100%)	72 (100%)[a]	1.000
ΔP, mmHg	4.2 ± 2.9	5.1 ± 3.1	5.1 ± 3.9	0.316
Q, mL/min	1037 ± 385	1124 ± 417	1137 ± 463	0.384
Qp/Qs, mean ± SD			1.22 ± 0.12	

ΔP = mean interatrial pressure gradient; C_d = discharge coefficient; D_{eff} = effective diameter; D_{vc} = vena *contracta* diameter; Q = flow

a. Three cases with echocardiographic imaging, but no colour Doppler views of the shunt; b. Thrombus seen in left atrial appendage in one patient

ESC Heart Fail. 2024 Oct;11(5):2499-2509. doi: 10.1002/ehf2.14859. Epub 2024 May 22.

In vivo fluid dynamics of the Ventura interatrial shunt device in patients with heart failure

Michael Pfeiffer 1, John Boehmer 1, John Gorcsan 1, Shunsuke Eguchi 1, Yoshiyuki Orihara 1, Michal Laufer Perl 2, Neal Eigler 3, William T Abraham 4, Julio Nuñez Villota 5, Elizabeth Lee 6, Antoni Bayés-Genís 7, Gil Moravsky 8, Saibal Kar 9, Michael R Zile 10, Richard Holcomb 11, Stefan D Anker 12, Gregg W Stone 13, Josep Rodés-Cabau 14, JoAnn Lindenfeld 15, Jeroen J Bax 16

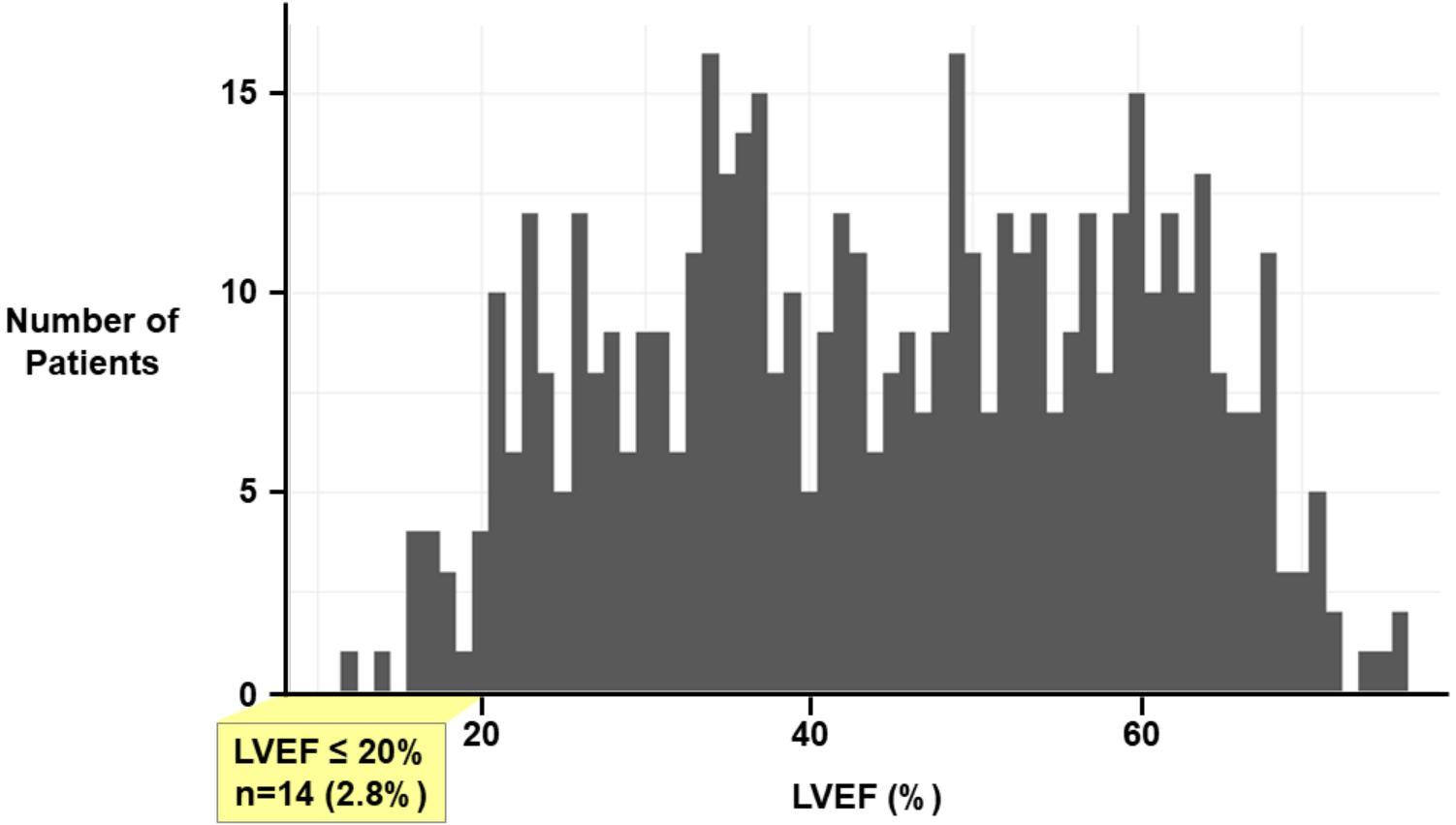
Patient Sex Distribution

	ITT Total N = 508		HFrEF Total N = 206		HFpEF Total N = 302		p-value*
	n	%	n	%	n	%	
Male	319	62.8%	168	81.6%	151	50.0%	< 0.0001
Female	189	37.2%	38	18.4%	151	50.0%	

Overall Demographics US vs OUS (HFrEF)

	Total N = 206		US N = 97		OUS N = 109	
	n	%	n	%	n	%
Race: White	184	89.3%	76	78.4%	108	99.0%
Race: Black	16	7.8%	15	15.5%	1	0.9%
Ethnicity: Hispanic	25	12.1%	14	14.4%	11	10.1%

LVEF Values at Baseline Reflect Epidemiology



Events in Patients with LVEF ≤ 20 at Baseline

	Patients with LVEF ≤ 20 at Baseline	
	Shunt N = 6	**Control** N = 8
HFH events	2	17
Death	2	2
HT/LV events	0	2
WHF events	3	2
HF events	7	23

Changes in MR and TR – ITT Population

	Baseline				12 Months			
	Treatment (N = 250)	Control (N = 258)	Difference (95% CI)	p-value	Treatment (N = 250)	Control (N = 258)	Difference (95% CI)	p-value
Mitral Regurgitation								
Moderate or greater	**20%**	**15%**	**4.9** (-1.7, 11.4)	0.15	**11%**	**10%**	**0.6** (-5.2, 6.5)	0.83
Moderate	**18%**	**14%**	**4.8** (-1.5, 11.2)	0.14	**10%**	**10%**	**-0.3** (-5.9, 5.3)	0.91
Mod – Severe	**1%**	**1%**	**0.0** (-2.3, 2.5)	1.00	**1%**	**0.5%**	**1.0** (-1.2, 3.8)	0.36
Severe	**0**	**0**	**0**	N/A	**0**	**0**	N/A	N/A
Tricuspid Regurgitation								
Moderate or greater	**20%**	**18%**	**2.7** (-4.1, 9.6)	0.43	**16%**	**11%**	**4.8** (-1.7, 11.2)	0.15
Moderate	**19%**	**16%**	**3.1** (-3.6, 9.7)	0.36	**13%**	**11%**	**2.8** (-3.3, 9.0)	0.36
Mod – Severe	**1%**	**0.4%**	**0.8** (-1.1, 3.2)	0.36	**2%**	**0.5%**	**1.9** (-0.5, 5.1)	0.12
Severe	**0**	**1%**	**-1.2** (-3.4, 0.4)	0.25	**0**	**0**	N/A	N/A

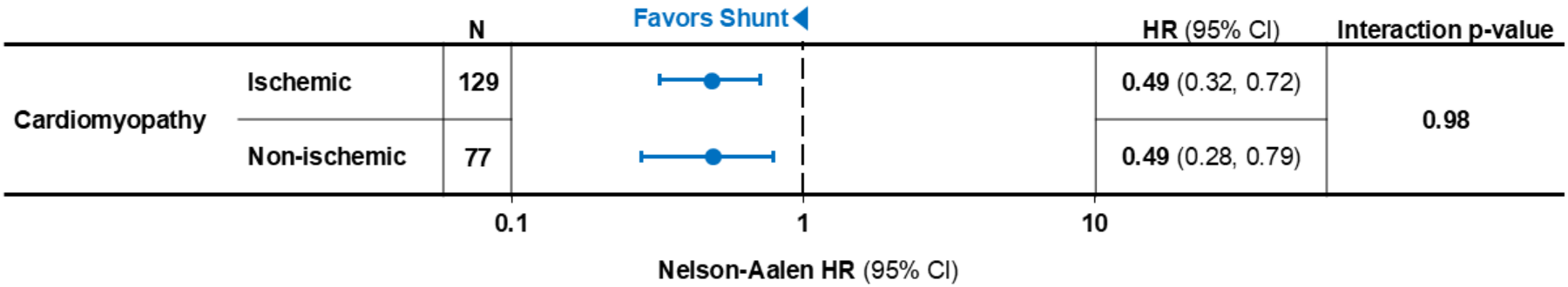
Changes in MR and TR – HFrEF

	Baseline				12 Months			
	Treatment (N = 101)	Control (N = 105)	Difference (95% CI)	p-value	Treatment (N = 101)	Control (N = 105)	Difference (95% CI)	p-value
Mitral Regurgitation								
Moderate or greater	**24%**	**18%**	**5.7** (-5.4, 16.8)	0.32	**14%**	**10%**	**4.4** (-5.2, 14.1)	0.37
Moderate	**22%**	**15%**	**6.5** (-4.0, 17.1)	0.23	**10%**	**10%**	**0.9** (-8.1, 10.0)	0.84
Mod – Severe	**2%**	**3%**	**-0.9** (-6.5, 4.6)	1.00	**3%**	**0**	**3.5** (-1.1, 9.9)	0.25
Severe	**0**	**0**	N/A	N/A	**0**	**0**	N/A	N/A
Tricuspid Regurgitation								
Moderate or greater	**12%**	**16%**	**-3.9** (-13.5, 5.6)	0.42	**8%**	**10%**	**-1.7** (-10.4, 7.0)	0.69
Moderate	**12%**	**14%**	**-2.0** (-11.4, 7.3)	0.67	**6%**	**10%**	**-4.1** (-12.2, 4.1)	0.33
Mod – Severe	**0**	**0**	N/A	N/A	**2%**	**0**	**2.3** (-2.3, 8.2)	0.50
Severe	**0**	**2%**	**-1.9** (-6.8, 2.0)	0.50	**0**	**0**	N/A	N/A

Event Rates and Rate Ratio for Baseline Resting Pulmonary Vascular Resistance (HFrEF)

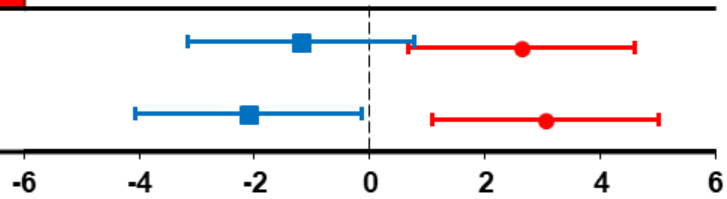
	PVR < 2.0 Wood Units				PVR ≥ 2.0 Wood Units			
	Shunt N = 44	Control N = 43	RRR (95% CI)	p-value	Shunt N = 55	Control N = 60	RRR (95% CI)	p-value
Death, HT/LV, HFH, WHF	**22** (30.2%/yr)	**42** (68.5%/yr)	**0.44** (0.25, 0.76)	0.0021	**53** (66.8%/yr)	**88** (102.2%/yr)	**0.65** (0.46, 0.93)	0.0169

Cardiomyopathy (HFrEF): All Heart Failure Events (All-cause Death, LVAD/HT, All HFHs, All Out-patient Worsening HF Events)



Win Ratio vs GST vs Recurrent Events Analysis

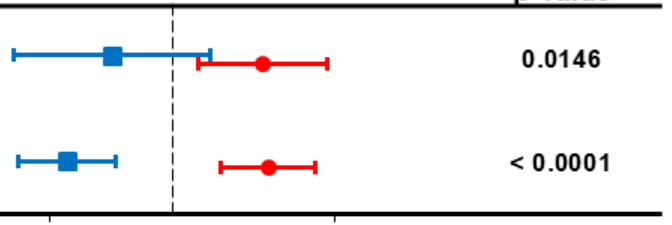
	HFrEF p-value	T-Score (95% CI) HFrEF	T-Score (95% CI) HFpEF
Primary Endpoint (Win Ratio)	0.23	-1.20 (-3.16, 0.76)	2.62 (0.66, 4.58)
GST primary + 6 secondary (without KCCQ)	0.04	-2.11 (-4.07, -0.15)	3.05 (1.09, 5.01)



T-Score (95% CI)

Gail-Simon GST (with KCCQ) p-value: 0.0201

	Hazard Ratio (95% CI) HFrEF	Hazard Ratio (95% CI) HFpEF	Interaction p-value
Primary Endpoint (Win Ratio [Inverted])	0.71 (0.41, 1.24)	1.63 (1.13, 2.34)	0.0146
Recurrent events analysis (primary endpoint components, without KCCQ)	0.55 (0.42, 0.73)	1.68 (1.29, 2.19)	< 0.0001



Hazard Ratio (95% CI)

Missing Echo Data

Pentara

Missing Values but has Echo

AVISIT	TRT	HFrEFFL	RAA	RVEDA	RVSA
Baseline	CONTROL ARM	0	1	0	0
Baseline	V-WAVE-SHUNT ARM	0	0	0	0
Baseline	CONTROL ARM	1	1	0	0
Baseline	V-WAVE-SHUNT ARM	1	2	0	0
Month 12	CONTROL ARM	0	4	3	3
Month 12	V-WAVE-SHUNT ARM	0	2	2	2
Month 12	CONTROL ARM	1	0	2	2
Month 12	V-WAVE-SHUNT ARM	1	2	4	4

Missing Echo

AVISIT	TRT	HFrEFFL	N
Month 12	CONTROL ARM	0	15
Month 12	V-WAVE-SHUNT ARM	0	21
Month 12	CONTROL ARM	1	12
Month 12	V-WAVE-SHUNT ARM	1	14

ACC / AHA Guidelines: HF with Improved EF

“The ACC/AHA also notes that, while the EF may now be in the "preserved" or "mid-range" category, the clinical trajectory and residual cardiac dysfunction of HFimpEF are distinct from de novo HFpEF, and the evidence base for management aligns with HFrEF rather than HFpEF. This distinction is supported by the observation that improvement in LVEF does not equate to normalization of cardiac structure or function, and ongoing therapy is necessary.”

Heidenreich, 2022

Outcomes in Patients with Improved LVEF

HF Events death, transplant, LVAD, all HFH, all WHF	**Shunt Hazard Rate** (95% CI)	**Control Hazard Rate** (95% CI)	**Hazard Rate Ratio** (95% CI)
HFrEF improved LVEF*	**0.51** (0.19, 0.95) N = 20	**0.79** (0.29, 1.52) N = 19	**0.64** (0.17, 2.16)
HFrEF non-improved LVEF	**1.04** (0.74, 1.48) N = 81	**2.30** (1.56, 3.43) N = 86	**0.45** (0.26, 0.77)
HFpEF	**1.17** (0.95, 1.51) N = 149	**0.69** (0.54, 0.93) N = 153	**1.69** (1.14, 2.52)

These findings suggest that HFrEF patients with improved LVEF do not behave like de novo HFpEF patients and continue to benefit from interatrial shunting.

* Improvement in LVEF from ≤ 40% at baseline to > 40% at 12 months

Site Reported SAE Heart Rhythm Events in HFrEF Stratum (MedDra Coded)

Heart Rhythm Event	Shunt (N = 101) N pts (N Events)	Control (N = 105) N pts (N Events)
Atrial Fibrillation / Flutter	6 (6)	5 (5)
Ventricular Tachycardia	8 (11)	9 (12)
Ventricular Fibrillation	0	1 (1)
Arrythmia - other	1 (1)	1 (1)
Syncope	2 (2)	2 (2)
CRT, new	2	1
Pacemaker, new	1	0
Lead Dislodgement	0	1

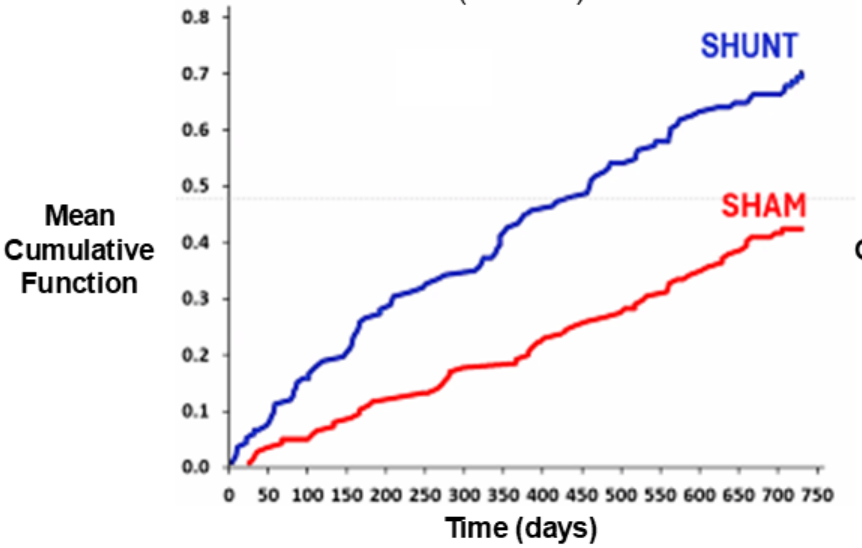
RELIEVE-HF HFpEF Patients Higher Risk than REDUCE LAP HF II Patients

Baseline Characteristic	RELIEVE-HF HFpEF Total N=302	REDUCE LAP HF II[1] Total N=578
Age, y	73.8	72.5
Female, %	50.0	61.4
Diabetes, %	47.7	36.3
Ischemic Cardiomyopathy, %	34.8	16.2
Atrial fibrillation, %	67.9	53.1
ARNI, %	18.2	0.0
SGLT2, %	33.8	2.6
NT-proBNP, pg/ml median	1553	444
eGFR, mL/min/1.73 m2	47.0	56.0
NYHA functional class, %		
II	2.0	21.8
III	97.3	78.2
E/e'	15.8	12.5
LAVI, ml/m2	40.7	31.6
TAPSE	17.0	20
Cardiac Output, L/min	4.6	5.2
PVR, WU	2.2	1.5

1. Gustafsson et al. JACC., 2024

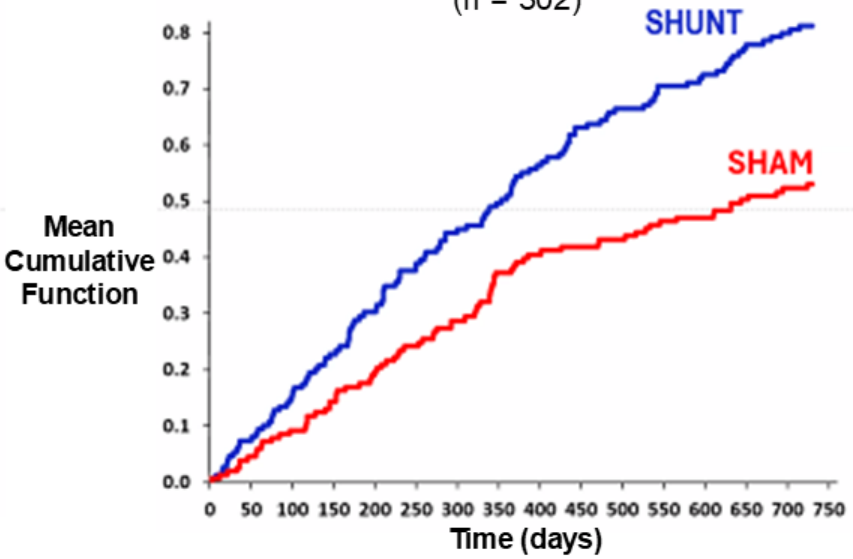
REDUCE LAP-HF HFH + Outpatient WHF Events Substantiate RELIEVE-HF Conclusions in HFpEF

REDUCE LAP HF II
Non-responders
(n = 265)



Gustafsson F, et al. JACC Heart Fail., 2024

RELIEVE-HF
HFpEF Stratum
(n = 302)



Adapted from Stone, et al. Circulation 2024

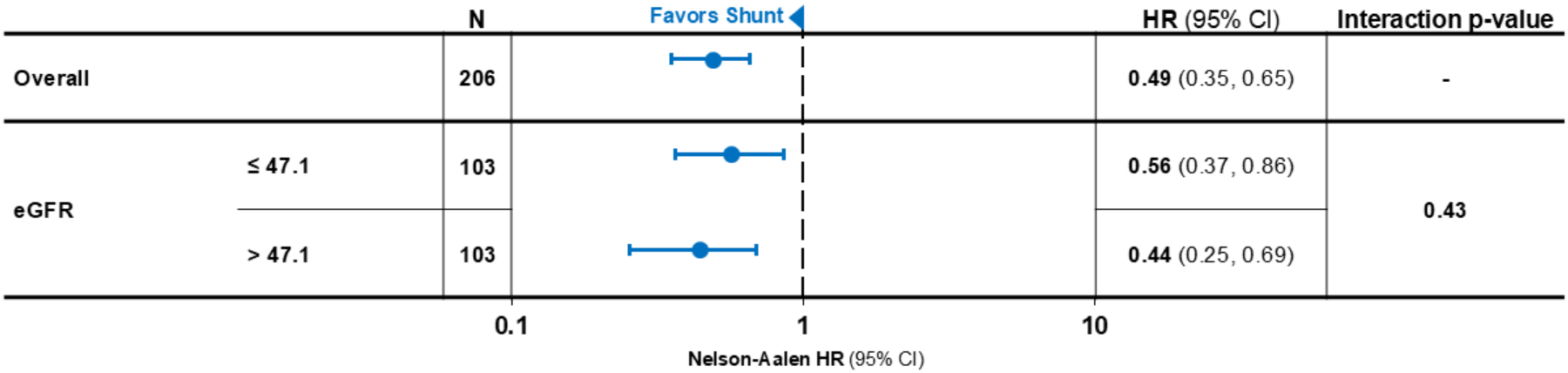
Replicating REDUCE non-responder outcomes gives credence to the totality of RELIEVE-HF data

Table 11: Additional Safety Endpoints

	Shunt group (N=250)	Control 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%)	-	-	-

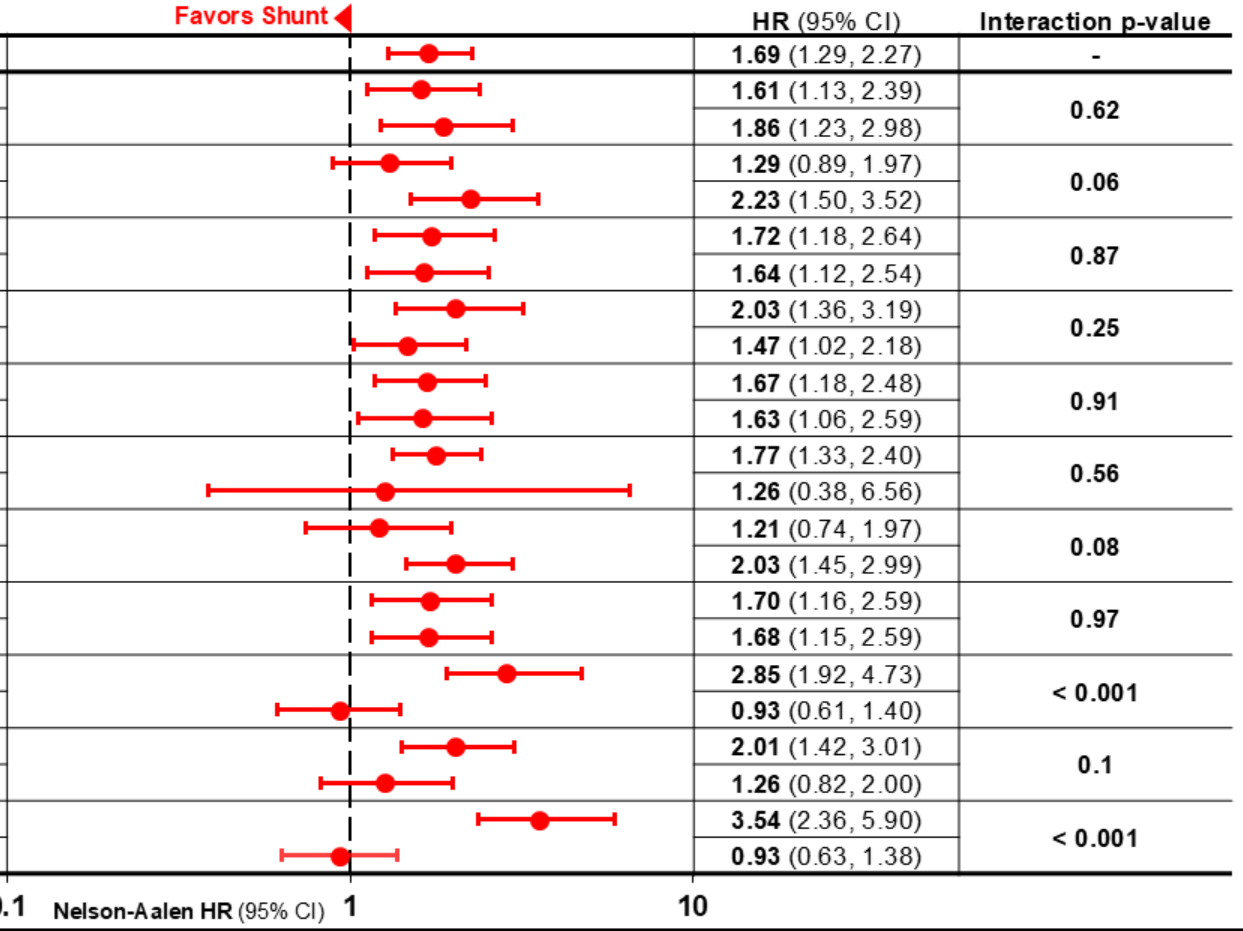
* MACNE was device-related or procedure-related.
** The 7 strokes in patients who were treated with the Shunt were classified by the CEC as being due to cerebrovascular disease (n=3), embolic due to atrial fibrillation (n=2) and undetermined (n=2). The 5 strokes in Control group patients who were treated with a placebo-procedure were classified by the CEC as being due to cerebrovascular disease (n=1), embolic due to atrial fibrillation (n=2), subarachnoid hemorrhage (n=1) and undetermined (n=1). Only one stroke occurred within 30 days of randomization, that being in the Control group.
† Does not include 1 additional patient in the placebo group with an ischemic stroke and hemorrhagic transformation.
1. Event rates were number of events (Kaplan-Meier time-to-first event estimates. Not done for MACNE as there were no events.
2. Hazard ratio [95% confidence interval].

Subgroup Analysis (HFrEF): All Heart Failure Events (All-cause Death, LVAD/HT, All HFHs, All Out-patient Worsening HF Events)

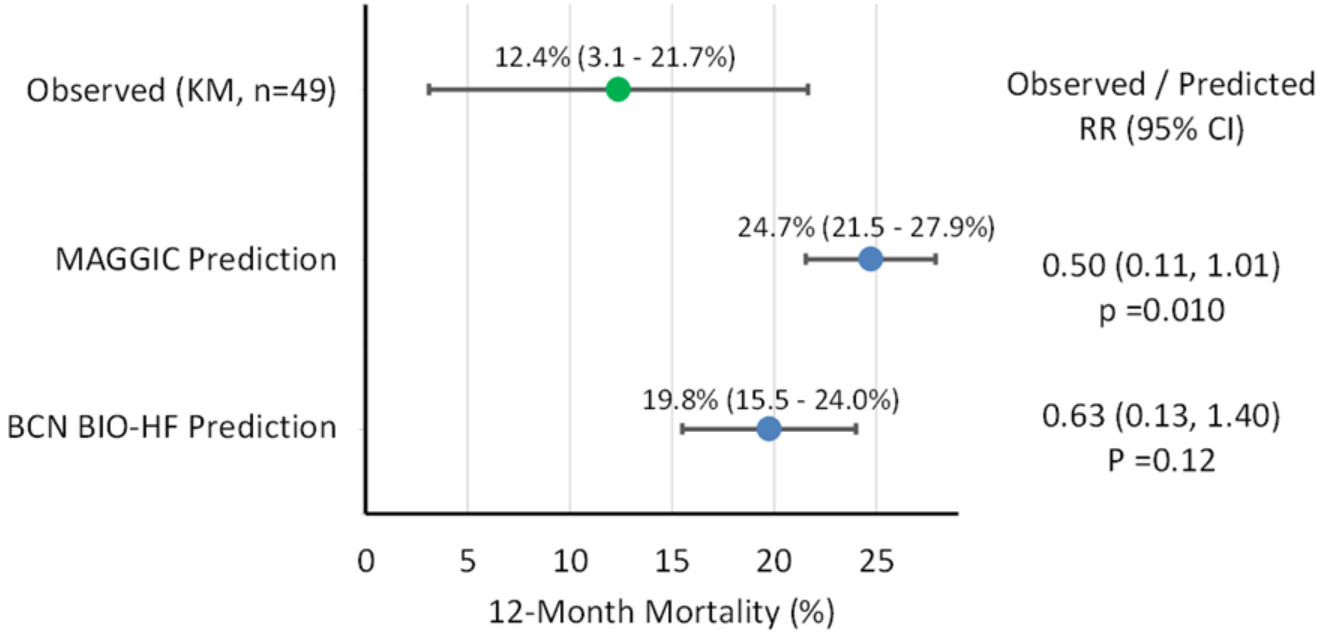


Subgroup Analysis (HFpEF): All Heart Failure Events (All-cause Death, LVAD/HT, All HFHs, All Out-patient Worsening HF Events)

		N	HR (95% CI)	Interaction p-value
Overall		302	**1.69** (1.29, 2.27)	-
Age	≤ 75	162	**1.61** (1.13, 2.39)	0.62
	> 75	140	**1.86** (1.23, 2.98)	
Sex	Male	151	**1.29** (0.89, 1.97)	0.06
	Female	151	**2.23** (1.50, 3.52)	
Geography	US	153	**1.72** (1.18, 2.64)	0.87
	Non-US	149	**1.64** (1.12, 2.54)	
BMI	≤ 30.9	154	**2.03** (1.36, 3.19)	0.25
	> 30.9	148	**1.47** (1.02, 2.18)	
Diabetes	Present	144	**1.67** (1.18, 2.48)	0.91
	Absent	158	**1.63** (1.06, 2.59)	
Hypertension	Present	264	**1.77** (1.33, 2.40)	0.56
	Absent	38	**1.26** (0.38, 6.56)	
Cardiomyopathy	Ischemic	105	**1.21** (0.74, 1.97)	0.08
	Non-ischemic	197	**2.03** (1.45, 2.99)	
BNP / NT-proBNP	≤ 177.5 / ≤ 1547	159	**1.70** (1.16, 2.59)	0.97
	> 177.5 / > 1547	143	**1.68** (1.15, 2.59)	
eGFR	≤ 47.3	151	**2.85** (1.92, 4.73)	< 0.001
	> 47.3	151	**0.93** (0.61, 1.40)	
6MWT	≤ 254.8	151	**2.01** (1.42, 3.01)	0.1
	> 254.8	151	**1.26** (0.82, 2.00)	
KCCQ	≤ 48.4	151	**3.54** (2.36, 5.90)	< 0.001
	> 48.4	151	**0.93** (0.63, 1.38)	



Shunt-Treated Roll-in Cohort Observed vs Predicted 12-month Mortality (HFrEF)



Observed Kaplan Meier rate (95% CI); Predictions mean (95% CI)
Rodés-Cabau et al. Eur J Heart Fail 2024

HFrEF Roll-in vs Randomized Shunt Patient Baseline Characteristics – Key Differences

Characteristic	Roll-in Shunt HFrEF	Randomized Shunt HFrEF
n	49	101
Age	68.9±11.0	69.8 ± 11.1
Female, %	8.2%	16.8%
BMI, kg/m²	31.1±5.8	29.1 ± 5.4
Therapies		
ICD, %	40.8%	88.10%
CRT, %	42.9%	48.50%
ARNI, %	59.2%	79.20%
SGLT2, %	22%	47.50%
Echo		
LVEF,%	28.2±6.7	30.0 ± 6.4
RVFAC, %	35.0±6.6	36.8 ± 6.9
TAPSE, mm	15.4±2.8	16.1 ± 3.4
Hemodynamics		
RAP, mmHg	11.6±4.6	8.9 ± 4.2
PAP mean, mmHg	31.6±8.7	25.6 ± 7.7
PCWP, mmHg	20.7±7.6	16.4 ± 6.6
PVR, Wood units	2.5±1.2	2.3 ± 1.3