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V-WAVE VENTURA® INTERATRIAL SHUNT SYSTEM

SPONSOR EXECUTIVE SUMMARY

CIRCULATORY SYSTEMS DEVICE ADVISORY COMMITTEE

MEETING DATE: 03 DECEMBER 2025

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

1 SYNOPSIS

1.1 Introduction

V-Wave is pursuing premarket approval (PMA) for the Ventura® Interatrial Shunt System for New York Heart Association (NYHA) Class III Heart Failure (HF) patients with left ventricular ejection fraction (LVEF) ≤ 40%, who remain symptomatic despite guideline-directed medical therapy (GDMT) and are judged by a Heart Team to be appropriate for shunt therapy to reduce the risk of hospitalization for HF. This system includes both the Ventura Shunt and the Ventura Delivery System.

There is a significant unmet need for therapies that improve prognosis in patients with HF with reduced ejection fraction (LVEF ≤ 40%; HFrEF), as these patients continue to be at significant residual risk of HF hospitalization and mortality despite current treatment options. HF is characterized by debilitating symptoms including shortness of breath, resulting from increased left atrial pressure and pulmonary venous congestion, which subsequently leads to HF hospitalization and often death. Although lowering left atrial pressure improves clinical outcomes in HF, it is difficult to achieve through pharmacological means (Lindenfeld et al., 2024).

Currently, there are no alternative therapies to improve clinical outcomes in NYHA Class III HFrEF patients who are treated with optimal GDMT, including the use of implantable cardioverter defibrillator (ICDs) and cardiac resynchronization therapy devices.

The Ventura Interatrial Shunt (hereafter referred to as the Shunt) is a permanent implant placed across the interatrial septum and is designed to shunt blood from the left-to-right atrium. In response to changes in the left-to-right atrial pressure gradient, the Shunt operates automatically to reduce left atrial pressure when needed, without patient or physician intervention. As a novel technology in the treatment of HF, a life-threatening and debilitating disease, the Shunt was granted Breakthrough Device Designation in 2019.

The pivotal RELIEVE-HF (**RE**ducing **L**ung congestion symptoms us**I**ng the v-wav**E** Shunt in ad**V**anc**E**d **H**eart **F**ailure) trial was a multicenter randomized, double-blind, sham (placebo procedure)-controlled, study where patients with symptomatic HF on optimal (i.e., maximally tolerated) GDMT, as adjudicated by a Central Eligibility Committee, received either the Shunt or the sham control procedure. The full trial Protocol and Statistical Analysis Plan have been previously published and are available online (Stone et al., 2024 Supplement 3). The trial randomized 508 patients over a 4-year period, more than 95% of whom were NYHA Class III. The median follow-up was 22 months.

From preclinical data and early feasibility studies of the Shunt, V-Wave and its Principal Investigators anticipated that both HFrEF (LVEF ≤ 40%) and HF with preserved ejection fraction (LVEF > 40%; HFpEF) patients could potentially benefit from the device. As a

result, the RELIEVE-HF study design included patients across the full spectrum of LVEF.

However, it was also understood that functional differences in the 2 clinical HF phenotypes could potentially affect the response to shunting. For this reason, randomization was stratified by LVEF group with the goal of ensuring a balanced representation of treatment assignment within each stratum in RELIEVE-HF. Interaction testing between these two strata was prespecified to assess the homogeneity of the treatment effects in the ITT population.

For the primary efficacy endpoint, an interaction was observed between the two LVEF strata (*P*=0.0146) and therefore the strata could not be combined for the analysis of effectiveness. Consequently, each LVEF stratum was separately analyzed, which demonstrated markedly contrasting directionally opposite outcomes. The win ratio primary effectiveness endpoint was not met in either stratum. In the RELIEVE-HF trial population, there was a signal for benefit in HFrEF patients and harm in HFpEF patients.

The four HF Event clinical components of the primary endpoint demonstrated benefit of Shunt treatment in HFrEF patients. Shunt treatment was associated with a concordant and clinically meaningful reduction in HF Event rates, particularly recurrent events, among patients with HFrEF (**Table 1**). Conversely, Shunt treatment in HFpEF patients was linked to an increase in such events. Similar findings were seen using a variety of comparative methods (see **Section 10.7.3**).

Table 1: Risk of All Primary Endpoint HF Events Through 2 Years in HFrEF (LVEF ≤ 40%)

	Shunt Group N=101 Events (Hazard rate at 2 yrs)	Control Group N=105 Events (Hazard rate at 2 yrs)	Nelson-Aalen Hazard Rate Ratio at 2 Years (95% CI)	Reduction (%)
Total primary endpoint HF Events	76 (0.93)	134 (1.92)	0.49 (0.36, 0.65)	51
All-cause death	13 (0.15)	20 (0.31)	0.49 (0.20, 1.08)	52
HTLV	1 (0.02)	6 (0.09)	0.16 (0.00, 1.10)	85
All HFHs	41 (0.52)	78 (1.13)	0.46 (0.29, 0.69)	54
All outpatient worsening HF	21 (0.25)	30 (0.38)	0.64 (0.33, 1.18)	36

CI: confidence interval; HF: heart failure; HFH: heart failure hospitalization; HFrEF: heart failure with reduced ejection fraction; HTLV: heart transplant; LVAD or left ventricular assist device; LVEF: left ventricular ejection fraction.
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

In an effort to understand the biological mechanisms of the observed effects, additional analyses were conducted to examine cardiac structure and function using serial

echocardiograms (read by an independent Echocardiographic Core Laboratory) from the RELIEVE-HF LVEF stratified cohorts.

The findings showed marked differences in baseline cardiac structure and function in the two groups (Zile et al., 2025). After shunt treatment, HFrEF patients had reductions in median left ventricular (LV) end-diastolic volume and LV end-systolic volume consistent with reverse LV remodeling. In prior studies, LV reverse remodeling has been associated with improved clinical outcomes (Kramer et al., 2010). Additionally, increased right ventricular (RV) compliance allowed HFrEF patients to accommodate the volume transferred from the left atrium to the right atrium without increased pulmonary artery pressure. In HFpEF patients, there was no reverse LV remodeling, and there was evidence of worsening right heart dilatation and pulmonary hypertension. In prior studies, worsening right heart dilatation and pulmonary hypertension have been associated with worse clinical outcomes (Zile et al., 2025).

The primary safety endpoint at 30 days was achieved for the ITT cohort. In fact, there were no device- or procedural-related major adverse cardiovascular or neurologic events (MACNE) at 30 days and through 2 years of follow-up in either the HFrEF or HFpEF strata. In addition, stroke, MI, and thromboembolic events occurred infrequently and at similar rates in the HFrEF Shunt and Control groups.

Collectively, the RELIEVE-HF study findings regarding safety, effectiveness, and mechanism of action support a favorable benefit-risk profile for Shunt treatment among HFrEF patients, particularly considering the unmet clinical need.

V-Wave will implement strong post-market controls that will serve as safeguards to ensure patient welfare. Along with the proposal for a limited indication, V-Wave has outlined a comprehensive set of post-approval commitments aimed at continued clinical evidence generation and data collection assuring oversight of the commercial release process. These proposals align with post-approval requirement expectations from past approvals of structural heart devices, including mandates for local heart teams, extensive physician training in patient selection, a controlled commercial roll-out, collaborative design of a robust post-approval study with the Food and Drug Administration (FDA), and the establishment of an independently-managed registry enrolling all United States (US) patients treated with the commercial device outside of the post-approval study.

Thus, the totality of the evidence and robust post-market controls provide reasonable assurance of safety and effectiveness for the Ventura Shunt, supporting its approval in patients with NYHA functional Class III HF who remain symptomatic despite optimal GDMT and have an LVEF of ≤ 40%.

1.2 Background and Unmet Need

HF is a major public health problem affecting the developed world and causes a tremendous human toll due to persisting high morbidity and mortality despite decades of advances in medical and device therapies and the use of guideline-directed treatment.

In the US, 7 million people ages 20 and older have HF; prevalence continues to rise and is expected to reach 8.5 million by 2030 (Bozkurt et al., 2025; Heidenreich et al., 2013; Van Nuys et al., 2018). Globally, 56 million people currently have HF. The risk of developing HF rises with each decade of life with a 24% lifetime risk, meaning that 1 in 4 of the US population will develop HF in their lifetime (Bozkurt et al., 2025). There are nearly 1 million new patients with HF in the US each year.

HF accounts for approximately 45% of all cardiovascular deaths (Bozkurt et al., 2025). Patients with HF often acutely decompensate with worsening signs and symptoms of HF(Hall et al., 2010). US heart failure hospitalizations have continued to increase with 659,615 HFrEF patients and 495,095 in HFpEF patients in 2019 (Bozkurt et al., 2025). Most of these patients present with severe symptoms and are NYHA functional Class III or IV (Adams et al., 2005; National Institute for Cardiovascular Outcomes Research (NICOR), 2021; Poon et al., 2022). Readmission rates for acute decompensated HF (ADHF) are nearly 50% at 6 months following initial hospitalization. Patients admitted with ADHF have a 90-day mortality of 10% and a 1-year risk-adjusted mortality of 30% (Fonarow et al., 2007). Medicare data show that in 39,982 patients admitted for HF, the 5-year all-cause mortality was >75% irrespective of LVEF (Shah et al., 2017). Taken together, these observations underscore the unmet need for new therapies that improve HF clinical outcomes.

HF is classified based on LVEF, which is the percent of LV end-diastolic volume ejected with each heartbeat. Normal LVEF ranges from 55% to 70%; however, in HF, LVEF may be markedly reduced. HF is commonly divided into 2 clinical phenotypes: 1) HFrEF, when LVEF is ≤ 40%; and 2) HFpEF, when LVEF is > 40% (McDonagh et al., 2024). Worsening symptoms in both HFrEF and HFpEF are characterized by increased left atrial pressure and pulmonary venous congestion (Ritzema et al., 2010).

Although elevated left atrial pressure is the common cause for worsening HF symptoms in the 2 phenotypes, cardiac structure and function differ between them (see **Section 2.2.1**). In HFrEF, the heart muscle is weakened, with thin ventricular walls and a dilated left ventricle with reduced systolic function; this ultimately leads to reduced pumping of blood by the left ventricle to the body. In contrast, in HFpEF, the heart muscle is stiffened, often with thick ventricular walls, which interferes with relaxation and filling of the ventricles. Moreover, HFpEF is characterized by a complex interaction of diastolic dysfunction, vascular stiffening, chronotropic incompetence, and right heart involvement. Due to these differences, responses to the same therapies may vary.

For patients with HFrEF, GDMT includes 5 classes of medications: renin-angiotensin system (RAS) inhibitors, beta blockers, mineralocorticoid receptor antagonists (MRA),

sodium-glucose cotransporter type 2 inhibitors (SGLT2i), and diuretics. For patients with HFpEF, GDMT currently includes diuretics and SGLT2i along with blood pressure and atrial fibrillation control. The guidelines for patients with HFrEF also include several implantable cardiac devices. Even with these GDMT therapies, these patients continue to have a high residual risk of morbidity and mortality, and alternative treatment approaches are urgently needed. The Class I guidelines for SGLT2i in HFrEF and HFpEF were separately incorporated during the course of enrolling RELIEVE-HF.

1.3 Device Overview

1.3.1 Development Rationale

Prior to launching RELIEVE-HF, the development of the Ventura Shunt, a novel, alternative treatment approach for HF, was based on substantial preclinical and clinical evidence that supports the benefits of interatrial shunting in HF and includes:

- Sustained elevation of left atrial pressure causes pulmonary congestion leading to symptoms of HF (Ritzema et al., 2010). Reducing elevated left atrial pressure ameliorates and prevents episodes of HF (Abraham et al., 2011; Abraham et al., 2016; Adamson et al., 2014; Brugts et al., 2023; Lindenfeld et al., 2021; Ritzema et al., 2010). In patients with HFrEF, meta-analyses have shown that implantable hemodynamic monitoring-guided therapy reduces the rate of heart failure hospitalization (HFH) and improves survival (Lindenfeld et al 2024).
- Computer simulation studies suggested reduced left-sided filling pressure after interatrial shunting based on exercise hemodynamics from a cohort of patients with “early” HFpEF (Kaye et al 2014). Human feasibility studies of a different Interatrial Shunt Device in HFpEF patients showed reductions in exercise-induced elevations of LAP (Feldman et al 2018; Kaye et al 2016).
- In a validated ovine model of chronic HFrEF, implantation of prototype V-Wave Shunts decompressed the left atrium, improved LV systolic dysfunction, and prevented the development of pulmonary congestion, pulmonary hypertension, and death, compared to controls (Eigler et al 2017).
- In feasibility human studies with an earlier version of the V-Wave Shunt, hemodynamic benefits of shunting were demonstrated that were associated with clinical improvements in both HFrEF and HFpEF (Rodes-Cabau et al., 2018).

1.3.2 Design Features and Implantation Procedure

The Shunt is a permanent implant designed to shunt blood from the left to the right atrium for treatment of patients with advanced chronic HF. The Ventura Delivery System (hereafter referred to as the Delivery System), while custom, is similar in design and function to other vascular implant delivery catheters.

The Shunt is implanted across the interatrial septum following femoral venous access and a standard transseptal catheterization procedure. Shunt implantation is conducted

under general anesthesia or conscious sedation with fluoroscopic and transesophageal (TEE) or intracardiac echocardiographic (ICE) guidance. After crossing the interatrial septum, the Shunt is implanted across the mid portion of the fossa ovalis. After Shunt implantation, a rise in left arial pressure results in an increase in the interatrial pressure gradient that automatically increases blood flow through the shunt from the left-to-right atrium. This increase in flow reduces left atrial volume, thereby lowering left atrial pressure.

1.4 Proposed Indication for Use

In light of the RELIEVE-HF results demonstrating safety and effectiveness in the HFrEF (LVEF ≤ 40%) group, where > 95% of patients were NYHA Class III, the Sponsor is seeking the following limited indication:

The Ventura® Shunt is indicated for NYHA Class III HF patients who remain symptomatic despite GDMT, 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 HF.

1.5 RELIEVE-HF Study

1.5.1 Study Design

RELIEVE-HF was a randomized, double-blind, sham-controlled, multicenter study that evaluated transcatheter implantation of the Shunt in symptomatic patients with HF with any LVEF. Enrolled patients were NYHA functional Class II, III, or ambulatory Class IV, despite optimal GDMT as assessed by a Central Eligibility Committee. Exclusion criteria included marked LV dilatation, severe pulmonary hypertension, or moderate or greater RV dysfunction. Details on key inclusion and exclusion criteria are in **Section 4.1.1**.

Following procedural screening with TEE or ICE and right heart catheterization, qualifying patients stratified by LVEF (HFrEF versus HFpEF) were immediately randomized 1:1 in a blinded fashion to transcatheter implantation of the Shunt or sham (Control) as described in **Section 4.1**.

During the pre-trial design phase, it was anticipated that patients across the LVEF spectrum could respond similarly to shunting but given the known differences between HFrEF and HFpEF patients, the possibility that they could respond differently also remained. In this regard, randomization was stratified by LVEF group (≤ 40% and > 40%), which was the only clinical variable stratified. While the study was powered to detect a treatment difference in the overall intention-to-treat (ITT) population, interaction testing of the prespecified LVEF strata was prespecified to examine the homogeneity of treatment effect.

All safety and effectiveness events were adjudicated by an independent Clinical Events Committee (CEC) that was blinded to treatment assignments unless and until they determined that a MACNE event was likely device or procedure related for safety reasons.

The Primary Safety Endpoint was a composite of device-related or procedure-related MACNE occurring in the Shunt arm within 30 days after randomization compared to a prespecified performance goal of 11%.

The Primary Effectiveness Endpoint was a hierarchical composite of the following HF Events and Kansas City Cardiomyopathy Questionnaire (KCCQ) in the overall pooled LVEF ITT Population:

1. All-cause death;
2. Heart transplantation or left ventricular assist device implantation (HTLV);
3. HFH, including qualifying ER visits ≥ 6 hours;
4. Worsening heart failure (WHF) treated as an outpatient, including ER HF visits < 6 hours; and
5. KCCQ Overall Summary Score (OSS) change from baseline with ≥ 5-point between-group difference through 2-year follow-up.

The Primary Effectiveness Endpoint was evaluated with a sum of ranks test statistic using the method of Finkelstein and Schoenfeld, expressed using the unmatched win ratio (Redfors et al., 2020), calculated as the total number of Shunt Group patient wins divided by the number of Control Group wins and 95% confidence interval (CI) after all pairwise comparisons. A win ratio > 1 indicates more favorable results for experimental treatment (Shunt Group). Additional details on statistical analyses are provided in **Section 4.3**.

1.5.2 Patient Population

RELIEVE-HF enrolled symptomatic HF patients on GDMT into a 1:1 randomized (Shunt treatment group [N=250 patients] or Control group [N=258 patients]), double-blind, sham-controlled cohort. A total of 508 patients were randomized at 114 sites in 11 countries. The Shunt was successfully implanted in all 250 patients assigned to shunt treatment group and in 1/258 (0.4%) patient in the sham-controlled group due to a site randomization error. The Shunt was also successfully placed in 96/97 Roll-in patients and 22/22 Crossover patients. Thus, the Shunt implant procedure success rate was 369/370 or 99.7%.

The rate of compliance with follow-up visits was high and did not differ between strata or treatment group within strata. At the time of primary analysis (median of 22 IQR [13.3, 23.9] months) follow-up was complete in 98.4% of patients. Eight patients chose to exit the trial prior to primary analysis follow-up. No patients were lost to follow-up.

Baseline demographics were generally balanced between Shunt and Control groups, with a median age of 73 years (additional details in **Section 5.2.1**). Baseline medical history was also similar between the Shunt and Control groups; ~97% of all patients were NYHA functional Class III, median N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 1,850 pg/mL, and median LVEF was 45.3% (see additional details in **Section 5.2**).

There were substantial differences between the HFrEF and HFpEF strata. In addition to differences in LVEF, patients with HFrEF received the 4 Class I pillars of GDMT (RAS inhibitors, beta blockers, MRA, and SGLT-2) recommended drug therapies at rates exceeding the HFpEF stratum as well as other contemporary HF studies. The use of defibrillators and cardiac resynchronization devices was also very high in the HFrEF stratum (see additional details in **Section 5.2.2**). In sum, particularly in the HFrEF population, the use of guideline-directed drug and device therapies was excellent.

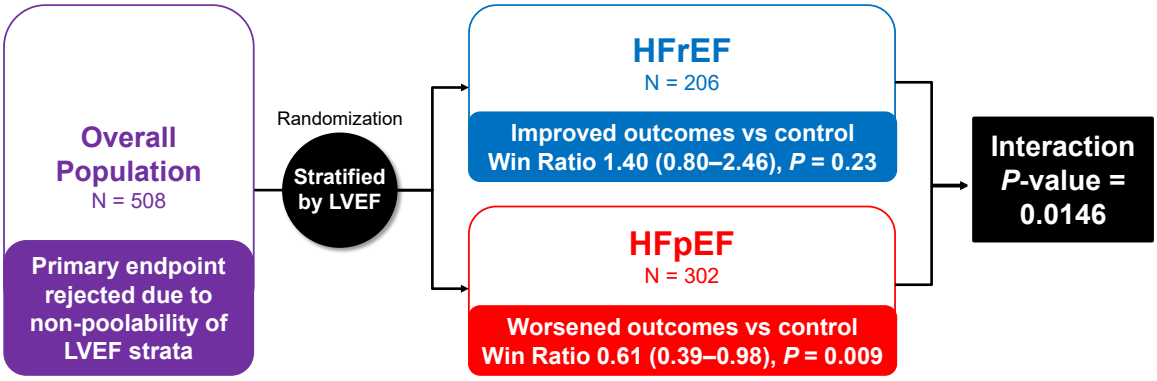
1.5.3 Safety Findings

RELIEVE-HF met its primary safety endpoint; there were 0 (97.5% CI: 0, 1.5) device- or procedure-related MACNE events at 30 days in the Shunt Group (ITT Population). Secondary safety endpoints for the ITT Population are described in **Section 4.2.1**. There were low, similar rates (less than 1%) of device- or procedure-related MACNE or Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding in the Shunt and Control groups at 30 days follow-up (**Table 18**). Through 2 years of follow-up, there were no device- or procedure-related MACNE events in Shunt-treated patients. Also, through 2 years of follow-up, there were no differences in MACNE of any cause (i.e., whether device- or procedure-related or not) or BARC types 3 or 5 bleeding between the Shunt and Control groups.

1.5.4 Effectiveness Findings

The prespecified LVEF strata interaction *P*-value for the primary effectiveness endpoint was 0.0146, indicating that there was a statistically significant difference in the treatment effect between the HFrEF and HFpEF patients, with opposing effects in the two stratification groups (**Figure 1**). It was evident that the 302 patients with HFpEF had worse clinical outcomes following treatment with the Shunt, with a win ratio (95% CI) of 0.61 (0.39, 0.98), nominal *P*=0.009. In the HFrEF population (N=206), the win ratio was 1.40 (0.80–2.46) with nominal *P*=0.23, directionally in favor of Shunt treatment. In the first 4 tiers of the hierarchy, there were more wins in the Shunt arm than in the Control arm in HFrEF patients. However, for the fifth tier with the KCCQ-OSS outcome comprising 27% of win/loss decisions, there were similar numbers of wins in each arm.

Figure 1: Effectiveness Outcomes (Win Ratio) Overall and by LVEF



HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction.
Note: Primary endpoint is a composite of all-cause death, heart transplant/LVAD implant, HF hospitalizations, worsening HF Events, and change in KCCQ-OSS score.

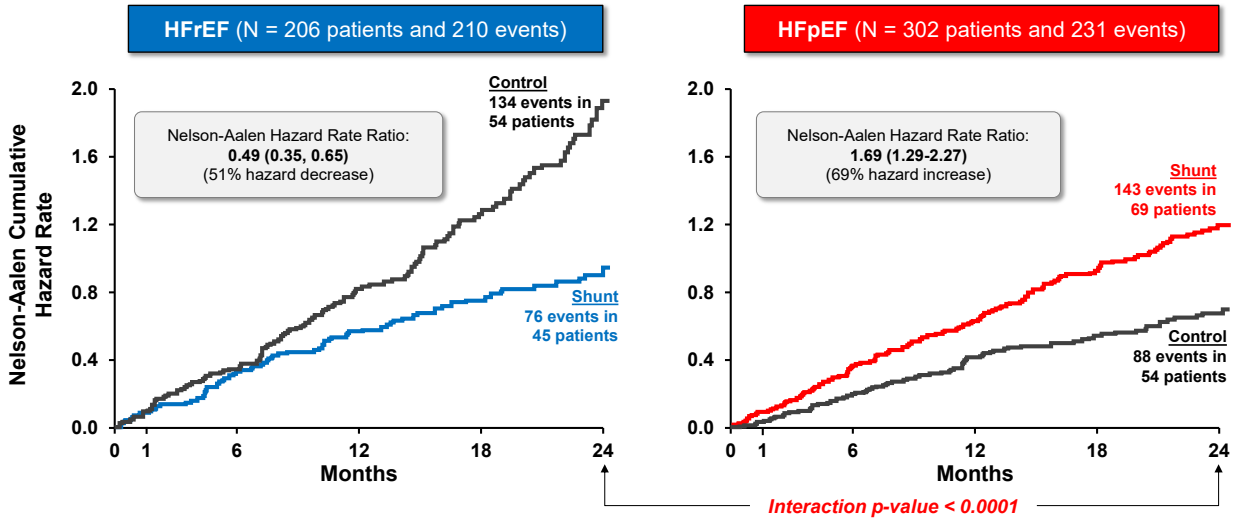
Due to the interaction effect and the unique nature of the opposing treatment effects (known as a crossover interaction) in prespecified strata, Shunt effectiveness was subsequently assessed in each stratum individually. These individual analyses are critical to evaluation of the totality of evidence supporting a favorable benefit-risk assessment in HFrEF patients, while acknowledging these analyses are considered post hoc with nominal *P*-values.

Patients with HFrEF (LVEF ≤ 40%) in the Shunt group achieved consistent benefit across multiple clinically relevant efficacy measures. HFrEF patients experienced a high rate of HF Events, with 210 adjudicated events where the majority were HFH (see **Section 7.2**). The less than significant win ratio results are explained by the number of patients excluded from contributing to Tiers 3 (HFH) and 4 (WHF) of the win ratio by having Terminal Events (Tier 1 or Tier 2). There was a disproportionate number of Control group patients with HFH or WHF events that were not accounted for in the primary endpoint (17 control patients with 50 non-terminal events, compared to 8 shunt patients with 15 non-terminal events). This discrepancy resulted from the structure of the win ratio, which compares patients sequentially by highest-tier outcomes and censors comparisons once a “win” is established. Otherwise, the Shunt recipients in this stratum had a 51% reduction in HF Events (all-cause death, HTLV, HFH and WHF) compared with control.

Shunt and Control patients in both LVEF strata had large improvements in KCCQ through 24 months, with no between-group differences. These findings are most likely indicative of a strong placebo effect in this double-blind, sham-controlled trial. Relevantly, pre-trial expectations for KCCQ benefit after Shunt implantation were derived from unblinded device trials with or without concurrent controls, and from pharmacological trials in less symptomatic patients with higher baseline KCCQ.

Although the win ratio analysis was the prespecified analysis for the Primary Effectiveness Endpoint, it only counts one win, loss, or tie per patient pair and does not reflect all events that patients experience, thereby underestimating the total burden of disease. In contrast, prespecified secondary recurrent event analyses such as the Nelson-Aalen cumulative hazard rate analysis and the Joint Frailty analysis of recurrent HFH controlled for competing Terminal Events (death or HTLV), includes first and recurrent events to represent the risk of all adverse outcomes and appropriately reflect the overall burden of disease. The Nelson-Aalen cumulative hazard rates over 2 years show that there were opposite treatment effects in the HFrEF and HFpEF strata for the combined 4 clinical components of the Primary Effectiveness Endpoint (**Figure 2**).

Figure 2: Nelson-Aalen Cumulative Hazard Analysis for HF Events (All-Cause Death, Heart Transplant/LVAD, HF Hospitalization, Worsening HF) by LVEF



HF: heart failure; LVAD: left ventricular assist device; LVEF: left ventricular ejection function.
The clinical outcomes components of the hierarchical composite primary endpoint were the cumulative incidence of all events, including all-cause death, LVAD or heart transplant procedures, HF hospitalizations, or worsening HF outpatient events. The Nelson-Aalen cumulative hazard rate function describes the estimated rate at which events have occurred, given that the individual has survived up to that time point, i.e., at any given time, the Nelson-Aalen cumulative hazard rate denotes the expected number of events per patient followed for that length of time. The number at the end of each curve is the 2-year hazard rate.
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.

For each of the 4 HF Event components of the primary endpoint, there were consistent trends favoring Shunt treatment compared to Control in patients with HFrEF (**Table 1**). These hard clinical outcomes were markedly reduced by treatment with the Shunt in patients with HFrEF already treated with maximally tolerated GDMT. The most profound effect was a 54% reduction in HFH that was highly nominally statistically significant. Sensitivity analyses were performed with multiple validated recurrent events models (**Section 10.7**) including Joint Frailty, negative binomial, Lin Wey Yang Ying (LWYY), Prentice-Williams-Peterson total time model (PWP-TT), and areas under the curve (AUC) all confirming benefit in HFrEF and harm in HFpEF.

To address the concern of multiplicity related to interaction testing and sequential evaluation of endpoints, a post hoc Global Statistical Test (GST) was used to quantify the totality of evidence by accounting for the prespecified hierarchy of the primary and secondary endpoints. The GST accounts for multiplicity by effectively not “double counting” correlated events between the series of successive tests. The GST calculations relied on the original prespecified primary and secondary endpoints methods in the statistical analysis plan (SAP). The overall evidence shows that benefit within the HFrEF stratum gets stronger as endpoints are added, with nominal *P*=0.040 for primary plus first 7 secondary endpoints and nominal *P*=0.035 if only hard clinical endpoints are included.

Additionally, the overall Type-I error including the primary and 7 secondary endpoints was estimated with a post hoc permutation-based interaction test (**Section 7.6**). The permutation-based testing resulted in a 2-sided Type-1 error rate of 5.28%, most of which comes from the scenario where the prespecified randomization strata would demonstrate homogeneity in treatment effect, which was not the case in RELIEVE-HF. These results suggest that the resulting Type-1 error inflation was minimal, and the results were not likely to be a false positive finding.

1.6 Biological Mechanism

Echocardiographic data from RELIEVE-HF revealed differences in cardiac structure and function in patients with HFrEF and HFpEF that provide a biologically plausible explanation for the differences in clinical responses to shunt placement (Zile et al., 2025). Data from 12-month transthoracic echocardiographic (TTE) changes of 17 cardiac structure/function parameters were compared with baseline using a validated 2-stage imputation process for missing data and covariate adjusted quantification of the differences between Shunt and Control treatment groups separately for the HFrEF and HFpEF strata. Echocardiographic data was provided by an independent Echocardiographic Core Laboratory based at The Pennsylvania State University.

In Shunt-treated vs Control patients with HFrEF, there were reductions in mean LV end-diastolic volume index (-11.9 [95%CI -21.3, -2.5] ml/m^2, nominal *P*=0.01) and LV end-systolic volume index, (-8.9 [95%CI -17.2, -0.7] ml/m^2, nominal *P*=0.01), indicative of reverse LV remodeling. There were no significant changes in RV, right atrial (RA), or inferior vena cava (IVC) sizes, or pulmonary artery systolic pressure (PASP). In contrast, Shunt-treated vs Control patients with HFpEF did not exhibit LV reverse remodeling, but had increased RV, RA, and IVC dimensions, and increased PASP (4.7 [95%CI: 0.9, 8.5] mmHg, nominal *P*=0.02).

Additionally, LV and RV diastolic compliance were decreased in HFpEF vs HFrEF at baseline and decreased further after Shunt treatment in HFpEF. All echo parameter changes at 12-months noted above were, on average greater than 10% compared to baseline, a threshold often considered clinically important. The magnitudes of the reductions in LV diastolic and systolic volumes in HFrEF patients were of the same order as those seen in other HF studies that were associated with a significant reduction in all-cause mortality (see **Figure 32**, **Appendix 10.4.2**).

These data do not prove causality between specific changes in cardiac structure/function and outcomes; however, they are highly correlative and provide biologically plausible mechanisms that explain, at least in part, the markedly discordant clinical outcomes after Shunt treatment in patients with HFrEF and HFpEF from RELIEVE-HF.

1.7 Benefit-Risk Summary

The robust clinical data presented in this briefing document establish a reasonable assurance of safety and effectiveness of the Shunt for the proposed limited indication.

The Shunt fills a large unmet medical need for an effective treatment of a life-threatening irreversible and debilitating disease/condition. The RELIEVE-HF trial is the first of its kind for HFrEF patients that remain symptomatic and at high risk for mortality and morbidity, especially for hospitalization, despite optimal GDMT. There are no commercially available alternative medical products or medical interventions for these patients. Approval of the Shunt can thus benefit a large group of highly symptomatic HFrEF patients who have a poor prognosis and have run out of viable options.

Acknowledging that RELIEVE-HF did not achieve its primary endpoint, the data nonetheless demonstrate strong clinical benefits for HFrEF patients. RELIEVE-HF was a well-executed, double-blind device trial with 98.4% clinical follow-up at primary analysis. There were few major protocol deviations and no confounding interventions. There were more than 100 sites in 11 countries with a majority of patients from North America. The analyses of clinically important HF outcomes, especially for recurrent events, HFH alone and the combination comprising all HF Events show marked consistency across event types and comparative methods with narrow confidence intervals. Although Type-I error was not prospectively controlled, it was estimated based on the actual results of RELIEVE-HF and was only marginally higher than 0.05. Moreover, there was a clear correlation between LV remodeling and clinical outcomes consistent with a biologically plausible method underlying the beneficial effects of Shunt treatment in HFrEF patients. Combined, these findings support the assertion that the extent of uncertainty for the benefits is acceptably low.

The primary safety endpoint was met, and there were no significant safety endpoint concerns. In 370 consecutive Shunt implants, there were no device or procedure related MACNE events through 2 years of follow-up. All additional safety assessments and comparisons of safety events between Shunt and Control groups have shown no differences in the HFrEF stratum.

To help ensure that approval of the V-Wave Shunt will continue to offer HFrEF patients benefits that outweigh the risks, V-Wave is committed to working with the FDA to establish robust post-market controls to support approval. In addition to the proposed limited indication of HFrEF patients, V-Wave is proposing conditions of approval that will serve as safeguards to support a safe and responsible commercial roll-out, as well as ongoing clinical evidence generation and data collection. The post-marketing proposal conforms with those conditions required for other, higher risk, structural heart devices including mitral/tricuspid valve edge-to-edge repair, TAVR, and left atrial appendage occluder devices. These conditions at a minimum include:

- A requirement for a local heart team comprising a physician implanter and a HF specialist to best ensure appropriate patient selection that conforms to device indication labeling and minimizes risk of enrolling patients less likely to benefit.
- Extensive physician and allied healthcare professional training.
- A controlled commercial roll-out such that learning curve and adequate commercial support are established.
- A robust US-based post-approval study.
- Establishing a comprehensive registry that enrolls all US patients treated with a commercial device to assure monitoring of overall results well into the future.

These considerations establish that the totality of data and post-market planning demonstrates a favorable benefit-risk profile for the Ventura Shunt for the treatment of patients with NYHA functional Class III HF who remain symptomatic despite GDMT and have a LVEF of ≤ 40% (HFrEF).

V-Wave provides in **Table 2** an application of the regulatory framework to the Shunt's benefit-risk profile that demonstrates that the combined safety profile and clear benefit to patients with HFrEF (LVEF ≤ 40%) yields a favorable overall benefit-risk profile for this population, supporting its approval in this subset of patients.

Table 2: Ventura Shunt Benefit-Risk Assessment Based on RELIEVE-HF

Factor	Assessment in RELIEVE-HF	Supporting Evidence
Clinical Benefit	RELIEVE-HF demonstrated meaningful reductions in recurrent HF Events, especially HF hospitalizations, and reductions in terminal events (all-cause death, LVAD, transplant) in a population of Class III HFrEF patients (LVEF ≤ 40%) on maximally tolerated GDMT.	Event reductions consistent across combined primary and secondary endpoints. Multiple recurrent event models; nominally significant reductions in terminal events; largest effect on hospitalizations.
Clinical Risk	Device- and procedure-related MACNE=0% at 2 years. No evidence of excess adverse events in HFrEF. Potential harm from unindicated treatment of HFpEF patients due to LVEF measurement variability is manageable and preventable with post-approval safeguards.	Independent CEC adjudication confirms excellent safety. Echo and HF Events data confirm LVEF safety margin.
Mechanistic Plausibility	In HFrEF, the Shunt decompresses the LA and favorably remodels the LV. In HFpEF, shunting leads to adverse right heart remodeling and worsening pulmonary hypertension.	Echo core lab quantified changes at 12 months and correlation with HF Events data.
Uncertainty	The prespecified interaction test was significant and required further exploration of the results of the primary effectiveness endpoint in the HFrEF and HFpEF patients for the ITT population. Evaluation of permutation tests showed that the endpoint in the HFrEF population narrowly missed (Type-1 error=0.075). GST testing of the primary and secondary endpoints was nominally	Well conducted double-blind sham-controlled trial with prespecified stratification by LVEF. Permutation, GST, and multiple sensitivity analyses demonstrate consistency across diverse models.

	significant. Positive results were robust and consistent across multiple recurrent event frameworks: prespecified Joint Frailty and Nelson-Aalen, with sensitivity Poisson, negative binomial, LWYY, PWP-TT, and AUC analyses. The totality of the results shows that uncertainty of a benefit for Ventura Shunt treatment in HFrEF patients is likely low.	
Patient Perspective	Patients/advocates emphasize urgent need and willingness to accept modest uncertainty for reduced hospitalizations, improved quality of life, and survival benefit, especially when associated with a strong safety profile.	Patient advocacy groups: https://www.aahfn.org https://www.heartfailurepf.org/ https://www.globalcyctforum.com/patient-trialists Letter from Rhonda Monroe (**Appendix 10.1**)
Unmet Medical Need	Very high. Despite GDMT, ~75% of hospitalized HFrEF patients die within 5 years. In the US, ~0.8–1.0M persistently symptomatic despite therapy, with ~130k new high-risk patients annually.	National HF epidemiology and outcomes data.
Regulatory Context	Breakthrough Device: Approval consistent with the 21st Century Cures Act, which permits approval in settings of unmet need despite some uncertainty. Here, uncertainty is likely low, benefit is consistent, and risk is minimal.	FDA Breakthrough Designation; Cures Act framework.

AUC=area under the curve; CEC=Clinical Events Committee; FDA=Food and Drug Administration; GDMT=guideline-directed medical therapy; HF=heart failure; GST=global statistical test; HFrEF=HF with reduced ejection fraction; ITT=intention-to-treat; LA=left atrium; LV=left ventricle; LVAD=LV assist device; LVEF,LV ejection fraction; LWYY=Lin-Wei-Yang-Ying model; MACNE=major adverse cardiovascular or neurological events; PWP-TT=Prentice-Williams-Peterson total time model; US=United States.

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List of Abbreviations

Abbreviation	Definition
6MWT	6-Minute Walk Test
ACC	American College of Cardiology
ACEi	Angiotensin-converting enzyme inhibitor
ADHF	Acute decompensated heart failure
AF	Atrial fibrillation
AHA	American Heart Association
ANCOVA	Analysis of covariance
APVR	Anomalous pulmonary venous return
ARB	Angiotensin receptor blocker
ARNi	Angiotensin receptor-neprilysin inhibitor
ASD	Atrial septal defect
BARC	Bleeding Academic Research Consortium
BMI	Body mass index
BNP	B-type natriuretic peptide
CABG	Coronary artery bypass graft
CEC	Clinical Events Committee
CI	Confidence interval
CNS	Central nervous system
CRT	Cardiac resynchronization therapy
ER	Emergency Room
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GDMT	Guideline-directed medical therapy
GLS	Global longitudinal strain
GST	Global statistical test
GWTG	Get With The Guidelines
HF	Heart failure
HFH	Heart failure hospitalization
HFpEF	Heart failure with preserved ejection fraction (LVEF > 40%)
HFrEF	Heart failure with reduced ejection fraction (LVEF ≤ 40%)
HR	Hazard ratio
HRR	Hazard rate ratio
HT	Heart transplant
IAP	Interatrial pressure

ICD	Implantable cardioverter defibrillator
ICE	Intracardiac echocardiography
ITT	Intention-to-treat
IVC	Inferior vena cava
IQR	Interquartile range
KCCQ-OSS	Kansas City Cardiomyopathy Questionnaire Overall Summary Score
LAP	Left atrial pressure
LV	Left ventricular
LVAD	Left ventricular assist device
LVEDD	Left ventricular end-diastolic dimension
LVEDVi	Left ventricular end-diastolic volume index
LVEF	Left ventricular ejection fraction
LVESVi	Left ventricular end-systolic volume index
LWYY	Lin Wey Yang Ying model
MACNE	Major adverse cardiovascular or neurologic events
MAR	Missing at random
MCID	Minimal clinically important difference
MCMC	Markov chain Monte Carlo
MDRD	Modification of diet in renal disease
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonists
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PA	Pulmonary artery
PADP	Pulmonary artery diastolic pressure
PAP	Pulmonary artery pressure
PASP	Pulmonary artery systolic pressure
PCI	Percutaneous coronary intervention
PCWP	Pulmonary capillary wedge pressure
PFO	Patent foramen ovale
PMA	Premarket approval
QOL	Quality of life
RA	Right atrial
RAA	Right atrial area
RAP	Right atrial pressure

RAS	Renin-angiotensin system
RELIEVE-HF	REducing Lung congestion symptoms usIng the v-wavE Shunt in adVancEd Heart Failure
RHC	Right heart catheterization
RRR	Relative risk ratio
RV	Right ventricular
RVED	Right ventricular end-diastolic
RVFAC	Right ventricular fractional area change
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SGLT2i	Sodium-glucose cotransporter type 2 inhibitors
TAPSE	Tricuspid annual plane systolic excursion
TEE	Transesophageal echocardiogram
TIA	Transient ischemic attack
TTE	Transthoracic echocardiogram
UADE	Unanticipated adverse device effects
US	United States
ULN	Upper limit of normal
WHF	Worsening heart failure

2 BACKGROUND AND UNMET NEED

Summary

- Approximately 7 million Americans are currently diagnosed with HF, with a lifetime risk of 24%.
- HF is characterized by increased left atrial pressure and pulmonary venous congestion and is often classified into 2 clinical phenotypes: HFrEF (LVEF ≤ 40%) and HFpEF (LVEF > 40%).
    - Cardiac structure and function differ between the phenotypes, which may result in different responses to the same treatments.
- Despite advances in treating patients with HF with both pharmacological treatments and devices, patients continue to have a high combined residual risk of morbidity and mortality.
    - Increased left heart filling pressures are associated with increased morbidity and mortality; targeting a reduction in left atrial pressure can reduce morbidity and mortality.
- There is an urgent clinical need for novel therapies to improve symptoms and prognosis in these patients.

2.1 Overview of HF

2.1.1 Clinical Condition and Disease Burden

HF is one of the major public healthcare problems facing the developed world. Despite decades of advances in medical therapy and device management, HF continues to take a tremendous human toll on patients and their families due to persisting high morbidity and mortality rates.

HF is a complex syndrome resulting from structural or functional impairments that disrupt the ability of the left ventricle to fill or eject blood, resulting in the heart being unable to pump blood adequately to meet the requirements of metabolizing tissues (Yancy et al., 2013). HF is characterized by episodes of acute decompensation that manifest as increasing symptoms, which may require hospitalization when sufficiently severe.

More than 56 million people worldwide are living with HF with prevalence estimates ranging from 1% to 3% for all ages (Ambrosy et al., 2014; Groenewegen et al., 2020; Lippi et al., 2021; Virani et al., 2021). According to data from the National Health and Nutrition Examination Survey 2017–2020, 7 million Americans ages 20 years and older now have HF, and the prevalence is expected to rise to 8.5 million by 2030 (Bozkurt et al., 2025; Heidenreich et al., 2013; Van Nuys et al., 2018). The lifetime risk of HF has increased to 24%, meaning 1 in 4 of the US population will develop HF during their

lifetime (Bozkurt et al., 2025). The prevalence of HF rises for each decade of life and is 8%-9% among Medicare beneficiaries. In the US, there are approximately 960,000 newly diagnosed cases annually. In addition to being common and debilitating, HF carries with it a tremendous disease burden; patients must manage multiple medications, provider visits, and tests, and often face depression, frailty, dietary and lifestyle limitations, and the inability to work.

2.1.2 HF Hospitalization

HF is a leading cause of hospitalization in the US and is the second most common primary reason for acutely hospitalizing patients ages 65 years or older (McDermott & Roemer, 2006). There are more than 1 million hospitalizations annually in the US where the primary cause of admission is ADHF, with 80%-90% of patients having a history of preexisting chronic HF. HFH in the US continues to increase; in 2018, 679,815 admissions were reported in patients with LVEF ≤ 40% and 495,095 in patients with LVEF > 40%.

Most (77%) patients presenting to the hospital are severely symptomatic with NYHA functional Class III or IV symptoms, indicating severe limitations with symptoms at rest (Adams et al., 2005; National Institute for Cardiovascular Outcomes Research (NICOR), 2021; Poon et al., 2022). When ADHF develops, respiratory symptoms such as tachypnea and dyspnea predominate. Approximately 90% of patients with ADHF present to the hospital with symptoms, signs, and/or laboratory evidence of pulmonary congestion (Adamson et al., 2003; Fonarow et al., 2005; Fonarow et al., 2004; Schiff et al., 2003). Ultimately, if this process is not reversed, pulmonary edema may ensue, and the likelihood of death increases significantly. Readmission rates following a hospitalization for ADHF average 18–25% at 30 days and nearly 50% at 6 months (Chun et al., 2012; Cleland et al., 2003; Gheorghiade et al., 2004; Krumholz et al., 2009).

2.1.3 HF Mortality

HF mortality rates have been on the rise for the last decade, with HF a primary or secondary cause in more than 400,000 deaths in the US in 2020 (Tsao et al., 2023).

Patients admitted with ADHF have an in-hospital mortality of 4%, a 90-day mortality of 10%, and according to the OPTIMIZE-HF Registry and other studies, a one-year risk-adjusted mortality rate of 30% (Chen et al., 2011; Fonarow et al., 2007; Gheorghiade et al., 2005). Shah et al (Shah et al., 2017) analyzed 5-year outcomes in 39,982 Medicare and Get With The Guidelines (GWTG) HF patients aged 65 years or older hospitalized with HF between 2005 and 2009, and found that 5-year mortality averaged 75%-76%, regardless of LVEF. Recurrent hospitalizations are associated with poor outcomes. In a large Canadian database review, the median survival after the first, second, third, and fourth HFH were 2.4, 1.4, 1.0, and 0.6 years, respectively (Setoguchi et al., 2007). Most patients were alive 2 years after the first HF hospitalization, but approximately half died within 1 year after the third hospitalization. These observations of mortality risk increase

with subsequent HFH have been repeatedly confirmed (Huusko et al., 2020; Lahoz et al., 2020; Lindmark et al., 2021) and underscore the importance of reducing recurrent, rather than just first, hospitalizations for HF.

2.2 HFrEF (LVEF ≤ 40%) and HFpEF (LVEF > 40%)

Heart failure is commonly divided into 2 clinical phenotypes: 1) HFrEF, defined as LVEF ≤ 40%; and 2) HFpEF, defined as LVEF > 40% (McDonagh et al., 2024). In patients with LVEF ≤ 40% in the US, the most frequent causes of HF are ischemic heart disease, hypertension, idiopathic cardiomyopathy, valvular heart disease, and myocarditis.

Patients with HFpEF tend to be older, are more commonly female, hypertensive, and have type 2 diabetes mellitus. The prevalence of patients with HFpEF presenting to the hospital with ADHF is growing, approaching but still less than the rates seen with HFrEF (Hogg et al., 2004; Oktay et al., 2013; Owan et al., 2006).

2.2.1 Pathophysiology of LVEF ≤ 40% and LVEF > 40%

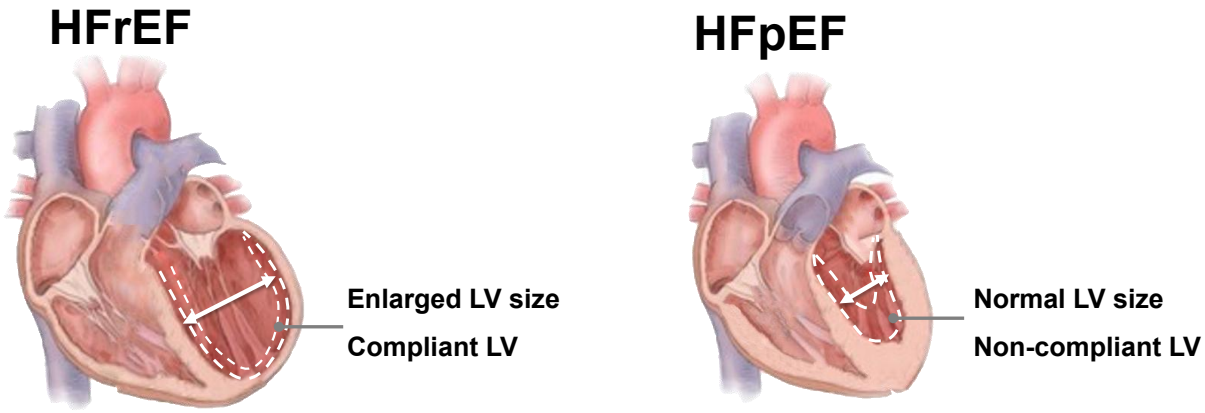
Cardiac structure and function differ in patients with HFrEF (LVEF ≤ 40%) and HFpEF (LVEF > 40%). HFrEF is characterized by systolic dysfunction, enlargement of the left ventricle, a relatively thin LV wall, and increased compliance of both ventricles (**Figure 3**).

In HFrEF, cardiomyocyte loss results in eccentric LV remodeling and reduced contractility. The LV is enlarged in both diastole and systole, and the mass-to-volume ratio is low. The right ventricle may also enlarge as HF progresses, and the left ventricle is relatively compliant during diastole. As the ventricle reaches its maximum volume, filling pressure rises exponentially, resulting in pulmonary congestion. The right ventricle is typically more compliant than the left ventricle and can therefore handle larger volume increases before failing.

HFpEF is characterized by diastolic dysfunction, normal left ventricle size, a thick left ventricle wall, and increased stiffness of both ventricles. In HFpEF, cardiomyocyte dysfunction occurs with increased LV diastolic stiffness. Recently, it has been appreciated that similar diastolic stiffening also occurs in the right ventricle, and this worsens prognosis (Obokata et al., 2019; Rommel et al., 2018). Moreover, HFpEF is characterized by a complex interplay of diastolic dysfunction, vascular stiffening, and chronotropic incompetence (Guazzi et al., 2020; Sarma et al., 2020; Zile et al., 2004).

The key structural and functional differences in the 2 clinical HF phenotypes may contribute to the difference in responses to pharmacologic therapies discussed in **Section 2.2.2.1** and could differentially affect the response to shunting. For example, in HFrEF, a more compliant right ventricle may be more able to accept an increase in redistributed blood volume without resulting in a large rise in right heart filling pressures. In contrast, a less compliant right ventricle may not be able to accept such an increase in redistributed blood volume; this could result in larger, undesirable increases in right heart pressures.

Figure 3: HF is Classified Based on LVEF and Commonly Divided Into 2 Clinical Phenotypes



HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; LV=left ventricle; RV=right ventricle.

2.2.2 Standard of Care in HFrEF (LVEF ≤ 40%) and HFpEF (LVEF > 40%)

2.2.2.1 Drugs

The mainstay therapy for patients with HFrEF are 5 classes of medications that regulate the neurohormonal milieu: RAS inhibitors, beta blockers, MRA, SGLT2i, and diuretics. These drug classes are mandated as GDMT in widely accepted published clinical guidelines (Heidenreich et al., 2022). RAS inhibitors include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and angiotensin receptor-neprilysin inhibitors. These agents have been shown to reduce morbidity and mortality and, in some cases, to result in beneficial ventricular remodeling in randomized trials. SGLT2 inhibitors have been shown to decrease cardiovascular events in 2 large randomized clinical trials. Specifically, dapagliflozin and empagliflozin reduced the risk of HFH and death in patients with LVEF ≤ 40% regardless of diabetes as a comorbidity (Abdelmasih et al., 2021; Chaudhary et al., 2021). Although SGLT2i decrease cardiac events for those at risk, they do not reduce natriuretic peptide levels or cardiac filling pressures and have little effect on symptoms, exercise tolerance, and quality of life metrics. The current European Society of Cardiology (ESC), American College of Cardiology (ACC)/American Heart Association (AHA), and Canadian HF Guidelines include a recommendation for SGLT2i as a Class I indication regardless of diabetes status in HFrEF (McDonald et al., 2021). Nonetheless, symptoms, especially dyspnea on exertion and poor exercise tolerance, require management of excess fluid volume with dietary sodium restriction as well as chronic use of loop diuretics in most patients. Fluid removal with loop diuretics, both oral and intravenous, is the most common approach to relieving worsening symptoms of HF. Even so, there is high residual morbidity and mortality for patients with HFrEF who are on GDMT.

There are fewer treatment options for patients with HFpEF. Two large, randomized trials of pharmacologic therapy for HFpEF with the SGLT2i empagliflozin and dapagliflozin

have achieved their primary endpoints (Anker et al., 2021; Solomon et al., 2022) resulting in Class I indications in US guidelines in 2023. Even with the modest improvements in mortality and reductions in HFH in patients with HFpEF treated with an SGLT2i, the residual risk for morbidity and mortality remains high and exceeds the treatment effect of these agents. Moreover, these agents do not clinically or substantially improve quality of life; the average improvement in KCCQ score is less than 5 points. Nevertheless, the current ESC, ACC/AHA, and Canadian HF practice guidelines recommend SGLT2i as a Class I indication for all patients with HF and type 2 diabetes mellitus who are at increased risk for cardiovascular events.

Note that the above Class I guideline drug therapy indications listed above were in effect either prior to or during the enrollment of RELEIVE-HF. Currently, newer trials with finerinone and GLP1 agonists may eventually result in Class I indications.

2.2.2.2 Devices

Several devices are FDA approved for patients with LVEF ≤ 35%, including cardiac resynchronization therapy (CRT), Implantable Cardioverter Defibrillators (ICD), transvalvular mitral valve repair with the MitraClip device in patients with severe mitral regurgitation and moderate LV dysfunction, and LVAD for patients with end-stage disease (Abraham et al., 2002; Bristow et al., 2004; Cleland et al., 2005; Stone et al., 2018).

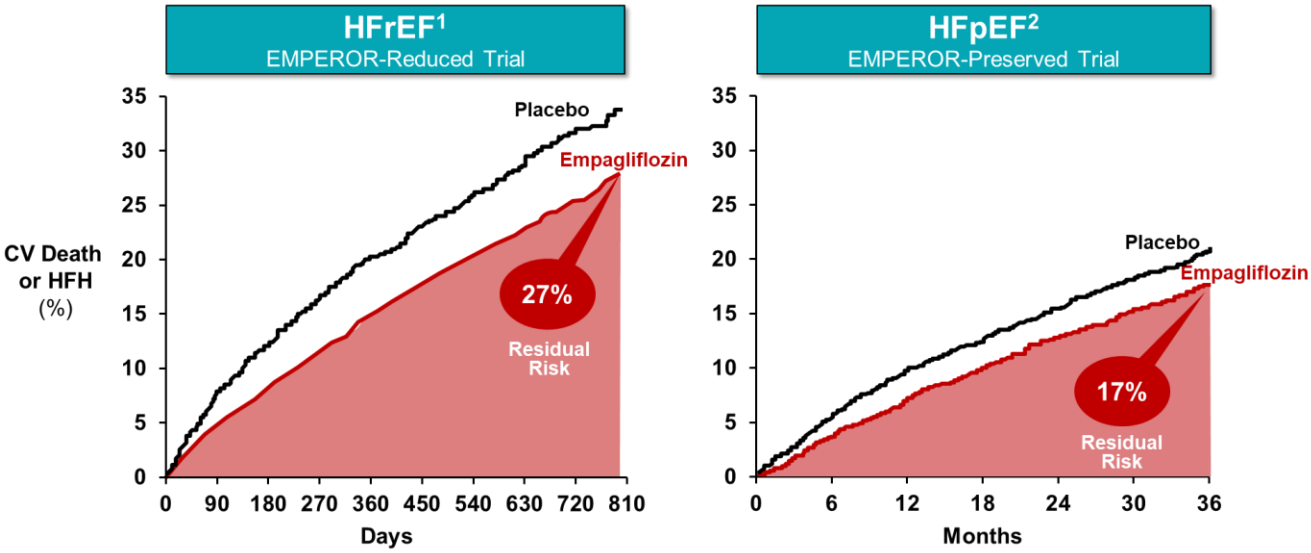
No effective device therapies are currently FDA approved for patients with LVEF > 40%. Implantable hemodynamic monitoring may be helpful in these patients, though it is an invasive procedure and rarely utilized at present (Adamson et al., 2014).

2.2.3 Residual Morbidity and Mortality

Despite advances in GDMT, patients with HFrEF and HFpEF have persistently high residual cardiovascular risk; hence, there remain substantial unmet medical and societal needs to reduce morbidity and mortality associated with HF.

The risk of cardiovascular death in patients with HFrEF and HFpEF was examined in the EMPEROR-Reduced (Packer et al., 2020) and EMPEROR-Preserved (Anker et al., 2021) trials, respectively, which evaluated empagliflozin in addition to optimized GDMT (**Figure 4**). Of note, empagliflozin is now considered a Class 1 GDMT. In patients with HFrEF who were NYHA Class II, although the addition of empagliflozin reduced event rates, 27% still died or were hospitalized with HF over 2.2 years of follow-up. Similarly, in patients with HFpEF who were NYHA Class II, 17% of patients still died or were hospitalized for HF over 3 years of follow-up. Importantly, in RELIEVE-HF most enrolled patients had NYHA Class III, who have even higher cardiovascular risk than NYHA Class II patients. Therefore, the residual cardiovascular risk in patients with HF, and particularly in HFrEF, represents a critical unmet need and important target for the development of novel HF therapies.

Figure 4: Residual Morbidity and Mortality for Patients on Guideline-Directed Drug and Cardiac Implantable Electronic Device Therapies



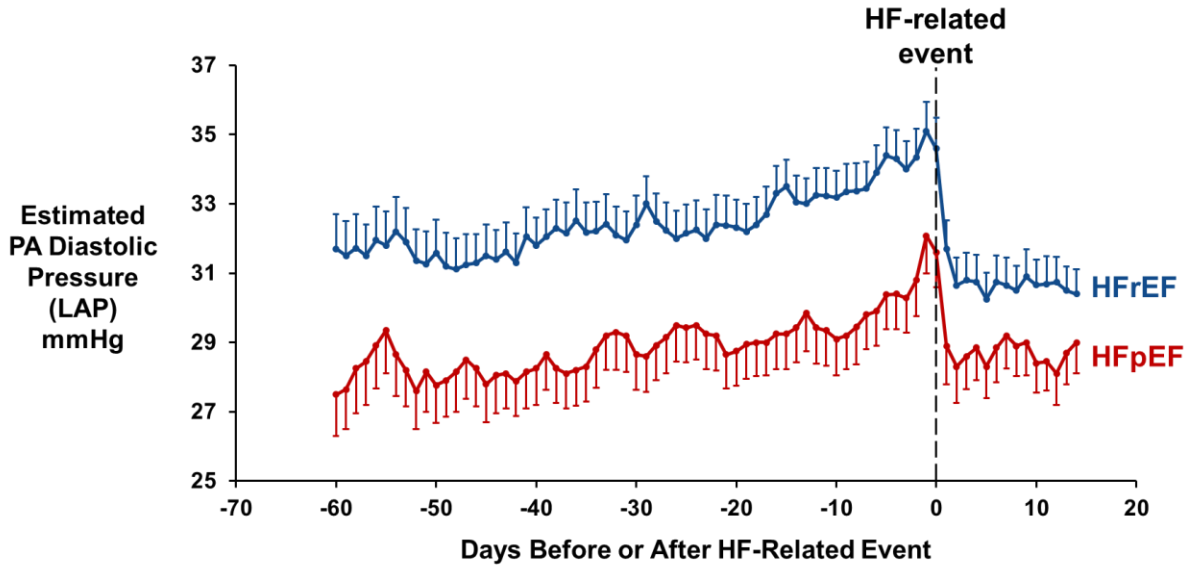
HFH=heart failure hospitalization; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction
Both trials included predominantly NYHA Class II patients.
1. Adapted from Packer et al., 2020
2. Adapted from Anker et al., 2021

2.2.3.1 Hemodynamic Mechanisms Contributing to Residual Morbidity and Mortality

The residual cardiovascular risk observed in the EMPEROR trials may result from two well-characterized hemodynamic mechanisms. In the first clinical setting, patients with HF develop gradual, progressive volume overload characterized by increased filling pressures, quantifiable as increased LV, left atrial, or pulmonary artery diastolic pressure. These increased pressures are associated with increased rates of HF Events and cardiovascular mortality. In the second clinical setting, patients develop rapid, reversible increases in filling pressure that occur with activity; these pressure changes substantially limit activities and reduce quality of life.

Data from Zile et al. (2008) demonstrated this relationship; pressures were measured in ambulatory patients with HF using implanted hemodynamic monitors that measured pulmonary artery diastolic pressure as a surrogate for left atrial pressure. Filling pressures steadily increased over the weeks preceding clinically recognized HF Events, in both patients with HFpEF and HFrEF (**Figure 5**). Following hospitalization and treatment, pressures returned to baseline levels. These and other data support the broad consensus that increased left atrial pressure plays a central causative role in HF morbidity.

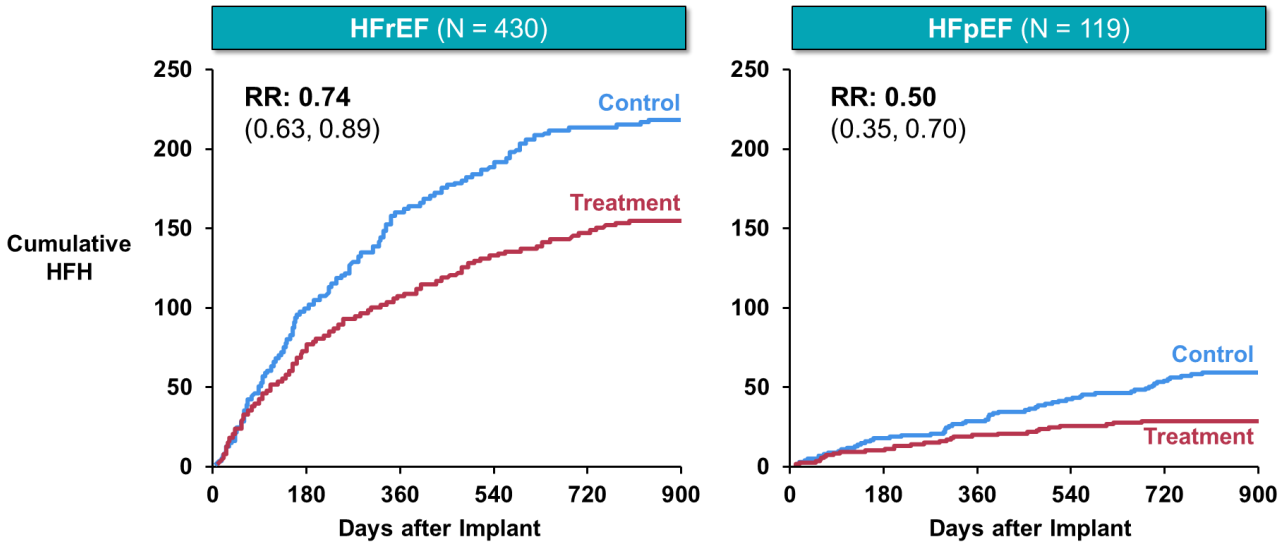
Figure 5: HF Events are Preceded by Gradual Increases in Pulmonary Capillary Wedge Pressure (Left Atrial Pressure) Despite GDMT (COMPASS-HF Trial)



GDMT=guideline-directed medical therapy; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; LAP=left atrial pressure; LVEF=left ventricular ejection fraction.
Notes: HFrEF=LVEF < 50%; HFpEF=LVEF ≥ 50%
Source: Zile et al., 2008

Data from the CHAMPION trial (Adamson et al., 2014) indicate that targeting elevated left atrial pressure reduces morbidity and mortality. In CHAMPION, patients were implanted with a wireless device that monitored pulmonary artery (PA) pressure (PA diastolic pressure is a proxy for left atrial pressure); the pressure data allowed pharmacologic therapy to be hemodynamically guided. Results of the CHAMPION trial demonstrated that hemodynamic monitoring of pulmonary artery pressure reduced decompensation leading to HFHs compared to standard management strategies in patients with HFpEF and HFrEF (**Figure 6**). In patients with HFpEF, HFHs were reduced by 46% in the treatment group compared to Control; HFHs were reduced by 24% in patients with HFrEF.

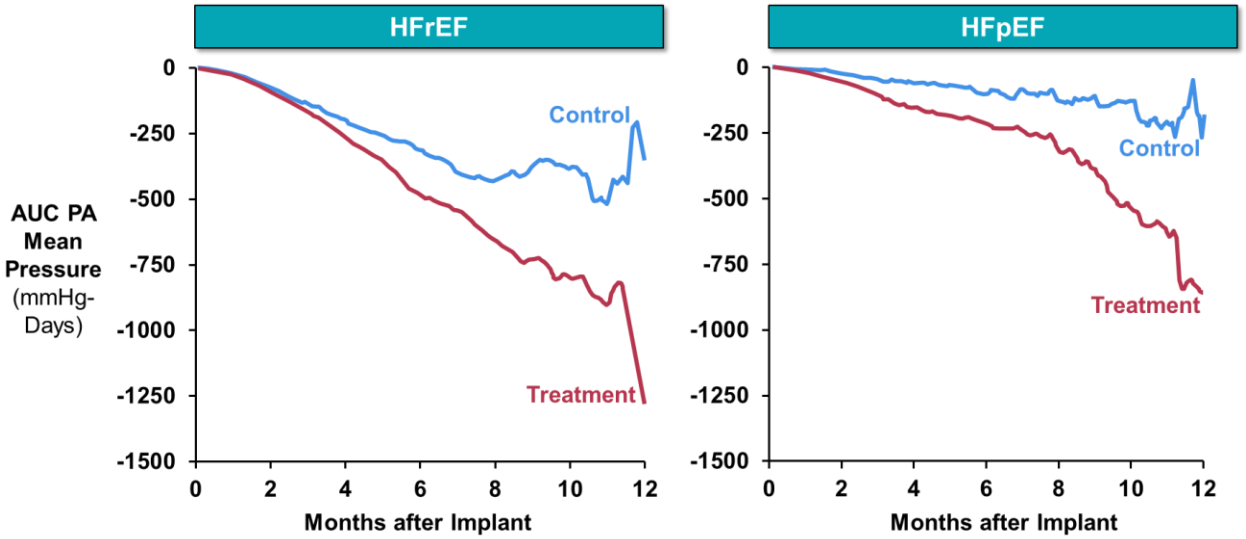
Figure 6: Wireless Pulmonary Artery Pressure Monitoring Guides Management to Reduce Decompensation in HF (CHAMPION Trial)



HFH=heart failure hospitalization; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction
Source: Adamson et al., 2014

The mechanism underlying the success of hemodynamically-guided therapy observed in the CHAMPION trial is the reduction of filling pressures, which was also observed in the GUIDE-HF trial (Zile et al., 2022). In GUIDE-HF, 1,000 patients who were NYHA Class II through IV with HF hospitalization in the prior 12 months or had elevated natriuretic peptides were implanted with the same pulmonary artery pressure sensor used in CHAMPION and randomized to either a hemodynamically-guided therapy group or to a control group. The results of GUIDE-HF demonstrated that pulmonary artery pressure was substantially reduced by hemodynamically-guided therapy in patients with both HFrEF and HFpEF, resulting in large part from changes in diuretic dose (85% of patients) and up-titration of other HF medications (15% of patients) (**Figure 7**). Although the adjustment of medications resulted in reduction of left atrial pressure, there were practical limitations to this method of treating HF. Effective application of this management strategy required patient compliance and provider engagement. The response rates were not sufficiently rapid to adjust to rapid changes in PA pressures, and medication changes could produce or worsen drug and dose intolerance.

Figure 7: Reduction of Pulmonary Artery Pressure is the Mechanism Underlying the Success of Hemodynamically-Guided Therapy (GUIDE-HF Trial)



AUC=area under the curve; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; PA=pulmonary artery.
Source: Zile et al., 2022

2.3 Summary of Patient Unmet Medical Need

As evidenced by data from EMPEROR-Reduced, the residual mortality in patients with HFrEF remains high despite GDMT. Although hemodynamically-guided pharmacologic therapy can reduce morbidity and mortality, it is limited in its applicability by requirements for patient compliance, provider engagement, slow response rate, and dose/drug intolerance. Beyond GDMT, there are currently no FDA approved therapies that improve morbidity and mortality in patients with advanced (NYHA functional Class III) HFrEF (LVEF ≤ 40%) who are not yet considered candidates for LVAD implantation or heart transplantation and remain at high risk for morbid and mortal events. Alternative, novel therapies are needed; the V-Wave Interatrial Shunt represents such an alternative to lowering left atrial pressure and consequently reducing morbidity and mortality.

3 PRODUCT DESCRIPTION

Summary

- The Shunt was developed based on computer modeling, animal studies, existing theoretical concepts, clinical observations from other therapies, and clinical feasibility studies. Key observations included the finding that elevated left atrial pressure directly contributes to pulmonary congestion, that left atrial pressure exceeds right atrial pressure (RAP) in most patients with heart failure, and that congenital atrial septal defects may improve outcomes in patients with HF.
- The Shunt is a permanent implant engineered to facilitate blood volume redistribution from the higher-pressure left atrium to the lower-pressure right atrium.
- The Shunt is constructed on an hourglass-shaped, self-expanding Nitinol frame encapsulated with ePTFE and has an internal diameter of ~5 mm.
- The Shunt is implanted across a patient's interatrial septum via a right-sided femoral vein catheterization procedure, using its custom delivery catheter and a commercially available introducer sheath.
- The implantation procedure requires approximately 80 minutes to complete and an overnight stay in the hospital.

3.1 Early Rationale and Evidence Supporting Interatrial Shunting

The Shunt is a transcatheter-implanted medical device designed to reduce the incidence of worsening HF in patients with chronic symptomatic HF. The development of the Shunt relied on the following concepts and observations:

- Sustained elevation of left atrial pressure directly causes pulmonary congestion, leading to symptoms of HF (Ritzema et al., 2010). Reducing elevated left atrial pressure ameliorates and prevents episodes of HF (Abraham et al., 2011; Abraham et al., 2016; Adamson et al., 2014; Brugts et al., 2023; Lindenfeld et al., 2021; Ritzema et al., 2010). In patients with HFrEF, meta-analyses have shown that implantable hemodynamic monitoring-guided therapy reduces HFH and improves survival (Lindenfeld et al., 2024).
- Purposefully created iatrogenic atrial septal defects (iASDs) have been shown to improve clinical outcomes in patients with HFpEF; atrial septostomy has been used in patients with intractable HF to reduce left-sided filling pressure (Bauer et al., 2018; Gossett et al., 2006).
- Computer simulation studies suggested reduced left-sided filling pressure after interatrial shunting based on exercise hemodynamics from a cohort of patients with "early" HFpEF (Kaye et al., 2014). Feasibility studies of another Interatrial

Shunt Device in HFpEF patients were consistent with clinical benefit and reductions in exercise-induced elevations of LAP (Feldman et al., 2018; Kaye et al., 2016).

- In a validated ovine model of ischemic cardiomyopathy resulting in HFrEF physiology, implantation of prototype V-Wave interatrial shunts decompressed the left atrium, improved LV systolic dysfunction, and prevented the development of pulmonary congestion, pulmonary hypertension, and death, compared to controls (Eigler et al., 2017).
- In feasibility human studies with an earlier version of the V-Wave Shunt, hemodynamic benefits of patent shunts were demonstrated and were associated with clinical improvements in both HFrEF and HFpEF (Rodes-Cabau et al., 2018).

3.1.1 Elevated LA Pressure Directly Causes Pulmonary Congestion

Pulmonary congestion results from high left atrial pressure, which increases hydrostatic pressure that is transmitted backward into the pulmonary veins and capillaries causing fluid to leak from the capillaries into the lung interstitial space. When pulmonary congestion is of cardiac origin, elevated left atrial pressure is the predominant causal factor (Guyton & Lindsey, 1959).

Implantable hemodynamic monitoring systems have been developed for outpatient HF management with the goal of reducing episodes of decompensation (Ritzema et al., 2010). Ritzema et al. reported a feasibility study (HOMEOSTASIS) using physician-directed patient self-management of implanted left atrial pressure sensor measurements in 40 patients with NYHA Class III and IV symptoms and a history of HF hospitalization during the prior 12 months, irrespective of systolic function. When compared to the initial period of being blinded to left atrial pressure data, patient self-management using left atrial pressure data resulted in reduction of HF Events, including HF hospitalization and all-cause death. Use of the device was also associated with better optimized neurohormonal antagonist and diuretic dosing and a reduction of early clinical events. In HOMEOSTASIS, hemodynamic decompensation nearly always preceded clinical decompensation, suggesting that outpatient hemodynamic monitoring linked to a self-management therapeutic strategy could change current management of advanced HF and potentially facilitate more optimal therapy and improved outcomes.

Abraham et al. and Adamson et al. have reported extensively on the results of the CHAMPION trial of the CardioMEMS Implantable Pulmonary Artery Pressure (PAP) monitoring system (Abraham et al., 2011; Abraham et al., 2016; Adamson et al., 2014). The CHAMPION trial was a patient-blinded trial of 550 patients with NYHA functional Class III and a history of HF hospitalization during the prior 12 months, irrespective of LVEF, on best tolerated guideline-driven drug and device therapies. In the treatment group, PAP trends were used to adjust medications, which were primarily loop diuretics. The CardioMEMS device reduced HF hospitalization in both LVEF groups, and these

observations have since been corroborated in additional studies (Brugts et al., 2023; Lindenfeld et al., 2021).

A meta-analysis by Lindenfeld et al., 2024 found that management of patients with HFrEF using implantable hemodynamic monitoring significantly reduces mortality and HFH. The reduction in hospitalizations occurred early in the first year of monitoring whereas reduced mortality was observed after the first year. A majority of data demonstrating the reduction in mortality came from a study using the same left atrial pressure monitor as used in Ritzema et al.

3.1.2 Left Atrial Pressure Exceeds Right Atrial Pressure in an Overwhelming Majority of Patients with HF

Interatrial shunting will only effectively lower left atrial pressure if there is a positive pressure gradient (left atrial pressure – RA pressure exceeds 0 mmHg) to support left-to-right shunt flow in the heart when left atrial pressure is elevated. Drazner et al. reported retrospective Swan-Ganz pulmonary artery catheterization results for 1,000 consecutive patients with HF being evaluated for heart transplantation who received tailored therapy with diuretics and vasodilators (Drazner et al., 1999). Although pulmonary capillary wedge pressure (PCWP) fell, RA pressure also decreased, maintaining a mean gradient of 9 mmHg before and after therapeutic intervention. In the second subgroup of 381 patients with moderate-to-severe tricuspid regurgitation, RA pressure was higher than in patients with mild tricuspid regurgitation. PCWP showed similar changes in moderate-to-severe compared with mild to no tricuspid regurgitation. Thus, moderate-to-severe tricuspid regurgitation did not reduce the IAP gradient. These data indicate that a reverse resting IAP gradient is unlikely to occur in a NYHA functional Class III/IV HF population, irrespective of etiology, existing RV dysfunction, pulmonary hypertension, or tricuspid regurgitation.

3.1.3 Atrial Septal Defects: Natural History and Interaction with Left and Right Ventricular Dysfunction and Atrial Septostomy

There is wide consensus among American, European, and Canadian cardiology communities that ASDs that are more than 10 mm in diameter are associated with clinically significant and pathological left-to-right shunting (Baumgartner et al., 2010; Warnes et al., 2008; Webb & Gatzoulis, 2006). A left-to-right atrial shunt is considered significant when the pulmonary-to-systemic blood flow ratio (Qp:Qs) is greater than 1.5, if it causes dilation of the right heart chambers, or if paradoxical embolism has occurred. Although there are limitations in estimating ASD diameter or Qp:Qs, shunting with a Qp:Qs of 1.5 is usually associated with right heart dilation and adverse long-term outcomes. ASDs that are 5 mm to 10 mm in diameter, with smaller flow ratios, generally have excellent outcomes and are not indicated for device or surgical closure since the risk of developing right heart volume overload is small. ASDs with a diameter of 5 mm or less, Qp:Qs < 1.5, and lacking RV dilation do not require intervention.

Acute pulmonary congestion is a recognized complication of ASD closure in adult patients with LV dysfunction (Ando et al., 2004; Davies et al., 1970; Peters et al., 2006; Schubert et al., 2005; Tomai et al., 2002; Viaene et al., 2010). When severe LV dysfunction is present, the ASD functions as a pressure-release valve for the left ventricle. When ASD closure is being considered in adults with suspected LV dysfunction, it is recommended to first occlude the defect with a balloon and measure the rise in left atrial pressure to unmask the potential to develop overt clinical HF.

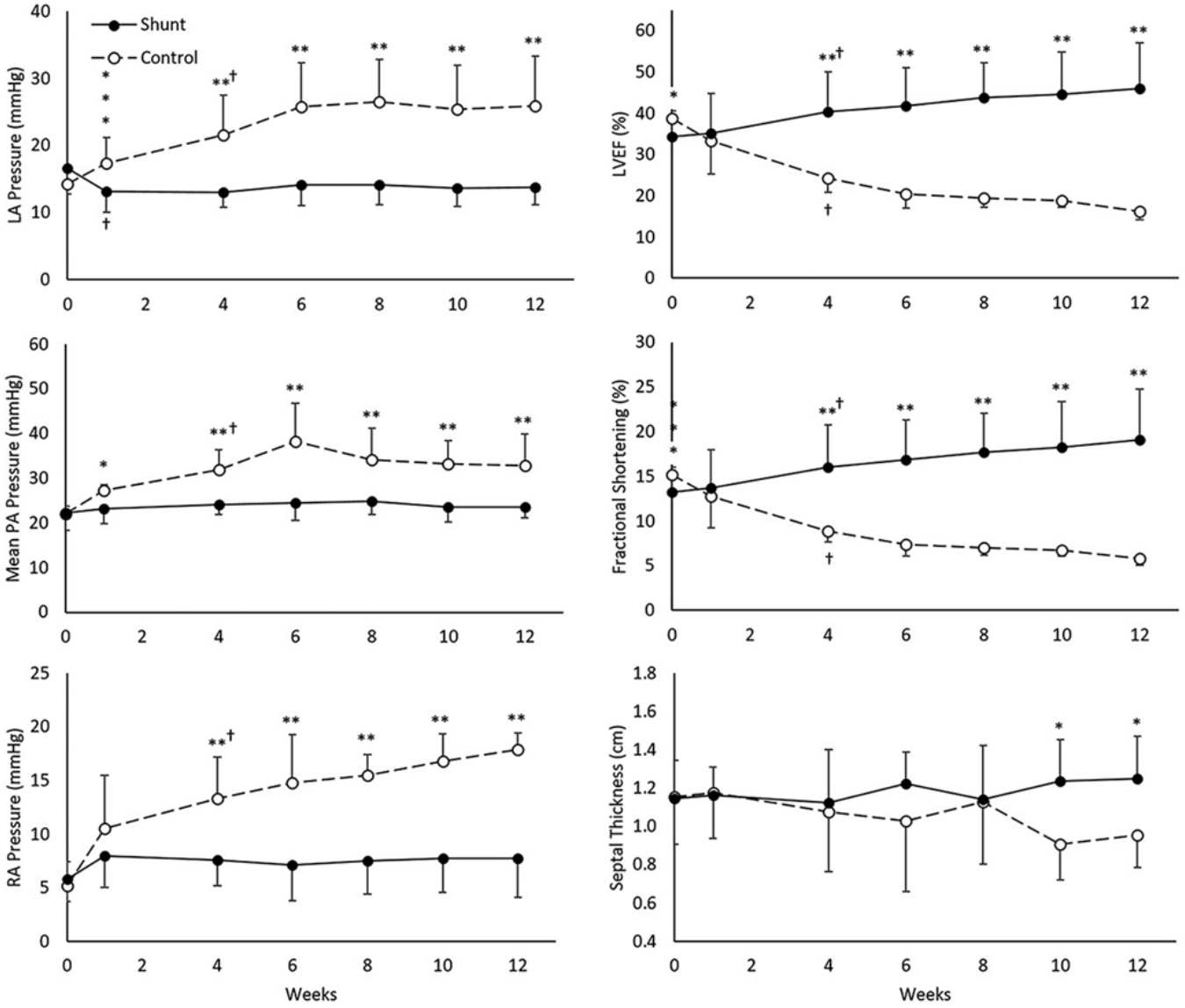
Atrial septostomy has been used for the reduction of left-sided pressure (Bauer et al., 2018; Gossett et al., 2006). Danon et al. demonstrated that atrial septostomy by stenting, mainly in infants, resulted in immediate reduction of mean left atrial pressure. At follow-up (range 0–27 months), the mean decrease in stent diameter was 0.85 mm with no serious complications (Danon et al., 2005). Leonard et al. reported similar results in 5 infants who underwent stent implantation across the atrial septum for the treatment of left atrial hypertension (Leonard et al., 2006). Blade and balloon atrial septostomy have been used for left heart decompression in patients with severe ventricular dysfunction and intractable pulmonary edema requiring circulatory support with extracorporeal membrane oxygenation (Seib et al., 1999). In this study of 10 patients, left atrial mean pressure fell from a mean of 30.5 to 16 mmHg when ASDs ranging in size from 2.5 to 8 mm (mean, 5.9 mm) were created.

These observations support the concept that interatrial shunting can lower left atrial pressures and reduce pulmonary congestion due to HF.

3.1.4 Effect of an Interatrial Shunt Device in a Large Animal Model of Ischemic Cardiomyopathy with LVEF ≤ 40%

An earlier version of the Ventura Shunt stabilized and reversed progressive LV systolic dysfunction and prevented pulmonary hypertension in an established animal model of ischemic dilated cardiomyopathy. Eigler et al. reported on an experimental model in which 21 sheep were subjected to repeat circumflex coronary artery microembolization until LV dysfunction with reduced LVEF and elevated left atrial pressure were documented (LVEF 36±6%, LA pressure 16±4 mmHg) (Eigler et al., 2017). Following study group assignment, animals were chronically instrumented during thoracotomy. Predicate first generation valved 5.1 mm diameter shunts were implanted in 14 sheep; 7 were sham procedure controls. Hemodynamic and echocardiographic responses were serially evaluated for 12 weeks. Comparisons at study termination showed statistically significant improved outcomes (LA pressure, mean PA pressure, RA pressure) in the Shunt Group compared to the Control Group (**Figure 8**).

Figure 8: Time Course of Hemodynamic Echocardiographic Parameters Following Induction of Heart Failure in an Ovine Model of Ischemic Cardiomyopathy with LVEF ≤ 40%



Plots showing time course of hemodynamic and echocardiographic parameters starting at baseline (time 0) after induction of heart failure for shunt group (●) and Control group (○) sheep. LA=left atrial; PA=pulmonary arterial; RA=right atrial; LVEF=left ventricular ejection fraction. *P < 0.05 shunt versus Control; **P < 0.01 Shunt versus Control; †P < 0.05 versus baseline. Error bars=standard deviations.
Source: Eigler et al., 2017

These findings were supported by gross pathological observations and there was a survival advantage in the Shunt Group compared to the Control Group (13/14 survivors versus 4/7 survivors at 12 weeks, respectively; nominal P=0.047). The implanted shunts had Qp:Qs 1.2±0.1 and all devices were patent at necropsy. These data aided in establishing preclinical proof-of-principle for interatrial shunting in HFrEF as a possible therapeutic approach.

3.1.5 First-in-Human Experience With the V-Wave System

Rodes-Cabau et al. (2018) conducted a first-in-human study that assessed the feasibility, safety, and exploratory efficacy of interatrial shunting in 38 high-risk patients with HFrEF (n=30) and HFpEF (n=8). This single-arm open-label study of patients with NYHA functional Class III or IV HF on optimal therapy was performed at 6 centers. Clinical, functional, echocardiographic, and hemodynamic evaluations were performed at baseline, 3 months, 12 months, and annually thereafter (median follow-up 28 months). The shunt device used was an earlier version that had a one-way tissue valve disposed on the RA end of the shunt.

The shunt device was successfully implanted in all cases without peri-procedural mortality. The rate of major device- or procedure-related complications during the first 12 months was 2.6%; peri-procedural cardiac tamponade occurred in 1 patient. At 3- and 12-month follow-up, there were improvements in NYHA functional class, quality of life, and 6-minute walk distance, without changes in objective measures of left- or right-sided function. All shunts were patent at 3 months, but 5 of 36 (14%) had occluded, and another 13 of 36 (36%) were stenotic at the valve by 12 months. Compared with patients with occluded/stenotic shunts, patients with widely patent shunts had lower long-term rates of death, LVAD placement or heart transplantation, and HF hospitalization, and a reduction of PCWP. Subsequent device modification, specifically the change to a valveless Ventura Shunt, improved the durability of patency.

Based on these findings, interatrial shunts were introduced into clinical studies, including the Ventura Shunt in the RELIEVE-HF study.

3.2 Device Overview

The V-Wave Ventura Interatrial Shunt System consists of a permanently implanted Shunt device placed between the left and right atria at the location of the fossa ovalis during a minimally invasive cardiac catheterization procedure using the dedicated Ventura Delivery System. By redistributing blood from the left to the right atrium, the Shunt is intended to reduce left-sided cardiac filling pressures and thereby morbidity and mortality in NYHA Class III HF patients who remain symptomatic despite GDMT and have a LVEF of ≤ 40%.

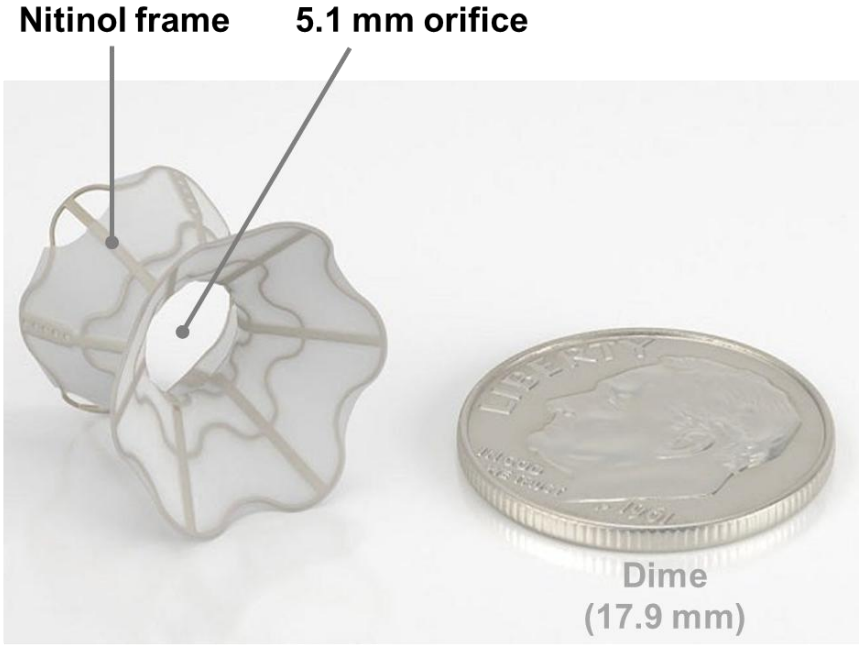
The system is implanted using the off-the-shelf Cook Medical 14Fr Mullins Introducer Sheath (Cook RCFW-14.0-38-85-RB-MTS). The V-Wave Cook Compatible Cartridge (Model: CRC00) will be available for use with the Cook Introducer Sheath. The Cartridge, which is Class I, is provided sterile in a standalone package.

Each component of the Ventura system is briefly described below.

3.2.1 Ventura Interatrial Shunt

The Shunt is a permanent implant designed to shunt blood from the left-to-right atrium thereby improving symptoms in patients with advanced chronic HF. The Shunt is constructed on an hourglass-shaped, self-expanding super elastic Nitinol frame, with expanded polytetrafluoroethylene (ePTFE) encapsulation to limit tissue ingrowth and to channel blood flow. An image of the Shunt is shown in **Figure 9**. The nitinol frame is laser-cut from a single piece of nitinol tubing, which undergoes a final shape-setting process and is then electropolished. The frame is comprised of 6 axially aligned bars and 5 circumferentially aligned sinusoidal struts. It is fully encapsulated in ePTFE except for the 3 E-shaped nitinol loops where the Delivery System engages the Shunt. The internal diameter at the neck is 5.1±0.1 mm, and the total length of the Shunt is ~12 mm. The external diameter at the RA end is ~11 mm and ~14 mm at the left atrial end. Testing has established that the Shunt is MR Conditional, i.e., safe to use in a specific magnetic resonance imaging (MRI) environment under certain conditions.

Figure 9: V-Wave Ventura® Interatrial Shunt System



3.2.2 Ventura Delivery System

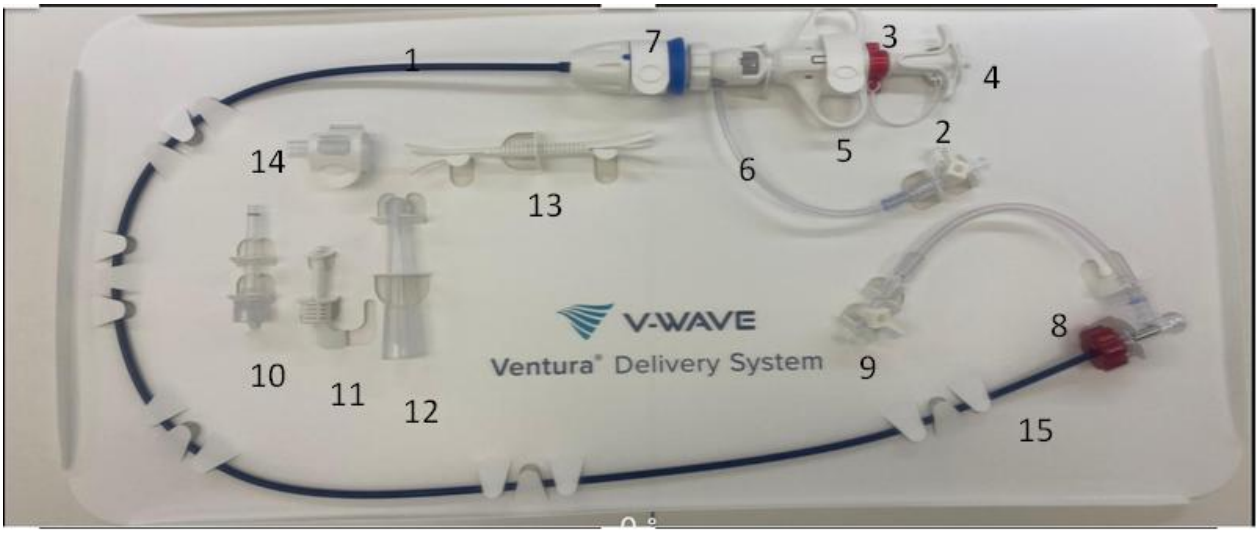
The Delivery System is custom but similar in design and function to other vascular implant delivery catheters. The Delivery System retains the Shunt until deployment, tracks over a guidewire to the desired position in the vasculature in an over-the-wire configuration and releases the Shunt. The Delivery System includes a Delivery Catheter and accessory tools (**Figure 10**). The distal end of the Delivery Catheter has retractable hooks embedded in the main tip that affix the Shunt to the Delivery Catheter and allows for controlled disengagement during device deployment. The proximal end of the

Delivery Catheter consists of the handle with a safety lock, a hemostatic valve with flush port, and a length adjustment knob apparatus.

The Delivery System will be supplied with accessory tools that include a guidewire insertion tool, length adjustment pin, and tools for crimping the Shunt (pusher, loader, and an empty Ventura cartridge) for crimping of non-crimped Shunt and in case the Shunt requires crimping during the implant procedure.

The single use Delivery System is provided sterile.

Figure 10: Ventura Delivery System



1. Delivery System Shaft; 2. Delivery Catheter Handle; 3. Safety Lock; 4. Guidewire Lumen Luer; 5. Handle Flush Port; 6. Handle Hemostatic Valve; 7. Length Adjustment Knob and Lock Nut; 8. Tuohy Borst Adapter; 9. Distal Flush Port; 10. Ventura Cartridge; 11. Length Adjustment Pin; 12. Loader; 13. Pusher; 14. Guidewire Insertion Tool; 15. Becker Ca.

3.2.3 Ventura Shunt Implantation Procedure

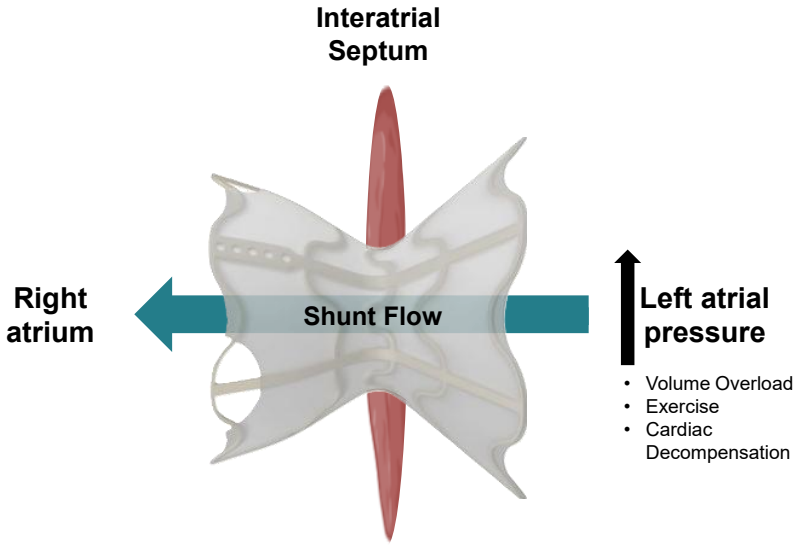
The Shunt is implanted across the central portion of the interatrial septum using a right-sided femoral vein catheterization procedure with an off-the-shelf Cook Medical 14 French Mullins Introducer Sheath. A Class I device cartridge is provided sterile in a standalone package. The implantation procedure is conducted under general anesthesia or conscious sedation with fluoroscopic and TEE or ICE guidance. After crossing the wall between the left and right atrium by transseptal catheterization, the Shunt is delivered across the septum and implanted across the central portion of the fossa ovalis in a controlled manner such that its hourglass shape holds it firmly in place. Placement of the Shunt results in a Qp:Qs ratio of approximately 1.2:1.

In RELIEVE-HF, with all protocol assessments, the entire procedure lasted approximately 80 minutes and required an overnight stay in the hospital.

3.2.4 Ventura Shunt Mechanism of Action

The novel hourglass design of the Shunt is engineered to facilitate blood volume redistribution from the higher-pressure left atrium to the lower-pressure right atrium (**Figure 11**). When a left-to-right pressure gradient exists in the presence of the Shunt, flow from the left atrium to right atrium increases automatically as left atrial pressure increases. This flow through the Shunt decompresses the left atrium and helps reduce left atrial pressure. The pressure gradient vs flow characteristics of the Shunt was assessed by serial TEE in the RELIEVE-HF open-label Roll-in patient cohort (n=97) (published in Pfeiffer et al. 2024 and summarized in **Appendix 10.3**) and found to closely correlate with fluid dynamic models and bench testing. Moreover, the shunt was found to remain patent and maintain a durable orifice size for at least 12 months.

Figure 11: The Ventura Shunt Mechanism of Action



3.3 Proposed Indication

The proposed indication for the Ventura Shunt System is for NYHA Class III HF patients who remain symptomatic despite GDMT, 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.

4 RELIEVE-HF STUDY DESIGN, METHODS, AND EXECUTION

Summary

- RELIEVE-HF was a randomized, double-blind, sham-controlled trial examining the safety and effectiveness of the Shunt in symptomatic patients with HF in which randomization was stratified by reduced (≤ 40%) versus preserved (> 40%) LVEF.
- The primary safety endpoint was the percentage of Shunt Group patients experiencing device- or procedure-related MACNE during the first 30 days after randomization.
- The primary effectiveness endpoint was a prespecified hierarchical composite of all-cause death, heart transplant or LVAD, HFH, worsened HF, and change from baseline in KCCQ-OSS.
- Following interim analysis, V-Wave elected to increase the sample size from 400 to 500 patients. This was done to address limitations in power calculations based upon low event rates due to COVID-19, to increase power for primary endpoint components (particularly for HFH and WHF recurrent events) and secondary endpoints, and to provide additional safety information.

RELIEVE-HF (**RE**ducing **L**ung congestion symptoms us**I**ng the v-wav**E** Shunt in ad**V**anc**E**d **H**eart **F**ailure) was a randomized, double-blind, sham-controlled, multicenter trial that evaluated transcatheter implantation of the Shunt in symptomatic patients with HF with any LVEF. The study was approved by the institutional review board or ethics committee at each center, and all patients provided written informed consent.

Key features of the study intended to support scientific rigor and unbiased collection, and evaluation of data included the following independent committees, laboratories, and individuals: 1) Central Eligibility Committee; 2) CEC; 3) echocardiography core lab; 4) data management and biostatistics; and 5) Data Safety Monitoring Board oversight.

4.1 Study Design

The full trial Protocol and SAP have been previously published and are available online (Stone et al., 2024 Supplement 3). The protocol and SAP were designed by the principal investigators and Sponsor. Patients were screened for enrollment at 114 sites in the US, Canada, Israel, Germany, Spain, Switzerland, Belgium, Poland, the Netherlands, Australia, and New Zealand. Key enrollment criteria appear in **Section 4.1.1** below. In brief, eligible patients had HF with either reduced (≤ 40%) or preserved (> 40%) LVEF and remained symptomatic NYHA functional Class II-IVa (ambulatory) despite a stable maximally-tolerated GDMT regimen per published clinical HF guidelines (McDonagh et al., 2024; McDonald et al., 2021).

A Central Eligibility Committee including HF specialists confirmed all entry criteria prior to enrollment. Sites first familiarized themselves with the V-Wave system by implanting the Shunt in up to 2–3 Roll-in Cohort patients if needed and followed them in an open-

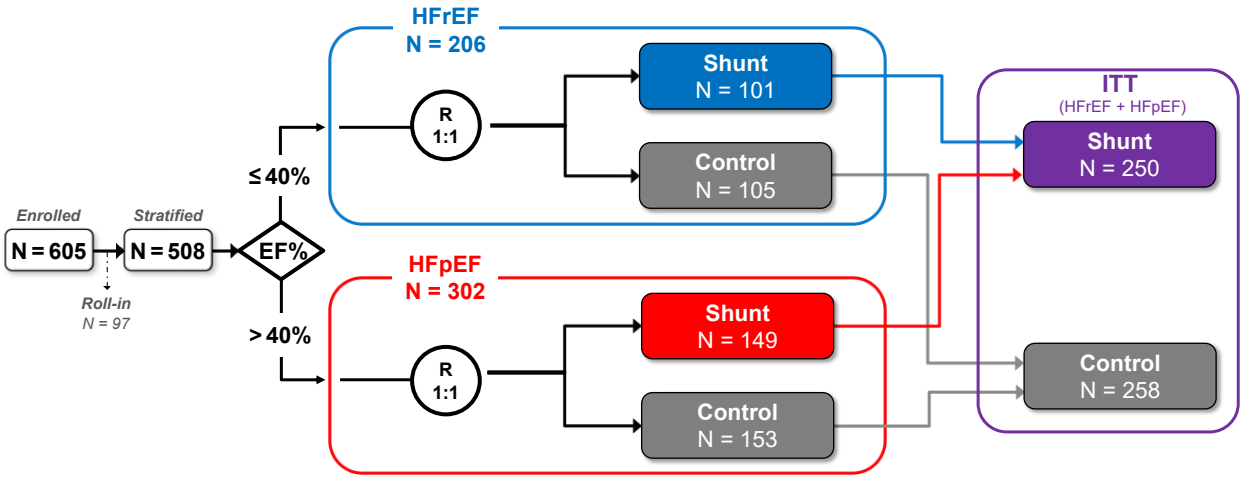
label manner. After sites became familiar with the Shunt procedure via the Roll-in Cohort, subsequent eligible patients were randomized 1:1 in a blinded fashion to transcatheter implantation of the Shunt or a sham procedure (**Figure 12**).

Given uncertainty as to whether the response to shunt implantation would vary in HF patients according to LVEF, randomization was stratified by reduced (≤ 40%) versus preserved (> 40%) LVEF determined by the echocardiographic core laboratory and by site. LVEF was the only clinical variable stratified.

Patients randomized to the sham procedure (Control Group) had a mock transseptal catheterization and device placement performed using a script. Measures to ensure blinding during the procedure, post-procedure, and follow-up are described in **Table 3**. All healthcare providers, research personnel, and outcome assessors were blinded during follow-up. Blinding effectiveness was assessed with a patient questionnaire before hospital discharge and at 1 year (**Section 5.2.4**).

Post-procedure, patients were treated with open-label oral aspirin 75–100 mg/day and a masked platelet receptor P2Y12 inhibitor (clopidogrel, 75 mg/day for Shunt Group patients or matching placebo for Control Group patients) for 6 months if not otherwise taking dual antiplatelet therapy or oral anticoagulation for a clinical indication. All study medication was accounted for. Clinical follow-up and TTE were performed through 2 years. Patients were unblinded following the 2-year visit, after which crossover to the Shunt was performed in Control patients who still met all original enrollment criteria. All Shunt-treated patients are followed through 5 years.

Figure 12: RELIEVE-HF Study Diagram



HFrEF=heart failure with reduced ejection fraction; HFpEF=heart failure with preserved ejection fraction; LVEF=left ventricular ejection fraction; R=randomized.

Table 3: Measures to Maintain Blinding in RELIEVE-HF

	Patients	Post-Procedure Personnel
During Procedure	• Received general anesthesia or deep conscious sedation • Wore eye masks and music-playing headphones	• Only unblinded study personnel allowed in procedure room • Cath lab personnel were not involved in any other aspects of the study
Post-Procedure	• Admitted to hospital for overnight stay • Treated with aspirin • Patients not already on clinically indicated oral anticoagulant or DAPT were provided with blinded study medication (clopidogrel or placebo) to provide study required antiplatelets	• Post-intervention procedure script provided to Implanter to utilize for consistent messaging for general post-study/procedural care
During Follow-Up	• Patient questionnaire assessment of blinding administered at time of hospital discharge and 12-month follow-up visit to assess success of blinding efforts	• Blinded study personnel did all follow-up visits and study assessments • Blinded HF physicians did not directly view echo imaging • Unblinding logs maintained to document any study personnel who became unblinded to a patient

DAPT=dual antiplatelet therapy; HF=heart failure

4.1.1 Key Inclusion and Exclusion Criteria

The key inclusion criteria for RELIEVE-HF were:

- Ischemic or non-ischemic cardiomyopathy with any LVEF and documented HF for at least 6 months
- NYHA functional Class II, III, or ambulatory Class IV despite maximally tolerated Class I GDMT and cardiac rhythm management device therapy for HF as assessed by a Central Eligibility Committee
- HF hospitalization within the prior 12 months and/or elevated (body mass index [BMI]-adjusted) B-type natriuretic peptide (BNP)/NT-proBNP (both required for NYHA II)
- 6-Minute Walk Test (6MWT) ≥ 100 meters to ≤ 450 meters

The key preliminary exclusion criteria at baseline for RELIEVE-HF were:

- Resting systolic blood pressure (SBP) < 90 or > 160 mmHg
- Intractable HF
- Severe pulmonary hypertension defined as PASP > 70 mmHg by echo/Doppler or pulmonary vascular resistance > 4.0 WU on right heart catheterization that cannot be reduced by vasodilator therapy

- RV dysfunction, defined as tricuspid annual plane systolic excursion (TAPSE) < 12 mm or RV fractional area change (RVFAC) ≤ 25% on TTE
- LV end-diastolic dimension (LVEDD) > 8 cm on TTE
- ASD (atrial septal defect), PFO (patent foramen ovale), ASD with anomalous pulmonary venous return (APVR), corrected congenital heart defect, and severe valvular lesions

Additionally, the key final exclusion criteria assessed during cardiac catheterization at the study intervention visit, just prior to randomization, were:

- Anatomical anomaly that precludes implanting the shunt across the fossa ovalis including:
    - Minimal fossa ovalis thickness > 6 mm or lengths < 10 mm; ASD or PFO with more than trace shunting; atrial septal aneurysm; intracardiac thrombus
- Hemodynamic, heart rhythm, or respiratory instability including:
    - Mean PCWP) < 7 mmHg or > 35 mmHg; RA pressure ≥ left atrial pressure (or PCWP) when left atrial pressure (PCWP) is ≥ 7 mmHg; cardiac index < 1.5 L/min/m^2; severe pulmonary hypertension as previously defined, systolic blood pressure < 90 or > 160 mmHg; need for intravenous vasopressor or inotrope medication; malignant arrhythmias; acute respiratory distress or hypoxemia

A complete listing of RELIEVE-HF eligibility criteria has been published (Stone et al., 2024).

4.1.2 Rationale for LVEF Stratification

There are well-recognized dissimilarities in underlying cardiac pathophysiology and differential responses to pharmacological and cardiac rhythm management interventions between HFrEF (LVEF ≤ 40%) and HFpEF (LVEF > 40%) (**Section 2.2**). RELIEVE-HF prespecified stratified randomization by LVEF. V-Wave considered the potential that the 2 populations may react differently to the Shunt. Interaction testing was prespecified to assess the homogeneity of the treatment effect.

4.2 Endpoint Definitions

All clinical endpoints were adjudicated by an independent CEC that was blinded to treatment group assignments. For MACNE events that were adjudicated as definitely or probably related to the device or procedure, the CEC was then unblinded after the initial assessment and relatedness was re-adjudicated in an unblinded fashion to assure correct assessment and patient safety.

4.2.1 Safety Endpoints

4.2.1.1 Primary Safety Endpoint

The primary safety endpoint was the percentage of Shunt Group patients experiencing device- or procedure-related MACNE during the first 30 days after randomization. MACNE is a composite of the following: all-cause death, stroke, systemic embolism, need for open cardiac surgery, or major endovascular surgical repair.

Percutaneous drainage of a pericardial effusion, percutaneous catheter snaring and removal of an embolized but otherwise uncomplicated study device and non-surgical treatment of access site complications were excluded from the definition of MACNE.

All events contributing to the primary safety endpoint were adjudicated and classified by an independent CEC.

4.2.1.2 Additional Safety Data

Additional safety data were the following:

- MACNE and BARC types 3 and 5 bleeding at 30 days
- Percentage of Treatment Group patients with device-related MACNE at 12 months
- Incidence of all serious adverse events (SAEs) by type at study duration
- Incidence of cerebrovascular events at study duration with subclassification of central nervous system (CNS) infarction, CNS hemorrhage, and transient ischemic attack (TIA) and their relationship to device or study procedures (per NeuroARC's neurological standardized endpoints for assessing how the brain functions after surgical or catheter-based cardiovascular interventions)
- Incidence of myocardial infarction (MI) events at study duration after implantation
- Incidence of systemic embolization events at study duration after implantation
- Incidence of pulmonary embolism events at study duration after implantation
- Incidence of shunt implant embolization at study duration after implantation
- Device-related MACNE annually through 5 years

4.2.2 Effectiveness Endpoints

4.2.2.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint was a prespecified hierarchical composite of the following:

1. All-cause death
2. Heart transplant or LVAD implantation (HTLV)
3. HFH (including qualifying Emergency Room [ER] visits ≥ 6 hours)

4. Worsened HF treated as outpatient (WHF; including ER HF visits < 6 hours)
5. KCCQ-OSS change from baseline with ≥ 5-point between-group difference through 2-year follow-up

4.2.2.2 Secondary Effectiveness Endpoints

The prespecified hierarchy for testing secondary effectiveness endpoints, if the primary effectiveness endpoint was met, was as follows:

1. KCCQ-OSS changes from baseline to 12 months
2. All-cause mortality and HFH
3. Time to all-cause death, LVAD/transplant or HF hospitalization
4. Time to all-cause death or first HF hospitalization
5. Cumulative HF hospitalization
6. Time-to-first HF hospitalization
7. Primary effectiveness endpoint including all-cause death, LVAD/transplant, HFH, and worsening HF treated as outpatient, but without inclusion of KCCQ
8. 6MWT changes from Baseline to 12 months

4.3 Statistical Analyses

4.3.1 Study Populations

Roll-in Population:

Sites first familiarized themselves with the V-Wave system by implanting the Shunt in up to 2–3 Roll-in Cohort patients if needed and followed them in an open-label manner. Implantation performance of the first Roll-in patient at a site was assessed during the implant by a Sponsor-provided qualified proctor. Roll-in patients were otherwise followed and analyzed identically as randomized patients with the exception that they had TEE/Doppler examinations at baseline and 6- and 12-month follow-up to quantify Shunt patency. These results showed that 56/56 patients with 1-year TEEs had widely patent Shunts (published in Pfeiffer et al 2024 and summarized in **Appendix 10.3**).

Intention-to-Treat Population (ITT):

Patients who were randomized to the Shunt or Control groups, irrespective of LVEF strata assignment, were pooled and analyzed according to their original assignment regardless of treatment received. No crossovers were allowed during the primary follow-up period. The ITT population was the primary analysis population.

Per Protocol Population (PP):

Randomized patients who met all initial and final inclusion/exclusion criteria, had no major protocol deviations which may have impacted study outcomes, were treated according to randomization (i.e., Shunt Group patients who underwent a Shunt implant

procedure, and Control Group patients who did not undergo a Shunt implant procedure), and who had available follow-up data for the endpoint being evaluated.

Safety Population:

Randomized patients who met the initial inclusion and exclusion criteria, signed an informed consent form, and underwent any invasive procedure associated with evaluation of the final exclusion criteria.

4.3.2 Primary Safety Endpoint Analysis

Assuming an alpha level of 0.025 (one-sided), a sample size of 200 evaluable Shunt Group patients from the randomized cohort would achieve a power of 87% to detect a difference between the expected safety endpoint rate of 5% and a performance goal of 11%. The performance goal was predicated on studies of left atrial appendage occlusion with the WATCHMAN device.

Hence, the primary safety endpoint was the percentage of Shunt Group patients experiencing device-related MACNE during the first 30 days after randomization was tested with an exact binomial test, at a one-sided significance level of 0.025, against the 11% performance goal.

4.3.3 Primary Effectiveness Endpoint Analysis with Finkelstein-Schoenfeld Method and Win Ratio

The primary effectiveness endpoint was evaluated with a sum of ranks (T_{Shunt}) test statistic in the Shunt Group using the method of Finkelstein and Schoenfeld (Finkelstein & Schoenfeld, 1999), based on adjudicated endpoint events when the last enrolled patient had a minimum 12-month follow-up since randomization. The *P*-value is calculated from the Finkelstein-Schoenfeld test, and the unmatched win ratio with 95% CI is used to measure the ratio of wins in the Shunt Group as described by Pocock (Pocock et al., 2012). The treatment effect, or unmatched win ratio approach, was used to evaluate the effect size or magnitude of effect of the primary effectiveness endpoint. The win ratio was calculated as the total number of Shunt Group patient ‘wins’ divided by the number of Control Group patient ‘wins’ and 95% CI after all pairwise comparisons. A win ratio > 1 indicates the occurrence of more positive results for the experimental Shunt treatment. An overview of the principles of the win ratio can be found in (Redfors et al., 2020); further description of the test statistic can be found in Table S8 of Stone et al 2024.

The trial was powered to examine primary outcomes in all randomized patients. The results in each LVEF strata were pre-specified but not powered. Rather, the similarity or dissimilarity of response by LVEF stratum was evaluated by interaction testing to assess the homogeneity of the treatment effect.

All patients had a scheduled minimum follow-up period of 12 months, and all data collected through 24 months of follow-up was included in the final analysis.

Analysis by the Finkelstein-Schoenfeld method compared every pair of Shunt Group and Control Group patients based on the following prespecified hierarchy of events:

1. All-cause death: whichever patient experienced death later “wins” the comparison. If neither patient died, the comparison proceeded to the next component of the prespecified hierarchy.
2. Heart transplant or LVAD implant: whichever patient experienced a heart transplant or LVAD implant later “wins” the comparison. If neither patient experienced the event, the comparison proceeded to the next component in the hierarchy.
3. HFH: whichever patient experienced fewer HFH events “wins” the comparison. If patients had the same number of HFH events, the first HFH times were compared, and if one patient had an event at least 7 days earlier than the comparator patient, the later HFH event would “win” the comparison. If both patients experienced the same number of events and the first HFH event times were within 7 days of each other, the comparison proceeded to the next hierarchical component.
4. Worsened HF: whichever patient experienced fewer worsening HF Events, over the longest time period in common between 2 patients, would “win” the comparison. If both patients experienced the same number of events, the comparison proceeded to the final component.
5. KCCQ overall score: whichever patient achieved an improvement of ≥ 5 points in KCCQ change from baseline “wins” the comparison. As the final level in the prespecified hierarchy, if both patients or neither patient achieved a 5-point improvement in KCCQ-OSS, the patient comparison would result in a tie.

To prevent inflation of Type-I error, the final Finkelstein-Schoenfeld statistic for the primary effectiveness analysis is derived from data wherein prespecified weights were assigned before and after the interim analysis (Cui et al., 1999).

4.3.4 Interim Analysis with Adaptive Sample Size Re-Estimation

For the primary 30-day safety endpoint, 200 evaluable Shunt Group patients provided 87% power to detect a difference between the expected rate of 5% and a performance goal of 11%, a metric agreed upon with FDA, evaluated using an exact binomial test at a 1-sided α=0.025. Based on 10,000 simulated trials, 400 total patients (200 per arm) provided 90% power to detect a sum of ranks greater than zero in the Shunt Group, with 1-sided α=0.025. Thus, 400 patients were planned for enrollment.

A single interim analysis of the primary effectiveness outcome with adaptive sample size re-estimation by an independent third party was planned when 200 enrolled patients completed 6-month follow-up or the study enrollment was predicted to be completed within 3 months, whichever occurred first.

Based on the results of the interim analysis, the Data Safety Monitoring Board recommended the study continue as originally planned and to leave the sample size unchanged. However, V-Wave elected to increase enrollment by 100 patients to approximately 500 patients. This was done to address limitations in power calculations based upon the possibility of low event rates due to COVID-19, to increase power for primary endpoint components (particularly for HFH and WHF recurrent events) and secondary endpoints, and to provide additional safety information. The Sponsor and investigators remained blinded until the time of primary analysis.

4.3.5 Additional Statistical Methods

Additionally, the components of the primary effectiveness endpoint were assessed individually and pooled as the cumulative incidence of all events, or as the time-to-first event. All endpoints were assessed in the overall ITT Population, as well as in the separate HFrEF and HFpEF strata.

Hence, the secondary endpoints and their respective evaluation methods are as follows:

- HF and non-HF Events were analyzed by Nelson-Aalen for event groupings. The cumulative hazard ratio function describes the estimated rate at which events will have occurred, given that patients survived until that time point.
- HF Events including all-cause death and heart transplant/LVAD were analyzed by Cox regression using prespecified covariates to estimate the hazard ratio between the Shunt and Control groups.
- HFH and worsened HF, adjusting for all-cause mortality for competing events including all-cause death and HTLV, were analyzed using a semi-parametric joint model with common frailty term to induce an association between the 2 distributions. The joint frailty model was based on the approach described by (Rogers et al., 2014) and expanded upon by (Rogers et al., 2016).
- KCCQ was analyzed by analysis of covariance (ANCOVA) to test the difference in mean changes from baseline to 12 months.

General Statistical Methods

Categorical variables were compared by Chi-square test or Fisher's exact tests. Continuous variables were compared by the two-sample t-test for normally distributed data or otherwise by the Wilcoxon rank sum test. Follow-up event rates were estimated using the Kaplan-Meier method and were compared by log-rank test. Hazard ratios and 2-sided 95% CIs were estimated by Cox proportional hazards models, including treatment as a covariate. Cumulative event rates were estimated using joint frailty, where death and LVHT were competing events, Poisson statistics, and the Nelson-Aalen estimator. All statistical tests were 2-sided unless otherwise specified and were performed at the 5% significance level, unless otherwise noted.

5 RELIEVE-HF PATIENT POPULATION

Summary

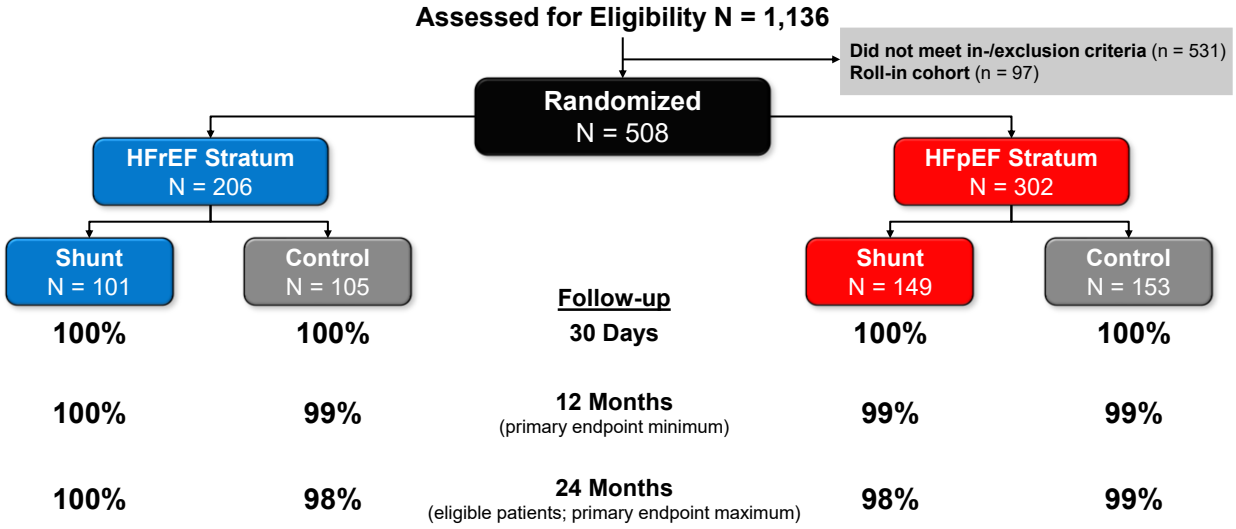
- In RELIEVE-HF, 206 patients were enrolled in the HFrEF stratum (101 Shunt and 105 Control), and 302 patients were enrolled in the HFpEF stratum (149 Shunt and 153 Control).
- Patients in the overall ITT Population were elderly, with a mean age of approximately 72 years with multiple comorbidities.
- Patients with HFrEF received guideline-directed Class I drug therapies at rates exceeding HFpEF patients and other contemporary HF clinical trials.
- The Shunt was successfully implanted in all 250 (100%) patients randomized to the Shunt Group.
- As expected, based on disease pathophysiology, HFrEF patients had enlarged LV end-diastolic and end-systolic volumes, while HFpEF patients had LV end-diastolic and end-systolic volume measurements in the normal range.
- Blinding assessments confirmed that the patient blinding procedures used in RELIEVE-HF were largely effective.

5.1 Disposition

Figure 13 shows the disposition diagram for the RELIEVE-HF study. A total of 1,136 patients were screened for enrollment at 114 sites in the US and other countries. Investigators presented all potential cases to the Central Eligibility Committee. In total, 605 patients were enrolled in the study, 97 in the Roll-in Cohort, and 508 in the randomized cohort (250 to Shunt and 258 to Control). One-year follow-up was completed in > 99% of patients and the median follow-up duration was 22.0 months. Over the entire duration of primary follow-up, 8 (1.6%) patients withdrew from the study (2 from the HFrEF stratum and 6 from the HFpEF stratum), and no randomized patient was lost to follow-up. Thus 500/508 (98.4%) of patients completed primary follow-up.

According to randomization stratified by LVEF, 206 patients were enrolled in the HFrEF stratum (101 to the Shunt Group and 105 to the Control Group), and 302 patients were enrolled in the HFpEF stratum (149 to the Shunt Group and 153 to the Control Group).

Figure 13: Patient Disposition in the RELIEVE-HF Study



5.2 Demographics and Baseline Characteristics

5.2.1 Demographics and Baseline Medical Characteristics

Patient demographics and baseline characteristics for all Shunt Group and Control Group patients in the ITT randomized cohort are shown in **Table 4** and for patients stratified and randomized by LVEF ≤ 40% and > 40% in **Table 5**. Patients in the overall ITT Population were elderly, with a mean age of approximately 72 years, and approximately 63% were male. The majority (90.4%) of patients were Caucasian, and mean BMI was 30.8 kg/m^2. Of 508 enrolled randomized patients, 250 (49.2%) were from the US and 285 (56.1%) were from North American (US and Canada).

The RELIEVE-HF study aimed to enroll patients at high risk for subsequent HF morbid and mortal events. Common comorbidities included ischemic heart disease, hypertension, hyperlipidemia, diabetes, chronic kidney disease, atrial fibrillation, smoking, and chronic obstructive pulmonary disease; patients in the overall ITT Population had a median of 5 comorbidities. A majority (96.5%) were NYHA functional Class III HF despite optimized GDMT. All patients had at least one HF hospitalization during the year prior to enrollment and/or an elevated outpatient BNP or NT-proBNP level, and other indicators of high risk such as poor health status and low average 6MWT were present. These established risk factors are understood to enrich a HF population for HF-related clinical events (Bui et al., 2011; Ford et al., 2015; Grundtvig et al., 2020; O'Connor et al., 2019).

There were differences in baseline demographic characteristics between the HFrEF and HFpEF strata. Patients in the HFrEF stratum tended to be younger on average (approximately 68 years) than those with HFpEF (approximately 74 years) and proportionally more male (81.6% versus 50.0%). Patients in the HFrEF stratum were more frequently of Hispanic ethnicity and had lower BMI. In terms of medical characteristics, patients in the HFrEF and HFpEF strata had the same average number

of comorbid conditions, with ischemic cardiomyopathy and prior MI occurring more frequently in patients with HFrEF, whereas insulin-requiring diabetes, non-ischemic heart disease, and atrial fibrillation occurred more frequently in patients with HFpEF. Patients with HFpEF had lower levels of BNP and N-terminal pro-BNP than patients with HFrEF. These findings were not unexpected given the differences in the pathophysiology of HF in HFrEF compared to HFpEF.

Table 4: Demographics and Baseline Characteristics – ITT Population

	Treatment group (N=250)	Control group (N=258)
Age, years	72.6 ± 10.0	70.4 ± 10.5
Sex, male	162 (64.8%)	157 (60.9%)
Race, Caucasian	227 (90.8%)	232 (89.9%)
Ethnicity, Hispanic	20 (8.0%)	26 (10.1%)
Body mass index, kg/m^2	30.5 ± 6.2	31.2 ± 6.1
Duration of heart failure — mos.	70.5 ± 66.3	75.1 ± 71.9
HFH during prior 1yr	0.76 ±0.97	0.68 ± 0.88
Diabetes mellitus	124 (49.6%)	125 (48.4%)
- Insulin-treated	49 (19.6%)	48 (18.6%)
Hypertension	209 (83.6%)	216 (83.7%)
Hyperlipidemia	201 (80.4%)	195 (75.6%)
Current or previous smoker	133 (53.2%)	137 (53.1%)
Prior stroke or transient ischemic attack	43 (17.2%)	48 (18.6%)
Chronic obstructive lung disease	43 (17.2%)	52 (20.2%)
Ischemic cardiomyopathy	114 (45.6%)	120 (46.5%)
Non-ischemic cardiomyopathy	136 (54.4%)	138 (53.5%)
At least one HFH in the prior year	128 (51.2%)	127 (49.2%)
Known coronary artery disease	169 (67.6%)	160 (62.0%)
Prior myocardial infarction	104 (41.6%)	103 (39.9%)
Prior PCI	103 (41.2%)	96 (37.2%)
Prior CABG	65 (26.0%)	58 (22.5%)
History of atrial fibrillation or flutter	170 (60.8%)	159 (61.2%)
- Baseline rhythm was atrial fibrillation or flutter	76 (30.4%)	64 (24.8%)
NYHA Class - I	0 (0.0%)	0 (0.0%)
- II	9 (3.6%)	7 (2.7%)
- III	239 (95.6%)	251 (97.3%)
- IV	2 (0.8%)	0 (0.0%)
KCCQ overall summary score	52.1 (35.4, 66.9)	50.8 (34.6, 66.4)
Six-minute walk distance	265 (196, 325)	2701 (198, 330)
Troponin I or T >ULN	79/227 (34.8%)	109/240 (45.4%)
B-type natriuretic peptide (pg/mL)	238 (117, 413)	221 (101, 518)
N-terminal pro-B-type natriuretic peptide (pg/mL)	1939 (1066, 3259)	1597 (852, 2868)
eGFR, mL/min/1.73 m^2	45.5 (37.5, 59.8)	48.5 (37.2, 60.8)
- < 60 mL/min/1.73 m^2	188 (75.2%)	188 (72.9%)

Continuous data are mean ± SD or median (interquartile range). CABG=coronary artery bypass graft surgery; eGFR=estimated glomerular filtration; HFH=heart failure hospitalization; ITT=intention-to-treat; KCCQ=Kansas City Cardiomyopathy Questionnaire; NYHA=New York Heart Association; PCI=percutaneous coronary intervention; ULN=upper limits of normal.

Table 5: Demographics & Baseline Characteristics - HFrEF and HFpEF Strata

	Heart failure with reduced ejection fraction (≤ 40%)		Heart failure with preserved ejection fraction (> 40%)	
	Treatment group (N=101)	Control group (N=105)	Treatment group (N=149)	Control group (N=153)
Age, years	69.8 ± 11.1	66.5 ± 10.6	74.6 ± 8.6	73.0 ± 9.5
Sex, male	84 (83.2%)	84 (80.0%)	78 (52.3%)	73 (47.7%)
Race, Caucasian	91 (90.1%)	93 (88.6%)	136 (91.3%)	139 (90.8%)
Ethnicity, Hispanic	10 (9.9%)	15 (14.3%)	10 (6.7%)	11 (7.2%)
Body mass index, kg/m^2	29.1 ± 5.4	30.4 ± 5.7	31.4 ± 6.6	31.8 ± 6.3
Duration of heart failure — mos.	97.4 ± 80.5	98.0 ± 82.9	52.3 ± 46.8	59.3 ± 58.5
HFH during prior 1yr	0.97 ± 1.11	0.78 ± 0.99	0.68 ± 0.85	0.61 ± 0.79
Diabetes mellitus	50 (49.5%)	55 (52.4%)	74 (49.7%)	70 (45.8%)
- Insulin-treated	14 (28.0%)	18 (32.7%)	35 (47.3%)	30 (42.9%)
Hypertension	81 (80.2%)	80 (76.2%)	128 (85.9%)	136 (88.9%)
Hyperlipidemia	80 (79.2%)	75 (71.4%)	121 (81.2%)	120 (78.4%)
Current or previous smoker	61 (60.4%)	60 (57.1%)	72 (48.3%)	77 (50.3%)
Prior stroke or TIA	17 (16.8%)	15 (14.3%)	26 (17.4%)	33 (21.6%)
Chronic obstructive lung disease	18 (17.8%)	20 (19.0%)	25 (16.8%)	32 (20.9%)
Ischemic cardiomyopathy	65 (64.4%)	64 (61.0%)	49 (32.9%)	56 (36.6%)
Non-ischemic cardiomyopathy	36 (35.5%)	41 (39.0%)	100 (67.1%)	97 (63.4%)
At least one HFH in the prior year	55 (54.5%)	53 (50.5%)	73 (49.0%)	74 (48.4%)
Known coronary artery disease	77 (76.2%)	76 (72.4%)	92 (61.7%)	84 (54.9%)
Prior myocardial infarction	58 (57.4%)	60 (57.1%)	46 (30.9%)	43 (28.1%)
Prior PCI	45 (44.6%)	49 (46.7%)	58 (38.9%)	47 (30.7%)
Prior CABG	36 (35.6%)	29 (27.6%)	29 (19.5%)	29 (19.0%)
History of atrial fibrillation or flutter	65 (64.4%)	59 (56.2%)	105 (70.5%)	100 (65.4%)
- Baseline rhythm was afib or flutter	27 (26.7%)	19 (18.1%)	49 (32.9%)	45 (29.4%)
NYHA Class - I	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- II	4 (4.0%)	6 (5.7%)	5 (3.4%)	1 (0.7%)
- III	97 (96.0%)	99 (94.3%)	142 (95.3%)	152 (99.3%)
- IV	0 (0.0%)	0 (0.0%)	2 (1.3%)	0 (0.0%)
KCCQ overall summary score	56.0 (35.9, 72.1)	54.2 (39.1, 69.8)	49.0 (34.8, 64.3)	47.4 (32.3, 62.8)
Six-minute walk distance	295 (216, 355)	263 (204, 345)	240 (186, 316)	275 (193, 321)
Troponin I or T >ULN	37/88 (42.0%)	50/98 (51.0%)	42/139 (30.2%)	59/142 (41.5%)
B-type natriuretic peptide (pg/mL)	301 (203, 751)	319 (155, 651)	178 (105, 325)	177.5 (79, 391)
N-terminal pro-B-type natriuretic peptide (pg/mL)	2231 (1300, 3944)	1867 (954, 3772)	1654 (873, 2766)	1454 (779, 2544)
eGFR, mL/min/1.73 m^2	44.5 (37.3, 58.0)	50.4 (39.2, 60.8)	46.6 (37.5, 59.8)	47.3 (36.6, 60.1)
- < 60 mL/min/1.73 m^2	76 (75.2%)	74 (70.5%)	112 (75.2%)	114/153 (74.5%)

Continuous data were mean ± standard deviation or median (interquartile range). Afib=atrial fibrillation; CABG denotes coronary artery bypass graft surgery; eGFR=estimated glomerular filtration rate calculated from the Modification of Diet in Renal Disease (MDRD) formula; HFH=heart failure hospitalization; HFpEF=heart failure with preserved ejection fraction (LVEF > 40%); HFrEF=heart failure with preserved ejection fraction (LVEF ≤ 40%); LVEF=left ventricular ejection fraction; KCCQ=Kansas City Cardiomyopathy Questionnaire; NYHA=New York Heart Association; PCI=percutaneous coronary intervention; TIA=transient ischemic attack; ULN=upper limits of normal.

5.2.2 Baseline Medication and Electrical Therapies

Medications at baseline for Shunt Group and Control Group patients are summarized in **Table 6** for the overall ITT Population and **Table 7** for the HFpEF and HFrEF strata.

Patients with HFrEF received guideline-directed Class I drug therapies at rates exceeding patients with HFpEF and other contemporary HF clinical trials, including RAS inhibitors, beta blockers, MRAs, and SGLT2i. Importantly, the SGLT2 agents did not have a Class I indication in the US for patients with HFrEF until the April 2022 ACC/AHA/HFSA Guidelines for the Management of Heart Failure were published (Heidenreich et al., 2022). By that time, most RELIEVE-HF patients were already enrolled. The utilization of cardiac implantable electronic devices was high in the LVEF≤ 40% population, with 89% having either an ICD or cardiac resynchronization therapy with defibrillator (CRT-D), and 45% having either cardiac resynchronization therapy with pacemaker (CRT-P) or CRT-D.

As expected, patients with HFpEF were less frequently treated with the four pillar drug classes, as they did not have Class I guideline indications. The 2022 ACC/AHA/HFSA Guidelines for the Management of Heart Failure assigned SGLT2i a Class IIa indication and RAS inhibitors (angiotensin-converting enzyme inhibitor [ACEi], angiotensin receptor blocker [ARB], angiotensin receptor-neprilysin inhibitors [ARNi]), MRAs, and beta blockers a Class IIb indication for the treatment of patients LVEF> 40% (Heidenreich et al., 2022). Drug utilization was generally evenly distributed between the HFpEF Shunt and Control groups except for MRA use, which was more commonly used in the HFpEF Control group than in the Shunt group.

Table 6: Baseline Medical and Electrical Therapies – ITT Population

	Treatment group (N=250)	Control group (N=258)
Beta blockers	224 (89.6%)	222 (86.0%)
Renin-angiotensin system inhibitors, any	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%)
Mineralocorticoid receptor antagonists	145 (58.0%)	174 (67.4%)
Sodium-glucose cotransporter-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%)

ACEi=angiotensin-converting enzyme inhibitors; ARB=angiotensin II receptor blockers; ARNi=angiotensin receptor-neprilysin inhibitor**;** CRT=cardiac resynchronization therapy; CRT-D=CRT-defibrillator; CRT-P=CRT-pacemaker; ICD=implantable cardiac defibrillator.

Table 7: Baseline Medical and Electrical Therapies – HFrEF and HFpEF Strata

	Heart failure with reduced ejection fraction (≤ 40%)		Heart failure with preserved ejection fraction (> 40%)	
	Treatment group (N=101)	Control group (N=105)	Treatment group (N=149)	Control group (N=153)
Beta blockers	99 (98.0%)	101 (96.2%)	125 (83.9%)	121 (79.1%)
Renin-angiotensin system inhibitors, any	95 (94.1%)	93 (88.6%)	81 (54.4%)	92 (60.1%)
- ACEi	7 (6.9%)	7 (6.7%)	25 (16.8%)	31 (20.3%)
- ARB	8 (7.9%)	7 (6.7%)	31 (20.8%)	31 (20.3%)
- ARNi	80 (79.2%)	79 (75.2%)	25 (16.8%)	30 (19.6%)
Mineralocorticoid receptor antagonists	74 (73.3%)	77 (73.3%)	71 (47.7%)	97 (63.4%)
Sodium-glucose cotransporter-2 inhibitors	48 (47.5%)	56 (53.3%)	45 (30.2%)	57 (37.3%)
Vasodilators	8 (7.9%)	13 (12.4%)	25 (16.8%)	21 (13.7%)
- Long-acting nitrates	7 (6.9%)	11 (10.5%)	22 (14.8%)	14 (9.2%)
- Hydralazine	2 (2.0%)	8 (7.6%)	8 (5.4%)	12 (7.8%)
Diuretics	93 (92.1%)	98 (93.3%)	137 (91.9%)	141 (92.2%)
Antiplatelet agents	51 (50.5%)	52 (49.5%)	55 (36.9%)	59 (38.6%)
Chronic oral anticoagulation	63 (62.4%)	54 (51.4%)	89 (59.7%)	87 (56.9%)
ICD or CRT-D	89 (88.1%)	95 (90.5%)	26 (17.4%)	28 (18.3%)
CRT-D or CRT-P	49 (48.5%)	43 (41.0%)	21 (14.1%)	16 (10.5%)

ACEi=angiotensin-converting enzyme inhibitors; ARB=angiotensin II receptor blockers; ARNi=angiotensin receptor-neprilysin inhibitor**;** CRT=cardiac resynchronization therapy; CRT-D=CRT-defibrillator; CRT-P=CRT-pacemaker; ICD=implantable cardiac defibrillator.

5.2.1 Baseline Echocardiography and Hemodynamics

Baseline TTE parameters for the Shunt and Control groups are summarized in **Table 8** for the ITT Population and in **Table 9** for the HFrEF and HFpEF strata. In the overall ITT Population, mean LVEF in the Shunt and Control groups were similar at 45.5% and 44.4%, respectively.

As expected, based on disease pathophysiology, patients in the HFrEF stratum had enlarged LV end-diastolic volumes, LV end-systolic volumes, and LA volumes, reduced cardiac output/index, mild pulmonary hypertension, and RV dysfunction as evaluated by RVFAC and TAPSE.

Patients in the HFpEF stratum had LV end-diastolic volume and LV end-systolic volume measurements in the normal range. Enlarged LA volumes, reduced cardiac output/index, and pulmonary arterial pressure and RV function parameter values were similar to those observed in the HFrEF stratum.

Table 10 and **Table 11** show hemodynamic parameters at right heart catheterization performed immediately prior to randomization in the ITT and the LVEF strata, respectively. On average, patients had elevations of RA, PA and pulmonary capillary wedge pressures, reduction of cardiac output/index and elevation of pulmonary vascular resistance, irrespective of LVEF strata or treatment assignment. The one exception was that HFpEF patients tended to have higher systolic blood pressure, which is consistent with this HF phenotype.

Table 8: Baseline Transthoracic Echocardiography – ITT Population

	Shunt Group (N=250)	Control Group (N=258)
LVED volume (biplane) (mL)	123.3 (87.0, 175.5)	126.0 (96.0, 181.5)
LV end-systolic volume (biplane) (mL)	66.3 (37.5, 115.5)	70.0 (40.5, 117.0)
LVEF (biplane) (%), mean ±SD	45.5 ± 15.1	44.4 ± 14.9
LVEF (biplane) (%), median (IQR)	45.4 (33.4, 58.9)	45.3 (33.3, 57.4)
LVEF ≤ 40%	101/250 (40.4%)	105/258 (40.7%)
LVEF > 40%	149/250 (59.6%)	153/258 (59.3%)
Left atrial 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)
RVFAC (%)	37.7 (33.3, 42.9)	37.5 (33.3, 42.9)
TAPSE (mm)	16.5 (14.0, 20.0)	17.0 (14.0, 19.0)
PA systolic pressure. (mmHg)	32.0 (24.0, 41.0)	32.0 (25.0, 40.0)
RVED area index (cm^2/m^2)	9.8 (8.2, 11.9)	10.4 (8.4, 12.4)
Inferior vena diameter max (cm)	1.6 (1.2, 2.0)	1.6 (1.2, 1.9)
Mitral regurgitation moderate or greater	49 (19.6%)	38 (14.7%)
Tricuspid regurgitation moderate or greater	50/247 (20.2%)	45/257 (17.5%)

LV=left ventricular; LVED=left ventricular end-diastolic; LVEF=left ventricular ejection fraction; PA=pulmonary artery; RVED=right ventricular end-diastolic; RVFAC=right ventricular fractional area change; TAPSE=tricuspid annular plane systolic excursion

Continuous data were median (interquartile range) or mean ± standard deviation. LVEF data were shown both ways.

Table 9: Baseline Transthoracic Echocardiography – HFrEF and HFpEF Strata

	HFrEF (LVEF ≤ 40%)		HFpEF (LVEF > 40%)	
	Shunt Group (N=101)	**Control Group (N=105)**	**Shunt Group (N=149)**	**Control Group (N=153)**
LVED volume (mL)	188.5 (155.5, 238.0)	187.5 (140.0, 249.5)	97.5 (73.0, 122.0)	106.0 (80.5, 128.5)
LV end-systolic volume (mL)	131.0 (103.5, 167.5)	128.5 (92.5, 184.0)	42.0 (28.0, 61.5)	47.0 (33.0, 64.5)
LVEF (biplane) (%), mean ±SD	30.0 ± 6.4	29.2 ± 6.7	56.1 ± 8.8	54.8 ± 8.7
LVEF (biplane) (%), median (IQR)	31.1 (24.9, 35.4)	30.2 (23.8, 34.8)	56.3 (49.4, 62.6)	54.3 (47.6, 62.2)
Left atrial volume (mL)	84.5 (65.5, 109.5)	77.5 (61.5, 104.0)	75.3 (62.0, 97.3)	74.3 (58.5, 101.0)
Stroke volume (mL)	54.0 (42.0, 67.0)	51.0 (45.0, 62.0)	54.0 (41.0, 66.0)	56.0 (44.0, 69.0)
Stroke volume index (mL/m^2)	26.9 (21.4, 33.3)	24.7 (21.0, 31.5)	26.5 (22.2, 31.6)	28.6 (22.6, 34.5)
Cardiac output (L/min)	3.76 (2.95, 4.66)	3.76 (3.05, 4.66)	3.60 (2.79, 4.48)	3.92 (3.11, 4.73)
Cardiac index (L/min/m^2)	1.89 (1.56, 2.30)	1.77 (1.46, 2.28)	1.79 (1.49, 2.10)	1.95 (1.57, 2.32)
RVFAC (%)	36.8 (32.0, 41.7)	35.0 (31.6, 40.0)	38.1 (33.3, 42.9)	38.9 (34.8, 45.0)
TAPSE (mm)	16.0 (13.0, 19.0)	15.0 (14.0, 18.0)	17.0 (15.0, 20.0)	17.0 (15.0, 20.0)
PA systolic pressure (mmHg)	29.5 (22.0, 39.0)	32.0 (25.0, 41.0)	34.0 (26.0, 41.0)	32.0 (26.0, 40.0)
RV end- diastolic area index (cm^2/m^2)	10.4 (8.7, 12.4)	10.9 (9.0, 13.5)	9.3 (8.0, 11.3)	9.9 (8.3, 11.3)
Inferior vena cava diameter Max (cm)	1.6 (1.2, 1.9)	1.6 (1.2, 2.0)	0.7 (0.4, 1.0)	0.7 (0.4, 1.0)
Mitral regurgitation moderate or greater	24 (23.8%)	19 (18.1%)	25 (16.8%)	19 (12.4%)
Tricuspid regurgitation moderate or greater	12/98 (12.2%)	17 (16.2%)	38 (25.5%)	28/152 (18.4%)

HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; IQR=interquartile range; LV=left ventricular; LVED=left ventricular end-diastolic; LVEF=left ventricular ejection fraction; PA=pulmonary artery; RV=right ventricular; RVFAC=right ventricular fractional area change; TAPSE=tricuspid annular plane systolic excursion

Continuous data were median (interquartile range) or mean ± standard deviation. LVEF data are shown both ways.

Table 10: Baseline Hemodynamics (Right Heart Catheterization) – ITT Population

	Treatment group (N=250)	Control group (N=258)
Heart rate, bpm	68.4 ± 13.6	68.3 ± 13.3
Systolic blood pressure, mmHg	118.4 ± 18.7	118.8 ± 19.8
Diastolic blood pressure, mmHg	65.4 ± 12.2	65.5 ± 11.2
Mean right atrial pressure, mmHg	9.6 ± 4.3	9.1 ± 4.1
Systolic pulmonary artery pressure, mmHg	38.7 ± 10.9	38.2 ± 10.7
Mean pulmonary artery pressure, mmHg	26.1 ± 7.2	25.7 ± 7.2
Pulmonary vascular resistance, Wood units	2.3 ± 1.1	2.2 ± 1.3
Pulmonary capillary wedge pressure, 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/m^2	2.3 ± 0.7	2.3 ± 0.7

Data are mean ± standard deviation.

Table 11: Baseline Hemodynamics (Right Heart Catheterization) – HFrEF and HFpEF Strata

	HFrEF (LVEF ≤ 40%)		HFpEF (LVEF > 40%)	
	Treatment group (N= 101)	Control group (N= 105)	Treatment group (N=149)	Control group (N=153)
Heart rate, bpm	69.9 ± 12.4	69 ± 10.2	67.4 ± 14.4	67.1 ± 15.0
Systolic blood pressure, mmHg	112.9 ± 17.4	111.1 ± 17.1	122.1 ± 18.7	123.9 ± 19.8
Diastolic blood pressure, mmHg	65.5 ± 12.3	65.8 ± 10.0	65.3 ± 12.1	65.3 ± 11.9
Mean right atrial pressure, mmHg	8.9 ± 4.2	9.3 ± 4.4	10.0 ± 4.4	9.1 ± 4.0
Systolic pulmonary artery pressure, mmHg	37.0 ± 10.8	39.6 ± 12.3	39.8 ± 10.9	37.3 ± 9.5
Mean pulmonary artery pressure, mmHg	25.6 ± 7.7	27.1 ± 8.6	26.3 ± 6.8	24.8 ± 5.9
Pulmonary vascular resistance, Wood units	2.3 ± 1.3	2.4 ± 1.4	2.4 ± 1.0	2.0 ± 1.1
Pulmonary capillary wedge pressure, mmHg	16.4 ± 6.6	17.2 ± 6.9	16.5 ± 5.7	16.0 ± 5.4
Cardiac output, L/min	4.5 ± 1.4	4.6 ± 1.6	4.5 ± 1.6	4.6 ± 1.4
Cardiac index, L/min/m^2	2.2 ± 0.6	2.3 ± 0.7	2.3 ± 0.7	2.3 ± 0.7

Bpm, beats per minute
Data are mean ± standard deviation.

5.2.2 Procedural Characteristics

Table 12 summarizes data from the intervention procedure for all patients randomized to the Shunt and Control groups in the ITT Population. The Shunt was successfully implanted in all 250 (100%) patients randomized to the Shunt Group, and in 1 patient in the Control Group due to a site randomization error. There were no cases of migration, embolization, or thrombosis of the Shunt during or after implantation. All patients were discharged from the catheterization laboratory alive and without MACNE. Overnight hospital stay was mandated by the protocol; median length of stay was 1 day (1 overnight).

Additional implantation experience in RELIEVE-HF not shown in **Table 12** included the 96/97 open-label Roll-in cohort patients that were successfully implanted with the Shunt. In one patient, the implant procedure was abandoned prior to attempted Shunt implant due to a non-hemodynamically significant pericardial effusion following transseptal catheterization. Pericardiocentesis was not required. The patient returned at a later date and was successfully implanted. Also, there were 22 Control patients that crossed over after primary analysis. All were successfully implanted with the Shunt. Thus, the Shunt implantation procedure success rate was 369/370 (99.7%).

Patients in the Shunt group had a median procedure time of 80 minutes, which was 37 minutes longer than in the Control group. The procedure duration included right heart catheterization, TEE or ICE, randomization, shunt implant or Control procedure, implant sheath removal, and acquisition of study data after Shunt implantation. Fluoroscopy time averaged 14 minutes in the Shunt group, which was similar to other percutaneous coronary intervention procedures. Radiation exposure as measured by estimated entrance skin exposure, air kerma area product, or effective dose, was similar to diagnostic coronary angiography and notably lower than percutaneous coronary intervention or other structural heart or electrophysiology ablative procedures (Laskey et al., 2010; Leung & Martin, 1996; Lickfett et al., 2004; Mettler et al., 2008; Pantos et al., 2009; Vijayalakshmi et al., 2007).

TEE/ICE Doppler examination of newly implanted shunts immediately following completion of the procedure revealed that 96.0% of shunts had continuous left atrial to RA flow and the remaining 4.0% had intermittent bidirectional flow. Net shunt flow in conjunction with cardiac output as measured during right heart catheterization was used to estimate Qp:Qs, which averaged 1.25 ± 0.11. The position of the Shunt was consistently near orthogonal (85 degrees) to the tangent of the interatrial septum at the location of transseptal crossing.

Table 12: Study Intervention Procedural Data – ITT Population

	Shunt Group (N=250)	Control Group (N=258)
Shunt implant attempt	250 (100%)	1 (0.4%)[a]
Shunt implanted successfully	250 (100%)	1 (0.4%)
Hospital duration post-procedure (days)	1 (1, 1)	1 (1, 1)
Procedure details		
TEE/ICE baseline septal anatomy		
Fossa ovale length (mm)	21.1 ± 6.1	20.6 ± 6.6
Fossa ovale thickness (mm)	1.5 ± 0.5	1.6 ± 0.6
Fossa ovale excursion motion (mm)	3.0 ± 1.9	2.9 ± 1.9
Procedure duration (min)	80 (59, 100)	43 (30, 55)
Radiation exposure [b]		
Fluoroscopy time (minutes)	14.0 (10.2, 20.4)	4.0 (2.1, 6.9)
Estimated effective dose (mSv)	4.4 (2.4, 7.0)	1.0 (0.5, 2.1)
Estimated kerma area product (Gy•cm^2)	24.5 (13.1, 39.2)	5.4 (2.9, 11.8)
Estimated entrance skin exposure (mGy)	414 (258, 624)	83 (42, 178)
Contrast administered (mL)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Heparin administered (units)	9000 (7000, 12,000)	-
Activated clotting time (s)	291 (246, 342)	-
TEE/ICE post implant		
Shunt flow direction (recorded by Core Lab)	247 (98.8%)	-
Left-to-right	237 (96.0%)	-
Right-to-left	0 (0.0%)	-
Bidirectional	10 (4.0%)	-
Shunt mean pressure gradient (mmHg)	3.2 ± 2.1	-
Shunt flow (mL/min)	1010 ± 321	-
Qp:Qs (estimated)	1.25 ± 0.11	-
Shunt axis angle to fossa (degrees)	85 (77, 88)	-

ICE=intracardiac echocardiography; ITT=intent-to-treat; Qp:Qs=pulmonary-to-systemic flow ratio
TEE=transesophageal echocardiography
a. Due to site error (misinterpretation of the randomization code). Continuous data were median (interquartile range) or mean ± standard deviation.
b. Radiation exposure was estimated by measurements provided from each site's commercial x-ray systems from multiple manufacturers. If dose units were not provided or obviously incorrect, these were estimated by correlation against the fluoroscopy time by a skilled medical physicist.
These results should be considered approximate. Qp:Qs was estimated from the Shunt flow (Q_{Shunt}) and pre-Shunt cardiac output Qs as (Q_{Shunt} - Q_s)/Q_s.

5.2.3 Post-Procedure Antiplatelet/Anticoagulation Treatment

All patients who received a Shunt were to be treated with a 6-month course of either: 1) aspirin (≥ 75 mg daily) and a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel at

clinically indicated doses); or 2) warfarin or a direct-acting oral anticoagulant (dabigatran, apixaban, rivaroxaban, edoxaban, or other approved agent at clinically indicated doses). Patients already receiving one of these regimens for a clinical indication unrelated to the Shunt implant (e.g., prior coronary stent or atrial fibrillation) could remain on their medications as indicated. Patients who were not on either of these regimens were treated with protocol-mandated dual antiplatelet therapy for 6 months. In this latter instance, to maintain patient and study site personnel blinding, all patients regardless of treatment assignment who were not on an antiplatelet/anticoagulant for a clinical indication were provided study medications. Clopidogrel (75 mg) and placebo clopidogrel (75 mg) were provided to sites for maintenance. Aspirin (75 to 100 mg) was also provided to patients by the sites.

Table 13 and **Table 14** summarize anticoagulation and antiplatelet treatments received after study procedure at discharge from the hospital for the ITT and LVEF ≤ 40% and > 40% populations, respectively. Approximately 1 in 3 patients in the Shunt Group were concomitantly taking anticoagulant and antiplatelet therapy for preexisting clinical indications.

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.

Table 14: Post-Procedure Antiplatelet/Anticoagulation Treatment at Implant Procedure Discharge – HFrEF and HFpEF Strata

	HFrEF (LVEF ≤ 40%)		HFpEF (LVEF > 40%)	
	Shunt Group (N=101) n (%)	Control Group (N=105) n (%)	Shunt Group (N=149) n (%)	Control Group (N=153) n (%)
Antiplatelet agents, open-label	55 (54.5)	58 (55.2)	66 (44.3)	74 (48.4)
Antiplatelet agents, study medications [a]	22 (21.8)	23 (21.9)	33 (22.1)	40 (26.1)
Chronic oral anticoagulation	64 (63.4)	58 (55.2)	94 (63.1)	92 (60.1)

HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with preserved ejection fraction; LVEF=left ventricular ejection fraction

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.

5.2.4 Study Unblinding Analyses

Unblinding was assessed by patient-completed blinding survey questionnaires at the time of hospital discharge from the enrollment/randomization visit (post-procedure, pre-discharge) (**Table 15**) and at the 12-month follow-up visit prior to protocol-mandated unblinding (**Table 16**).

Survey data were categorized as possibly unblinded if patients were certain or suspected their treatment assignment for any reason and were correct in that assessment > 50% of the time. Patients were considered unblinded if they reported an incident, e.g., overhearing a conversation of research staff or being told of their treatment assignment by an echocardiographer or other personnel, and were correct in their belief of treatment assignment. Patients were also considered to be unblinded if documentation only occurred in the site logs.

At post-procedure, pre-hospital discharge, 504 (99.2%) patients completed the questionnaire, and 413 (81.3%) patients did not know or did not suspect their treatment assignment. Of the 94 (18.7%) patients that were certain of or suspected their treatment assignment, 47 (50%) were correct in their belief; this is the equivalent of chance and yields no evidence of substantial unblinding having occurred in this study. Three patients reported an unblinding incident (overheard a conversation during the procedure), but only 2 of them were correct about their treatment assignment.

Table 15: Blinding Questionnaire Results at Post-Procedure Pre-Discharge – ITT Population

Post-procedure Pre-discharge Eligible Randomized Patients Unblinding Questionnaire Completed	All Patients (n=508) 504 (99.2%)	Shunt Group (n=250) 250 (100.0%)	Control Group (n=258) 254 (98.4%)
Patient does not know/suspect assignment	413 (81.3%)	204 (81.6%)	206 (81.1%)
Patient certain/suspects assignment	94 (18.7%)	46 (18.4%)	48 (18.9%)
Believes received placebo procedure	19 (3.8%)	9 (3.6%)	10 (3.9%)
Believes received the Shunt	75 (14.9%)	37 (14.8%)	38 (15.0%)
Possibly unblinded (belief > 50% correct)	0 (0.0%)	14 (5.6%)	0 (0.0%)
Unblinded (correctly reported incident)	2 (0.4%)	2 (0.8%)	0 (0.0%)

At 1 year of follow-up, 96.6% of eligible patients completed unblinding questionnaires, and 261 (58.4%) patients did not know or suspect their treatment assignment whereas 186 (41.6%) were certain of or suspected their treatment assignment. The number of patients correctly reporting an unblinding incident was small (2.5%), and all but 1 were in the Shunt Group.

Table 16: Blinding Questionnaire Results at One Year – ITT Population

At 1 Year Eligible Randomized Patients Unblinding Questionnaire Completed	All Patients (n=463) 447 (96.6%)	Shunt Group (n=227) 222 (99.8%)	Control Group (n=235) 225 (95.7%)
Patient does not know/suspect assignment	261 (58.4%)	130 (58.6%)	131 (50.2%)
Patient was certain /suspects assignment	186 (41.6%)	92 (41.4%)	94 (41.8%)
Believes received placebo procedure	72 (16.1%)	25 (11.3%)	47 (20.9%)
Believes received the Shunt	114 (25.5%)	67 (30.2%)	47 (20.9%)
Possibly unblinded (belief > 50% correct)	21 (4.7%)	21 (9.5%)	0 (0.0%)
Unblinded (correctly report incident)	11 (2.5%)	10 (4.5%)	1 (0.4%)

ITT=intent-to-treat

Table 17 compares Bang's New Blinding Index at post-procedure and at 1-year calculated from questionnaire responses (Bang et al., 2004). In Bang's Index, a 0 represents perfect blinding whereas a score of 1 is unblinding. Estimates for Shunt and Control patients showed only small percentages (< 8%) had correct guesses beyond chance with 95% CIs that were consistent with random guessing. These estimates include the effects of patient bias that assumed active treatment due to feeling improved and Control group assignment due to not feeling improved.

Table 17: Blinding Indices at Pre-Discharge and at One Year in ITT Patients

Time of survey	Treatment Group	Bang's New Blinding Index [a,b]	95% CI Lower Bound	95% CI Upper Bound	Interpretation: if CI includes 0, then "random guessing"
Post-procedure	Shunt	0.056	-0.001	0.113	5.6% guessed Shunt beyond chance
	Control	0.028	-0.084	0.140	2.8% guessed Control beyond chance
One-year	Shunt	0.050	-0.020	0.119	5.0% guessed Shunt beyond chance
	Control	0.078	-0.022	0.178	7.8% guessed Control beyond chance

CI=confidence interval; ITT=intent-to-treat
Assumes 50:50 Shunt vs. Control when no guess made.
a. Bang et al., 2004
b. Poltavskiy E, Nandi R, Wertheim H. Blinding Indexes - Generalized and Unified Framework - a SAS® Macro. https://www.wuss.org/proceedings/2023/WUSS-2023-Paper-102.pdf

There are multiple limitations to this analysis but foremost was that patients who were certain or suspected their treatment assignment mostly did so based on symptoms improving or not improving. The near perfect concordance between feeling improved and guessing assignment to Shunt or not feeling better and guessing assignment to Control, strongly suggests that symptom changes highly bias patients' beliefs about randomization assignments.

Based on integrating all the results of the patient blinding questionnaires including the validated Bang's blinding indices, and the site-recorded unblinding logs, patient blinding procedures used in RELIEVE-HF were largely effective and the magnitude of unblinding was small and not likely to materially affect outcome measures.

6 RELIEVE-HF CLINICAL SAFETY RESULTS

Summary

- The study met its primary safety endpoint; there were 0 (97.5% CI: 0, 1.5) device-related or procedure-related MACNE occurring within 30 days in the 250 patients in the ITT Shunt Group.
- Overall, in 348 patients implanted (250 ITT Shunt + 1 ITT Control + 97 Roll-in) with the Shunt, the 2-year rate of device- or procedure-related MACNE was 0%.
- Rates of bleeding measured by BARC 3 or 5 grading at 30 days were low and not different between Shunt and Control groups.
- Peri-procedural complications were rare and did not increase in the Shunt group and shunt embolization did not occur through 2 years of follow-up.
- Other events that may be attributed to an interatrial shunt, including stroke, MI, or embolization, occurred infrequently and at a similar rate as in the blinded Control group. SAEs were less frequent in Shunt-treated HFrEF patients compared with Controls and more frequent in HFpEF patients. There were no unanticipated adverse device effects (UADEs).

6.1 Primary Safety Endpoint Results

The study met its primary safety endpoint, defined as the percentage of Shunt Group patients experiencing device-related MACNE during the first 30 days after randomization, compared to a pre-specified performance goal of 11% (**Table 18**). There were 0 (97.5% CI: 0, 1.5) device- or procedure-related MACNE within the first 30 days after randomization or through long-term follow-up at 2 years.

Table 18: Primary Safety Endpoint – ITT Population

Parameter	Shunt Group (N=250) % (n)	97.5% CI (*P*-value)
Device-related or procedure-related MACNE [a] during the first 30 days after randomization [b]	0.0 (0)	0, 1.5 (< 0.0001)
All-cause death	0.0 (0)	
Stroke	0.0 (0)	
Systemic embolism	0.0 (0)	
Open cardiac surgery	0.0 (0)	
Major endovascular surgical repair	0.0 (0)	

CI=confidence interval; ITT=intent-to-treat; MACNE=Major Adverse Cardiovascular and Neurological Events
[a] MACNE defined as all-cause death, stroke, systemic embolism, open cardiac surgery or major endovascular surgical repair.
[b] The proportion of patients with MACNE events tested against a performance goal of 11% with an exact binomial test, with a one-sided significance level of 0.025.

The same Primary Safety Endpoint event criteria were also examined in all 348 Shunt-treated patients (including 250 ITT Shunt, 1 ITT Control, and 97 Roll-in) at 30 days and 2 years (**Table 19**). Again, no (0%) episodes of MACNE that were adjudicated as device- or procedure-related were reported through 2 years.

Table 19: Extended Primary Safety Endpoint – All Shunt-Treated Patients (ITT and Roll-in Populations)

Parameter	Shunt Through 30 Days (N=348) % (n)	Shunt Through 2 Years (N=348) % (n)
Device-related or procedure-related MACNE [a]	0.0 (0)	0.0 (0)
All-cause death	0.0 (0)	0.0 (0)
Stroke	0.0 (0)	0.0 (0)
Systemic embolism	0.0 (0)	0.0 (0)
Open cardiac surgery	0.0 (0)	0.0 (0)
Major endovascular surgical repair	0.0 (0)	0.0 (0)

CI=confidence interval; ITT=intent-to-treat; MACNE=Major Adverse Cardiovascular and Neurological Events
[a] MACNE defined as all-cause death, stroke, systemic embolism, open cardiac surgery or major endovascular surgical repair.

6.2 Additional Safety Data

Additional safety endpoints for the ITT Population are shown in **Table 20**. There were low, similar rates (< 1%) of device- or procedure-related MACNE or BARC type 3 or 5 bleeding in the Shunt and Control groups at 30 days follow-up. In the Shunt Group, there were 2 (0.8%) BARC type 3 bleeds associated with the implantation procedure: one at the femoral venous access site; the second was due to excessive blood loss during the procedure. Both patients fully recovered. There were no intracerebral BARC type 5 bleeds in the Shunt group. At the time of primary follow-up (1 year through up to 2 years), there were no device- or procedure-related MACNE events and a trend toward more BARC 3 bleeding episodes in Shunt group patients. At 2 years of follow-up, there were low rates of stroke (none related to device or procedure), MI, systemic embolization, and pulmonary embolism; rates did not differ between Shunt and Control groups. The rate of stroke in this aged population with severe HF, hypertension, and a high incidence of atrial fibrillation was within the range expected for patients with HF (Barkhudaryan et al., 2021; Cuadrado-Godia et al., 2010; Yang et al., 2023). Safety information for the 97 patients in the Roll-in Cohort has been published (Rodés-Cabau et al 2024) and is summarized in **Appendix 10.3**.

Similar results were observed in the HFrEF and HFpEF strata (**Table 21**) with the exception that the 2-year rates of bleeding tended to be lower in Shunt group HFrEF patients. Thus, excess BARC bleeding was confined to the HFpEF stratum.

Table 20: Secondary Safety Endpoints and Additional Safety Data – ITT Population

Parameter	Shunt Group (N=250) n (%)	Control Group (N=258) n (%)	Relative Risk Hazard Ratio (95% CI)[f]	Nominal *P*-value
MACNE [a] or BARC types 3 or 5 bleeding at 30 days [b]	2 (0.8)	-	-	-
MACNE [a] or BARC types 3 or 5 bleeding at 2 years [b]	12 (5.2)	-	-	-
BARC types 3 or 5 bleeding at 30 days [b]	2 (0.8)	1 (0.4)	2.07 (0.19, 22.9)	0.54
BARC types 3 or 5 bleeding at 2 years [b]	12 (5.2)	5 (2.0)	2.52 (0.89, 7.16)	0.07
MACNE [a] at 1 year [b]	0 (0.0)	-	-	-
MACNE [a,c] through 2 years [b]	0 (0.0)	-	-	-
Cerebrovascular events at 2 years, any [b]	11 (5.1)	6 (2.5)	1.92 (0.71, 5.18)	0.19
CNS infarction (stroke) [b,d]	7 (3.3)	5 (2.1)	1.46 (0.46, 4.60)	0.52
CNS hemorrhage (intracerebral or subarachnoid) [b,e]	0 (0.0)	1 (0.5)	-	0.33
Transient ischemic attack [b]	4 (1.9)	1 (0.4)	4.12 (0.46, 36.9)	0.17
Myocardial infarction at 2 years [b]	8 (3.8)	13 (6.6)	0.63 (0.26, 1.52)	0.30
Systemic embolization events at 2 years [b]	0 (0.0)	0 (0.0)	-	-
Pulmonary emboli events at 2 years [b]	2 (1.0)	0 (0.0)	-	0.16
Shunt implant embolization at 2 years [b]	0 (0.0)	-	-	-

BARC=Bleeding Academic Research Consortium; CI=confidence interval; CNS=central nervous system; ITT=intent-to-treat; MACNE=major adverse cardiovascular and neurological events; -=not applicable.
a. MACNE was device-related or procedure-related.
b. Event rates were the number of events (Kaplan-Meier time-to-first event estimates). Not done for MACNE as there were no events.
c. These data are through the duration of available follow-up with median follow-up at 22 months.
d. The 7 strokes in patients who were treated with the Shunt were classified by the Clinical Events Committee 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 Clinical Events Committee 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; it occurred in the Control Group.
e. Does not include 1 additional patient in the Control Group with an ischemic stroke and hemorrhagic transformation.
f. Hazard ratio (95% CI).
Notes: Data through 2 years was the maximum follow-up available.
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.

Table 21: Secondary Safety Endpoints and Additional Safety Data – HFrEF and HFpEF Strata

	HFrEF (LVEF≤ 40%)			HFpEF (LVEF> 40%)		
Parameter	**Shunt Group (N=101) n (%)**	**Control Group (N=105) n (%)**	**Hazard Ratio (95% CI)**	**Shunt Group (N=149) n (%)**	**Control Group (N=153) n (%)**	**Hazard Radio (95% CI)**
MACNE [a] or BARC types 3 or 5 bleeding at 30 days [b]	0 (0.0)	-	-	2 (1.3)	-	-
MACNE [a] or BARC types 3 or 5 bleeding at 2 years [b]	1 (1.0)			11 (8.0)		
BARC types 3 or 5 bleeding at 30 days [b]	0 (0.0)	1 (1.0)	-	2 (1.3)	0 (0.0)	-
BARC types 3 or 5 bleeding at 2 years [b]	1 (1.0)	3 (3.1)	0.34 (0.04,3.26)[e]	11 (8.0)	2 (1.3)	5.92 (1.31, 26.7)[e]
MACNE [a] at 1 year [b]	0 (0.0)	-	-	0 (0.0)	-	-
MACNE [a] at 2 years [b]	0 (0.0)	-	-	0 (0.0)	-	-
Cerebrovascular events at 2 years, any [b]	4 (4.1)	3 (3.2)	1.38 (0.31, 6.15)[e]	7 (5.7)	3 (2.0)	2.49 (0.64, 9.63)[e]
CNS infarction (stroke) [b,c]	3 (3.1)	2 (2.2)	1.54 (0.26, 9.23)[e]	4 (3.3)	3 (2.0)	1.42 (0.32, 6.34)[e]
CNS hemorrhage (intracerebral or subarachnoid) [b,d]	0 (0.0)	1 (1.2)	-	0 (0.0)	0 (0.0)	-
Transient ischemic attack [b]	1 (1.0)	1 (1.0)	1.04 (0.07, 16.6)[e]	3 (2.4)	0 (0.0)	-
Myocardial infarction at 2 years [b]	1 (1.1)	3 (3.5)	0.34 (0.04, 3.24)[e]	7 (5.6)	10 (8.5)	0.73 (0.28, 1.91)[e]
Systemic embolization events at 2 years [b]	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Pulmonary emboli events at 2 years [b]	1 (1.7)	0 (0.0)	-	1 (0.7)	0 (0.0)	-
Shunt implant embolization at 2 years [b]	0 (0.0)	-	-	0 (0.0)	-	-

HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; MACNE=major adverse cardiovascular and neurological events; -=not applicable.
a. MACNE was all cause, whether or not device-related or procedure-related.
b. Event rates were number of events (Kaplan-Meier time-to-first event estimates).
c. In HFrEF, the 3 strokes in patients who were treated with the Shunt were classified by the Clinical Events Committee as being due to cerebrovascular disease (n=1), embolic due to atrial fibrillation (n=1, cause of death) and undetermined (n=1) The 2 strokes in Control Group patients who were treated with a placebo procedure were classified by the Clinical Events Committee as being due to cerebrovascular disease (n=1), subarachnoid hemorrhage (n=1). Only one stroke occurred within 30 days of randomization, that being in the Control Group. In HFpEF, the 4 strokes in patients who were treated with the Shunt were classified by the Clinical Events Committee as being due to cerebrovascular disease (n=2), embolic due to atrial fibrillation (n=1) and undetermined (n=1) The 3 strokes in Control Group patients who were treated with a placebo procedure were classified by the Clinical Events Committee as being embolic due to atrial fibrillation (n=2) and undetermined (n=1).
d. Does not include 1 additional Control patient with ischemic stroke and hemorrhagic transformation.
e. Hazard ratio (95% CI).
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 stratum patients with MACNE of any cause, whether or not device- or procedure-related are summarized in **Table 22**. These adverse events tended to be less frequent in Shunt compared with Control patients, 16.6% vs. 32.7% but did not reach significance.

HFpEF stratum patients with MACNE of any cause, whether or not device- or procedure-related are summarized in **Table 23**. These AEs were more frequent in the Shunt group compared with Control, 19.4% vs 10.7%, respectively (HR 2.69 [1.30, 5.58]).

Table 22: All-Cause MACNE at 2 Years – HFrEF (LVEF ≤ 40%)

Parameter	Shunt Group (N=101) n (%)	Control Group (N=105) n (%)	Hazard Ratio (95% CI)
All-cause MACNE [a] during the first 2 years [b]	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)
All-cause Stroke	3 (1.1)	2 (2.2)	1.54 (0.26, 9.23)
All-cause Systemic embolism	0 (0.0)	0 (0.0)	-
All-cause Open cardiac surgery	1 (1.5)	6 (9.0)	0.16 (0.02, 1.32)
All-cause Major endovascular surgical repair	0 (0.0)	0 (0.0)	-

HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; MACNE=major adverse cardiovascular and neurological events; -=not applicable.
a. MACNE was all cause, whether or not device-related or procedure-related.
b. Event rates were number of events (Kaplan-Meier time-to-first event estimates).
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 23: All-Cause MACNE at 2 Years – HFpEF (LVEF > 40%)

Parameter	Shunt Group (N=101) n (%)	Control Group (N=105) n (%)	Hazard Ratio (95% CI)
All-cause MACNE [a] during the first 2 years [b]	26 (19.4)	10 (7.2)	2.69 (1.30, 5.58)
All-cause death	22 (16.4)	7 (5.2)	3.24 (1.38, 7.59)
All-cause Stroke	4 (3.3)	3 (2.0)	1.42 (0.32, 6.34)
All-cause Systemic embolism	0 (0.0)	0 (0.0)	-
All-cause Open cardiac surgery	0 (0.0)	0 (0.0)	-
All-cause Major endovascular surgical repair	0 (0.0)	1 (0.7)[c]	-

HFpEF=heart failure with preserved ejection fraction; LVEF=left ventricular ejection fraction; MACNE=major adverse cardiovascular and neurological events; -=not applicable.
a. MACNE was all cause, whether or not device-related or procedure-related.
b. Event rates were number of events (Kaplan-Meier time-to-first event estimates).
c. Due to aortic dissection and repair 10 months after randomization.
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.

6.3 Serious Adverse Events

For completeness, **Table 24** is a compilation of MeDdra (Medical Dictionary for Regulatory Activities) major system organ classes of site-reported (not CEC adjudicated) SAEs and Serious Adverse Device Effects (SADEs) and Unanticipated Device Effects (UADEs) for the HFrEF and HFpEF strata populations. In the HFrEF stratum, 64 Shunt patients had 172 SAEs, far fewer than in Control patients where 69 patients had 282 SAEs (Poisson rate ratio 0.59 [0.49, 0.72], nominal $P < 0.001$). The opposite effect was seen in the HFpEF stratum where Shunt patients had significantly more SAEs than Controls (RR=1.81 [1.54, 2.12], nominal $P < 0.001$). SADEs were infrequent in HFrEF patients and more common in Shunt-treated HFpEF patients. There were no UADEs reported in the entire trial. These data are consistent with a Shunt-related safety benefit in HFrEF and a signal of harm in HFpEF.

Table 24: MeDdra Coded Site-Reported Serious Adverse Events and Adverse Device Effects up to 2 Years – HFrEF and HFpEF Strata

	HFrEF (LVEF ≤ 40%)		HFpEF (LVEF > 40%)	
Parameter	**Shunt Group (N=101) n pts (n events)**	**Control Group (N=105) n pts (n events)**	**Shunt Group (N=149) n pts (n events)**	**Control Group (N=153) n pts (n events)**
Any SAE	64 (172)	69 (282)	111 (420)	91 (240)
Blood and lymphatic	0 (0)	4 (4)	10 (10)	0 (0)
Cardiac	47 (84)	53 (140)	75 (178)	52 (102)
Endocrine	0 (0)	1 (1)	5 (5)	3 (3)
Eye	0 (0)	1 (1)	1 (1)	1 (1)
Gastrointestinal	9 (13)	10 (10)	21 (26)	14 (16)
General	6 (8)	7 (8)	8 (9)	2 (2)
Hepatobiliary	2 (3)	2 (3)	3 (4)	2 (4)
Immune system	0 (0)	1 (1)	1 (1)	0 (0)
Infection	5 (7)	15 (17)	26 (33)	18 (23)
Injury	3 (3)	9 (11)	23 (28)	14 (15)
Investigation	0 (0)	1 (2)	0 (0)	2 (2)
Metabolism and nutrition	3 (3)	4 (4)	8 (10)	5 (5)
Musculoskeletal & connective tissue	2 (2)	3 (3)	6 (6)	1 (1)
Neoplasm	2 (2)	3 (10)	5 (6)	4 (5)
Nervous system	4 (4)	4 (5)	13 (13)	7 (8)
Product issues	0 (0)	1 (1)	0 (0)	0 (0)
Psychiatric	0 (0)	0 (0)	1 (1)	0 (0)
Renal Urinary	9 (11)	14 (19)	23 (33)	14 (16)
Reproductive	0 (0)	0 (0)	2 (2)	1 (1)
Respiratory	12 (14)	12 (22)	20 (26)	17 (24)
Skin	2 (2)	0 (0)	3 (3)	1 (1)
Surgical procedures	5 (6)	6 (6)	11 (12)	4 (4)
Vascular	8 (10)	10 (14)	11 (13)	7 (7)
Any SADE	6 (6)	4 (12)	13 (19)	2 (2)
UADE	0 (0)	0 (0)	0 (0)	0 (0)

SAE=serious adverse event; SADE=serious adverse device effect; UADE=unanticipated adverse device effect.

6.4 Safety Conclusions

The RELIEVE-HF study met its primary safety endpoint, with 0 (97.5% CI: 0, 1.5%) device- or procedure-related MACNE events at 30 days in the Shunt Group (ITT Population). There was no device- or procedure-related MACNE through 2 years of follow-up in the overall ITT Population, and the rates of all-cause MACNE were low. The frequency of BARC type 3 or type 5 bleeding was also low and was similar between the Shunt and Control groups. The frequency of MACNE due to any cause trended to favor Shunt treatment in HFrEF patients and Control in HFpEF patients. Also, the frequency of SAEs was reduced with Shunt treatment in HFrEF patients and increased in HFpEF. There were no unexpected adverse device effects (UADE). Similar procedural and device safety was observed in the 97 Roll-in Cohort patients (Rodes-Cabou et al 2024).

7 RELIEVE-HF CLINICAL EFFECTIVENESS RESULTS

Summary

- Among all randomized patients, the win ratio for the primary effectiveness outcome at 2 years in the Shunt group compared with the Control group in the combined ITT population was not significantly different. For the primary efficacy endpoint, an interaction was observed between the two LVEF strata (*P*=0.0146), and therefore the strata could not be combined for the analysis of effectiveness. Consequently, each LVEF stratum was separately analyzed.
- Analysis of the primary effectiveness endpoint by prespecified LVEF stratification revealed that the Shunt improved HF Event outcomes compared to Control in patients with HFrEF (LVEF ≤ 40%) though it did not achieve statistical significance. There was a signal for harm in the HFpEF (LVEF > 40%) stratum.
- In patients with HFrEF, the Shunt was effective at reducing the two-year hazard rate for HF Events (death, heart transplantation or LVAD implantation, all HFH, and all outpatient WHF events) from 1.92 events in the Control group to 0.93 events in the Shunt group, a 51% reduction in HF Events (nominal *P* < 0.0001). This included a 54% reduction in all HFH and a 58% reduction in Terminal Events (death or heart transplant/LVAD implantation).
- For the HFrEF stratum for the primary win ratio endpoint, permutation test estimation of Type-1 error (false positive rate) for the entire decision tree was only mildly inflated.

7.1 Primary Effectiveness Results (Overall; ITT Population)

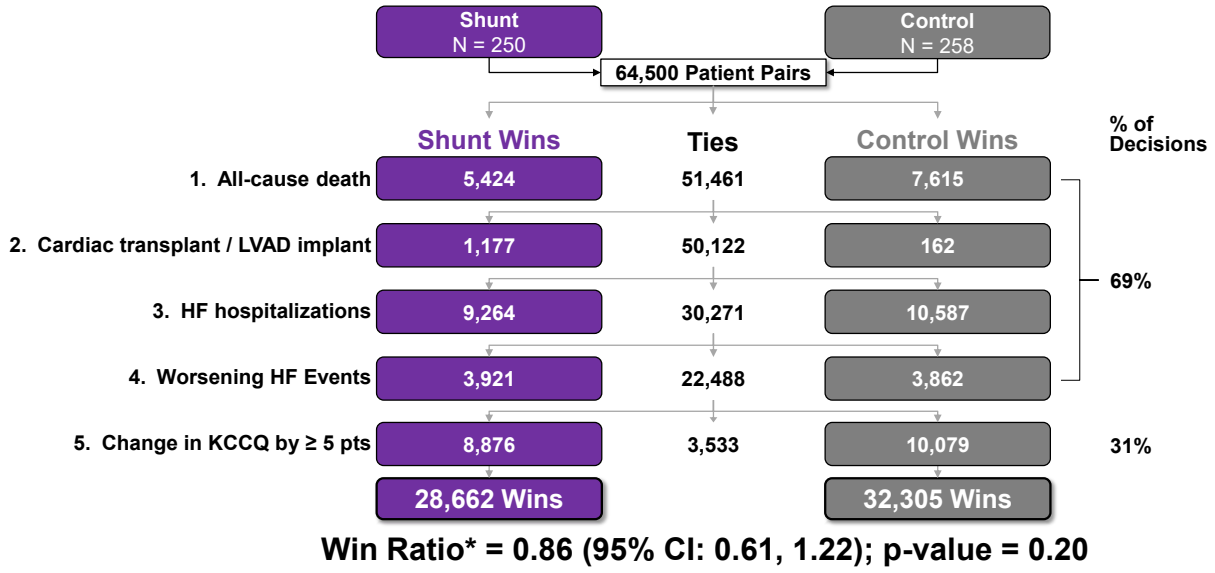
RELIEVE-HF did not meet its Primary Effectiveness Endpoint (**Figure 14**) as described in the SAP. The prespecified analysis for pooling of the LVEF strata yielded opposite treatment effects in HFrEF and HFpEF patients with an interaction *P*-value=0.0146.[1] This finding of strongly opposing interaction effect, also known as a crossover interaction, indicates that the strata should not be combined for the analysis of effectiveness. As homogeneity of the LVEF strata was a basic assumption of the null hypothesis for the ITT win ratio analysis, and since that assumption was violated, the win ratio for the ITT population is uninterpretable. The results for the ITT win ratio analysis are presented for exploratory or descriptive purposes only.

Thus, for completeness, the win ratio for the ITT population was 0.86 [0.61, 1.22] with a nominal *P*-value, P=0.20 (2 tailed). Notably, 69% of win ratio decisions were based on hard clinical events, i.e., the first 4 components of the hierarchy including all-cause

[1] Errata: The interaction *P*-value was initially reported as 0.0275. It was determined there was a coding error in the calculation of confidences intervals for the phase-weighted win ratio. The correct interaction *P*-value is 0.0146. FDA has been updated on this error which had no material effect on interpretation of outcomes.

death, heart transplantation or LVAD, recurrent HFH, and worsening HF as an outpatient. The fifth component, KCCQ-OSS, represented 31% of the decisions.

Figure 14: Non-Inferential Win Ratio Analysis for the Primary Hierarchical Composite Effectiveness Endpoint (Overall; ITT Population)



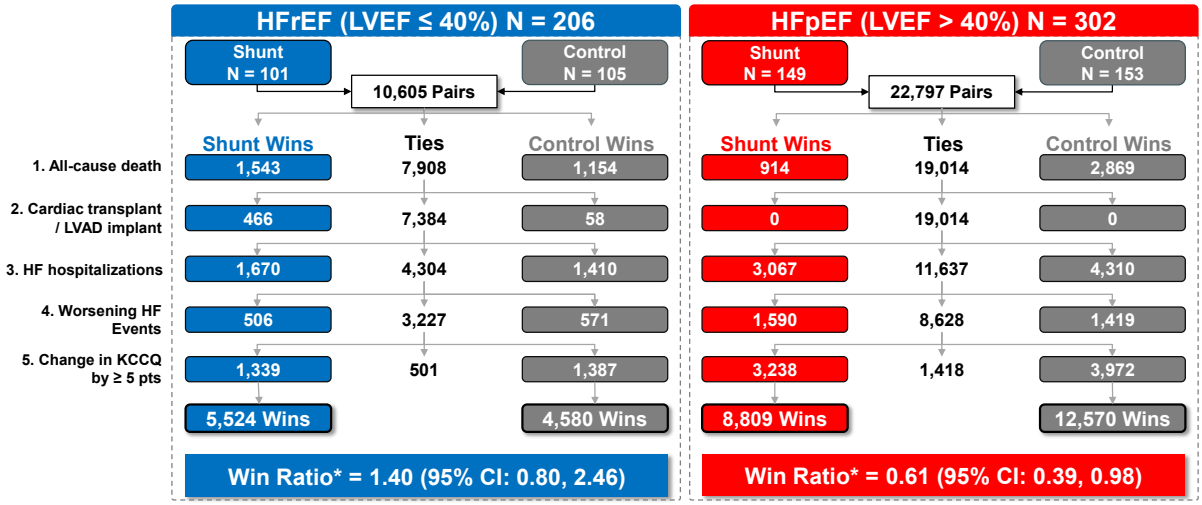
HF=heart failure; ITT=Intent-to-treat; KCCQ=Kansas City Cardiomyopathy Questionnaire; LVAD=left ventricular assist device. * The Win ratio was phase-weighted for the interim analysis. The numbers of wins, losses, and ties for all pairs of patients at each level of the win ratio hierarchy are shown, as well as the method for calculation of the win ratio (number of wins in the Shunt Group divided by number of ties in the Shunt Group). The win ratio was then adjusted for the numbers of pairs of patients examined before vs. after the interim analysis according to the method of Cui L et al (1999).

7.1.1 Primary Effectiveness Outcome by LVEF Strata

Understanding that the original primary endpoint was no longer interpretable becomes of key importance in understanding the outcome of RELIEVE-HF. The study protocol, SAP, and administrative record prespecified that: 1) The HFrEF and HFpEF strata were the only clinical characteristics used for stratified randomization; 2) The Primary Effectiveness Endpoint would be tested for interaction between the LVEF strata. Based on standard statistical practice, if the interaction is significant and qualitatively different, the strata would not be pooled, and endpoints would be evaluated in each stratum individually.

Figure 15 shows the Primary Effectiveness Endpoint when the LVEF randomized strata were tested individually. In patients with HFrEF, the Shunt Group performed numerically better than the Control Group with the win ratio [95% CI] of 1.40 [0.80, 2.46], signifying a 40% improvement favoring the Shunt. However, given the number of patients enrolled, the 95% CI included 1.0, not achieving statistical significance. Conversely, in patients with HFpEF, the Control Group performed better than the Shunt Group (0.61 [0.39, 0.98]) consistent with evidence of harm.

Figure 15: Win Ratio Analysis for the Primary Hierarchical Composite Effectiveness Endpoint by LVEF



Interaction p-value = 0.0146

HF=heart failure; KCCQ=Kansas City Cardiomyopathy Questionnaire; LVAD=left ventricular assist device. * The Win ratio was weighted for the interim analysis.

Acknowledging that neither LVEF strata achieved the win ratio primary effectiveness endpoint, a post hoc, integrated analytical approach was taken to gain an understanding of consistency, directionality, effect size and strength of the evidence in the reduced and preserved LVEF strata to ascertain if there is support for probable and reasonable assurances of effectiveness or harm. V-Wave requested FDA that HFpEF not be considered as a population indicated for Shunt use. As such, from this point forward, the major focus will be on results in the HFrEF stratum with contrasts to HFpEF results where applicable.

7.2 Limitations of the Win Ratio in RELIEVE-HF

Table 25 and **Table 26** summarize the number of CEC-adjudicated effectiveness clinical events in the HFrEF and HFpEF strata, respectively. Recurrent events were commonplace in RELIEVE-HF. For example, in the HFrEF stratum, 63 patients had 119 HFH, 99 patients had 210 HF Events, and 131 patients had 363 All Events episodes. Although there was a trend showing fewer first events in Shunt-treated patients, subsequent events were generally more frequent than first events in Control patients, and there was a much larger relative reduction in subsequent events with Shunt treatment. By example, for the composite of HF Events, Shunt patients had 54 first events compared to 69 first events in Controls, but the frequency of subsequent events was 34 vs. 74 in Shunt compared to Control patients. Although the randomized sample size was relatively small (N=206), the rate of recurrent events was high, with 41 vs 78 HFH events, 76 vs 134 HF Events, and 144 versus 219 total events (All Events) in the Shunt and Control groups, respectively. The large number of events relative to the population size allows stable estimation of treatment effects across recurrent event

models and supports the statistical reliability and the robustness of the observed between-group differences for assessing treatment effects on recurrent clinical outcomes. Similar conclusions regarding adequate size for reliable assessment of treatment effects can be made for the HFpEF stratum.

Table 25: CEC-Adjudicated Effectiveness Events in Reduced LVEF ≤ 40% Stratum (HFrEF, N=206)

	Shunt (N=101)			Control (N=105)			Shunt and Control Total Events
Parameter	First Events	Subsequent Events	Total Events	First Events	Subsequent Events	Total Events	
Single Events							
Death	13	-	13	20	-	20	33
Heart Transplant/ LVAD (HTLV)	1	-	1	6	-	6	7
Hospitalization for HF (HFH)	26	15	41	37	41	78	119
All-Cause Hospitalization (ACH)	55	54	109	63	100	163	272
Worsening HF outpatient (WHF)	16	5	21	19	11	30	51
Composite Events							
Terminal Events (Death, HTLV)	14	-	14	26	-	26	40
HF Events (Death, HTLV, HFH, WHF)	45	31	76	54	80	134	210
All Events (Death, HTLV, ACH, WHF)	63	81	144	68	151	219	363

HF=heart failure

Table 26: CEC-Adjudicated Effectiveness Events in Preserved LVEF > 40% Stratum (HFpEF, N=302)

	Shunt (N=149)			Control (N=153)			Shunt and Control Total Events
Parameter	First Events	Subsequent Events	Total Events	First Events	Subsequent Events	Total Events	
Single Events							
Death	22	-	22	7	-	7	29
Heart Transplant/ LVAD (HTLV)	-	-	0	-	-	0	0
Hospitalization for HF (HFH)	47	40	87	30	17	47	134
All-Cause Hospitalization (ACH)	93	165	258	82	80	162	420
Worsening HF outpatient (WHF)	29	5	34	25	9	34	68
Composite Events							
Terminal Events (Death, HTLV)	22	-	22	7	-	7	29
HF Events (Death, HTLV, HFH, WHF)	69	74	143	54	34	88	231
All Events (Death, HTLV, ACH, WHF)	103	211	314	89	114	203	517

HF=heart failure

HFrEF patients with Terminal Events (all-cause death, heart transplantation or LVAD) that would be counted in the first 2 tiers of the Primary Effectiveness Endpoint win ratio, were more likely to have higher cumulative recurrent HFH and WHF event rates compared with patients with no Terminal Events, irrespective of treatment group assignment (**Table 27**). Moreover, as summarized in **Table 28**, the proportions of events that were excluded from contributing to Tiers 3 and 4 of the win ratio by having Tier 1 or Tier 2 Terminal Events were disproportionately greater in the Control group (17 Control patients with 50 events, compared to 8 Shunt patients with 15 events). This resulted directly from the structure of the win ratio, which compares patients sequentially by highest-tier outcomes and censors' comparisons once a "win" is established and represents a censoring bias against the treatment benefit of the Shunt.

Table 27: Frequency of Other HF Events in HFrEF Stratum Patients with and without Terminal Events

Event Groups	Terminal Events	No Terminal Events	Rate Ratio
Shunt, N pt (pt-yr)	14 (10.8)	87 (144.4)	
HFH, N events	10	31	4.3 (1.9–9.1)
WHF, N events	5	16	4.2 (1.2–12.0)
Control, N pts (pt-yr)	26 (27.3)	79 (123.8)	
HFH, N events	40	38	4.8 (3.0–7.6)
WHF, N events	10	20	2.3 (1.0–5.1)

Terminal Events include all-cause death, heart transplantation, and left ventricular assist device implantation.
Abbreviations: HF=heart failure; HFH=HF hospitalizations; HFrEF=HF with reduced ejection fraction; WHF=worsening HF treated as an outpatient with intravenous therapy.
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 28: HF Hospitalizations and Worsening HF Outpatient Events Excluded from Primary Effectiveness Endpoint by Terminal Events in HFrEF stratum

		HFrEF Shunt group N=101	HFrEF Control group N=105	Nominal *P*-value[1]
Win Ratio Tier 3 HFH Events	Events total, N	41	78	
	Events not counted in WR, N (%)	10 (24.4%)	40 (51.3%)	0.004
Win Ratio Tier 4 WHF Events	Events Total, N	21	30	
	Events not counted in WR, N (%)	5 (24.0%)	10 (33.3%)	0.38
Win Ratio Tier 3, 4 HFH + WHF Events	Events Total, N	62	108	
	Events not counted in WR, N (%)	15 (24.2%)	50 (46.3%)	0.004

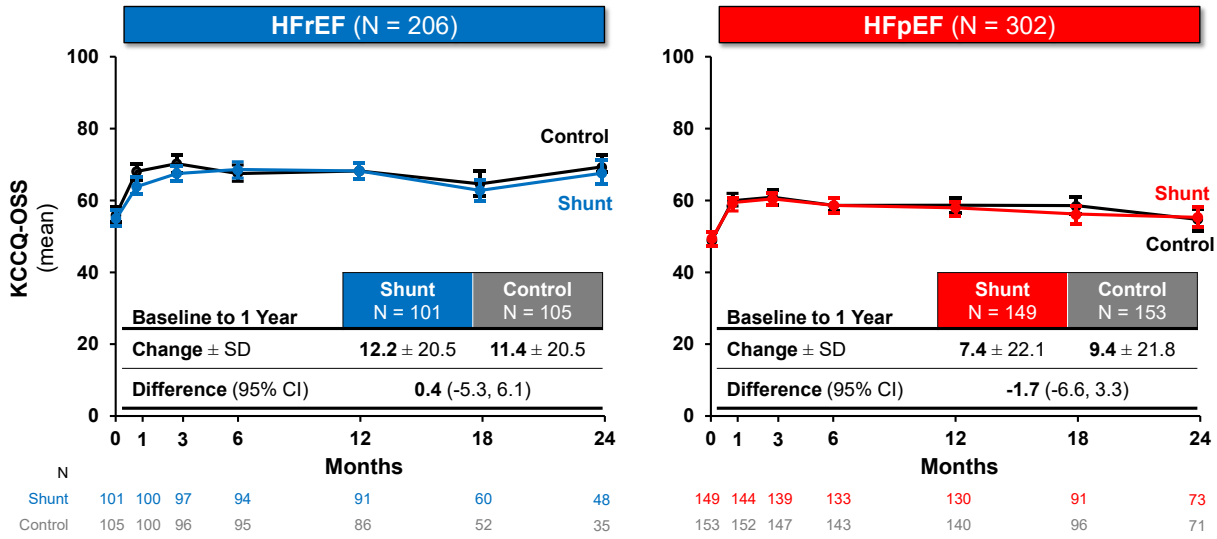
Abbreviations: HFH=heart failure hospitalizations; WHF=worsening heart failure events treated as outpatient with intravenous therapies; WR=win ratio.
[1] Exact test with mid-*P*-value.
Nominal P-values are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

The win ratio only counts one win, loss, or tie per patient pair and does not reflect all events that patients experience, thereby underestimating the total burden of disease. As a result, the win ratio is less informative than recurrent event models, which incorporate the entirety of events experienced by each patient. These findings highlight a key limitation of the win ratio framework in chronic conditions like HFrEF, where recurrent morbidity represents a substantial component of clinical burden and therapeutic benefit.

The other major limitation of the win ratio framework was the inclusion of KCCQ as the tie breaking fifth tier. **Figure 16** shows that the changes in KCCQ-OSS from baseline were similar for patients with HFrEF and HFpEF across all time points. KCCQ-OSS increased from baseline to follow-up by approximately 10 points in all patient groups, regardless of whether they had HFrEF or HFpEF, and regardless of whether they were

treated with the atrial shunt or a blinded sham procedure. Specifically, in the HFrEF strata, there was no between-group incremental improvement in KCCQ-OSS in Shunt-treated patients, even though the Shunt reduced the risk of HFHs by a large margin, as well as the terminal events of death, heart transplantation, or LVAD implantation. Perhaps even more strikingly, among patients with HFpEF, both randomized groups, including those treated with the Shunt, reported that they were feeling better by KCCQ assessment, despite the fact that there was a doubling of the rates of HFH and a tripling of mortality with shunt treatment. Thus, there appears to be a very strong placebo, Hawthorne, or other confounding effect with blinded KCCQ outcomes that lasts at least 2 years

Figure 16: Change in KCCQ-OSS Over Time by LVEF



CI=confidence interval; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; KCCQ-OSS=Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LVEF=left ventricular ejection fraction; QOL=quality of life; SD=standard deviation.
The QOL component of the hierarchical composite primary endpoint, the KCCQ-OSS during 2-year follow-up. Data are displayed as mean ± 95% Cis.
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.

Additional analyses of the KCCQ data, including a responder analysis and comparison to other published HF studies, are provided in **Appendix 10.5**

These limitations in the Primary Effectiveness Endpoint including event counting bias favoring Control and lack of between-group differences and other vagaries in KCCQ have prompted well-regarded statistical authors to conclude that the “win ratio was ill-suited to capture this diversity of effects across subgroups and components of the primary outcome” in specific reference to RELIEVE-HF (Pocock et al., 2024).

7.3 Secondary Effectiveness Endpoints Results

A summary of secondary clinical effectiveness outcomes in patients with HFrEF using the SAP specified methods for each endpoint is provided in **Table 29**. The results except for KCCQ showed consistent trends favoring shunt treatment for time-to-first event methods and nominally significant differences for the two recurrent event assessments of HFH (joint frailty model and Nelson-Aalen estimator). In both cases, the effect size was large, and the 95% upper confidence boundaries were substantially < 1.0.

Table 29: Secondary Endpoint Results in HFrEF (LVEF ≤ 40%)

Secondary Endpoints (covariate adjusted)	Shunt Group (N=101)	Control Group (N=105)	Difference, HR, HRR, RR, or Win Ratio [95% CI]
S1: KCCQ-OSS changes from Baseline to 12 months	12.2 ± 20.5	11.4 ± 20.5	Difference 0.4 [-5.3, 6.1][1]
S2: HFH adjusted for all-cause mortality	0.29	0.56	HR 0.52 [0.31, 0.86][2]
S3: Time-to-first death, LVAD/Transplant, or HFH event	0.36%	50.1%	HR 0.71 [0.45, 1.11][3]
S4: Time to death or first HFH	35.9%	49.5%	HR 0.72 [046, 1.13][3]
S5: Cumulative HFHs at study duration	0.52	1.13	HRR 0.46 [0.29, 0.69][4]
S6: Time-to-first heart failure hospitalization	28.7%	41.7%	HR 0.68 [0.41, 1.12][3]
S7: Primary Effectiveness Endpoint including mortality, LVAD/Transplant, HFH, and Worsening Heart Failure treated as outpatient, but without KCCQ			WR 1.31 [0.87, 1.97][5]
S8: 6MWT changes from Baseline to 12 months. Only If the null hypothesis for S7 is rejected.			NA[6]

CI=confidence interval; HF=heart failure; HFH=heart failure hospitalization; HFrEF=heart failure with reduced ejection fraction; KCCQ-OSS=Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LVAD=left ventricular assist device; LVEF=left ventricular ejection fraction; WHF=worsening heart failure.
1. Difference with 95% CI, adjusted for baseline value (ANCOVA).
2. Annualized rates and hazard ratio [95% CI] calculated in a joint frailty model adjusted for all-cause mortality
3. Event rate by Kaplan-Meier time-to-first event estimates. HR [95% CI] by univariate Cox regression that includes treatment assignment as an independent predictor.
4. Hazard rate ratio (95% CI) by Nelson-Aalen estimator.
5. Win ratio (95% CI).
6. Median (IQR) – data not normally distributed, 25.2% missing data at 12 months due to Covid 19 pandemic missed clinic follow-up visits. Was to be evaluated only if null hypothesis for S7 was rejected.
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.
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.

7.4 Stratified Recurrent Event Outcomes

As specified in the SAP, the HF clinical events comprising the primary effectiveness endpoint were examined for recurrent events by Nelson-Aalen estimator and joint frailty

methods. The advantage of the Nelson-Aalen approach is that it can graphically represent recurrent events with appropriate censoring of terminal events and patient exits unlike Kaplan-Meier estimates that censor patients after a single event. As a non-parametric method, there are no assumptions regarding event timing distribution, nor does it require that hazards be proportional. Comparisons between two Nelson-Aalen hazard rate functions for Shunt and Control groups can be made as either point estimates based on z-scores or assessment of the entire distribution of the curves by the Kolmogorov-Smirnov statistic (see **Appendix 10.7**). The advantages of the joint frailty model are that it also accounts for competing events such as death or HTLV (Terminal Events) that limit subsequent recurrent events such as HFH or WHF.

A variety of clinical event categories defined as single event types and composites with multiple event types were evaluated with these prespecified recurrent event methodologies. Sensitivity analyses were performed by including additional recurrent event models that have been used to analyze randomized HF trials. Details of the statistical methods and sensitivity analyses are provided in **Appendix 10.7**.

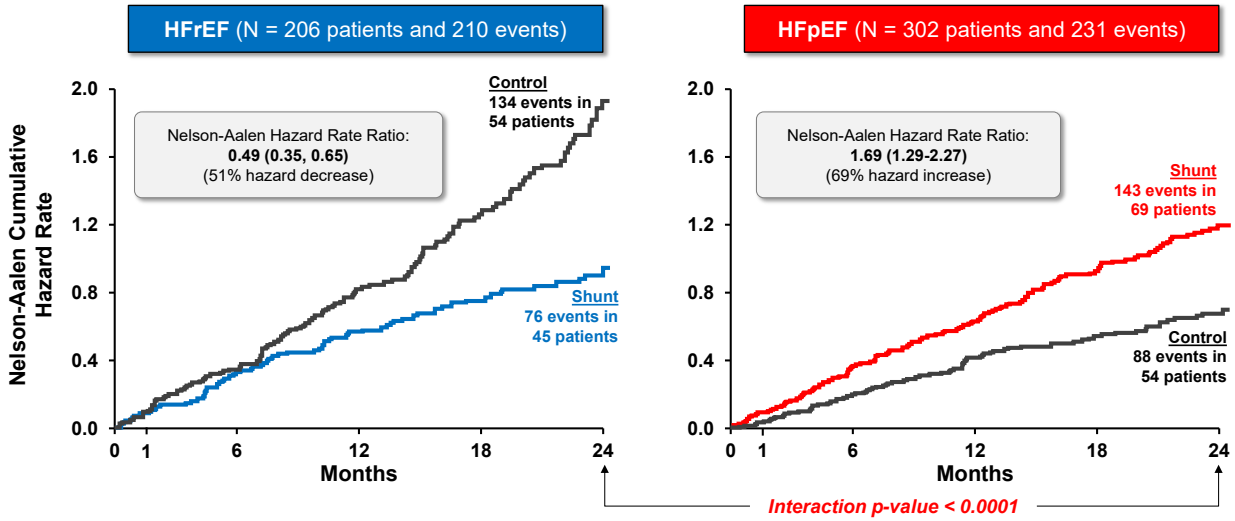
Figure 17 shows Nelson-Aalen cumulative hazard rates over 2 years for HF Events in each LVEF stratum. There were strong opposite treatment effects in the HFrEF and HFpEF strata for the combined 4 HF Event clinical components of the Primary Effectiveness Endpoint.

For HFrEF, there was a high HF Event rate in Control patients (an average of 1.92 events at 2 years), which comports well with the other studies of similarly selected patients described in a published meta-analysis of implantable hemodynamic monitoring studies (Lindenfeld et al 2024). The two curves continue to separate at 2 years with a hazard rate ratio (HRR) of 0.49 (95%CI; 0.35, 0.65) indicating a 51% reduction in HF Events. The number needed to treat (NNT) to prevent one HF Event at 2 years in HFrEF was 1.0 (95% CI: 0.7, 1.8) (per method of Cook, 2013).

By comparison, in HFpEF, the HF event rate in Controls was substantially lower than in HFrEF (0.69 events at 2 years), which is similar to the control event rate in a published double-blinded randomized trial of another interatrial shunt device (Gustafsson et al 2024 and summarized in **Appendix 10.8**). There was a strong signal of likely harm with Shunt treatment in the HFpEF stratum.

The very low *P*-value of interaction and the large and diametrically opposed treatment effects on hard cardiovascular event outcome measures, coupled with very low nominal *P*-values in each LVEF stratum indicate that these LVEF strata are highly likely to be substantively and significantly different.

Figure 17: Nelson-Aalen Cumulative Hazard Analysis for HF Events (All-Cause Death, Heart Transplant/LVAD, HF Hospitalization, Worsening HF) by LVEF



HF=heart failure; LVAD=left ventricular assist device; LVEF=left ventricular ejection function.
The clinical outcomes components of the hierarchical composite primary endpoint were the cumulative incidence of all events, including all-cause death, LVAD or heart transplant procedures, HF hospitalizations, or worsening HF outpatient events. The Nelson-Aalen cumulative hazard rate function describes the estimated rate at which events have occurred, given that the individual has survived up to that time point, i.e., at any given time, the Nelson-Aalen cumulative hazard rate denotes the expected number of events per patient followed for that length of time. The number at the end of each curve is the 2-year hazard rate.
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.

The forest plot in **Figure 18** details Nelson-Aalen hazard rate comparisons, cumulative HRRs, and interaction testing at 24 months for individual and composite event categories in each LVEF strata. Shunting improved clinical outcomes in HFrEF for all event types with 24-month HRRs nominally significant for all event categories except WHF and hospitalization not for HF. There were worse outcomes for all individual and composite event types in HFpEF patients except WHF. There were also nominally significant interactions between LVEF strata for all categories of events except WHF.

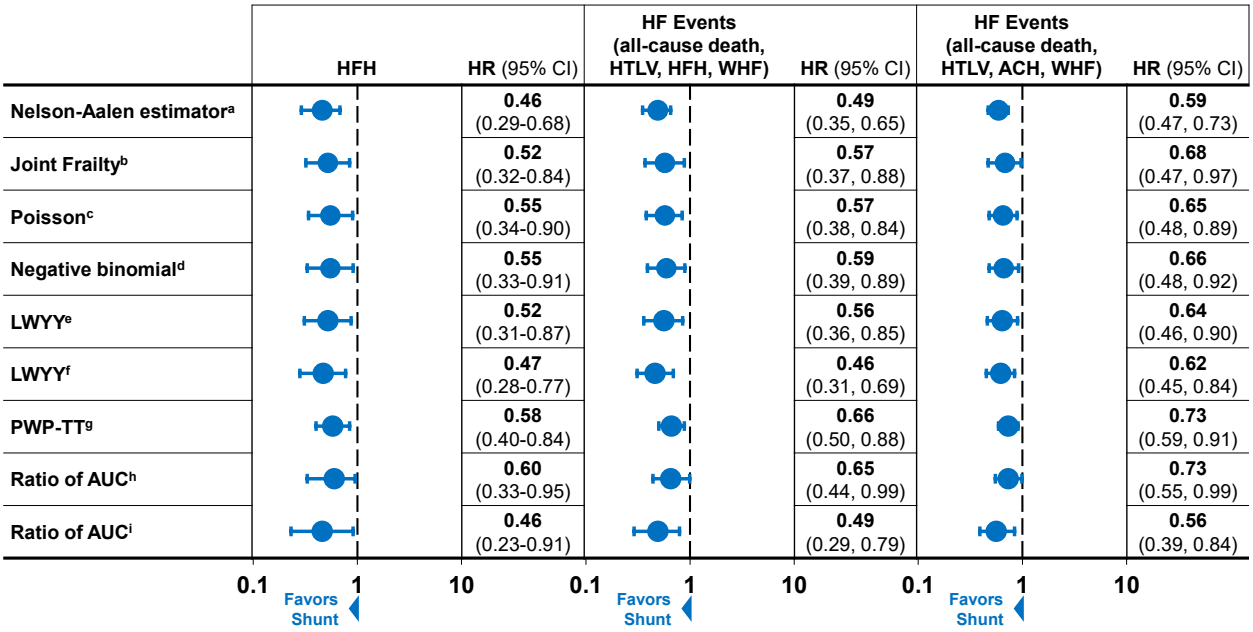
Figure 18: Nelson-Aalen Cumulative Hazard Rate Ratios (HRR) and Interaction Testing at 24 Months for LVEF ≤ 40% and > 40% Strata for All Event Categories, Single and Composites

		Hazard Rate (95% CI)		Hazard Ratio (95% CI)	Nominal Interaction P-value
		HFrEF	HRpEF		
Single Event Types	All-Cause Death	0.48 (0.20, 1.06)	3.38 (1.48, 12.7)		0.005
	Heart Transplant/LVAD (HT/LV)	0.15 (0.00, 0.98)	–		-
	Hospitalization for HF (HFH)	0.46 (0.29, 0.68)	1.96 (1.37, 2.95)		<0.001
	Hospitalization not for HF (NHFH)	0.76 (0.54, 1.07)	1.62 (1.27, 2.09)		<0.001
	All-Cause Hospitalization (ACH)	0.61 (0.47, 0.79)	1.72 (1.40, 2.12)		<0.001
	Worsening HF Outpatient (WHF)	0.64 (0.33, 1.17)	1.03 (0.61, 1.72)		0.25
Composite Event Types	Terminal Events (All-cause Death, HT/LV)	0.42 (0.18, 0.84)	3.38 (1.48, 12.5)		0.002
	WHF and HFH	0.51 (0.35, 0.70)	1.55 (1.16, 2.11)		<0.001
	All-cause Death, HT/LV, HFH	0.45 (0.31, 0.63)	2.14 (1.54, 3.12)		<0.001
	All-cause Death, HT/LV, ACH	0.58 (0.45, 0.74)	1.78 (1.47, 2.19)		<0.001
	HF Events (All-cause Death, HT/LV, HFH, WHF)	0.49 (0.35, 0.65)	1.69 (1.29, 2.27)		<0.001
	All Events (All-cause Death, HT/LV, ACH, WHF)	0.59 (0.47, 0.73)	1.65 (1.38, 1.99)		<0.001

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.

As a sensitivity analysis, **Figure 19** shows that in the HFrEF stratum Shunt treatment benefit was observed across multiple recurrent event models (see **Appendix 10.7** for additional details) and was seen consistently for individual and composite outcome categories that included large reductions in HFH, Terminal Events, HF Events and All Events (e.g., 54%, 58%, 51%, and 41% reductions, respectively, by the Nelson-Aalen estimator). The NNTs to prevent one event at 24 months were small: 4.3 (95%CI: 2.2, 18.6) per Terminal Event, 1.6 (95%CI: 1.6, 3.5) for HFH, 1.0 (95%CI: 0.7, 1.8) per HF Event and 0.8 (95%CI: 0.6, 1.4) for All Events. Over the 24-month period of follow-up, HF Event-free time increased by an average of 6.4 (95%CI: 0.5, 12.4; nominal *P*=0.034) months and All Event-free time by 8.2 (95%CI: 0.4, 16.0; nominal *P*=0.041) months. Compared with traditional time-to-first event analysis, recurrent event models more fully captured the clinical benefit, revealing a greater magnitude of treatment effect across the full spectrum of disease burden. Moreover, a major strength of this analysis rests in the use of and consistency between multiple recurrent event models, each incorporating different assumptions regarding the timing, dependency, and distribution of repeated events.

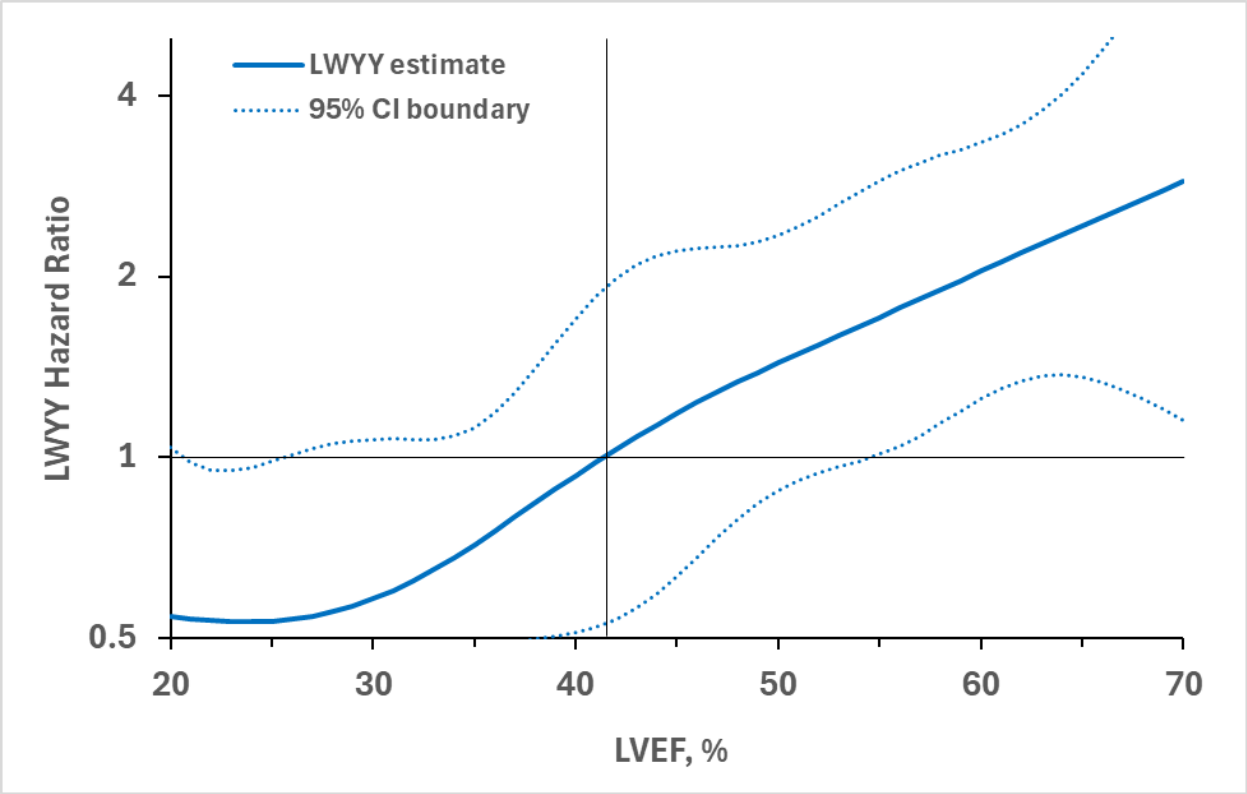
Figure 19: Recurrent Event Outcomes by 24 Months in the Reduced LVEF ≤ 40% (HFrEF) Stratum



Data are presented as HR, RR, or HRR (95%CI). Abbreviations: ACH=all-cause hospitalization; AUC=area under the curve; HF=heart failure; HFH=heart failure hospitalization; HR=hazard ratio; HRR=hazard rate ratio; HFrEF=heart failure with reduced ejection fraction; HTLV=heart transplantation or left ventricular assist device; LVEF=left ventricular ejection fraction; LWYY=Lin-Wei-Yang-Ying model; PWP-TT=Prentice-Williams-Peterson total time model; RR=rate ratio; WHF=worsening HF treated with intravenous therapy as an outpatient.
[a]Nelson-Aalen ratio of cumulative hazard comparison of point estimate at 24 months by z-test. [b]Joint Frailty with all-cause death and HTLV as competing events. [c]Poisson regression adjusted for over dispersion and zero inflation. [d]Negative Binomial adjusted for over dispersion and zero inflation. [e]LWYY model also known as Andersen-Gill model with robust standard error. [f]LWYY model stratified by time before/after 6 months. [g]PWP-TT model allows hazards of later events to be different from earlier events. [h]Area under the curve (AUC) ratio, based on Ghosh-Lin mean cumulative count curves. [i]AUC ratio with start time set to 6 months after randomization (landmark).
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.

Lastly, to evaluate if there is a continuous relationship between treatment effect and baseline LVEF, an LWYY recurrent event model regression using a restricted cubic spline fit was performed for HF Events (**Figure 20**). These data suggest that the lower the LVEF, the better the effect of Shunt treatment. A precise LVEF value where benefit changes to harm should not be inferred from these data due to the wide confidence intervals.

Figure 20: LWYY Model of All HF Event Due to the Wide Confidence Intervals, Using Continuous LVEF



7.5 Post Hoc Sensitivity Analysis Models Supporting the LVEF Cutoff Value of ≤ 40% for HFrEF

Echocardiographic LVEF measurements in a clinical setting may be less reproducible than the measurements in a trial setting where core laboratory quantification was used for LVEF stratified randomization. Multiple event rate analyses examined the effects of including patients with LVEF up to 45% to understand the optimal labeling for the upper cutoff value of LVEF for patients with HFrEF.

Table 30, **Table 31**, and **Table 32** explore consistency of HFrEF treatment effect in HFpEF patients with moderate reductions in LVEF from > 40% up to 45%. Although these patients had lower event rates, the relative benefit of interatrial shunting remained consistent with that seen in the prespecified HFrEF stratum.

Figure 21 further illustrates the robustness of the treatment effect across varying definitions of HFrEF based on LVEF upper boundary thresholds. As the upper boundary for LVEF progressively increased from 40% to 45%, both Nelson-Aalen HRR and LWYY model HR for HF Events remained stable and 95% upper confidence boundaries were consistently below 1.0, indicating that there was not a reversal in Shunt effectiveness in the patients with reduced LVEF ranging up to 45%.

Importantly, these analyses are presented to support the proposed labeling LVEF cutoff of ≤ 40%, not an increase in that cutoff to 45%, in demonstrating that there is a margin of safety through an LVEF of approximately 45%.

Table 30: Events and Rate Ratios for LVEF Ranging from > 40% to 43%

LVEF Range > 40% to 43%	Patients N	Events N (%/yr)	Rate Ratio (95% CI)
HFH			
Shunt	17	2 (7.5)	0.15 (0.02, 0.62)
Control	15	11 (48.9)	
HF Events			
Shunt	17	8 (30.1)	0.34 (0.14, 0.76)
Control	15	20 (88.7)	
All Events			
Shunt	17	27 (101.5)	0.64 (0.38, 1.05)
Control	15	36 (159.7)	

HF=heart failure; HFH=heart failure hospitalization; LVEF=left ventricular ejection fraction.
HF Events is the composite [all-cause death, heart transplantation or left ventricular assist device implantation (HTLV), HFH, and worsening HF treated as an outpatient (WHF)]; All Events is the composite [death, HTLV, all-cause hospitalization and WHF].
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 31: Events and Rate Ratios for LVEF Ranging from > 40% to 44%

LVEF Range > 40% to 44%	Patients N	Events N (%/yr)	Rate Ratio (95% CI)
HFH			
Shunt	20	5 (16.4)	0.40 (0.12, 1.12)
Control	18	11 (41.4)	
HF Events			
Shunt	20	12 (39.3)	0.52 (0.25, 1.06)
Control	18	20 (75.2)	
All Events			
Shunt	20	35 (114.6)	0.80 (0.50, 1.27)
Control	18	38 (143.0)	

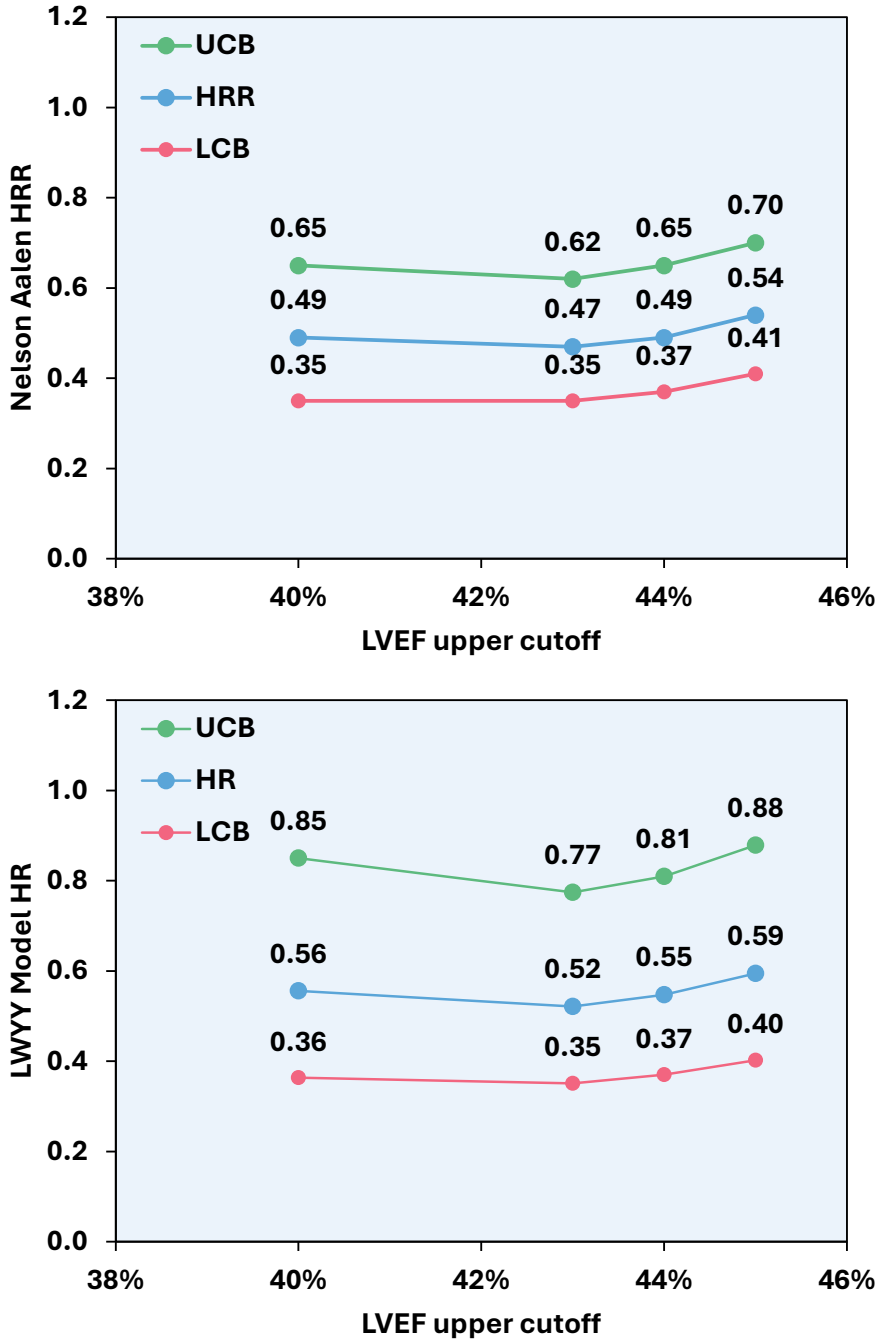
HF=heart failure; HFH=heart failure hospitalization; LVEF=left ventricular ejection fraction.
HF Events is the composite [all-cause death, heart transplantation or left ventricular assist device implantation (HTLV), HFH, and worsening HF treated as an outpatient (WHF)]; All Events is the composite [death, HTLV, all-cause hospitalization and WHF].
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 32: Events and Rate Ratios for LVEF Ranging from > 40% to 45%

LVEF Range > 40% to 45%	Patients N	Events N (%/yr)	Rate Ratio (95% CI)
HFH			
Shunt	23	7 (19.6)	0.54 (0.20, 1.34)
Control	23	13 (36.3)	
HF Events			
Shunt	23	19 (53.2)	0.83 (0.44, 1.53)
Control	23	23 (64.3)	
All Events			
Shunt	23	49 (137.1)	1.02 (0.69, 1.53)
Control	23	48 (134.1)	

HF=heart failure; HFH=heart failure hospitalization; LVEF=left ventricular ejection fraction.
HF Events is the composite [all-cause death, heart transplantation or left ventricular assist device implantation (HTLV), HFH, and worsening HF treated as an outpatient (WHF)]; All Events is the composite [death, HTLV, all-cause hospitalization and WHF].
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.

Figure 21: Nelson-Aalen (top) and LWYY Model (bottom) analyses of Serial Increments of HFrEF LVEF Upper Cutoff Value for HF Events

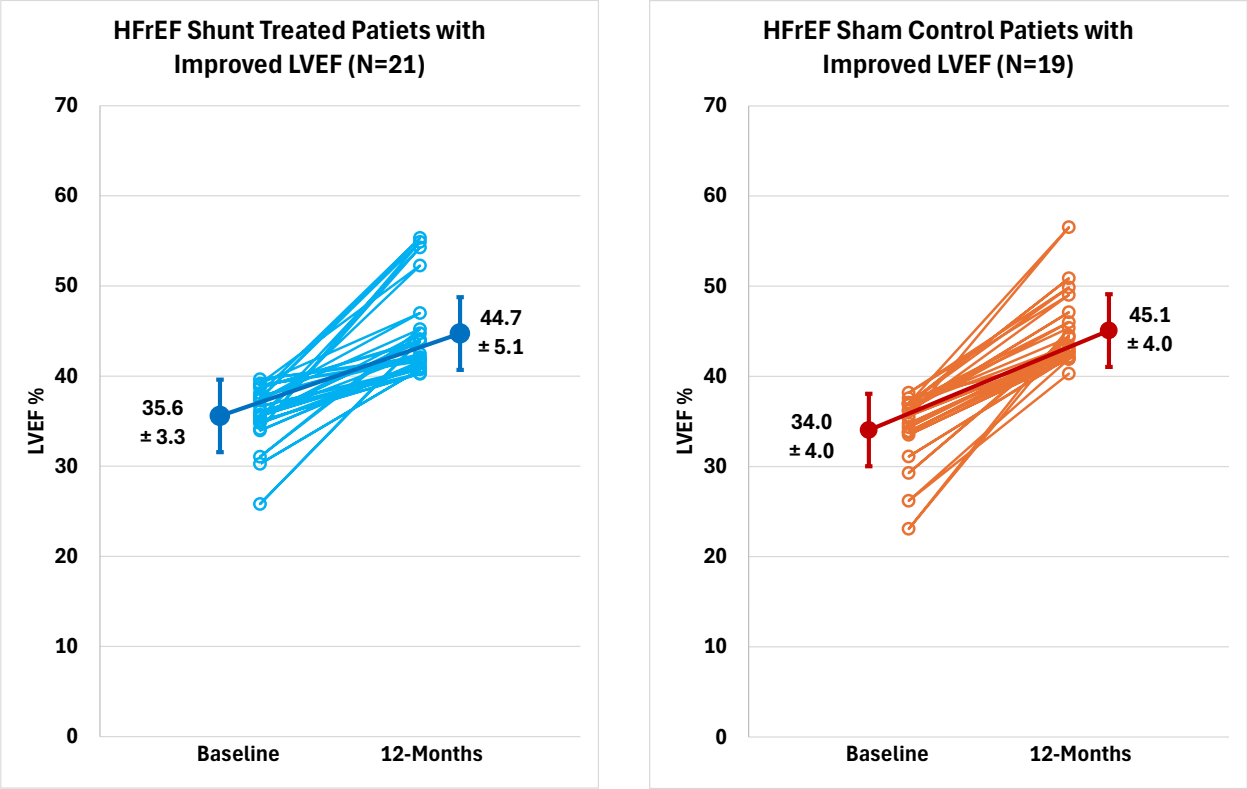


HF Events include all-cause death, heart transplantation or left ventricular assist device implantation, all heart failure hospitalizations and worsening heart failure treated with intravenous therapy as an outpatient. Abbreviations: HRR=hazard rate ratio; HF=heart failure; HR=hazard ratio; LCB=lower 95% confidence boundary; LWYY= Lin Wey Yang Ying model; UCB=upper 95% confidence boundary.
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.

Secondly, there is potential for LVEF measurements to change over time either spontaneously or in response to therapeutic interventions in patients whose baseline LVEF is ≤ 40%. Improvement in LVEF is known as HF with improved ejection fraction (HFimpEF) and is defined here as prior LVEF ≤ 40% with a follow-up LVEF > 40%. Additional analyses were conducted to determine whether HFimpEF patients were at increased risk of harm from Shunt treatment because they reached an ejection fraction that overlaps with the range of HFpEF.

There were similar numbers of HFrEF stratum Shunt and Control patients with improved LVEF at 12 months (**Figure 22**).

Figure 22: HFrEF Patients with Improved LVEF at 12 Months



HFrEF Control patients (left panel) and Shunt patients (right panel) meeting the definition of heart failure with improved LVEF – HfimpEF.

Table 33 shows HF Event rates and Nelson-Aalen HRR at the time of primary analysis between patients with HFimpEF, HFrEF patients without improved LVEF, and with the HFpEF stratum. Patients with HFimpEF had lower HF Event rates than patients with persistent HFrEF. The HF Event rate in HFimpEF was 0.51 at 24 months in Shunt-treated vs 0.79 in Controls, whereas the Shunt and Controls rates in the persistent HFrEF stratum were 1.04 and 2.30, respectively. In addition to lower HF Event rates, Shunt-treated HFimpEF patients maintained a benefit compared with Controls with HRR=0.64, but the 95% CI was wide due to small sample size. These outcomes in HFimpEF patients are distinctly different from outcomes seen in HFpEF patients that show worsening outcomes with Shunt treatment. These findings suggest that HFrEF patients with improved LVEF do not behave like de novo HFpEF patients and continue to benefit from the Shunt.

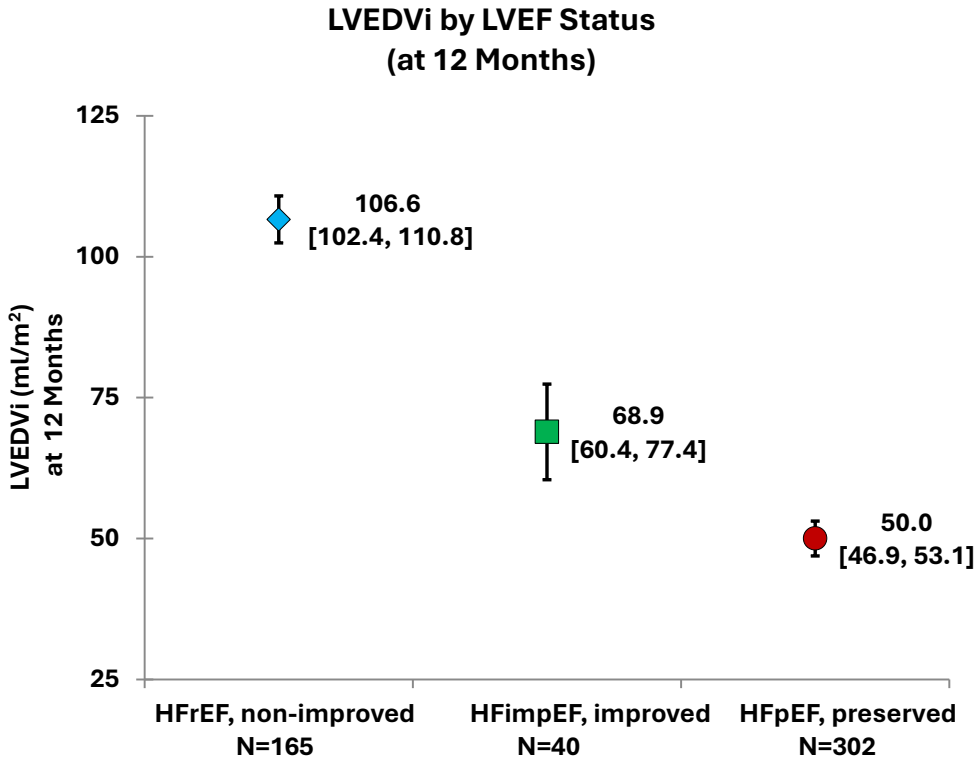
Table 33: Outcomes Patients with or without Improved LVEF

HF Events death, HTLV, HFH, WHF	Shunt Hazard rate	Control Hazard Rate	Hazard Rate Ratio (95% CI)
HFimpEF improved	0.51 N=20	0.79 N=19	0.64 (0.17, 2.16)
HFrEF non-improved	1.04 N=81	2.30 N=86	0.45 (0.26, 0.77)
HFpEF	1.17 N=149	0.69 N=153	1.69 (1.14, 2.52)

Hazard rates and rate ratios by Nelson-Aalen Estimator.
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.

Figure 23 shows echocardiographic LVEDVi at 12 months in patients with HFimpEF and compared with HFrEF patients that did not improve LVEF and HFpEF stratum patients. HFimpEF patients had LVEDVi that was intermediate between the groups, with the LV remaining moderately dilated compared with HFpEF. This suggests that marked reverse remodeling in HFrEF does not “create” HFpEF physiology or subject these patients to harm.

Figure 23: Left Ventricular End-Diastolic Volume Index (LVEDVi) Between-Group Differences



Data are ANOVA LS means [95% CI]
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.

In summary, these findings validate the 40% LVEF threshold for clinical use, providing a buffer zone of where patients near the lower LVEF boundary of the HFpEF stratum, did not suffer untoward Shunt-induced events and thus mitigate potential inappropriate treatment due to real-world echocardiographic LVEF measurement variability (Oh et al., 2012; Wood et al., 2014). Moreover, HFimpEF patients appear to benefit from Shunt treatment with no signal for harm. That HFimpEF patients maintained benefit is keeping with literature that HFimpEF patients continue to behave clinically like HFrEF and respond to HFrEF treatment and maintain responsiveness to disease-modifying therapies. Consistently, contemporary guideline statements characterize HFimpEF as a high-risk phenotype that warrants continued medical therapy despite improved LVEF (Heidenreich et al., 2022).

7.6 Quantifying Type-I Error for the Primary Effectiveness Endpoint

To address potential inflation of Type-I error (false positive rate) arising from a hierarchical, data-driven analysis strategy, a non-parametric permutation testing framework was implemented. Permutation testing is based on approximating all random rearrangements (permutations) of the observed data, providing a better estimate of the actual Type-I error compared to relying on theoretical distributions.

Prespecified permutation testing is an accepted statistical methodology for estimating and controlling Type-I error (Food and Drug Administration (FDA), October 2022). Permutation testing is the established method for quantifying Type-I error in the setting of complex decision trees, and it avoids specific parametric forms. Even when conducted post hoc, permutation testing remains highly informative, and the permutation test merely characterizes the Type-I error properties of that path.

In implementation, all patient data are fixed (e.g., outcomes, baseline characteristics, LVEF strata), but the treatment labels were randomly reassigned (100,000 times for the Primary Effectiveness Endpoint). For each of these permutations, the exact analysis plan is rerun—including the interaction test and whether to proceed with analysis of the full population or subgroups (in this case the two LVEF strata). This process mimics what might happen in a trial if there were truly no treatment effect, allowing quantification of how often a result as extreme as the one observed would arise by chance (Type-I error) under a given decision framework. By analyzing this empirically generated distribution, adjusted estimates of the Type-I error that reflect the structure and decisions of the analysis plan are obtained. This helps assess spurious claims of significance and supports inference even in the presence of interaction-driven analyses or exploratory subgroups.

For the Primary Effectiveness Endpoint, to estimate the Type-I error, the full 3-level decision tree was executed, including (1) the interaction test, and subsequent endpoint testing either in the ITT cohort (2) or by stratum (3), depending on the permuted interaction result. For each iteration, the test statistics and *P*-values corresponding to the pathway selected by the permutation were recorded. The empirical distribution of these permuted test statistics under the null hypothesis was then used to calculate the Type-I error in the current study.

Statistical analyses were verified by independent double coding using SAS 9.4 or R V4.3.2 (or later) software packages. All *P*-values are reported as 2-sided tests unless otherwise specified. When win ratio results are reported, results are calculated using the phase-weighted methods defined in the SAP.

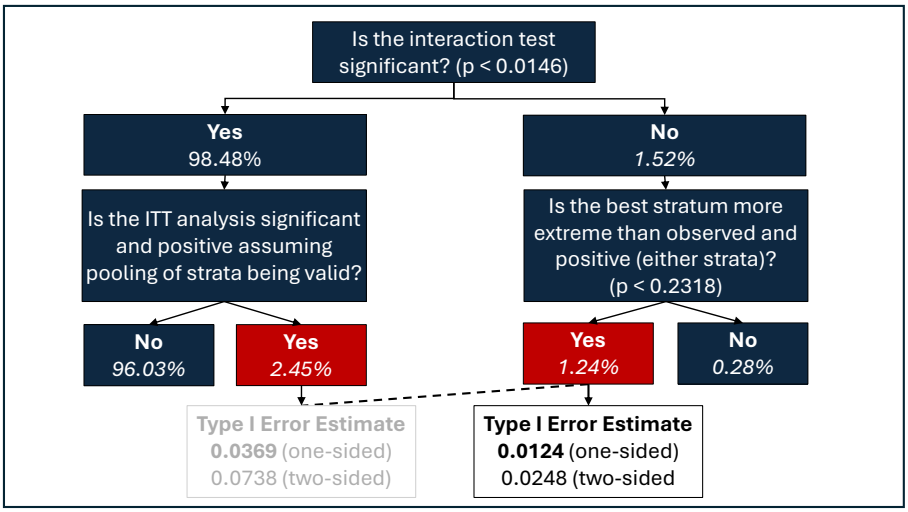
Figure 24 shows the decision tree for the prespecified Primary Effectiveness Endpoint with 2 branches that can lead to declaring significance. The prespecified interaction testing of the LVEF strata yielded opposite treatment effects in HFrEF and HFpEF patients with an interaction *P*=0.0146. The right-hand branch applies when there is significant interaction, and the best stratum is chosen. In this case, the permutation has

to outperform the study results to obtain a “false” positive that is more compelling than the observed study results. Only 1.24% of permutation results were more favorable than those observed (one-sided) when not considering the ITT population as a whole; a two-sided permutation test yielded nominal *P*=0.0248. The left-hand branch shows the possibility of falsely declaring significance for the overall ITT population (pooled HFrEF and HFpEF strata) test, which has a probability of 2.45%. The Type-I error for the entire decision tree is calculated by summing these 2 probabilities and is equal to 3.69%, one-sided, with two-sided Type 1 error of nominal *P*=0.0738.

Figure 24: Primary Effectiveness Endpoint Decision Tree Assessment of Inflation of Type-I Error by Permutation Tests (100,000 Permutations)

Opportunities for success resulting in inflation of type 1 error:
1. HFrEF or HFpEF
2. ITT (pooled)

“Yes” indicates a false positive, or a Type-I Error under the Null



8 POST-MARKETING PLAN

8.1 Post-Approval Study Plan

The post-approval study plan will collect additional data on the Ventura Shunt System and includes the following component studies:

- **Continued follow-up of RELIEVE-HF patients as specified in the RELIEVE-HF protocol.** All patients who received an implant (Roll-in patients, patients randomized to Shunt Treatment, and Control patients who have crossed over and received a Shunt), regardless of LVEF, will be evaluated in-clinic at Years 3, 4, and 5 (±60 days) post-implantation. Assessment of Adverse Events that occurred during the one year since the last contact will be collected, among other assessments as specified in the protocol.
- **A prospective, multicenter, single-arm, post-approval study in the indicated HFrEF population.** Goals of this study include comparison of clinical outcomes and safety assessments to prespecified performance goals and a focus on the enrollment and evaluation of outcomes in women and underrepresented minority populations.
    - Primary Safety Endpoint: The percentage of patients experiencing procedure- and device-related MACNE during the first 30 days after enrollment (Shunt implantation). MACNE is defined as all-cause death, stroke, systemic embolism, need for open cardiac surgery or major endovascular surgical repair.
    - Primary Effectiveness Endpoint: The composite endpoint of all-cause death and worsening heart failure events – cardiac transplantation or LVAD implantation, recurrent HFH (including ER HF Visits with duration ≥ 6 hours), and recurrent worsening HF Events treated as an outpatient (including ER HF visits < 6 hours).
    - Primary analysis will occur when the last patient enrolled has been followed for 12 months or the median duration of follow-up is at least 19 months (whichever comes later) to match follow-up duration in the RELIEVE-HF randomized HFrEF population.
- **An interatrial shunt registry**. V-Wave is collaborating with the Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) TVT Registry™ to develop a data collection document to monitor patient safety and real-world outcomes related to interatrial shunt devices. Registry measures will include:
    - Patient demographics, clinician, and facility characteristics
    - History/risk factors, cardiac status, and detailed health status
    - Indications for the procedure

- Pre, intra, and post-procedure data and adverse event rates
- Outcomes at 30 days and one year

8.2 Safeguards to Ensure Proper Patient Selection

To ensure proper use of the Shunt in a commercial clinical setting, V-Wave proposes the following labeling and other safeguards to operationalize safe and reliable patient selection to prevent use of the Shunt in HFpEF patients.

- Label restriction to HFrEF (≤ 40%) with HFpEF (> 40%) listed as contraindicated.
- Extensive training of Sponsor and site personnel.
- Heart Team oversight: HF specialist + implanter to adjudicate phenotype and imaging.
- Clear Instructions for Use contraindications on LVEF cutoff thresholds.
- Controlled commercial roll-out.
- Post-approval surveillance: all US cases enrolled in ACC NCDR registry or a structured Post-Approval Study for ongoing safety monitoring. Registry data by LVEF will be reported to FDA.

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10 APPENDICES

10.1 Patient Letter

BOOST
Better Outcomes
Optimal Scientific Therapies

July 7, 2025

VIA ELECTRONIC SUBMISSION

Angela Krueger
Deputy Director for Regulatory Policy
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration

RE: Letter on Behalf of Heart Failure Patients (b)(4)
(b)(4)

Ms. Krueger:

I submit this letter in support of V-Wave's application for premarket approval of the Ventura Shunt (b)(4). As a heart failure patient and founder of Better Outcomes Optimal Scientific Therapies (BOOST), a patient-driven nonprofit advocacy organization dedicated to improving outcomes for heart failure patients, I have a vested interest in innovative therapies that may offer relief from the frequent hospitalizations, high mortality, and debilitating symptoms associated with the condition.

BOOST, through partnership with stakeholders across the continuum of healthcare, keeps heart failure patients front and center in advocating for innovative technologies and therapies to address this highly burdensome disease. Chronic heart failure affects approximately 6.7 million patients in the United States, a population that grows significantly every year.

Heart failure patients with reduced ejection fraction (HFrEF) represent a subset of the chronic heart failure population who are particularly affected by the disease. HFrEF patients have a poor prognosis. More than 75% of patients who currently suffer from HFrEF are likely to die within five years. Most of these patients will also experience morbid events despite receiving guideline-directed medical therapy (GDMT). HFrEF patients do not have a suitable alternative treatment option to reduce morbidity and mortality when GDMT has been exhausted. While patients like me are hopeful that GDMT will help reduce our symptoms, we also advocate for innovative new treatments that may lead to more durable outcomes and more years to spend with family and friends.

The Ventura Shunt has the potential to address this unmet clinical need. V-Wave's RELIEVE-HF trial showed that the Ventura Shunt and its implantation procedure are safe, with no procedure- or device-related incidents of major adverse cardiovascular or neurological events observed after 30 days in the 369 patients implanted with the device. The trial also showed that the Ventura Shunt was effective in HFrEF patients, reducing heart failure-related events by 51% compared to patients in the control group.

While we acknowledge that uncertainty remains, we strongly believe that there is sufficient evidence to support approval of the Ventura Shunt, particularly given its status as a breakthrough device. Congress established the Breakthrough Device Designation Program to allow for additional uncertainty in the benefit-risk determination and to help innovative new

technologies reach patients who are out of options and face a high likelihood of serious morbidity or mortality.

HFrEF patients agree that the FDA should offer some flexibility for innovative technologies, like the Ventura Shunt, when there's uncertainty in the benefit-risk assessment—especially when data indicate their safety and effectiveness. Patients are willing to accept more uncertainty with a treatment that addresses a critical need for severe diseases like heart failure and want the option to choose potential benefits from innovative therapies such as the Ventura Shunt. We ask the FDA to let HFrEF patients make this decision.

Finally, V-Wave's proposed controlled commercial market rollout provides additional guardrails that benefit patients by allowing for the careful selection of qualified sites. The "V-Wave Heart Team" patient selection approach offers balanced group expertise, which is patient-preferred over a single referrer. Protocolized physician training during the controlled rollout will ensure all patients receive skilled care, and the 5-year patient follow-up will provide information on any adverse events and a robust set of data for analysis.

At BOOST, we believe that patient-centered innovation is essential to improving care. ***FDA's approval of the Ventura Shunt would mark a significant advancement in the treatment of heart failure by giving patients and providers a much-needed tool to reduce morbidity and mortality associated with this deadly disease***. We appreciate the FDA's ongoing engagement with V-Wave to bring the Ventura Shunt to HFrEF patients, many of whom could live longer due to the Ventura Shunt, rather than facing the overwhelming odds of mortality within the next five years.

Thank you for your consideration of BOOST's support of the Ventura Shunt. Please do not hesitate to contact me at (b)(6) if you have any questions.

Sincerely,

Rhonda E. Monroe, MBA
HFrEF Patient and Patient Advocate
Founder, Better Outcomes Optimal Scientific Therapies (BOOST)

Co-Chair CardioVascular Clinical Trialists (CVCT) Patient Advisory Board

10.2 Implications of Breakthrough Therapy Designation

Under Section 515 of the Food and Drug Cosmetic Act, FDA is required to determine whether a premarket approval application (PMA) for a Class III medical device provides a "reasonable assurance of safety and effectiveness" of the device under the conditions of use prescribed, recommended, or suggested in the proposed labeling[2] by considering, among other things, the "probable benefit to health from the use of the device weighed against any probable injury or illness from such use."[3]

Separate from the statutory and regulatory standards for PMA approval, the Breakthrough Devices Program was established by Congress "to apply efficient and flexible approaches to expedite the development of, and prioritize the Food and Drug Administration's review of, devices that represent breakthrough technologies."[4] The program is designed to "help patients have more timely access to…medical devices [designated as breakthrough devices] by expediting their development, assessment, and review, while preserving the statutory standards for premarket approval…consistent with the Agency's mission to protect and promote public health."[5] "The Breakthrough Devices Program is a voluntary program for certain medical devices…that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions."[6] V-Wave's Shunt received Breakthrough Device Designation on August 5, 2019.

Breakthrough Devices subject to a PMA must still meet the statutory standard of reasonable assurance of safety and effectiveness at the time of approval.[7] However, for FDA's PMA benefit-risk determination for a Breakthrough Device, FDA may accept a greater extent of uncertainty of the benefit-risk profile to support the PMA, 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 (e.g., a device that treats a life-threatening disease when no alternative treatments are available) and with adequate post-market controls. Generally, weighing the benefits against the risks for Breakthrough Devices with acceptance for a greater extent of uncertainty adds another dimension to the benefit-risk calculus. Specifically, FDA's benefit-risk determination includes weighing 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.

Generally, FDA is legally obligated to consider, irrespective of whether the subject device is designated as a Breakthrough Device, "whether the extent of data that

[2] *See* 21 U.S.C. §§ 360e(d)(1), 360e(d)(2)
[3] 21 C.F.R. § 860.7(b)(3)
[4] 21 U.S.C. § 360e-3(a).
[5] Guidance for Industry and Food and Drug Administration Staff: Breakthrough Devices Program (September 15, 2023). https://www.fda.gov/media/162413/download, at 5("Breakthrough Guidance").
[6] Breakthrough Guidance, at 1; *see also* 21 U.S.C. § 360e-3(b)(1).
[7] Breakthrough Guidance, at 7.

otherwise would be required for approval … with respect to effectiveness can be reduced through reliance on postmarket controls."[8]

Given that the Shunt has been awarded Breakthrough Device Designation, FDA may accept "greater extent of uncertainty" in the PMA product benefit-risk analysis and must also consider whether data that would otherwise be required to support effectiveness can be reduced through reliance on postmarket controls. The RELIEVE-HF clinical data presented are reliable and sufficient to establish a reasonable assurance of safety and effectiveness of the Shunt, particularly in light of the flexibility and efficiency FDA is encouraged by law to apply for Breakthrough Devices, and given the requirement by law that FDA consider whether additional effectiveness data can be obtained on a postmarket basis, therefore reducing the requirement for such additional data on a premarket basis to support approval.

10.3 Roll-in Shunt Cohort Safety and Patency Summary

The primary results of the (RELIEVE-HF) Roll-in (open-label) cohort and a second manuscript describing the in-vivo fluid dynamic properties of the Shunt from this cohort have been published (Pfeiffer et al., 2024; Rodés-Cabau et al., 2024).

Safety, procedure performance, and serial TEE outcomes were assessed during the 12 months after Ventura Shunt implantation in the RELIEVE-HF open-label roll-in cohort.

Eligibility required symptomatic HF despite optimal GDMT with ≥ 1 HF hospitalization (HFH) in the prior year or elevated natriuretic peptides. The safety endpoint was device or procedure-related MACNE at 30 days, compared to a prespecified performance goal. TEE was performed at Shunt implant and at 6- and 12-month follow-up. Shunt effective diameter (D_{eff}) was derived from the vena contracta, and flow was determined by the continuity equation (**Figure 25**).

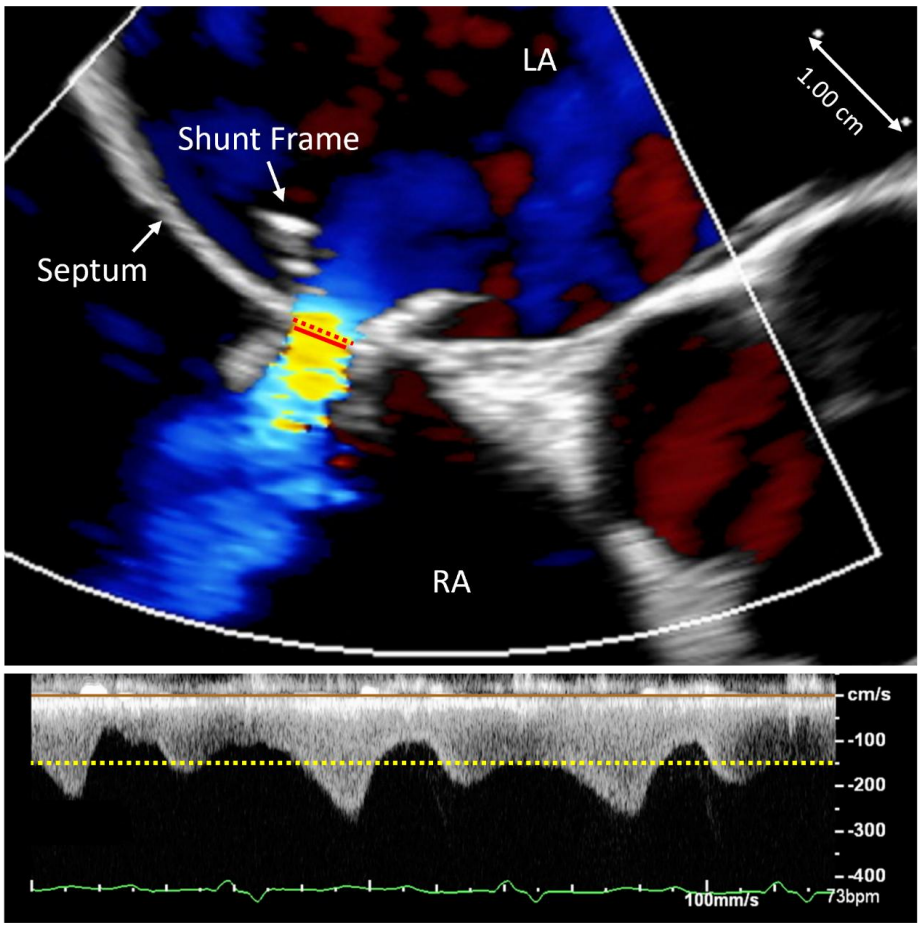
Ninety-seven patients were enrolled and implanted at 64 sites. Average age was 70±11 years, 97% were NYHA Class III, and half had LVEF ≤ 40% (**Table 34**). Shunt implantation was successful in 96/97 (99%) patients. One patient had a non-hemodynamically significant pericardial effusion after transseptal puncture and Shunt implantation was not attempted. The patient was successfully implanted at a later date. The safety endpoint, device or procedure-related MACNE at 12 months was achieved (event rate 0%, $P < 0.001$ – see **Table 35**). KCCQ-OSS was improved by 12–16 points at all follow-up timepoints (all $P < 0.004$), with similar outcomes in patients with reduced and preserved LVEF. Patency was confirmed in all instances, except for one stenotic Shunt at 6 months (**Table 36** and **Figure 26**). D_{eff} remained unchanged from baseline at 12 months (0.47±0.01 cm, nominal P=0.376), as did the trans-Shunt mean pressure gradient (5.1±3.9 mmHg, nominal P=0.316) and flow (1137±463 ml/min, nominal P=0.384). TEE measured flow versus pressure closely correlated ($R^2 \geq 0.98$) with a fluid

[8] 21 U.S.C. § 360c(a)(3)(C).

dynamics model. At 12 months, the pulmonary/systemic flow Qp/Qs ratio was 1.22±0.12.

In conclusion, in the 97-patient open-label Roll-in arm of RELIEVE-HF, interatrial shunting with the Ventura device was placed successfully in all patients and was safe. TEE findings showed that when implanted in patients with advanced HF, this small interatrial Shunt demonstrated predictable and durable patency and performance.

Figure 25: Transesophageal Echocardiographic (TEE) Images of a Widely Patent Shunt



D_{VC}	D_{frame}	D_{eff}	$\Delta\bar{P}$	Q
0.46 cm	0.51 cm	0.47 cm	9.0 mmHg	1586 ml/min
Nominal Lumen (12 months)				

Images from 12-month follow-up in a 67-year-old male with non-ischemic cardiomyopathy. Top: Color Doppler short axis view showing shunt frame and locations of the vena contracta and frame neck diameter measurements. Mid: Continuous wave Doppler through the shunt with dotted line indicating mean velocity. Bottom: Measured fluid dynamics values. D_{vc}=diameter vena contracta; D_{frame}=measured diameter of the frame neck; D_{eff}=effective diameter; $\Delta\bar{P}$=mean interatrial pressure gradient; Q=trans-shunt flow; RA=right atrium; LA=left atrium.

Table 34: Baseline Patient Characteristics of Roll-in Patients

Characteristic	HFrEF (LVEF < 40%)	HFpEF (LVEF ≥ 40%)	Nominal *P*-value
Number of patients	49	48	
Age, years	68.9±11.0	70.4±11.1	0.5065
Female	4 (8.2%)	24 (50.0%)	< 0.0001
BMI, kg/m^2	31.1±5.8	32.0±5.5	0.4138
Duration of HF, years	6.6±5.8	4.3±3.7	0.0048
HFH/patient in prior 12 months	0.96±1.10	1.13±1.35	0.9755
≥ 1 HFH in prior 12 months	28 (57.1%)	28 (58.3%)	1.00
Comorbidities			
Atrial fibrillation	20 (40.8%)	30 (62.5%)	0.0287
Permanent or persistent	11 (22.4%)	15 (31.3%)	0.2702
CKD ≥ stage 3a	37 (81.6%)	38 (79.2%)	0.6387
COPD	14 (28.6%)	12 (25.0%)	0.6561
Diabetes	25 (51.0%)	28 (58.3%)	0.4263
Hypertension	40 (81.6%)	43 (89.6%)	0.2672
Hyperlipidemia	36 (75.0%)	38 (79.2%)	0.4874
Ischemic etiology	32 (65.3%)	22 (44.9%)	0.0460
Prior MI	34 (69.4%)	20 (42.6%)	0.0050
Stroke	9 (18.4%)	8 (16.7%)	1.00
Therapies			
ICD	20 (40.8%)	3 (6.3%)	< 0.0001
CRT	21 (42.9%)	3 (6.3%)	< 0.0001
Pacemaker	1 (2.0%)	9 (18.8%)	0.0041
RAS (ACE, ARB, or ARNI)	45 (91.8%)	29 (60.4%)	0.0002
ARNI	29 (59.2%)	6 (12.5%)	< 0.0001
Beta Blocker	47 (95.9%)	35 (72.9%)	0.0010
MRA	35 (71.4%)	23 (47.9%)	0.0152
SGLT2i	11 (22%)	4 (8%)	0.0562
Loop diuretic	46 (93.9%)	46 (95.8%)	1.00
Loop and Thiazide Diuretic	8 (16.3%)	11 (22.9%)	0.3311
Anticoagulants	17 (34.7%)	17 (35.4%)	1.00
Antiplatelets	18 (36.7%)	15 (31.2%)	0.531
Anti-coagulant/platelet combination	9 (18.4%)	11 (22.9%)	0.474
Lab			
Hgb, gm/dl	13.6±2.0	12.3±1.7	0.0006
Creatinine, mg/dl	1.63±0.44	1.48±0.49	0.0999
eGFR, ml/min/1.73m^2	42.1 [32.9–55.1]	41.7 [35.7–56.5]	0.9742
Echo			

Characteristic	HFrEF (LVEF < 40%)	HFpEF (LVEF ≥ 40%)	Nominal *P*-value
LVEF, %	28.2±6.7	57.1±7.5	< 0.0001
RVFAC, %	35.0±6.6	37.6±5.4	0.0399
TAPSE, mm	15.4±2.8	16.3±2.9	0.0974
Hemodynamics			
HR, bpm	74.2±13.0	70.4±11.6	0.1287
BP systolic, mmHg	113.0±14.8	128.4±15.4	< 0.0001
RAP, mmHg	11.6±4.6	11.0±4.6	0.5258
PAP mean, mmHg	31.6±8.7	29.0±8.1	0.1388
PCWP, mmHg	20.7±7.6	18.4±6.5	0.1126
LA-RA gradient, mmHg	9.1±5.3	7.4±4.8	0.0995
CI, L/min/m^2	2.2±0.7	2.3±0.9	0.3917
PVR, Wood units	2.5±1.2	2.5±1.3	0.9740
Prognosis			
NYHA Class III, %	48 (98.0%)	46 (95.8%)	0.3672
NYHA Class IV, %	1 (2.0%)	2 (4.2%)	0.3672
KCCQ Overall Summary Score	50.9±22.3	40.6±18.7	0.0158
6MWT, m	287±86	245±88	0.0176
NT-proBNP, pg/ml	1730 [1220–3575]	1736 [969–3098]	0.2969
BNP, pg/ml	540 [238–1298]	220 [136–317]	0.0652
MAGGIC 1-yr mortality	25.1%±12.1%	16.8%±8.2%	0.0003
BCN BIO-HF 1-yr mortality	19.7%±15.4%	24.4%±13.7%	0.0248

Data expressed as number (rate per patient in %), mean ± standard deviation, or median [interquartile range].
HFrEF=HF with reduced ejection fraction (EF); HFpEF=HF with preserved EF; LVEF=left ventricular EF; BMI=body mass index; HFH=heart failure hospitalization; CKD=chronic kidney disease; MI=myocardial infarction; COPD=chronic obstructive pulmonary disease; ICD=implantable cardioverter defibrillator; CRT=cardiac resynchronization therapy; RASI=renin-angiotensin system inhibitor; ARNI=angiotensin receptor-neprilysin inhibitor; BB=beta blocker; MRA=mineralocorticoid receptor antagonist; SGLT2i=sodium-glucose cotransporter 2 inhibitors; Hgb=hemoglobin; eGFR=estimated glomerular filtration rate; RVFAC=right ventricular fractional area change; TAPSE=tricuspid annular plane systolic excursion; HF=heart rate; BP=blood pressure; RAP=right atrial pressure; PCWP=pulmonary capillary wedge pressure; LA=left atrium; RA=right atrium; PAP=pulmonary artery pressure; CI=cardiac index; PVR=pulmonary vascular resistance; NYHA=New York Heart Association; KCCQ=Kansas City Cardiomyopathy Questionnaire; 6MWT=6 minute walk test; NT-proBNP=N-terminal pro-brain natriuretic peptide; BNP=brain natriuretic peptide; MAGGIC=The Meta-Analysis Global Group in Chronic HF risk calculator; BCN BIO-HF=Barcelona Bio-HF risk calculator.
Nominal p-values are provided to illustrate the variability of the corresponding summary statistics; they are provided for descriptive purposes and should not be used to draw statistical inference.

Table 35: Procedural, 30-Day and 12-Month Safety Outcomes

Procedural/in-hospital	N=97
Technical Success	96 (98.9%)
Device embolization/dislocation	0 (0%)
Need for a second device	0 (0%)
Procedure duration, min	71 [56–90]
Contrast dose, ml	0 [0–0]
Fluoroscopy time, min	14 [11–20]
Estimated radiation effective dose, mSv	4.9 [2.6–8.2]
Bleeding (BARC) types 3 or 5	0 (0%)
Hospitalization length, days	1 [1–1]
Safety outcomes through 30 days	
MACNE, device or procedure-related (primary safety endpoint)	0 (0%)
Any MACNE	0 (0%)
Bleeding (BARC) types 3 or 5	0 (0%)
Device success	96 (98.9%)
Procedural success	96 (98.9%)
Safety outcomes through 365 days	
MACNE and components, device-related	
MACNE	0 (0%)
Death, all-cause	0 (0%)
Stroke	0 (0%)
Cardiac tamponade	0 (0%)
Device infection	0 (0%)
Reintervention or surgery	0 (0%)
MACNE and components, all-cause	
MACNE	13 (13.4%)
Death, all cause	13 (13.4%)
Cardiac	7 (7.2%)
Non-cardiac	6 (6.2%)
Stroke	0 (0%)
Systemic embolism	0 (0%)
Cardiac tamponade	0 (0%)
Reintervention or surgery	0 (0%)
Non-MACNE serious adverse events	
Cardiovascular hospitalization (non-HF-related)	19 (19.6%)
LVAD or heart transplant	1 (1.0%)
Myocardial infarction types 1 or 2	3 (3.1%)
Atrial fibrillation/flutter, new onset	2 (2.1%)
Atrial fibrillation/flutter, recurrent	5 (5.2)%
Non-cardiovascular hospitalizations	43 (44.3%)
Bleeding (BARC) type 3*	4 (4.1%)

Data expressed as number (rate/patient in %), or median [interquartile range].
*There were 0 BARC type 5 bleeds.
BARC=Bleeding Academic Research Consortium; LVAD=Left ventricular assist device; MACNE=Major adverse cardiovascular and neurological events.

Table 36: Echocardiographic Assessments of Shunt Function

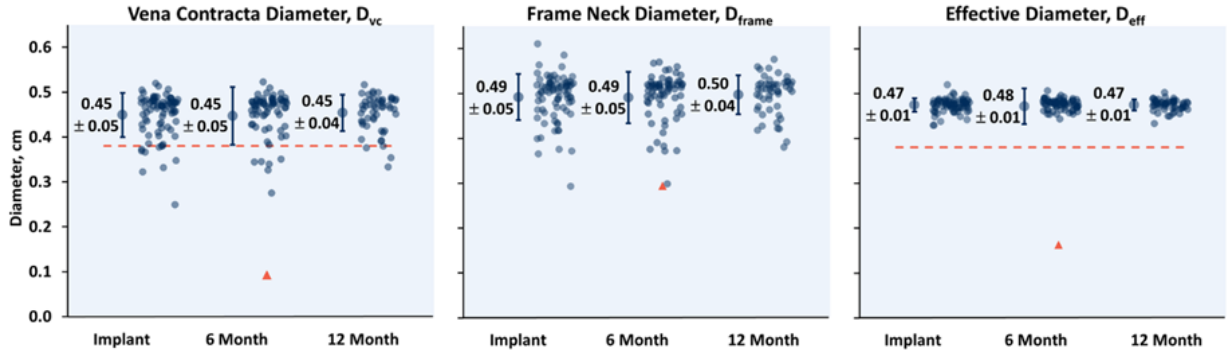
Parameter	Implant	6 Months	12 Months	Nominal *P*-Value
Eligible Patients				
N	97	90	82	
Studies analyzed				
TEE or TTE	97 (100%)	87 (97%)	75 (91%)	
TEE	86 (89%)	69 (77%)	56 (68%)	
Time to TEE, months	0 [0–0]	6.2 [5.7–6.6]	12.3 [11.9–12.9]	
Results				
Shunt patent	97 (100%)	87 (100%)	72 (100%)	1.000
Flow direction				
Left-to-Right	91 (94%)	85 (98%)	68 (94%)	0.895
Right-to-Left	0 (0%)	0 (0%)	0 (0%)	
Bidirectional	6 (6%)	2 (2%)	4 (6%)	
Shunt thrombi	0	0	0[a]	
D_{vc}, mm	4.5 ± 0.5	4.5 ± 0.6	4.5 ± 0.4	0.092
D_{eff}, mm	4.7 ± 0.1	4.7 ± 0.4	4.7 ± 0.1	0.376
C_d	0.87 ± 0.05	0.86 ± 0.10	0.86 ± 0.04	0.363
$\Delta\overline{P}$, 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

Data expressed as N (% eligible patients), median [IQR], or mean ± SD and are inclusive of a single stenotic shunt at 6 months. D_{vc}=*vena contracta* diameter; D_{eff}=effective diameter; C_d=discharge coefficient; $\Delta\overline{P}$ =mean interatrial pressure gradient; Q=flow.

[a]Thrombus seen in left atrial appendage in 1 patient.

Nominal p-values are provided to illustrate the variability of the corresponding summary statistics; they are provided for descriptive purposes and should not be used to draw statistical inference.

Figure 26: In Vivo Shunt Orifice Dimensions Over Time



Graphs showing individual patient transesophageal echocardiographic (TEE) measurements of *vena contracta*, frame neck, and effective diameters at implant and at 6- and 12-month follow-up. The stenotic threshold (red dashed line). Blue circles below this line indicate that the shunt orifice size was artifactually reduced due to non-coaxial imaging (pseudo stenotic). The red triangle represents a single patient with a stenotic shunt at 6-month follow-up. That patient exited the study upon receiving a left ventricular assist device (LVAD) at 8 months at which time the shunt was occluded. Mean ± standard deviation values are exclusive of stenotic shunt.

10.4 Zile 2025. Mechanistic Basis for Differential Effects of Interatrial Shunt Treatment in HFrEF vs HFpEF: The RELIEVE-HF Trial

The V-Wave investigators have recently published a peer-reviewed manuscript describing results of TTE performed at baseline and 12 months follow-up in the heart failure with reduced EF (LVEF ≤ 40%; HFrEF) and heart failure with preserved EF (LVEF > 40%; HFpEF) strata (Zile et al., 2025). These analyses were intended to identify potential mechanistic structural and functional responses to interatrial shunt treatment that might account for their differential clinical effects in patients with HFrEF vs HFpEF observed in the RELIEVE-HF trial. The presentation below has been adopted from that manuscript.

10.4.1 Methods

Transthoracic echocardiography. TTE was performed at baseline and serially during follow-up; for the present study the 12-month TTE was used as the follow-up study representing a time when changes in cardiac chamber size and function after shunt placement were likely to be stable, without excessive loss- to-follow-up at later time points. Studies were read at an independent Echo Core Laboratory (Penn State College of Medicine, Hershey, PA, USA). Seventeen echo parameters were assessed as listed in Tables 1–3. Echo results were indexed (where appropriate) for body surface area. In addition, LV and right ventricular (RV) chamber compliance (instantaneous operative end-diastolic chamber compliance or its inverse, chamber stiffness) was assessed at baseline using pressures obtained from qualifying pre-procedure right heart catheterization and echocardiographic measures of ventricular chamber volumes. Because assessments at 12 months relied entirely on echo parameters (right heart catheterization was not repeated at 12 months), LA volume and right atrial area were used as surrogates of LA and RA pressures as supported by data presented in the results. The end-diastolic pressure vs volume ratio was modeled as an exponential curve. Serial patient-paired changes from baseline to 12 months are reported below.

Statistical Analysis. A 2-step imputation model was used to account for missing echocardiographic data (Asch et al., 2019; Little et al., 2012). Missing parameter values from completed echocardiograms and missing 12-month echocardiographic studies, except those due to adjudicated HF-related death or trial exit due to cardiac transplantation or LVAD placement prior to 12 months, were assumed to be missing at random (MAR) and were imputed using Markov chain Monte Carlo (MCMC) multiple imputation (20 iterations). Using the MIAALYZE procedure in SAS, MCMC imputation was done separately by LVEF strata and treatment arm. Results were pooled using Rubin's rules for pooling. All echo data were included in the MCMC imputation as were sex, age, ischemic vs nonischemic etiology, diabetes, and hypertension history. For patients with a missing 12-month echocardiogram due to HF-related death, cardiac transplantation, or LVAD, the worst 12-month values in their LVEF group and treatment assignment were used. Worst values were directionally the same for all cases, whether baseline LVEF placed them in the HFrEF or HFpEF stratum. They were the largest

chamber or vessel size, E/e', PA pressure, the smallest LVEF, stroke volume, cardiac index, right ventricular fractional area change (RVFAC), TAPSE, and least negative LV global longitudinal strain.

Each TTE parameter was tested for normality and if criteria were not met, and the data were more normally distributed under a logarithmic transformation as judged by statistical testing and visually assessment of P-P and Q-Q plots, they were transformed prior to imputation and then back transformed. Baseline echocardiographic data within and between LVEF groups and changes in echocardiographic parameters from baseline to 12 months within and between LVEF groups were tested by analysis of covariance (ANCOVA). All results are stated as least square means and 95% confidence intervals. A 2-sided *P*-value < 0.05 was considered nominally significant without correction for multiplicity. All statistical analyses were run by an independent statistical group (Pentara, Millcreek, UT, US) and verified by independent double coding using SAS 9.4 or R V4.3.2 software.

10.4.2 Results

Echocardiographic data. All 508 patients randomized in the RELIEVE-HF study underwent a baseline TTE at a median of 1.1 (interquartile range [IQR] 0.7–1.4) months prior to randomization. Of these 508, 428 patients underwent a 12-month TTE at a median of 12.0 (IQR 11.5–12.5) months after randomization. A total of 80 studies at 12 months were not performed: 18 patients died due to HF or had a heart transplant or LVAD before the 12-month TTE; 12-month TTEs in 62 patients were assumed to be MAR. After imputation a total of 508 baseline and 12-month paired TTEs were included in the TTE database. There were 17 TTE parameters analyzed for each study at each time period. Of 17,272 total measurements (17 x 508 patients x 2 studies), 15,495 (89.7%) were analyzed by the Echo Core Laboratory without imputation while 1,777 (10.3%) parameters were imputed.

Baseline echocardiographic comparisons between HFrEF and HFpEF. As shown in **Table 37**, at baseline, within each EF group, there were no differences in any TTE parameters in patients assigned to shunt placement vs sham procedure group. However, at baseline, many of the echo parameters were different in HFrEF vs HFpEF patients.

Baseline left heart structure and function in HFrEF vs HFpEF: LV volumes were larger in HFrEF compared with HFpEF, and indices of LV systolic function (LVEF and LV global longitudinal strain [GLS]) were lower (**Table 37**). Indices of left-sided filling pressure (E/e', PA systolic pressure, LA volume) were increased to a similar degree in both HFrEF and HFpEF. LV diastolic compliance was greater in HFrEF compared with HFpEF at baseline; both the pulmonary capillary edge pressure (PCWP), from baseline right heart catheterization) vs left ventricular end-diastolic volume index (LVEDVi) and the LAV index (LAVi) vs LVEDVi relationships lie to the right in HFrEF (indicating the presence of a more compliant LV) (**Figure 33**).

Table 37: Baseline Echocardiographic Data in Patients with HFrEF and HFpEF

Parameter	Baseline Control HFpEF (N=153)	Baseline Shunt HFpEF (N=149)	Baseline HFpEF Difference	Baseline Control HFrEF (N=105)	Baseline Shunt HFrEF (N=101)	Baseline HFrEF Difference	HFrEF vs HFpEF Difference	Nominal P-value HFpEF vs. HFrEF
Heart rate, bpm	69.7 (67.7, 71.7)	68.6 (66.5, 70.6)	-1.1 (p =0.4329) 95% CI (-4.0, 1.7)	72.1 (69.6, 74.5)	70.6 (68.1, 73.0)	-1.5 (p =0.4022) 95% CI (-4.9, 2.0)	2.2 (-0.0, 4.4)	0.053
LV end-diastolic volume index, ml/m^2	54.5 (50.2, 58.9)	49.9 (45.5, 54.3)	-4.6 (p =0.1428) 95% CI (-10.8, 1.6)	96.9 (91.6, 102.1)	98.1 (92.8, 103.5)	1.3 (p =0.7379) 95% CI (-6.2, 8.8)	45.3 (40.4, 50.1)	< 0.0001
LV end-systolic volume index, ml/m^2	25.5 (21.9, 29.1)	22.6 (19.0, 26.2)	-2.9 (p =0.2623) 95% CI (-8.0, 2.2)	70.0 (65.7, 74.4)	69.4 (65.0, 73.8)	-0.7 (p =0.8341) 95% CI (-6.8, 5.5)	45.7 (41.7, 49.7)	< 0.0001
LV stroke volume index, ml/m^2	29.0 (27.7, 30.4)	27.3 (26.0, 28.7)	-1.7 (p =0.0809) 95% CI (-3.6, 0.2)	26.8 (25.2, 28.4)	28.8 (27.1, 30.4)	1.9 (p =0.1008) 95% CI (-0.4, 4.2)	-0.4 (-1.9, 1.1)	0.62
LV cardiac index, L/min/m^2	2.0 (1.9, 2.1)	1.8 (1.7, 1.9)	-0.2 (p =0.0194) 95% CI (-0.3, -0.0)	1.9 (1.8, 2.0)	2.0 (1.9, 2.1)	0.1 (p =0.3246) 95% CI (-0.1, 0.2)	0.0 (-0.1, 0.2)	0.36
LV ejection fraction, %	54.8 (53.4, 56.2)	56.1 (54.6, 57.5)	1.2 (p =0.2297) 95% CI (-0.8, 3.3)	29.2 (27.5, 30.9)	30.0 (28.2, 31.8)	0.8 (p =0.5287) 95% CI (-1.7, 3.3)	-25.8 (-27.4, -24.2)	< 0.0001
LV global longitudinal strain, %	17.1 (16.4, 17.7)	17.6 (16.9, 18.2)	0.5 (p =0.2978) 95% CI (-0.4, 1.4)	9.9 (9.1, 10.7)	9.6 (8.8, 10.4)	-0.3 (p =0.5370) 95% CI (-1.4, 0.7)	-7.6 (-8.3, -6.9)	< 0.0001
Left atrial volume index, ml/m^2	42.2 (38.9, 45.4)	40.0 (36.7, 43.3)	-2.2 (p =0.3637) 95% CI (-6.8, 2.5)	40.9 (36.9, 44.8)	45.2 (41.2, 49.2)	4.3 (p =0.1347) 95% CI (-1.3, 10.0)	1.9 (-1.7, 5.6)	0.29
E/e'	15.6 (14.1, 17.2)	15.5 (13.9, 17.0)	-0.1 (p =0.8977) 95% CI (-2.3, 2.0)	16.3 (14.5, 18.2)	18.2 (16.3, 20.1)	1.9 (p =0.1625) 95% CI (-0.8, 4.5)	1.7 (0.0, 3.4)	0.0498
RV end-diastolic area index, cm^2/m^2	10.0 (9.5, 10.5)	9.8 (9.3, 10.3)	-0.2 (p =0.5241) 95% CI (-1.0, 0.5)	11.5 (10.8, 12.1)	10.7 (10.0, 11.3)	-0.8 (p =0.0725) 95% CI (-1.7, 0.1)	1.2 (0.6, 1.7)	< 0.0001
RV stroke area index, cm^2/m^2	3.9 (3.7, 4.1)	3.8 (3.6, 3.9)	-0.2 (p =0.2124) 95% CI (-0.4, 0.1)	4.1 (3.8, 4.3)	3.9 (3.7, 4.2)	-0.1 (p =0.5005) 95% CI (-0.4, 0.2)	0.2 (-0.0, 0.4)	0.12
RV fractional area change, %	39.5 (38.4, 40.7)	38.9 (37.8, 40.1)	-0.6 (p =0.4631) 95% CI (-2.2, 1.0)	36.0 (34.7, 37.4)	37.6 (36.2, 38.9)	1.5 (p =0.1194) 95% CI (-0.4, 3.5)	-2.5 (-3.7, -1.2)	0.0001
TAPSE, mm	17.6 (17.0, 18.2)	17.6 (17.0, 18.2)	0.0 (p =0.9589) 95% CI (-0.8, 0.9)	15.8 (15.1, 16.6)	16.4 (15.6, 17.1)	0.5 (p =0.3257) 95% CI (-0.5, 1.6)	-1.5 (-2.2, -0.8)	< 0.0001
Right atrial area index, cm^2/m^2	9.7 (9.1, 10.3)	10.0 (9.4, 10.6)	0.3 (p =0.4665) 95% CI (-0.5, 1.2)	10.1 (9.4, 10.9)	10.2 (9.5, 11.0)	0.1 (p =0.8424) 95% CI (-0.9, 1.1)	0.3 (-0.3, 1.0)	0.33

Inferior vena cava diameter (max), cm	1.55 (1.46, 1.64)	1.63 (1.53, 1.72)	0.07 (p =0.2609) 95% CI (-0.1, 0.2)	1.65 (1.54, 1.75)	1.57 (1.46, 1.68)	-0.07 (p =0.3596) 95% CI (-0.2, 0.1)	0.02 (-0.08, 0.12)	0.68
PA systolic pressure, mmHg	33.3 (30.9, 35.8)	35.2 (32.8, 37.7)	1.9 (p =0.2794) 95% CI (-1.6, 5.4)	32.9 (29.9, 35.9)	31.5 (28.5, 34.5)	-1.4 (p =0.5197) 95% CI (-5.6, 2.8)	-2.1 (-4.9, 0.6)	0.12
TAPSE / PA systolic pressure, mm/mmHg	0.66 (0.59, 0.73)	0.58 (0.51, 0.66)	-0.08 (p =0.1524) 95% CI (-0.2, 0.0)	0.64 (0.55, 0.73)	0.66 (0.57, 0.75)	0.02 (p =0.7402) 95% CI (-0.1, 0.1)	0.03 (-0.05, 0.11)	0.51

Data are means (95% CI) for baseline and ANCOVA adjusted means (95% CI) for differences. HR=heart rate; RV=right ventricular; RVFAC=right ventricular fractional area change; TAPSE=tricuspid annular plane systolic excursions; E/e'=peak E-wave velocity by the peak e' velocity; PA=pulmonary artery.
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.

Baseline right heart structure and function in HFrEF vs HFpEF: RV end-diastolic area index (RVEDAi), was larger in HFrEF compared with HFpEF, and indices of RV systolic function (RVFAC), and TAPSE were lower (**Table 37**). Indices of right-sided filling pressures (RA area index [RAAi] and IVC diameter) were increased to a similar degree in both HFrEF and HFpEF. RV diastolic compliance was increased in HFrEF compared with HFpEF at baseline; both the RAP (from baseline right heart catheterization) vs the RV end-diastolic area index (RVEDAi) and the RAAi vs RVEDAi relationship lie to the right in HFrEF (indicating the presence of a more compliant RV) compared with HFpEF (which had a less compliant RV) (**Figure 34**).

Echocardiographic differences between HFrEF and HFpEF in response to shunt placement. Shunt vs control-induced changes in left heart structure and function from baseline to 12 months: In HFrEF patients, the difference between changes from baseline to 12 months in the Shunt-treated vs Control groups demonstrated net reductions in LVEDVi and end-systolic volume index (LVESVi) with shunt treatment. The decrease in LVEDVi (-11.9 [-21.3, -2.5] ml/m^2, nominal *P*=0.01) and LVESVi (-8.9 [-17.2, -0.7] ml/m^2, nominal *P*=0.03) indicated shunt-induced LV reverse remodeling (**Table 38**, **Figure 27**). In contrast, Shunt-treated HFpEF patients had no net changes in LVEDVi or LVESVi, and thus no LV remodeling (**Table 39**, **Figure 27**). The between LVEF group differences from baseline to 12 months in Shunt vs control in LVEDVi and LVESVi were significant (nominal *P*= 0.006 and 0.01 respectively). In both HFrEF and HFpEF, there were no net changes in left ventricular stroke volume index (LVSVi), cardiac index, LVEF or LV GLS, indicating maintenance of LV systolic function after Shunt placement (**Table 38** and **Table 39**).

LAVi was decreased with shunt treatment in HFrEF (-5.8 [-11.8, 0.2], nominal *P*=0.06) and increased in HFpEF (4.9 [0.4, 9.3], nominal *P*=0.03). The between LVEF group differences from baseline to 12 months in Shunt vs control in LAVi was significant (nominal *P*=0.004). After Shunt placement there were no significant changes in the instantaneous operative end-diastolic LV stiffness coordinate (LAVi vs LVEDVi) in either the HFrEF or HFpEF patients (**Figure 28A**).

Shunt vs control-induced changes in right heart structure and function: In HFrEF patients, the net difference between the changes from baseline to 12 months in the Shunt-treated vs. control groups demonstrated no significant changes in right ventricular end-diastolic area index (RVEDAi), RAAi, or IVC diameter with shunt treatment (**Table 37**, **Figure 28**). There were trends toward increases in RV stroke area index (RVSAi), but no change in RVFAC, and TAPSE (**Table 38**, **Figure 30**), consistent with maintenance of systolic performance after Shunt placement. In HFrEF patients treated with a Shunt, there was a net decrease in PASP compared to controls of -2.2 mmHg (**Table 38**, **Figure 31**) which did not reach statistical significance but, nonetheless, may have clinical relevance (Zile et al., 2025). In contrast, Shunt-treated HFpEF patients had net increases in RVEDAi, RAAi, and IVC diameter and PASP rose by an average of +4.7 (0.9,0.05) mmHg (nominal *P*=0.02) in shunt-treated vs controls, a statistically and

clinically relevant change (**Table 39**, **Figure 27** to **Figure 31**). The between LVEF group differences from baseline to 12 months in Shunt vs control in RAAi and PASP were (nominal *P*=0.01 and nominal *P*=0.06 respectively).

In contrast to the lack of difference in LV compliance, differential changes in RV compliance were noted after Shunt placement. As shown in **Figure 34**, at baseline, the RAP (and RAAi) vs RVEDAi relationship lies to the right in patients with HFrEF (indicating the presence of a more compliant RV) compared to patients with HFpEF (less compliant RV). After Shunt placement (**Figure 28B**) there were no significant changes in the instantaneous operative end-diastolic RV stiffness coordinate (RAAi vs RVEDAi) in HFrEF. In contrast, there was a change in HFpEF; the RAAi vs RVEDAi coordinate moved up to a stiffer portion of the curve.

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

	Control (N=105)			Shunt (N=101)				
Parameter	**Baseline**	**12 Months**	**12 Month – Baseline Difference**	**Baseline**	**12 Months**	**12 Month – Baseline Difference**	**Difference Shunt - Control**	**ANCOVA Nominal *P*-value**
Heart rate, bpm	72.1 (69.7, 74.4)	75.3 (72.8, 77.7)	3.2 (0.5, 6.0)	70.6 (68.2,73.0)	70.8 (68.2,73.3)	0.2 (-2.7, 3.0)	-3.1 (-7.0, 0.8)	0.12
LV end-diastolic volume index, ml/m^2	96.9 (89.8, 103.9)	105.0 (97.2, 112.9)	8.2 (1.3, 15.0)	98.1 (90.9,105.3)	94.5 (86.8,102.1)	-3.7 (-10.2, 2.9)	-11.9 (-21.3, -2.5)	0.01
LV end-systolic volume index, ml/m^2	70.0 (63.9, 76.2)	75.6 (68.7, 82.4)	5.5 (-0.4, 11.4)	69.4 (63.1,75.7)	66.0 (59.4,72.6)	-3.4 (-9.0, 2.1)	-8.9 (-17.2, -0.7)	0.03
LV stroke volume index, ml/m^2	26.8 (25.1, 28.5)	27.4 (25.4, 29.4)	0.6 (-1.6, 2.7)	28.8 (27.0,30.5)	28.1 (26.0,30.2)	-0.6 (-2.8, 1.6)	-1.2 (-4.1, 1.7)	0.41
LV cardiac index, L/min/m^2	1.9 (1.8, 2.0)	2.0 (1.8, 2.1)	0.0 (-0.1, 0.2)	2.0 (1.9, 2.1)	2.0 (1.8, 2.1)	-0.1 (-0.2, 0.1)	-0.1 (-0.3, 0.1)	0.44
LV ejection fraction, %	29.2 (27.6, 30.8)	30.5 (28.8, 32.2)	1.3 (-0.4, 3.0)	30.0 (28.4,31.7)	32.2 (30.4,34.0)	2.2 (0.4, 4.0)	0.9 (-1.5, 3.3)	0.46
LV global longitudinal strain, %	9.9 (9.2, 10.6)	9.7 (9.0, 10.4)	-0.2 (-0.9, 0.5)	9.6 (8.9, 10.3)	10.3 (9.6, 11.0)	0.7 (-0.0, 1.5)	1.0 (-0.1, 2.0)	0.06
Left atrial volume index, ml/m^2	40.9 (36.9, 44.9)	47.2 (43.0, 51.3)	6.3 (2.1, 10.5)	45.2 (41.1,49.3)	45.7 (41.5,49.9)	0.5 (-3.7, 4.8)	-5.8 (-11.8, 0.2)	0.06
E/e'	16.3 (14.2, 18.4)	19.5 (17.3, 21.6)	3.2 (1.2, 5.2)	18.2 (16.1,20.3)	17.6 (15.3,19.9)	-0.6 (-2.7, 1.6)	-3.7 (-6.7, -0.7)	0.02
RV end-diastolic area index, cm^2/m^2	11.5 (10.8, 12.2)	11.6 (10.8, 12.4)	0.1 (-0.7, 1.0)	10.7 (9.9, 11.4)	11.2 (10.4,12.0)	0.5 (-0.3, 1.4)	0.4 (-0.8, 1.6)	0.52
RV stroke area index, cm^2/m^2	4.1 (3.8, 4.3)	3.5 (3.3, 3.7)	-0.6 (-0.8, -0.3)	3.9 (3.7, 4.2)	4.0 (3.8, 4.3)	0.1 (-0.2, 0.4)	0.7 (0.2, 1.1)	0.002
RV fractional area change, %	36.0 (34.6, 37.4)	34.9 (33.4, 36.5)	-1.1 (-2.8, 0.7)	37.6 (36.1,39.0)	37.7 (36.1,39.3)	0.1 (-1.7, 1.9)	1.2 (-1.3, 3.8)	0.35
TAPSE, mm	15.8 (15.1,16.5)	15.4 (14.6, 16.1)	-0.5 (-1.3, 0.3)	16.4 (15.7,17.1)	16.8 (16.0,17.6)	0.4 (-0.4, 1.3)	0.9 (-0.3, 2.1)	0.14
Right atrial area index, cm^2/m^2	10.1 (9.4, 10.9)	11.1 (10.3, 11.8)	0.9 (0.1, 1.7)	10.2 (9.5, 11.0)	11.0 (10.2,11.8)	0.7 (-0.1, 1.5)	-0.2 (-1.3, 0.9)	0.74
Inferior vena cava diameter	1.65	1.78	0.13 (-0.01, 0.28)	1.57	1.68	0.11	-0.03 (-0.23, 0.18)	0.80

(max), cm	(1.53, 1.76)	(1.66, 1.90)		(1.46,1.69)	(1.55, 1.81)	(-0.05, 0.26)		
PA systolic pressure, mmHg	32.9 (29.7, 36.0)	36.7 (33.0, 40.5)	3.9 (-0.6, 8.3)	31.5 (28.3, 34.7)	33.1 (28.6,37.7)	1.7 (-3.4, 6.7)	-2.2 (-8.8, 4.4)	0.51
TAPSE / PA systolic pressure, mm/mmHg	0.64 (0.54, 0.73)	0.57 (0.47, 0.67)	-0.07 (-0.19, 0.06)	0.66 (0.56, 0.76)	0.70 (0.59, 0.81)	0.04 (-0.09, 0.17)	0.11 (-0.07, 0.29)	0.24

Data are means (95% CI) for baseline and ANCOVA adjusted means (95% CI) for differences. N is the number of patients with paired 12-month and baseline echocardiographic values. ANCOVA=Analysis of covariance; RV=right ventricular; RVFAC=right ventricular fractional area change; TAPSE=tricuspid annular plane systolic excursions; E/e'=peak E-wave velocity by the peak e' velocity; PA=pulmonary artery.
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.

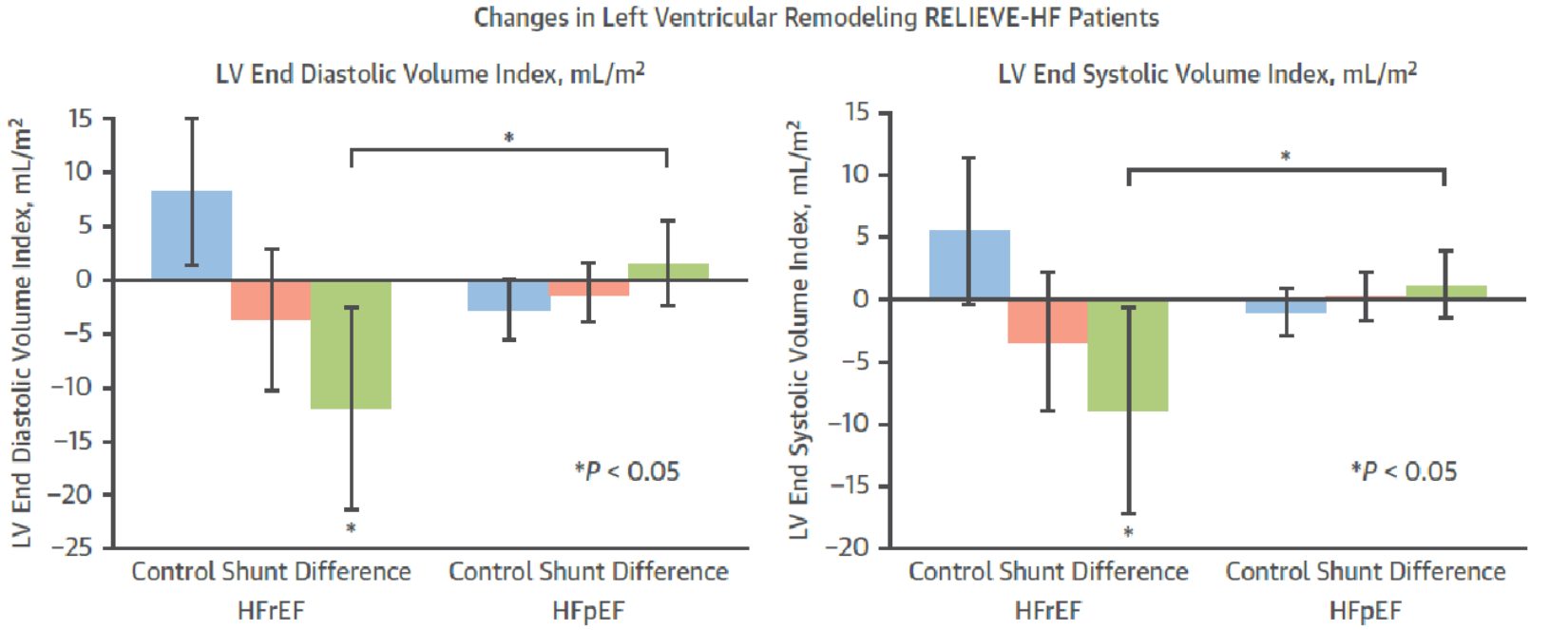
Table 39: Echocardiographic Data at Baseline and 12 Months in HFpEF (LVEF > 40%)

Parameter	Control (N=153)			Shunt (N=149)				
	Baseline	12 Months	12 Month – Baseline Difference	Baseline	12 Months	12 Month – Baseline Difference	Difference Shunt - Control	ANCOVA Nominal *P*-value
Heart rate, bpm	69.7 (67.7, 71.7)	69.6 (67.4, 71.8)	-0.1 (-2.3, 2.1)	68.6 (66.5, 70.6)	70.5 (68.2, 72.7)	1.9 (-0.4, 4.2)	2.0 (-1.2, 5.1)	0.22
LV end-diastolic volume index, ml/m^2	54.5 (51.6, 57.5)	51.8 (48.6, 54.9)	-2.8 (-5.6, 0.0)	49.9 (47.0, 52.9)	48.6 (45.5, 51.8)	-1.3 (-4.1, 1.5)	1.5 (-2.5, 5.5)	0.47
LV end-systolic volume index, ml/m^2	25.5 (23.5, 27.5)	24.5 (22.3, 26.7)	-1.0 (-2.9, 0.9)	22.6 (20.6, 24.6)	22.8 (20.6, 25.0)	0.2 (-1.7, 2.1)	1.2 (-1.5, 3.9)	0.38
LV stroke volume index, ml/m^2	29.0 (27.7, 30.3)	27.4 (26.0, 28.8)	-1.6 (-3.1, -0.2)	27.3 (26.0, 28.6)	24.9 (23.5, 26.3)	-2.4 (-3.8, -0.9)	-0.7 (-2.8, 1.3)	0.48
LV cardiac index, L/min/m^2	2.0 (1.9, 2.1)	1.9 (1.8, 2.0)	-0.1 (-0.2, -0.0)	1.8 (1.7, 1.9)	1.7 (1.6, 1.8)	-0.1 (-0.2, -0.1)	-0.0 (-0.2, 0.1)	0.6
LV ejection fraction, %	54.8 (53.3, 56.3)	55.0 (53.5, 56.6)	0.2 (-1.4, 1.8)	56.1 (54.5, 57.6)	54.8 (53.0, 56.5)	-1.3 (-3.0, 0.5)	-1.5 (-3.9, 0.9)	0.223
LV global longitudinal strain, %	17.1 (16.4, 17.8)	17.6 (16.9, 18.3)	0.5 (-0.2, 1.3)	17.6 (16.9, 18.2)	18.0 (17.3, 18.8)	0.5 (-0.3, 1.2)	-0.1 (-1.1, 1.0)	0.89
Left atrial volume index, ml/m^2	42.2 (39.0, 45.4)	39.3 (35.9, 42.8)	-2.8 (-6.0, 0.4)	40.0 (36.8, 43.3)	42.1 (38.7, 45.5)	2.0 (-1.0, 5.1)	4.9 (0.4, 9.3)	0.03
E/e'	15.6 (14.2, 17.0)	16.0 (14.6, 17.5)	0.4 (-0.9, 1.7)	15.5 (14.1, 16.9)	16.1 (14.6, 17.6)	0.6 (-0.7, 1.9)	0.2 (-1.7, 2.1)	0.832
RV end-diastolic area index, cm^2/m^2	10.0 (9.6, 10.5)	9.9 (9.4, 10.4)	-0.1 (-0.6, 0.4)	9.8 (9.3, 10.3)	11.0 (10.5, 11.5)	1.2 (0.7, 1.7)	1.3 (0.6, 2.1)	0.0006
RV stroke area index, cm^2/m^2	3.9 (3.7, 4.1)	3.9 (3.6, 4.1)	-0.1 (-0.3, 0.2)	3.8 (3.6, 3.9)	4.0 (3.8, 4.3)	0.3 (0.1, 0.5)	0.4 (0.0, 0.7)	0.04
RV fractional area change, %	39.5 (38.4, 40.7)	39.3 (38.1, 40.5)	-0.2 (-1.7, 1.2)	38.9 (37.8, 40.1)	38.7 (37.5, 40.0)	-0.2 (-1.7, 1.3)	0.0 (-2.0, 2.1)	0.97
TAPSE, mm	17.6 (17.0, 18.2)	17.5 (16.8, 18.1)	-0.1 (-0.9, 0.6)	17.6 (17.0, 18.3)	17.4 (16.7, 18.1)	-0.2 (-1.0, 0.5)	-0.1 (-1.1, 0.9)	0.84
Right atrial area index, cm^2/m^2	9.7 (9.1, 10.3)	10.0 (9.4, 10.6)	0.3 (-0.2, 0.7)	10.0 (9.4, 10.6)	11.6 (11.0, 12.2)	1.6 (1.1, 2.1)	1.3 (0.6, 2.0)	0.0002
Inferior vena cava diameter	1.55	1.53	-0.02 (-0.12, 0.08)	1.63	1.80	0.17 (0.06, 0.28)	0.19 (0.05, 0.34)	0.008

(max), cm	(1.47, 1.64)	(1.44, 1.62)		(1.54, 1.72)	(1.70, 1.89)			
PA systolic pressure, mmHg	33.3 (31.0, 35.7)	32.6 (29.9, 35.3)	-0.7 (-3.4, 2.0)	35.2 (32.9, 37.6)	39.2 (36.7, 41.8)	4.0 (1.4, 6.6)	4.7 (0.9, 8.5)	0.02
TAPSE / PA systolic pressure, mm/mmHg	0.66 (0.59, 0.73)	0.68 (0.60, 0.76)	0.02 (-0.05, 0.10)	0.58 (0.51, 0.65)	0.58 (0.50, 0.66)	-0.00 (-0.08, 0.08)	-0.03 (-0.14, 0.09)	0.65

Data are means (95% CI) for baseline and ANCOVA adjusted means (95% CI) for differences. N is the number of patients with paired 12-month and baseline echocardiographic values. ANCOVA =Analysis of covariance; LV=left ventricular; LVEF=left ventricular ejection fraction; RV=right ventricular; RVFAC=right ventricular fractional area change; TAPSE=tricuspid annular plane systolic excursions; E/e'=peak E-wave velocity by the peak e' velocity; PA=pulmonary artery. 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.

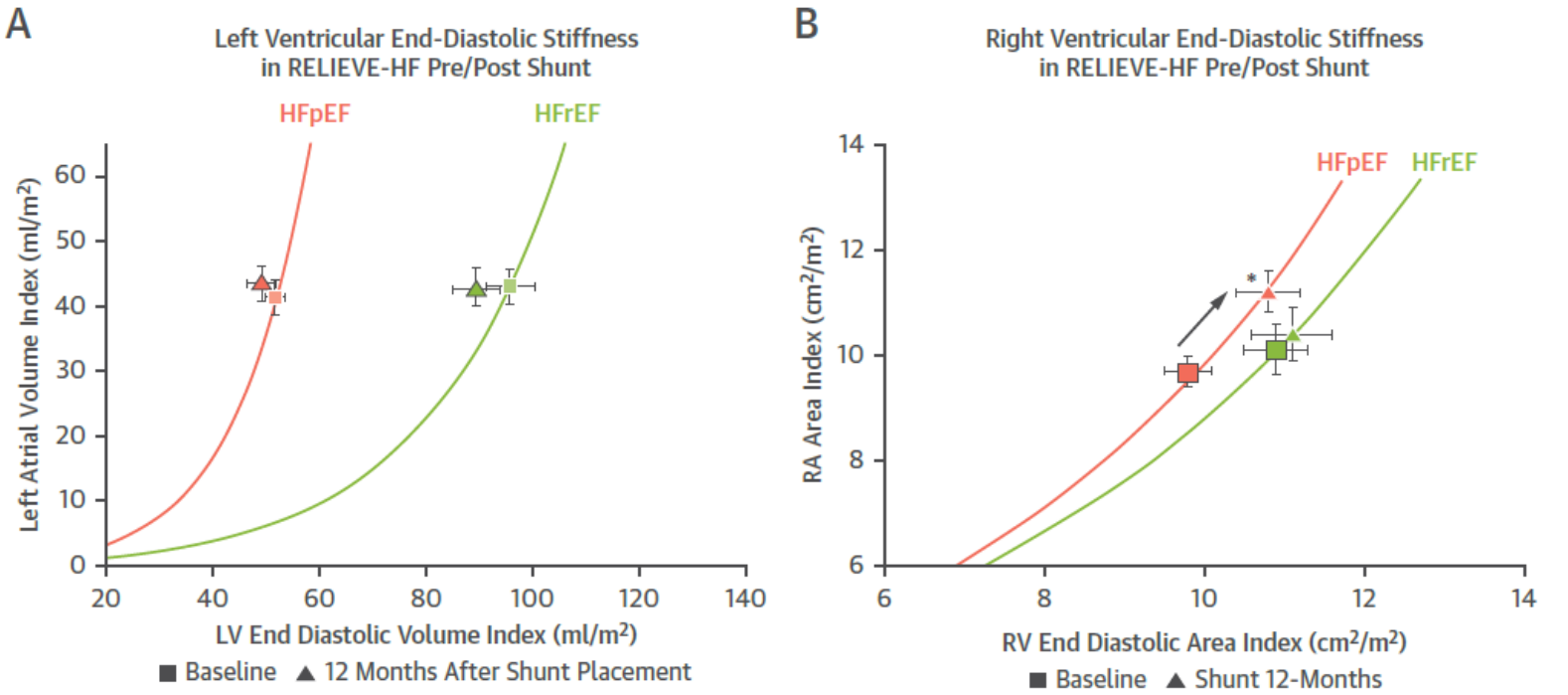
Figure 27: LV Remodeling During 12-Month Follow-up



Changes from baseline to 12 months in LV end-diastolic volume and end-systolic volume index in patients with HFrEF and HFpEF after randomization to an interatrial shunt vs control group. The difference between the 2 groups from baseline to follow-up (shunt minus control) is shown by the green bars. Data are least square means with 95% CIs. *$P < 0.05$. HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; RELIEVE-HF = REducing Lung congestion symptoms using the v-wavE shunt in adVancEd Heart Failure.

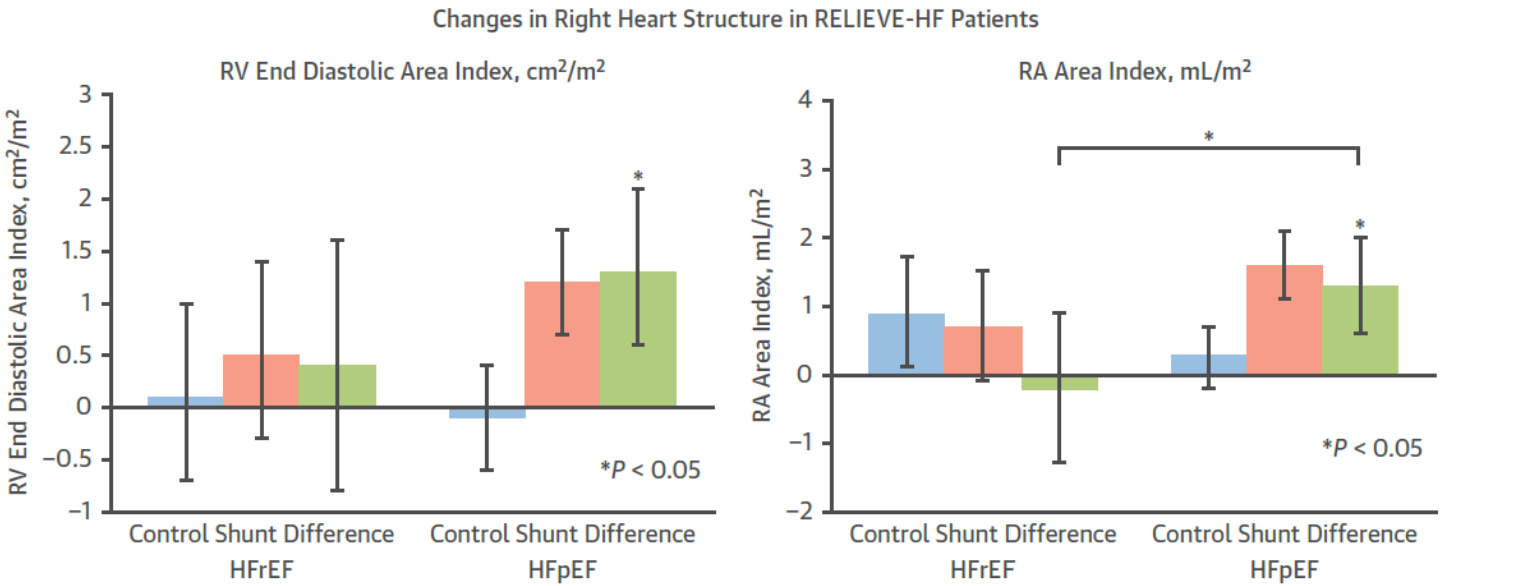
Nominal *P*-values are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

Figure 28: Diastolic Compliance at Baseline and at 12 Months After Shunt Placement



(A) LV diastolic compliance at baseline (squares) vs 12 months (triangles) after shunt placement in patients with HFrEF and HFpEF. There were no significant differences between baseline and 12 months after shunt placement in the ratio of left atrial volume index to LV end-diastolic volume index in either HFpEF or HFrEF; shunt placement did not alter LV diastolic stiffness. (B) RV diastolic compliance at baseline (squares) vs 12 months (triangles) after shunt placement in HFrEF vs HFpEF. There were no significant differences between baseline and 12 months after shunt placement in the ratio of RA area index to right ventricular end-diastolic area index in HFrEF; shunt placement did not alter RV diastolic stiffness. However, in HFpEF, after shunt placement, the ratio of right atrial area index to RV end-diastolic area index coordinate moved up an unchanged curve indicating an increase in instantaneous end-diastolic RV stiffness. Abbreviations as in Figures 1 and 3.

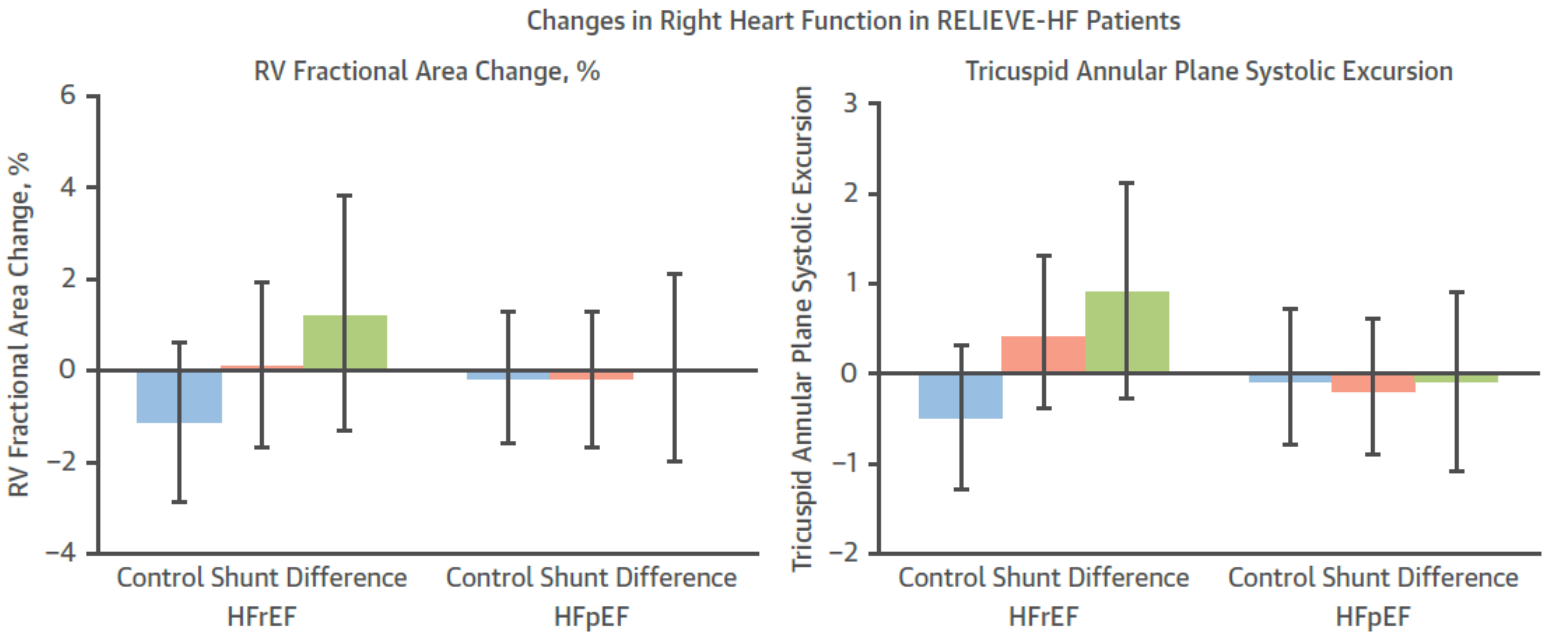
Figure 29: Changes in Right-Sided Heart Structure During 12-Month Follow-up



Changes from baseline to 12 months in RV end-diastolic area and RA area index in patients with HFrEF and HFpEF after randomization to an interatrial shunt vs control group. The difference between the 2 groups from baseline to follow-up (shunt minus control) is shown by the green bars. Data are least square means and 95% CIs. *$P < 0.05$. RA = right atrial; RV = right ventricular; other abbreviations as in Figure 1.

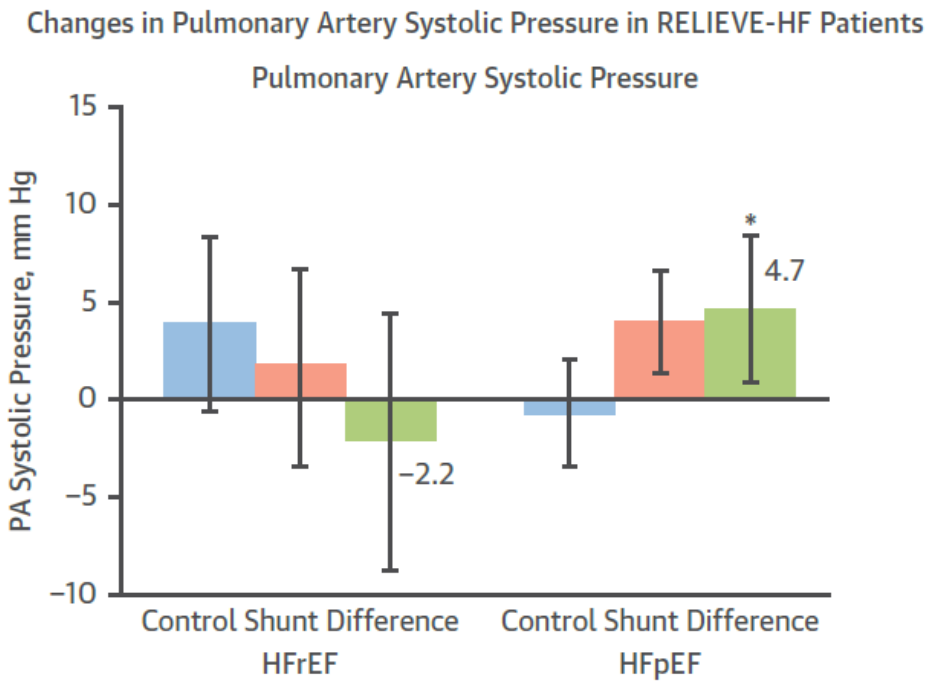
Nominal *P*-values are provided to illustrate the variability of the corresponding summary statistic; they are provided for descriptive purposes and should not be used to draw statistical inference.

Figure 30: Changes in Right-Sided Heart Function During 12-Month Follow-up



Changes from baseline to 12 months in RV fractional area change and tricuspid annular plane systolic excursion in patients with HFrEF and HFpEF after randomization to an interatrial shunt vs control group. The difference between the 2 groups from baseline to follow-up (shunt minus control) is shown by the green bars. Data are least square means and 95% CIs. *$P < 0.05$. Abbreviations as in Figures 1 and 3.

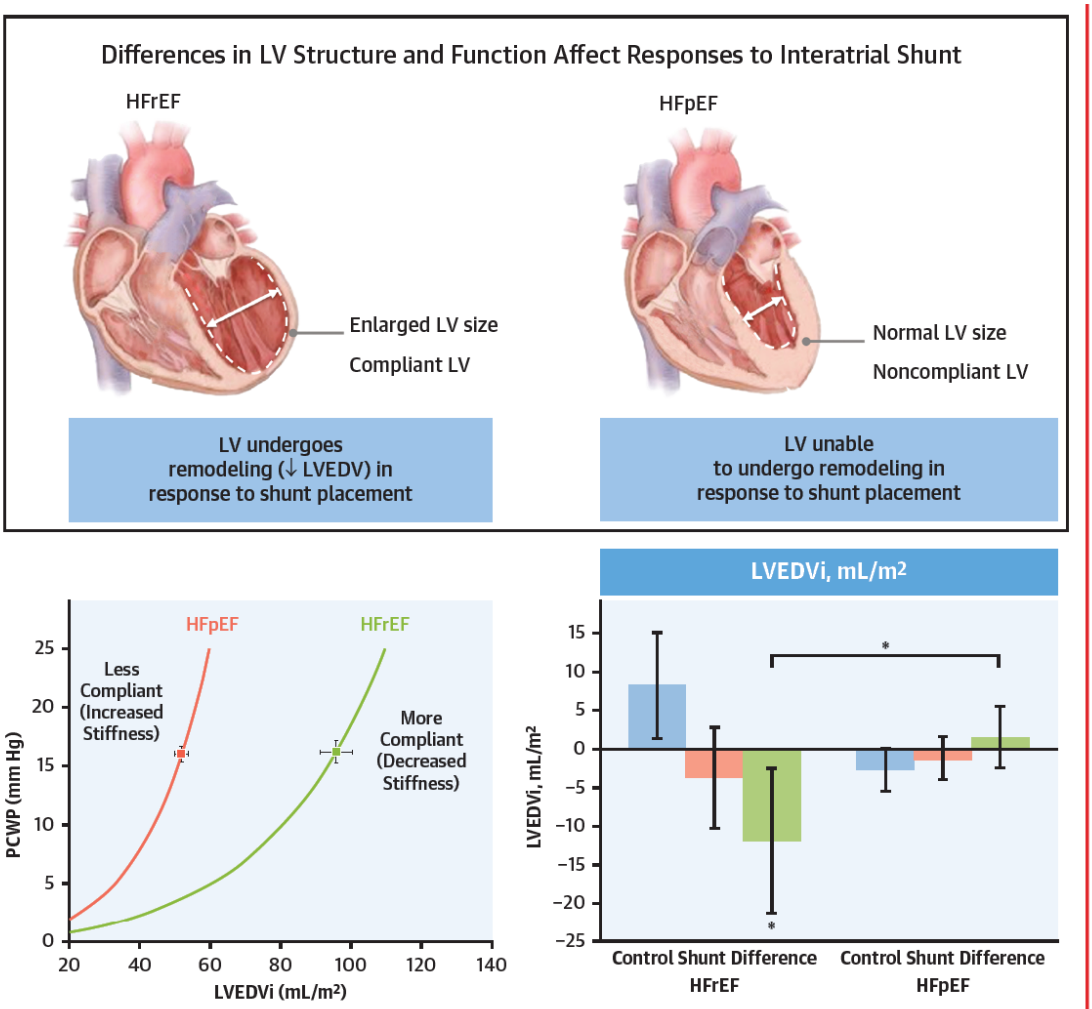
Figure 31: Changes in PA Systolic Pressure During 12-Month Follow-up



Changes from baseline to 12 months in PA systolic pressure in patients with HFrEF and HFpEF after randomization to an interatrial shunt vs control group. The difference between the 2 groups from baseline to follow-up (shunt minus control) is shown by the green bars. Data are least square means and 95% CIs. *$P < 0.05$. PA = pulmonary artery; other abbreviations as in Figure 1.

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.

Figure 32: Serial Changes in Transthoracic Echocardiography in HFrEF and HFpEF in the RELIEVE-HF Trial



Zile MR, et al. JACC Cardiovasc Imaging. 2025;■(■):■-■.

Differences in left ventricular (LV) and right ventricular (RV) structure and function at baseline and in their responses to an interatrial shunt were observed in patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). At baseline, the LV and RV were more compliant in patients with HFrEF than in HFpEF, which may explain their differences in response to volume redistribution from the left side of the heart to the right side of the heart after interatrial shunt placement. Specifically, in HFrEF, the more compliant RV was able to accommodate the increase in redistributed blood volume without resulting in a large increase in pulmonary artery (PA) pressure, and the LV underwent favorable reverse remodeling after shunt placement. In contrast, in HFpEF, the less compliant right ventricle was not able to accommodate this increase in redistributed blood volume, thus resulting in a large rise in PA pressure, and the LV did not demonstrate favorable remodeling during follow-up. *$P < 0.05$. LVEDV = left ventricular end-diastolic volume; LVEDVi = left ventricular end-diastolic volume index; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RELIEVE-HF = REducing Lung congestion symptoms using the v-wavE shunt in adVancEd Heart Failure; RVEDAi = right ventricular end-diastolic area index.

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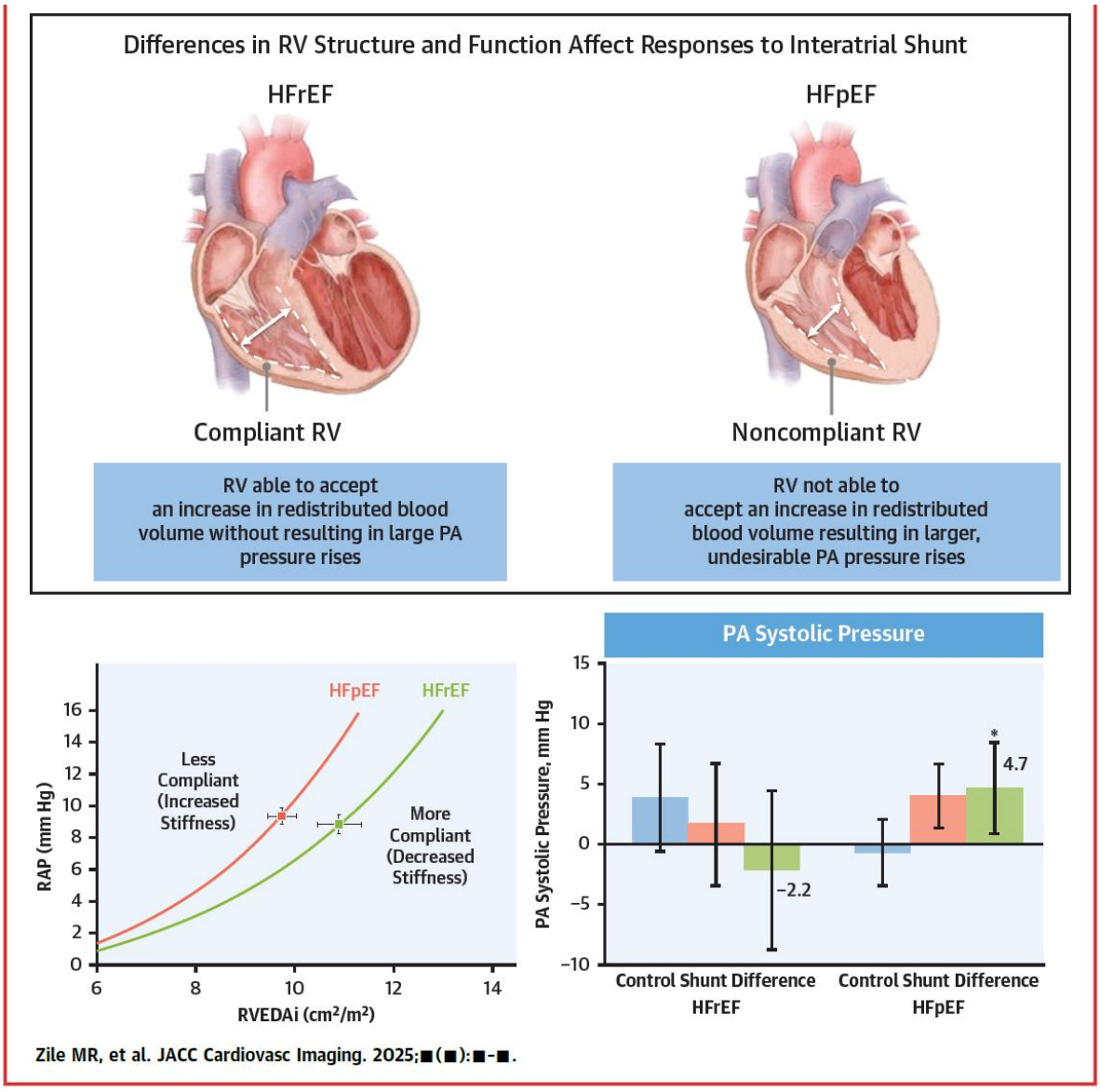


Zile MR, et al. JACC Cardiovasc Imaging. 2025;■(■):■-■.

10.4.3 Discussion

The RELIEVE-HF trial examined the effects of interatrial shunt placement on clinical outcomes in HF patients. While shunt treatment would be expected to reduce left atrial pressure (LAP) in all patients, the mechanisms through which a shunt reduces LAP (redistribution of blood flow from the left to the right heart) is quite different than the effect of other therapies that reduce pulmonary congestion such as diuretics. In HF the right heart must be able to accommodate the increase in blood flow after shunt placement. To examine these effects randomization in RELIEVE-HF was stratified by LVEF ≤ 40% (HFrEF) vs > 40% (HFpEF). Markedly dichotomous results of shunt placement on the composite of all HF Events (all-cause death, heart transplantation/LV assist device, all [recurrent] HFH, and all [recurrent] outpatient worsening HF Events) were observed in these prespecified cohorts. By Nelson-Aalen cumulative hazard rate analysis, the 2-year cumulative relative risk for all HF Events decreased by 51% in HFrEF but increased by 69% in HFpEF after shunt placement (Stone et al 2024) (**Figure 35**). Differences in cardiac structure and function between HFrEF and HFpEF that were present at baseline or changed after shunt placement were hypothesized to underlie these discordant outcomes (**Figure 32**). Specifically, 3 major structural and functional determinants that have been previously verified to impact clinical outcomes were hypothesized to play a pivotal role: LV remodeling (measured as LVEDV), RV diastolic function (measured as RV diastolic compliance), and PAP. As reported herein, the baseline and 12-month serial TTE findings support the conclusion that differences in these parameters provided a mechanistic basis for the discordant clinical responses in HFrEF and HFpEF observed after shunt placement in RELIEVE-HF.

Effect of shunt treatment on left heart remodeling. Adverse remodeling is indicated by an increase in LVEDVi (which may represent progression of disease) whereas favorable remodeling is indicated by a decrease in LVEDVi (characterized as reverse remodeling). A meta-analysis by Kramer that examined the results of 50 randomized drug and devices trials with 8,499 patients demonstrated a direct correlation between the reduction in LVEDVi, LVESVi, and mortality (Kramer et al., 2010). Therapies associated with reductions in LVEDVi (40 randomized controlled trials [RCTs], 5,037 patients) were correlated with clinically important reductions in mortality. Changes seen in this meta-analysis were of similar magnitude to that seen in the RELIEVE-HF study in the patients with HFrEF. For example, **Figure 36** conceptually plots the changes in LVEDV produced by shunt placement in HFrEF patients in the RELIEVE-HF study superimposed on the data plotted by Kramer et al. (Kramer et al., 2010). As shown in **Figure 36**, the results after interatrial shunt placement in RELIEVE-HF are consistent with these findings. In contrast, these kinds of changes in favorable reverse LV remodeling did not occur in RELIEVE-HF HFpEF patients treated with a Shunt. These data support the conclusion that shunt placement in patients with HFrEF resulted in significant LV reverse remodeling, which may provide a physiologic basis for the observed reductions in morbidity and mortality.

At baseline, the LV was more dilated and more compliant in HFrEF than in HFpEF, which in concert with the favorable effects of shunt placement on the right heart (as discussed below), enabled reverse remodeling of the LV in HFrEF but not in HFpEF. Moreover, LAV was decreased with shunt treatment in HFrEF and increased in HFpEF. These data support the conclusion that shunt placement in patients with HFrEF resulted in significant LV (and LA) reverse remodeling, contributing to the observed reductions in HF-related morbidity and mortality. In contrast, such favorable reverse LV (and LA) remodeling did not occur in the HFpEF patients treated with a shunt in RELIEVE-HF.

Effect of shunt treatment on RV structure, function, and chamber compliance. Consistent with the findings from RELIEVE-HF, previous studies have shown that RV compliance is increased in patients with HFrEF and decreased in patients with HFpEF (Rommel et al., 2018; Schwartzenberg et al., 2012). Moreover, in RELIEVE-HF, RV compliance further decreased during 12-month follow-up after Shunt placement in patients with HFpEF but not in HFrEF. In HFrEF, the greater compliance of the RV (which may extend to the PA bed, affecting pulmonary capacitance) likely enabled the right heart to accept an increase in redistributed blood volume from the LA to the RA after shunt placement without significant chamber enlargement. In contrast, in HFpEF, the non-compliant RV was unable to accommodate an increase in redistributed blood volume from the LA to the RA, resulting in increased chamber and vessel size (especially of the RA and IVC). These varying RV responses likely had a direct effect on PAP, an important determinant of morbidity and mortality.

Effect of shunt treatment on PAP. A strong relationship between changes in PAP and changes in morbidity and mortality have previously been reported in prior studies of implantable hemodynamic monitors (Lindenfeld et al., 2024; Zile et al., 2025; Zile et al., 2017; Zile et al., 2022). For example, Zile et al previously demonstrated that a 3-mmHg increase in PA diastolic pressure (PADP) was associated with a 24% increase in 6-month mortality, while a 3-mmHg decrease in PADP was associated with a 20% decrease in mortality (Zile et al., 2017). Similar predictive relationships were demonstrated between PASP and mortality in a meta-analysis of 5 studies with the CardioMEMs device; a 3-mmHg increase in PASP was associated with a 23.8% increase in 6-month mortality whereas a 3-mmHg decrease in PASP was associated with a 14.2% decrease in mortality (Zile et al., 2025). Findings after shunt placement in RELIEVE-HF patients were concordant with these previous studies. Compared with control, shunt placement resulted in a net decrease in PASP from baseline to 12 months of 2.2 mmHg in HFrEF and a net increase in PASP of 4.7 mmHg in HFpEF, likely contributing to the lower rate of mortality observed with shunt treatment in HFrEF and the increased rate of mortality observed with shunt treatment in HFpEF (Stone et al., 2024). Presumably, these differences reflect the inability of the non-compliant right heart (and pulmonary vascular bed) in HFpEF to accommodate the increased left-to-right blood flow after shunt placement, in contrast to the more compliant right heart in HFrEF.

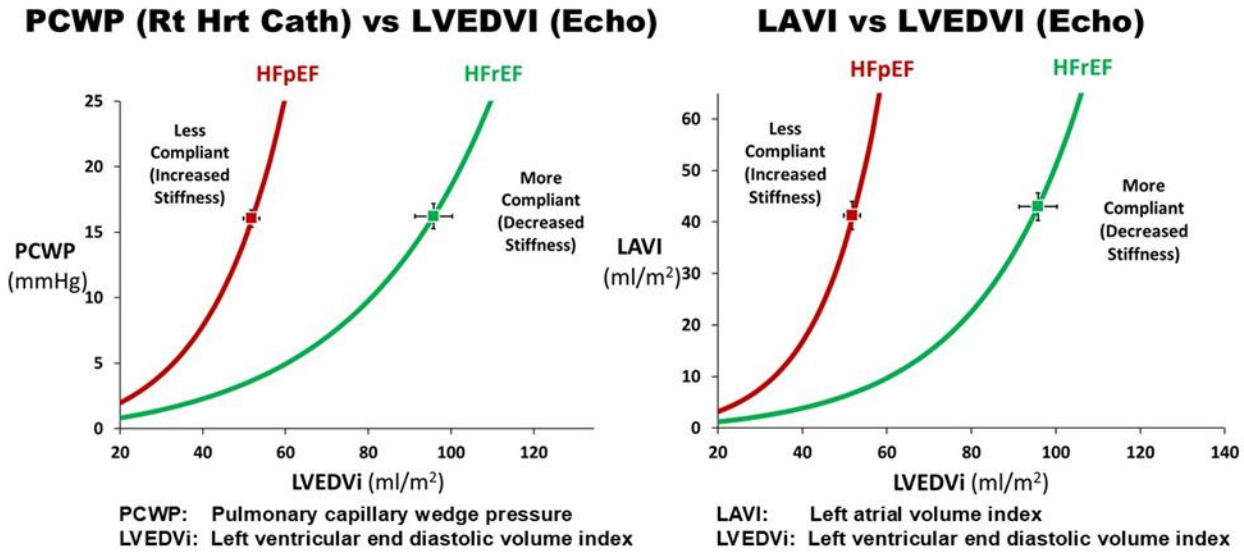
In summary, although exploratory, the one-year echocardiographic changes in RELIEVE-HF provide a biologically plausible pathophysiological mechanism underlying the diametrically opposite clinical outcomes in response to interatrial shunt placement observed in patients with HFrEF vs. HFpEF. The critical differences in cardiac structure and function between the LVEF groups at baseline and after shunt placement determined the ability of the LV to reverse remodel and the right heart to accommodate the increase in redistributed blood volume. The discordant HF-related outcomes in HFrEF and HFpEF in RELIEVE-HF as influenced by these structural and functional determinants are consistent with previous studies (Januzzi et al., 2019; Kramer et al., 2010; Lindenfeld et al., 2024; Mathias et al., 2016; Stolz et al., 2023; Zile et al., 2017; Zile et al., 2022). The favorable LV and RV structure and function in HFrEF allowed the right heart and pulmonary vascular bed to accommodate the increased blood flow from the LA to the RA after shunt placement without RV failure or increased PA pressures and with favorable LV remodeling, resulting in decreased morbidity and mortality in HFrEF. In contrast, the less favorable LV and RV structure and function in HFpEF resulted in the right heart being unable to accommodate the redistributed blood flow, resulting in right heart dilatation and increased PA pressures and without favorable LV remodeling. The net effect was increased morbidity and mortality in HFpEF after shunt placement.

Limitations. There are important limitations to acknowledge. First, as a post hoc analysis, the present results should be considered exploratory and hypothesis generating. Second, the reliance on completed 12-month echos would have introduced bias with drop-outs from more ill or deceased patients. Therefore, an accepted 2-stage imputation process (Asch et al., 2019) was used to provide a complete dataset and mitigate the effects of this potential bias. This resulted in imputation of 10.3% of missing data. As there is no ideal method to adjust for missing data due to poor HF outcomes, these results again reinforce the exploratory nature of the findings. Third, the 12-month measurements of LV and RV compliance were dependent on measurements LAVI and RAAI which served as surrogates of PCWP and RAP respectively. However, the LV and RV compliance curves using these surrogates were concordant with those using measured pressures. Fourth, TTE is unable to assess several physiological mechanisms that may underlie the response to shunt placement. For example, differences in pulmonary vasculature compliance and resistance may vary in HFrEF and HFpEF. Patients with HFpEF may have more pronounced microvascular disease and less capacity to recruit and dilate the pulmonary vasculature compared with patients with HFrEF (Guazzi et al., 2020; Li et al., 2024). Although serially assess pulmonary vascular resistance after shunt placement were not specifically investigated, the serial right heart findings observed on TTE are consistent with these prior findings. Finally, the results of the present study apply only to the patient profiles enrolled and specific device (the Ventura Shunt) used in RELIEVE-HF; clearly further combinatorial analyses will be needed.

Conclusions. Analysis of serial baseline and 12-month TTE data provide biologically plausible mechanisms explaining the markedly discordant clinical outcomes after shunt treatment in patients with HFrEF and HFpEF from the RELIEVE-HF trial. The changes in these objective measures of cardiac structure and function provide reassurance that the observed differences in clinical outcomes were not due simply to a play of chance.

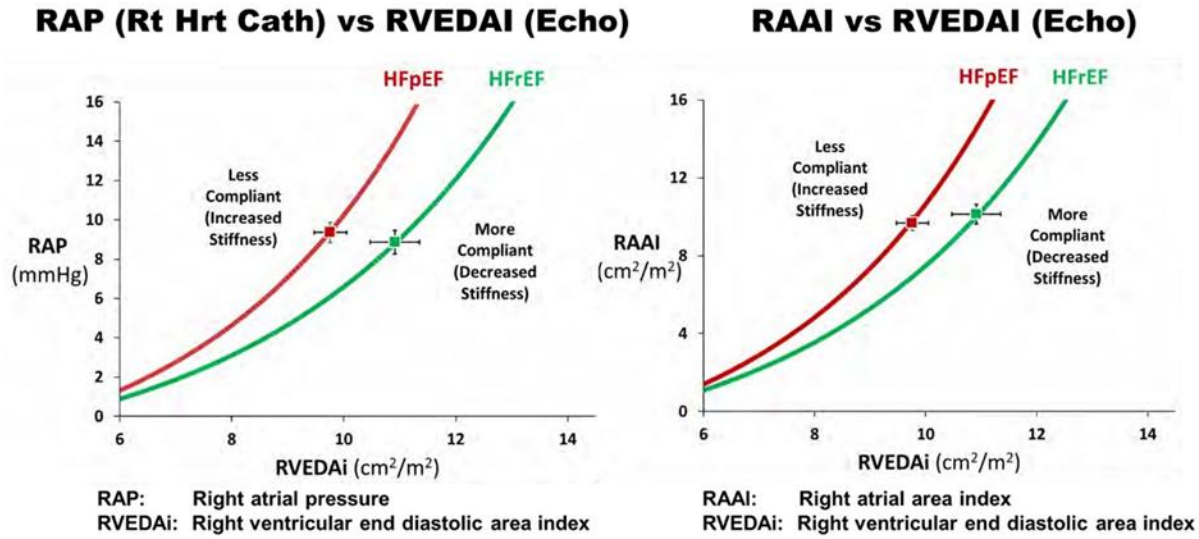
10.4.4 Supplemental Material

Figure 33: Baseline Left Ventricular Diastolic Compliance in Patients with HFrEF and HFpEF in RELIEVE-HF



LV diastolic compliance was characterized in 2 ways: 1) PCWP measurements obtained during right heart catheterization (RHC) vs left ventricular end-diastolic volume index (LVEDVi) measures obtained during TTE (left panel); and 2) Left atrial volume index (LAVi) vs LVEDVi measures (both from Echo) (right panel) were fit to an exponential model. The LV in patients with HFrEF (green curve) was more compliant (decreased stiffness) compared with the LV in patients with HFpEF (red curve). Note that the results were similar with both methods.

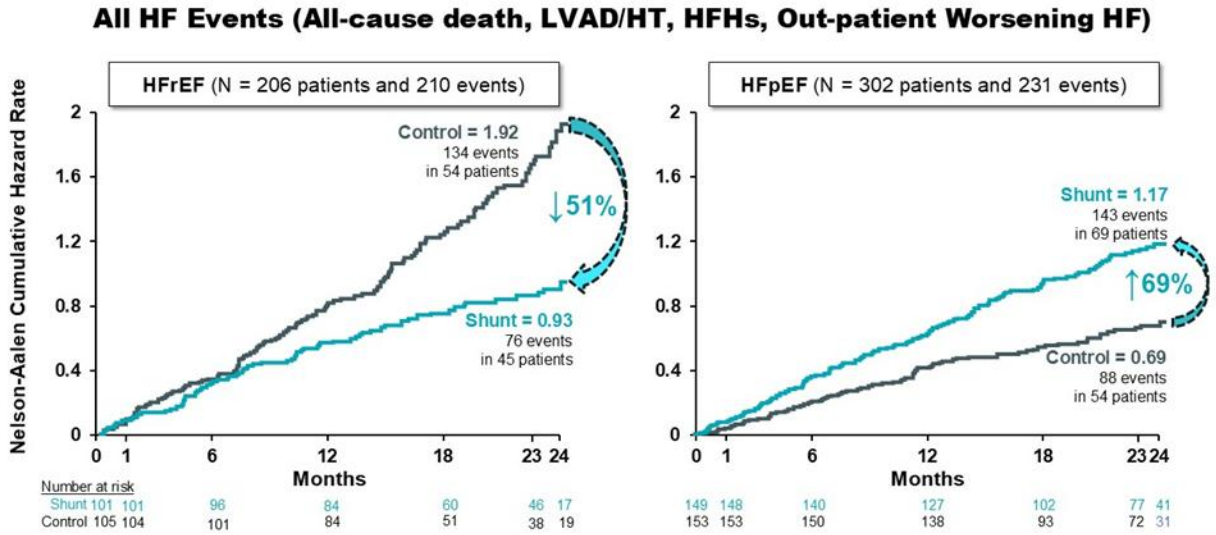
Figure 34: Baseline Right Ventricular Diastolic Compliance in Patients with HFrEF and HFpEF



RAP: Right atrial pressure
RVEDAi: Right ventricular end diastolic area index
RAAI: Right atrial area index
RVEDAi: Right ventricular end diastolic area index

RV diastolic compliance was characterized in 2 ways: 1) RAP measurements obtained during RHC vs right ventricular end-diastolic area index (RVEDAi) measures obtained during TTE (left panel); and 2) Right atrial area index (RAAi) vs RVEDAi measures (both from Echo) (right panel) were fit to an exponential model. The RV in patients with HFrEF (green curve) was more compliant (decreased stiffness) compared with the RV in patients with HFpEF (red curve). Note that the results were similar with both methods.

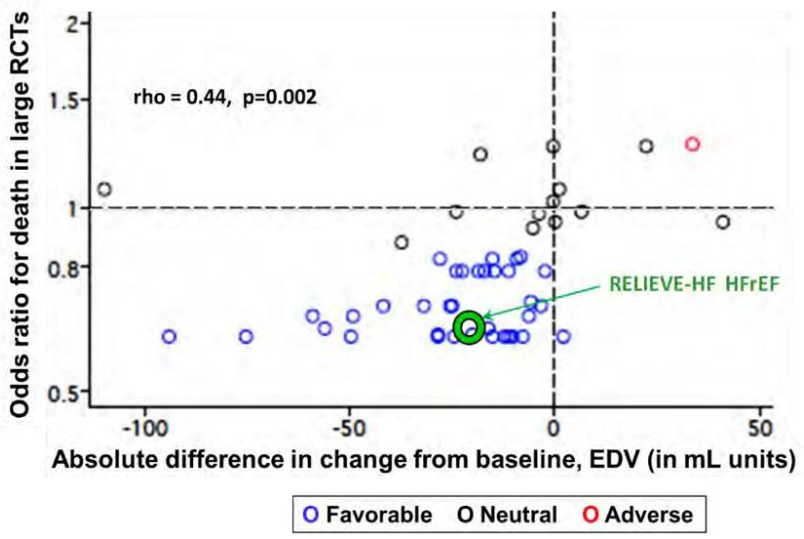
Figure 35: All Heart Failure Events in the RELIEVE-HF Trial in the Stratified Randomized HFrEF and HFpEF Strata



Modified with permission, Stone et al, Circulation: 150, 1931-1943, 2024

HF Events were all-cause death, heart transplantation or LVAD implantation, all HFH and all outpatient worsening HF Events. The y-axis represents the cumulative Nelson-Aalen hazard rate during follow-up in Shunt-treated compared with sham procedure treated patients. Patients with HFrEF had fewer HF Events with Shunt vs Control (annualized rate 49.0% vs 88.6%; nominal $P < 0.0001$), whereas patients with HFpEF had more cardiovascular events with shunt treatment (annualized rate 60.2% vs 35.9%; nominal $P=0.0001$; nominal $P_{interaction} < 0.0001$). During 2-year follow-up the Nelson-Aalen hazard rate was decreased by 51% in HFrEF and increased by 69% in HFpEF.

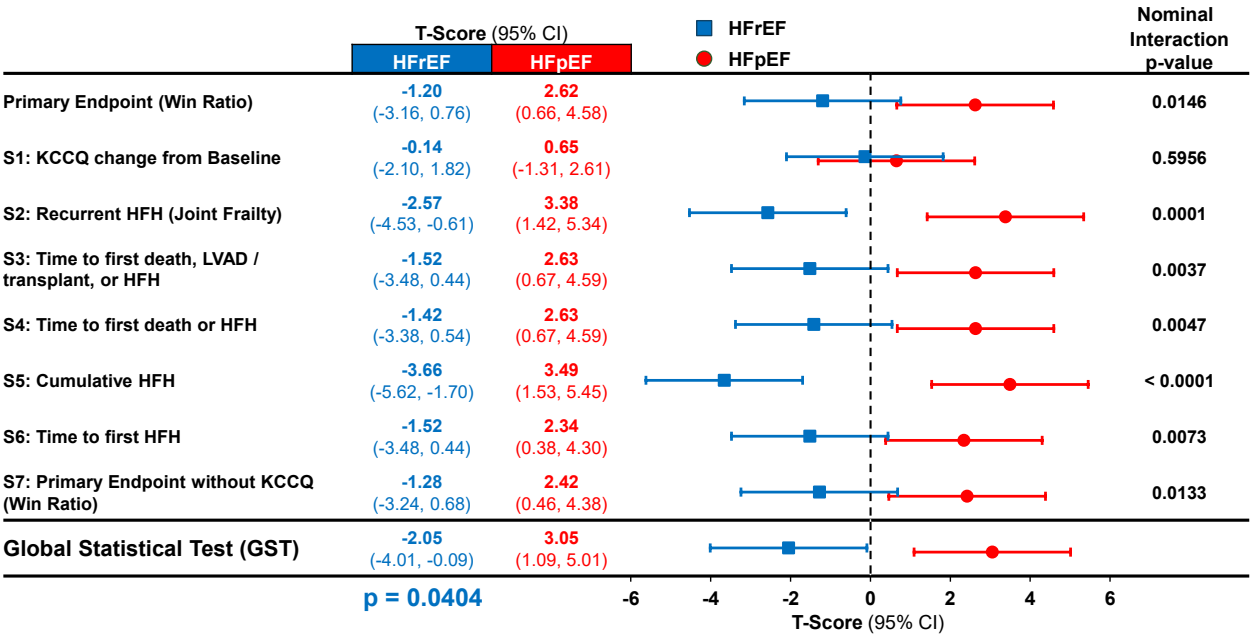
Figure 36: Relationship Between Change in LV End-Diastolic Volume and Mortality



10.5 Totality of Evidence Assessment of LVEF Strata for Primary and Secondary Endpoints (GST and Permutation Testing)

A GST was used to quantify the totality of evidence from the prespecified hierarchy of the primary and secondary endpoints, similar to a meta-analysis. Each endpoint adds to or subtracts from the evidence for a treatment effect, finally concluding whether a treatment works or not. GSTs are used to assess the totality of the evidence from an entire series of primary and secondary endpoints. Also, the GST correctly avoids "double counting" events by explicitly correcting for the correlation between the series of successive tests. The GST calculations relied on the original prespecified primary and secondary endpoints assessing elements of the primary endpoint in the SAP. The GST calculation was performed on the primary and 7 secondary endpoints, where the latter were components of the primary endpoint. The overall evidence (**Figure 37**) shows that benefit within the HFrEF stratum gets stronger as endpoints are added with nominal *P*=0.040 for primary plus first 7 secondary endpoints. The GST result improves slightly to nominal *P*=0.035 if the first secondary endpoint, change in KCCQ-OSS, is excluded due to its weak and inconsistent correlation with objective benefits in blinded HF trials.

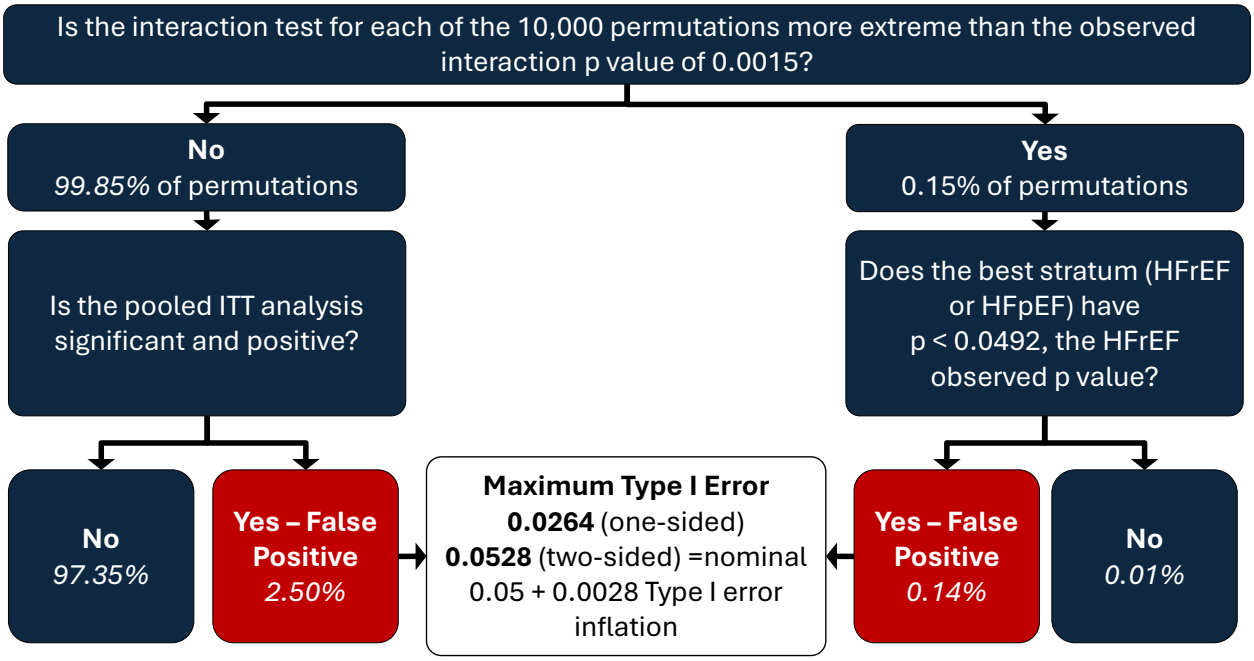
Figure 37: Totality of Evidence - Prespecified Primary and Secondary Analyses in Hierarchical Order with Global Statistical Test



Data have been transformed as T-score for direct comparisons of forest plot intervals.
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.

The overall Type-I error, including the Primary and 7 Secondary Effectiveness Endpoints, was quantified with a series of permutation-based interaction tests. Permutation tests can be used to estimate Type-1 error (false positive rate) by repeatedly randomly assigning patients to Shunt or Control. When applied to each step in the decision tree, the comparison of the observed to the permuted results quantifies the overall probability of Type-1 error. Each test had 100,000 permutations except for the joint frailty model, which was computationally intensive. The joint frailty model was permuted 10,000 times. The overall Type-I error estimate for the interaction branch of the decision tree, was nominal $P < 0.0014$. It is extremely unlikely, under the null, to observe a set of results as extreme as the present set of results. Viewed from another perspective, even if the entire alpha of 0.05 was spent on the primary endpoint, the total alpha spent for the primary and secondary endpoints based on the overall permutation test including both branches of the decision tree would add up to at most nominal P=0.0528 (**Figure 38**). As in **Section 7.3**, the null hypothesis was rejected for the ITT analysis due to a violation of the poolability assumption for of the LVEF strata, and thus the permutation estimate of nominal P=0.0528 for the entire decision tree can be considered a worst-case estimate of the probability of a Type-I error given the results observed.

Figure 38: RELIEVE-HF Primary and Hierarchical Effectiveness Endpoint Decision Tree: Assessment of Inflation of Type-I Error by Permutation Tests



Since the null is true for these random scenarios, "Yes" indicates a false positive, or a Type-I error under the null.

Taken together, these permutation and GST analyses add confidence that the findings in the HFrEF stratum are not likely to be grossly affected by multiple comparisons and inflated Type-1 error. Thus, in the HFrEF stratum, the Shunt maintained a treatment benefit, with low residual uncertainty, on the strength of either the prespecified or additional permutation-based analyses.

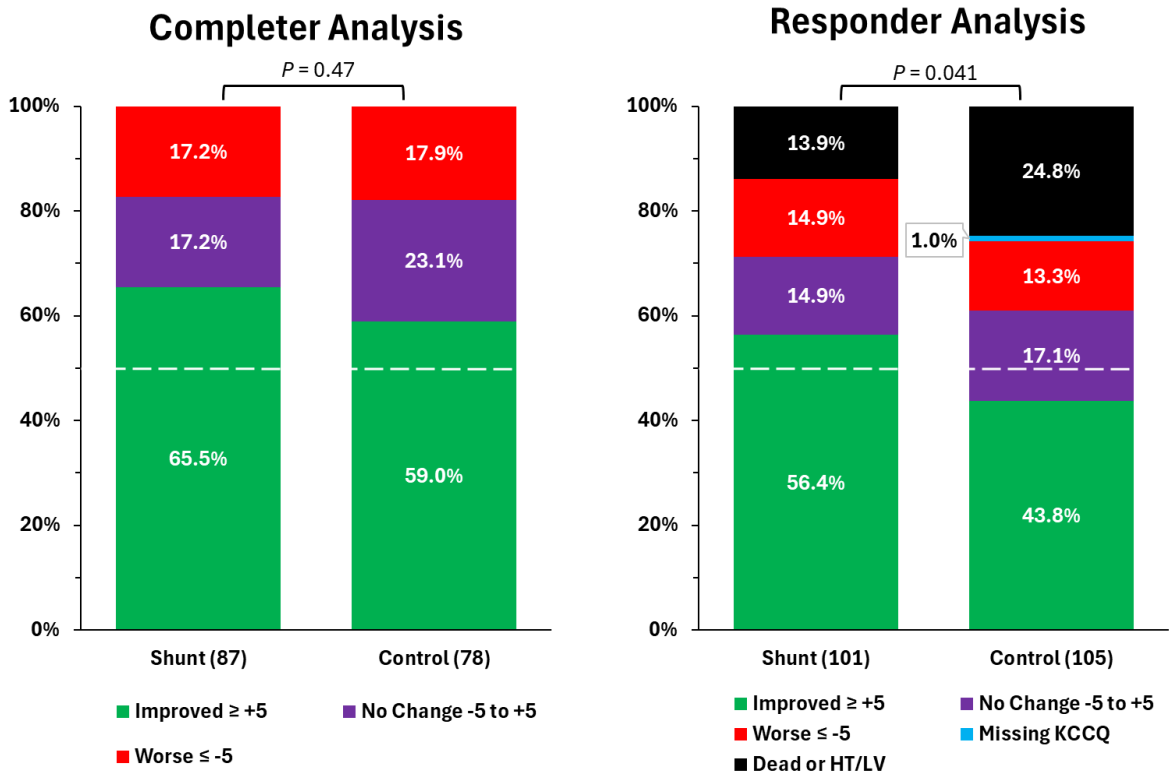
10.6 Additional KCCQ Analysis and Changes in NYHA Functional Class

The KCCQ-OSS secondary endpoint was specified as a test if the difference in the mean changes from baseline to 12 months was higher in the Shunt arm compared to the Control arm using ANCOVA to adjust for the differences in the baseline measurements. These results were already presented graphically in the discussion of the components of the primary effectiveness endpoint (**Section 7.2 Figure 16**). The mean change in KCCQ-OSS in patients with reduced LVEF was +12.2 ± 20.5-point improvement in the Shunt treatment arm and an 11.4 ± 20.5-point improvement in the Control group. These comparisons are a form of "completers analyses" since they describe the population remaining in the trial.

Additional assessments of KCCQ-OSS were performed that categorically ranked changes from baseline as improved (≥ +5 points), no change (> -5 to < 5 points), or worsening (≤ -5 points) at the time of primary analysis. **Figure 39** shows ranked results for KCCQ-OSS changes at the time of primary analysis in HFrEF for completers and also for responders where patients that died or were treated with HTLV (40 patients) or otherwise exited the study (1 patient) were ranked last. In completers, there were no

differences in KCCQ-OSS changes between Shunt and Control groups. When the disposition of all patients was examined in the responder analysis, Shunt-treated patients had improved outcomes, i.e. there were more Shunt patients with better outcomes, largely due to fewer deaths or HTLV events.

Figure 39: Change in KCCQ-OSS at Primary Follow-up in HFrEF Completers and Responders



Ordinal outcomes containing health status (KCCQ-OSS) and survival in the study in HFrEF stratum patients. Improved ≥ 5 point change from baseline; No Change ≥ -5 to < +5 points; Worse ≤ -5 point change from baseline *P*-values were Mann-Whitney U for ordinal scaled data. The dashed line is the median.
Nominal *P*-values are provided to illustrate the variability of the corresponding summary statistics; they are provided for descriptive purposes and should not be used to draw statistical inference.

The extent of knowledge at the onset of RELIEVE-HF was largely based on unblinded device trials, such as COAPT (Stone et al. 2018), and suggested that a device therapy with marked beneficial differences in clinical outcomes between treatment and control group would also manifest similar magnitude beneficial changes in patient reported outcomes (PROs) like KCCQ. In the context of other recently published studies, the finding neutral differences in mean KCCQ changes between treatment groups in the setting of marked differences in HF Event rates are, however, less surprising. Observations from recent device and drug trials demonstrate the limitations of the KCCQ and other health status assessments and their highly variable correlation with clinical outcomes in cardiovascular device trials. A summary of several of these trials is provided below.

Luo and colleagues (Luo et al., 2019) in the ACTION-HF trial compared the probability of all-cause mortality or HFH over the period of follow-up with change in KCCQ at 3 months and found an inverse relationship between the frequency of events in patients with a change in KCCQ of < +8 points. Paradoxically, when change in KCCQ was > +8, the relationship reversed direction such that despite a larger improvement in KCCQ, patients had higher morbidity and mortality.

The BeAT-HF Pivotal Trial of baroreflex activation therapy (BAT or barostimulation) demonstrated an improvement in the Minnesota Living with Heart Failure (MLWHF) Questionnaire score in the barostimulation group compared to controls (Zile et al., 2020). The trial was unblinded, and the incidence of death and rate of HFH did not appear to differ between the groups (Zile et al., 2024). Thus, there was no correlation between change in MLWHF score and hard outcomes in this trial.

The GUIDE-HF Trial of PAP guided HF management showed no improvement in the KCCQ score in treatment versus Control groups in either the overall analysis or in the pre-COVID impact analysis (Lindenfeld et al., 2021). Between-group comparison of treatment and Control patients demonstrated comparable improvements in the KCCQ score. The trial was single-blinded (patients), and the rate of HFH was reduced in the treatment versus Control group in the pre-COVID impact analysis. There was no correlation between change in KCCQ score and hard outcomes in this trial.

The MONITOR-HF Trial of PAP guided heart failure management demonstrated improvement in KCCQ score in treatment compared to Control patients. The trial was unblinded, and the rate of HFH was reduced in the treatment versus Control group (Brugts et al., 2023). In contrast to GUIDE-HF, there was a correlation between change in KCCQ score and hard outcomes in this trial.

The REDUCE LAP-HF II Pivotal Trial of interatrial shunting for HFpEF patients demonstrated no improvement in KCCQ score in the non-responder subgroup despite a doubling of HF Events with shunt treatment (Shah et al., 2022). Thus, there was no correlation between change in KCCQ score and harmful outcomes in this trial.

While beta blockers produce large reductions in morbidity and mortality in HFrEF, a review of other β-blocker trials has reported inconsistent but generally neutral effects on quality of life with drug treatment (Reddy & Dunn, 2000). In seven of 10 studies that used PROs, no significant improvement was seen with β blockers. The three beta-blocker studies reporting positive effects were small, each involving ≤ 67 patients.

As shown in **Table 40**, large double-blind HF drug trials including PARADIGM-HF, DAPA-HF, EMPEROR-Reduced/Preserved, FINEARTS-HF; which combined had in excess of 28,000 patients, consistently demonstrated robust reductions in death or HFH, yet only small KCCQ differences (1.3–2.8 points) (Anker et al., 2021; McMurray et al., 2014; McMurray et al., 2019; Packer et al., 2020; Solomon et al., 2024). These gains, though statistically significant, illustrate the limited sensitivity of KCCQ compared to hard endpoints. Between-group changes in KCCQ, thus do not strongly reflect major

drug and device effects in most blinded HF trials. Although only minimal changes in KCCQ were observed in these pharmacotherapy trials, there is widespread consensus that these interventions substantially benefit patients with HF, as reflected by their Class I indications in the guidelines and widespread adoption.

Table 40: Comparison of Large Pharma Trial Event-driven Primary Endpoints with Change in KCCQ in HFrEF and HFpEF

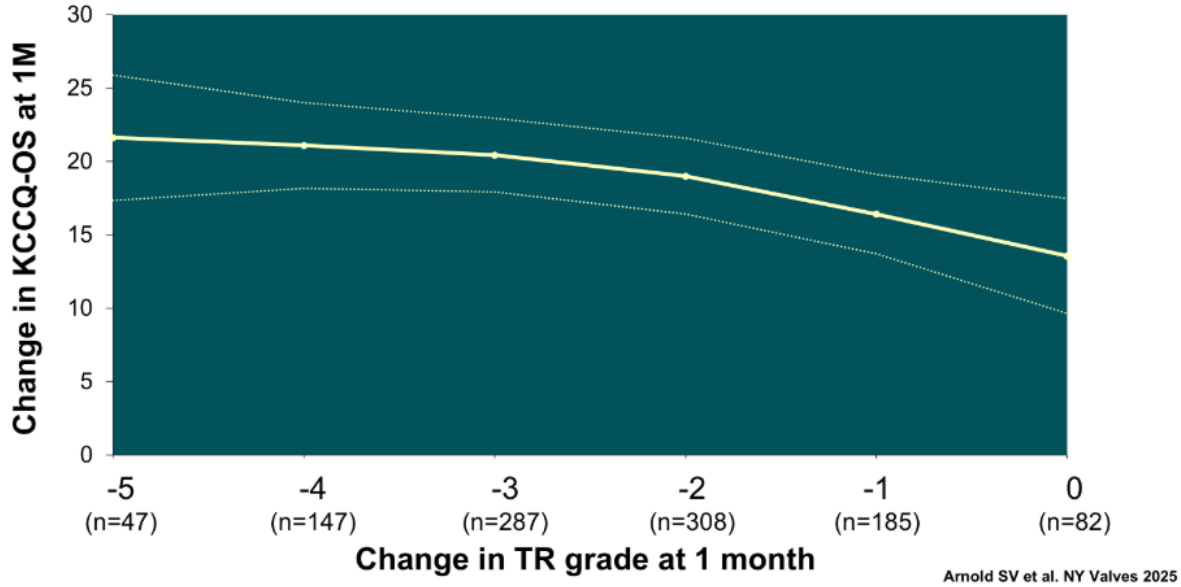
				Primary Endpoint		Between-Group Change in KCCQ (MCID=5 pts)
Study	N	Disease	Intervention	Clinical Events	HR or RRR	
EMPEROR-Reduced[1]	3,730	HFrEF	Empagliflozin	CV death or HF hospitalization	0.75	+1.7
EMPEROR-Preserved[2]	5,988	HFpEF	Empagliflozin	CV death or HF hospitalization	0.79	+1.3
DAPA-HF[3]	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 Interatrial Shunt	All-cause death, HTLV, all HFHs, all outpatient WHFs	0.49	+0.4
RELIEVE-HF (Preserved)[6]	302	HFpEF	Ventura Interatrial Shunt	All-cause death, HTLV, all HFHs, all outpatient WHFs	1.69	-1.7

CV=cardiovascular; HF=heart failure; HFH=heart failure hospitalization; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; HR=hazard ratio; HTLV=heart transplant or LVAD; KCCQ=Kansas City Cardiomyopathy Questionnaire; LVAD=left ventricular assist device; MCID=minimum clinically important difference; RRR=relative risk ratio; WHF=worsening heart failure
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.

The TRILUMINATE Pivotal Trial of tricuspid transvascular edge-to-edge repair (TEER) showed an improvement in the KCCQ score in the TEER group compared to controls (Sorajja et al., 2023). The trial was unblinded, and the incidence of death or tricuspid valve surgery and the rate of hospitalization for HF did not appear to differ between the groups. Thus, there was no correlation between change in KCCQ score and hard outcomes in this trial.

The TRI-QOL analysis (N=1,056, comprising 6 unblinded tricuspid valve repair studies — see **Figure 40**) showed ~13–15-point KCCQ gains even in patients with negligible or no tricuspid regurgitation reduction—consistent with large placebo/Hawthorne effects (Arnold, 2025).

Figure 40: Tri-QOL: Change in KCCQ-OS by Change in Tricuspid Regurgitation After TTVI

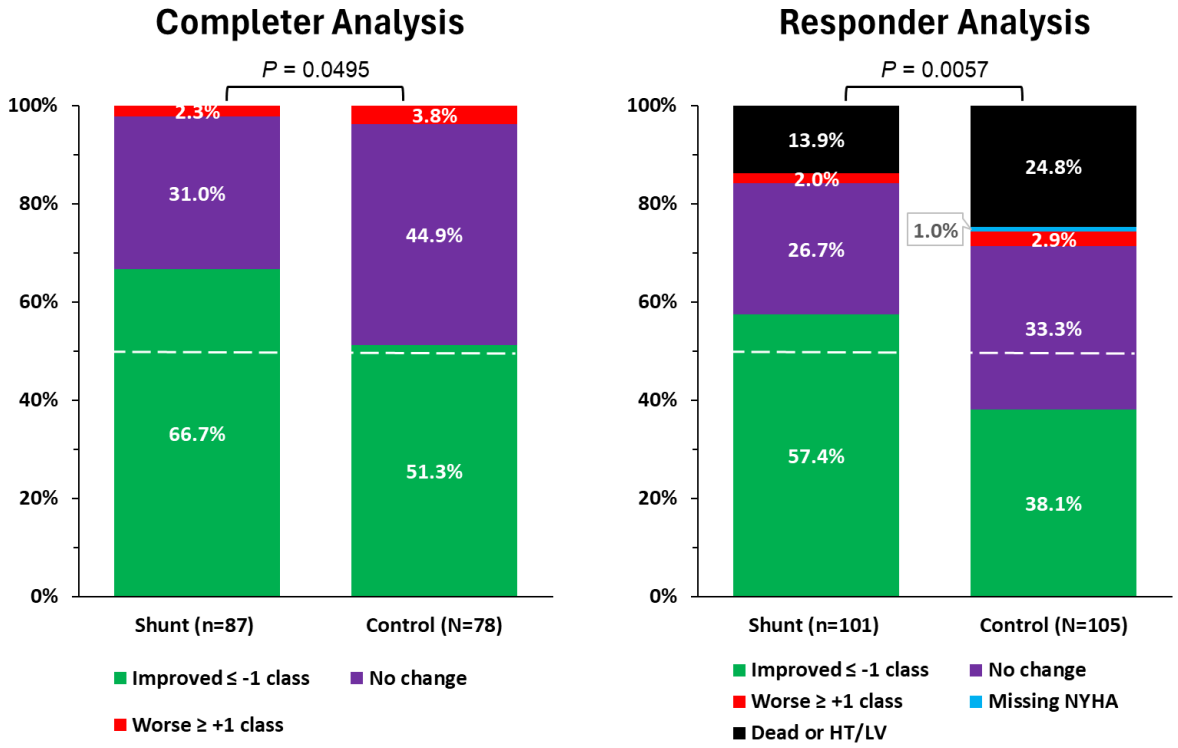


Presentation by Dr. Suzanne Arnold at New York Valves 2025 meeting showing that when open-label TEER procedure resulted in minimal or no change in tricuspid insufficiency, KCCQ improved on average by at least 13 points.

Finally, other data consistent with a strong placebo effect on KCCQ were apparent in RELIEVE-HF. For example, for 12-month blinding questionnaires in the ITT population, there were 154 patients who believed or suspected their treatment assignment because they had improved or worsened symptoms. Those that believed they received a Shunt (correctly in 59%) had an average +18.6-point improvement in ∆ KCCQ at 12-months, whereas those that believed they were Controls had only a +4.5-point improvement.

Clinician assessment of symptom status, NYHA class, shows that both completers and responders analyses correlated with outcomes in the HFrEF stratum (**Figure 41**). Perhaps KCCQ-OSS is more subjective as it is more likely to be affected by how the patient feels about their quality of life as it includes social and other factors and many of the assessments were performed during the Covid-19 pandemic. NYHA assessment by trained HF clinicians, however, may be less subjective as it is more rule-based relating symptoms to activity.

Figure 41: Change from Baseline in New York Heart Association (NYHA) Functional Class in HFrEF Completers and Responders at Time of Primary Follow-up



Ordinal outcomes containing NYHA functional class status and survival in RELIEVE-HF HFrEF stratum patients. Worse=increase in NYHA Class by at least 1 class from baseline; no change=NYHA class did not change from baseline (increase or decrease); improved =decrease in NYHA Class by ≥ 1 class; *P*-values are Mann-Whitney U for ordinal scaled data. The dashed line is the median.
Nominal *P*-values are provided to illustrate the variability of the corresponding summary statistics; they are provided for descriptive purposes and should not be used to draw statistical inference.

10.7 Additional Details on Stratified Recurrent Event Analyses

10.7.1 Methods

The Nelson-Aalen estimator was used to construct hazard rate functions, and HRR were compared by Kolmogorov-Smirnov testing and point estimate testing at 24 months by z-score (Aalen, 1978; Bluhmki et al., 2019; Borgan, 2005; Lin, 1997; Nelson, 1969). The joint frailty model already used for recurrent HFH was also used to quantify other recurrent events where Terminal Events were treated as competing events (Liu & Huang, 2008). As the primary endpoint was not met, these were performed post hoc, as were multiple additional recurrent event analyses including: Poisson and negative binominal models adjusted for over dispersion and zero inflation; Anderson Gill extension of the Cox proportional hazard model with robust standard errors, also known as the LWYY model with and without stratification by time after enrollment (Lin et al., 2000); the PWP-TT model (extension of Cox) stratified by the number of events (Prentice et al., 1981); and the ratio of AUC using the Gosh Lin estimator, an extension of restricted mean event-free survival time methodology, to generate event-free time gained or lost by treatment (Claggett et al., 2022; Ghosh & Lin, 2000). Landmark analysis was applied to AUC models to assess bias in favor of early events that may occur prior to the onset of benefit after shunt treatment (Dafni, 2011; Peterson et al., 2021). All models were fit separately for the HFpEF and HFrEF strata. The choice of recurrent event models was based on their use in prior clinical trials of HF therapies (Braga et al., 2018; Claggett et al., 2018; Gregson et al., 2023; Rogers et al., 2014). Interaction terms were incorporated into each model to test for differences in the magnitude of treatment effect and Gail Simon testing for qualitative (crossover) interactions were evaluated to determine if the direction of treatment effect differed between HFrEF and HFpEF (Gail & Simon, 1985). The NNT for each outcome category was calculated for the Nelson-Aalen estimates (Cook, 2013).

HFrEF patients were assessed for consistency of HF Events outcomes by annualized event rates in prespecified and post hoc subgroups. Bootstrap resampling with replacement (N=10,000) of the Nelson-Aalen estimates for HFH, HF Events and All Events categories, where patients were the sampling unit, to compare different samples of the enrolled HFrEF population that might have been selected from this group at random. HRRs and their logarithms were generated, and bias corrected accelerated CIs were obtained. A HRR 1.0 or Ln(HRR) 0 was indicative of alpha=0.05. Sensitivity analyses of the upper LVEF boundary of 40% were also performed.

Statistical analyses were verified by independent double coding using SAS 9.4 or R V4.3.2 software packages. *P*-values are two-sided without adjustment for multiplicity and should be considered indicative of the strength of the evidence, not a decision rule.

10.7.2 Results

Nelson-Aalen cumulative hazard rates and HRRs in the HFrEF and HFpEF strata patients are detailed in **Table 41** and plotted in **Figure 42**. In HFrEF at 24 months,

Terminal Events, HFH, HF Events, and All Events were reduced by 58%, 54%, 51%, and 41%, respectively. Similarly, the NNT to prevent one event was 4.3 (2.2–18.6) per Terminal Event, 1.6 (1.1–3.5) for HFH, 1.0 (0.7–1.8) per HF Event and 0.8 (0.6–1.4) for All Events. The curves start to separate at 3 months for HFH, at 7 months for HF Events and All Events, and at 12 months for Terminal Events. Thereafter, the differences progressively widened out to 24 months. Control hazard rates at 24 months were ≥ 2X higher in HFrEF compared to HFpEF. In HFpEF, there were early and persistent separations between treatment and control groups with markedly higher hazard rates in shunted patients.

Table 42 summarizes all recurrent event models in HFrEF patients. All models had nominally significant reductions in Shunt-treated patients for HFH, HF Events, and All Events outcome categories. Using the AUC model, shunt treatment increased HF Event-free time by 6.4 (0.5–12.4) months (nominal *P*=0.034), and All Event-free time by 8.2 (0.4–16.0) months (nominal *P*=0.041).

Table 43 details the same analytics for HFpEF patients and **Table 44** shows interaction testing of these models between the LVEF strata. HFpEF patients had worse outcomes with shunt treatment across all models and event categories, and there were strong quantitative and qualitative (crossover) interactions between the LVEF stratified groups.

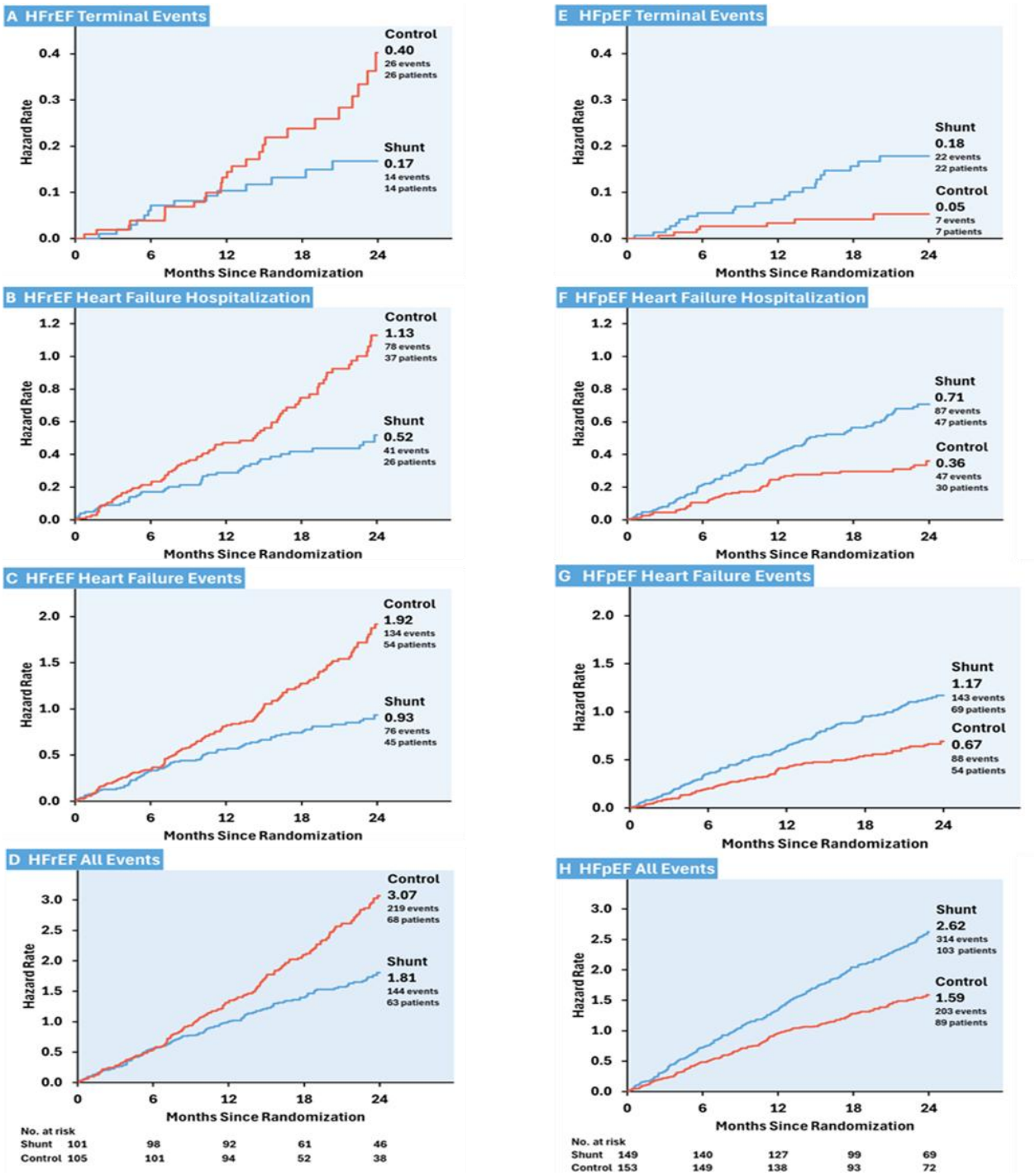
Figure 43 examines Shunt vs. control rate ratios for HF Events at 24 months when the HFrEF population is divided into 17 dichotomous prespecified and post hoc subgroups. All subgroups had rate ratios < 1.0 favoring benefit for Shunt-treated patients. **Figure 44** shows the original and log-transformed bootstrapped resampled distributions for HF Events. Similar bootstrap distributions were observed for HFH alone and the All Events composite. Irrespective of the outcome category, resampling and replacement consistently favored shunt treatment. Improved events rates for Shunt versus control were observed in 99.3%, 99.8% and 99.6% of samples for HFH, HF Events, and All Events categories, respectively. Log-transformed data were confirmed to be normally distributed by multiple methods. These findings provide internal validation that the observed treatment effects were not driven by random sampling variability and reinforce the reliability of results across increasingly inclusive event definitions.

Table 41: Nelson-Aalen Estimator Cumulative Hazard Rates and Hazard Rate Ratios for Event Types, Singly and in Combination for the Reduced and Preserved LVEF Strata

	Reduced LVEF ≤ 40% (HFrEF, N=206)			Preserved LVEF > 40% (HFpEF, N=302)			
Outcomes	**Shunt Hazard Rate**	**Control Hazard Rate**	**Hazard Rate Ratio (95% CI)**	**Shunt Hazard Rate**	**Control Hazard Rate**	**Hazard Rate Ratio (95% CI)**	**HFrEF vs HFpEF Interaction Nominal *P*-value**
Individual Event Types							
Death (all-cause)	0.15	0.32	0.48 (0.20–1.06)	0.18	0.05	3.38 (1.48, 12.7)	0.005
Heart Transplant/ LVAD (HTLV)	0.02	0.10	0.15 (0.00–0.98)	-	-	-	-
Hospitalization for HF (HFH)	0.52	1.13	0.46 (0.29–0.68)	0.71	0.36	1.96 (1.37, 2.95)	< 0.001
Hospitalization not for HF (NHFH)	0.87	1.15	0.76 (0.54–1.07)	1.45	0.90	1.62 (1.27, 2.09)	< 0.001
All-Cause Hospitalization (ACH)	1.39	2.28	0.61 (0.47–0.79)	2.16	1.26	1.72 (1.40, 2.12)	< 0.001
Worsening HF outpatient (WHF)	0.25	0.38	0.64 (0.33–1.17)	0.29	0.28	1.03 (0.61, 1.72)	0.25
Composite Event Types							
Terminal Events (Death, HTLV)	0.17	0.40	0.42 (0.18–0.84)	0.18	0.05	3.38 (1.48, 12.5)	0.002
HFH, WHF	0.77	1.51	0.51 (0.35–0.70)	0.99	0.64	1.55 (1.16, 2.11)	< 0.001
Death, HTLV, HFH	0.69	1.53	0.45 (0.31–0.63)	0.88	0.41	2.14 (1.54, 3.12)	< 0.001
Death, HTLV, ACH	1.56	2.68	0.58 (0.45–0.74)	2.34	1.31	1.78 (1.47, 2.19)	< 0.001
HF Events (Death, HTLV, HFH, WHF)	0.93	1.92	0.49 (0.35–0.65)	1.17	0.69	1.69 (1.29, 2.27)	< 0.001
All Events (death, HTLV, ACH, WHF)	1.81	3.07	0.59 (0.47–0.73)	2.62	1.59	1.65 (1.38, 1.99)	< 0.001

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.

Figure 42: Nelson-Aalan Hazard Rate Functions in HFrEF (A-D) and HFpEF (E-H) Strata for Shunt and Control Groups



Terminal Events (death, heart transplant or left ventricular assist device); Heart Failure hospitalizations (HFH); Heart Failure Events, (Terminal Events, HFH, and worsening heart failure treated as an outpatient (WHF)); and All Events, (Terminal Events, all-cause hospitalization and WHF).

Table 42: Recurrent Event Outcomes by 24 Months in the Reduced LVEF ≤ 40% (HFrEF) Stratum

HFrEF (LVEF ≤ 40%)	HFH	HF Events (all-cause death, HTLV, HFH, WHF)	All Events (all-cause death, HTLV, ACH, WHF)
Nelson-Aalen estimator[1]	0.46 (0.29–0.68)	0.49 (0.35–0.65)	0.59 (0.47–0.73)
Joint Frailty[2]	0.52 (0.32–0.84)	0.57 (0.37–0.88)	0.68 (0.47–0.97)
Poisson[3]	0.55 (0.34–0.90)	0.57 (0.38–0.84)	0.65 (0.48–0.89)
Negative Binomial[4]	0.55 (0.33–0.91)	0.59 (0.39–0.89)	0.66 (0.48–0.92)
LWYY[5]	0.52 (0.31–0.87)	0.56 (0.36–0.85)	0.64 (0.46–0.90)
LWYY[6]	0.47 (0.28–0.77)	0.46 (0.31–0.69)	0.62 (0.45–0.84)
PWP-TT[7]	0.58 (0.40–0.84)	0.66 (0.50–0.88)	0.73 (0.59–0.91)
Ratio of AUC[8]	0.60 (0.33–0.95)	0.65 (0.44–0.99)	0.73 (0.55–0.99)
Ratio of AUC[9]	0.46 (0.23–0.91)	0.49 (0.29–0.79)	0.56 (0.39–0.84)

Data are presented as HR, RR, or HRR (95%CI). Abbreviations: ACH=all-cause hospitalization; AUC=area under the curve; HF=heart failure; HFH=heart failure hospitalization; HR=hazard ratio; HRR=hazard rate ratio; HFrEF=heart failure with reduced ejection fraction; HTLV=heart transplantation or left ventricular assist device; LVEF=left ventricular ejection fraction; LWYY=Lin-Wei-Yang-Ying model; PWP-TT=Prentice-Williams-Peterson total time model; RR=rate ratio; WHF=worsening HF treated with intravenous therapy as an outpatient.
[1]Nelson-Aalen ratio of cumulative hazard comparison of point estimate at 24 months by z-test. [2]Joint Frailty with all-cause death and HTLV as competing events. [3]Poisson regression adjusted for over dispersion and zero inflation. [4]Negative Binomial adjusted for over dispersion and zero inflation. [5]LWYY model also known as Andersen-Gill model with robust standard error. [6]LWYY model stratified by time before/after 6 months. [7]PWP-TT model allows hazard of later events to be different from earlier events. [8]Area under the curve (AUC) ratio, based on Ghosh-Lin mean cumulative count curves. [9]AUC ratio with start time set to 6 months after randomization (landmark).
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 43: Recurrent Event Outcomes by 24 Months in the Preserved LVEF > 40% (HFpEF) Stratum

HFpEF (LVEF > 40%)	HFH	HF Events (all-cause death, HTLV, HFH, WHF)	All Events (all-cause death, HTLV, ACH, WHF)
Nelson-Aalen estimator[1]	1.96 (1.37–2.95)	1.69 (1.29–2.27)	1.65 (1.38–1.99)
Joint Frailty[2]	2.07 (1.35–3.20)	1.69 (1.17–2.46)	1.70 (1.27–2.29)
Poisson[3]	1.82 (1.16–2.86)	1.68 (1.19–2.38)	1.59 (1.23–2.05)
Negative Binomial[4]	1.83 (1.16–2.88)	1.67 (1.16–2.40)	1.58 (1.21–2.05)
LWYY[5]	1.92 (1.19–3.08)	1.68 (1.17–2.42)	1.60 (1.22–2.09)
LWYY[6]	1.56 (1.02–2.37)	1.41 (1.03–1.94)	1.45 (1.16–1.82)
PWP-TT[7]	1.67 (1.17–2.39)	1.50 (1.15–1.96)	1.41 (1.17–1.70)
Ratio of AUC[8]	1.81 (1.17–2.92)	1.63 (1.13–2.37)	1.50 (1.15–1.99)
Ratio of AUC[9]	1.77 (1.00–2.98)	1.56 (1.01–2.42)	1.57 (1.13–2.16)

Data are presented as HR, RR, or HRR (95%CI). Abbreviations: ACH=all-cause hospitalization; AUC=area under the curve; HF=heart failure; HFH=heart failure hospitalization; HR=hazard ratio; HRR=hazard rate ratio; HFrEF=heart failure with reduced ejection fraction; HTLV=heart transplantation or left ventricular assist device; LVEF=left ventricular ejection fraction; LWYY=Lin-Wei-Yang-Ying model; PWP-TT=Prentice-Williams-Peterson total time model; RR=rate ratio; WHF=worsening HF treated with intravenous therapy as an outpatient.
[1]Nelson-Aalen ratio of cumulative hazard comparison of point estimate at 24 months by z-test. [2]Joint Frailty with all-cause death and HTLV as competing events. [3]Poisson regression adjusted for over dispersion and zero inflation. [4]Negative Binomial adjusted for over dispersion and zero inflation. [5]LWYY model also known as Andersen-Gill model with robust standard error. [6]LWYY model stratified by time before/after 6 months. [7]PWP-TT model allows hazard of later events to be different from earlier events. [8]Area under the curve (AUC) ratio, based on Ghosh-Lin mean cumulative count curves. [9]AUC ratio with start time set to 6 months after randomization (landmark).
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 44: Quantitative and Qualitative Interaction Testing Between LVEF ≤ 40% (HFrEF) and LVEF > 40% (HFpEF) Strata

HFrEF (LVEF ≤ 40%)/ HFpEF (LVEF > 40%)	HFH	HF Events (all-cause death, HTLV, HFH, WHF)	All Events (all-cause death, HTLV, ACH, WHF)
Nelson-Aalen estimator[1]	0.23 (0.11–0.54) P_{int} < 0.001; P_{GS} < 0.001	0.29 (0.17–0.53) P_{int} < 0.001; P_{GS} < 0.001	0.36 (0.22–0.59) P_{int} < 0.001; P_{GS} < 0.001
Joint Frailty[2]	0.25 (0.13–0.48) P_{int} < 0.001	0.34 (0.19–0.459) P_{int} < 0.001	0.40 (0.25–0.64) P_{int} < 0.001
Poisson[3]	0.30 (0.16–0.60) P_{int} < 0.001	0.34 (0.20–0.57) P_{int} < 0.001	0.41 (0.27–0.61) P_{int} < 0.001
Negative Binomial[4]	0.30 (0.15–0.60) P_{int} < 0.001	0.35 (0.20–0.61) P_{int} < 0.001	0.42 (0.28–0.64) P_{int} < 0.001
LWYY[5]	0.27 (0.13–0.54) P_{int} < 0.001; P_{GS}=0.006	0.33 (0.19–0.58) P_{int} < 0.001; P_{GS}=0.003	0.40 (0.26–0.62) P_{int} < 0.001; P_{GS}=0.004
LWYY[6]	0.30 (0.15–0.58) P_{int} < 0.001	0.33 (0.20–0.54) P_{int} < 0.001	0.42 (0.29–0.63) P_{int} < 0.001
PWP-TT[7]	0.35 (0.21–0.58) P_{int} < 0.001	0.44 (0.30–0.66) P_{int} < 0.001	0.52 (0.39–0.69) P_{int} < 0.001
Ratio of AUC[8]	0.33 (0.15–0.65) P_{int} < 0.001	0.40 (0.24–0.71) P_{int}=0.004	0.48 (0.32–0.72) P_{int} < 0.001
Ratio of AUC[9]	0.26 (0.10–0.62) P_{int}=0.002	0.31 (0.16–0.60) P_{int} < 0.001	0.36 (0.21–0.60) P_{int} < 0.001

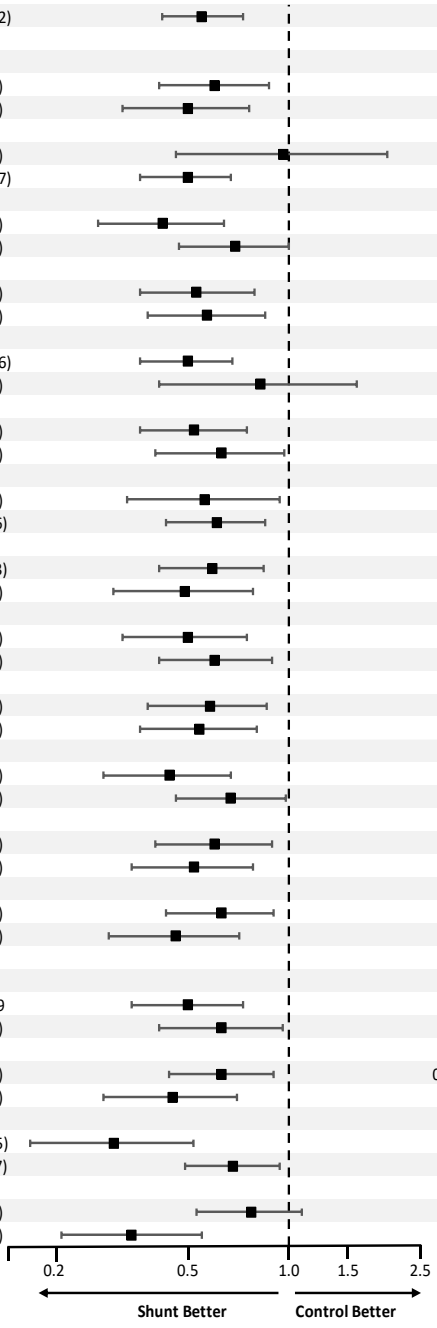
Data are presented as HR, RR, or HRR (95%CI); P_{int}=quantitative interaction test; P_{GS}=Gail Simon qualitative (crossover) interaction test. Abbreviations: ACH=all-cause hospitalization; AUC=area under the curve; HF=heart failure; HFH=heart failure hospitalization; HR=hazard ratio; HRR=hazard rate ratio; HFrEF=heart failure with reduced ejection fraction; HT/LV=heart transplantation or left ventricular assist device; LVEF=left ventricular ejection fraction; LWYY=Lin-Wei-Yang-Ying model; PWP-TT=Prentice-Williams-Peterson total time model; RR=rate ratio; WHF=worsening HF treated with intravenous therapy as an outpatient.

[1]Nelson-Aalen ratio of cumulative hazard comparison of point estimate at 24 months by z-test. [2]Joint Frailty with all-cause death and HTLV as competing events. [3]Poisson regression adjusted for over dispersion and zero inflation. [4]Negative Binomial adjusted for over dispersion and zero inflation. [5]LWYY model also known as Andersen-Gill model with robust standard error. [6]LWYY model stratified by time before/after 6 months. [7]PWP-TT model allows hazard of later events to be different from earlier events. [8]Area under the curve (AUC) ratio, based on Ghosh-Lin mean cumulative count curves. [9]AUC ratio with start time set to 6 months after randomization (landmark).

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.

Figure 43: Subgroup Analyses of Heart Failure Events within 24 Months in HFrEF (LVEF ≤ 40%) Stratum

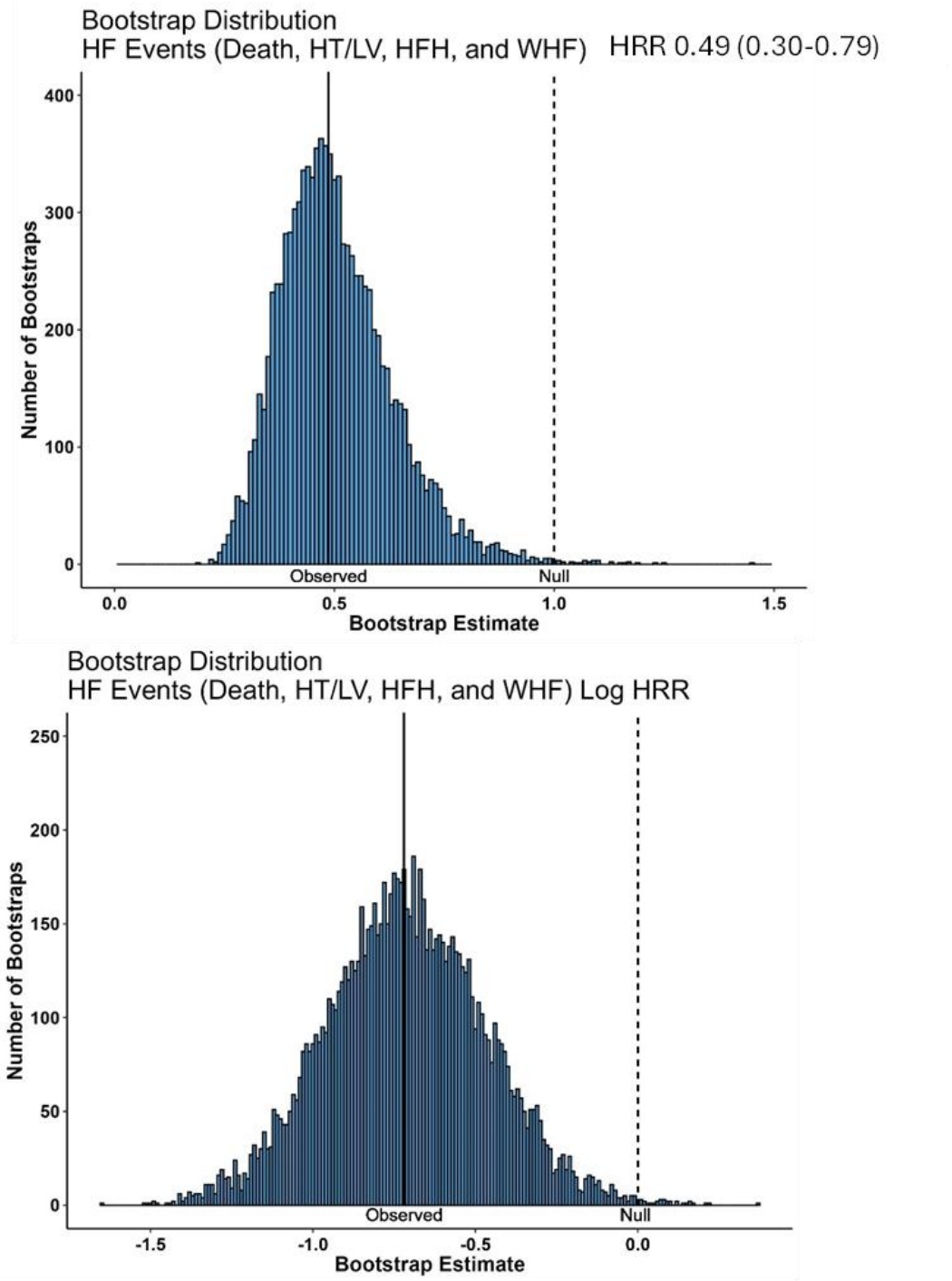
Subgroup	No. of Patients	Shunt Group *annualized rate % (no. of events/ no. of patient-yr)*	Control Group *annualized rate % (no. of events/ no. of patient-yr)*	Relative Risk (95%CI)
All patients	206	49.0 (76/155.2)	88.6 (134/151.2)	0.55 (0.42-0.73)
Prespecified subgroups				
Age				
≥ 70 yr	105	52.9 (46/87.0)	88.8 (63/71.0)	0.60 (0.41-0.87)
< 70 yr	101	44.0 (30/68.2)	88.5 (71/80.2)	0.50 (0.32-0.76)
Sex				
Female	38	55.2 (14/25.4)	57.6 (17/29.5)	0.96 (0.46-1.96)
Male	168	47.8 (62/129.8)	96.2 (117/121.7)	0.50 (0.36-0.67)
BMI				
≥ 30 kg/m^2	94	41.3 (28/67.8)	99.0 (70/70.7)	0.42 (0.27-0.64)
< 30 kg/m^2	112	55.0 (48/87.3)	79.5 (64/80.5)	0.69 (0.47-1.00)
Diabetes				
Yes	105	47.7 (37/77.6)	89.3 (71/79.3)	0.53 (0.36-0.79)
No	101	50.2 (39/77.6)	87.9 (63/71.7)	0.57 (0.38-0.85)
Hypertension				
Yes	161	49.4 (62/125.6)	98.9 (112/113.6)	0.50 (0.36-0.68)
No	45	47.4 (14/29.5)	58.0 (22/37.9)	0.82 (0.41-1.59)
Cause of cardiomyopathy				
Ischemic	129	43.0 (45/104.5)	83.2 (76/91.4)	0.52 (0.36-0.75)
Nonischemic	77	61.2 (31/50.6)	97.0 (58/59.8)	0.63 (0.40-0.97)
Baseline left ventricular ejection fraction				
≥ median 30.5%	103	26.8 (24/89.5)	47.6 (36/75.6)	0.56 (0.33-0.94)
< median 30.5%	103	79.2 (52/65.7)	129.6 (98/75.6)	0.61 (0.43-0.85)
Natriuretic peptides, BNP or NT-proBNP				
≥ median BNP 373, NT-pro BNP 2150 pg/ml	99	67.8 (50/73.7)	115.0 (82/71.3)	0.59 (0.41-0.84)
< median BNP 373, NT-pro BNP 2150 pg/ml	107	31.9 (26/81.4)	65.1 (52/79.9)	0.49 (0.30-0.78)
eGFR				
≥ median 47 ml/min/1.73m^2	103	44.9 (31/69.1)	90.0 (77/85.6)	0.50 (0.32-0.75)
< 47 median ml/min/1.73m2	103	52.2 (45/86.1)	86.9 (57/65.6)	0.60 (0.41-0.89)
6-minute walk distance				
≥ median 280 m	103	47.0 (40/8.1)	81.6 (60/75.3)	0.58 (0.38-0.86)
< median 280 m	103	51.4 (36/70.0)	95.3 (74/77.7)	0.54 (0.36-0.80)
KCCQ-OSS				
≥ median 55	104	38.4 (31/80.8	87.4 (69/78.9)	0.44 (0.28-0.67
< median 55	102	60.5 (45/74.3)	90.0 (65/72.3)	0.67 (0.46-0.98
Region				
United States	97	59.0 (39/66.2)	98.0 (71/72.4)	0.60 (0.40-0.89)
Rest of the world	109	41.6 (37/89.0)	80.0 (63/78.7)	0.52 (0.34-0.78)
Enrolled HFrEF patients per site				
≥ median 4	115	55.3 (49/88.5)	88.5 (75/84.8)	0.63 (0.43-0.90)
< 5 median 4	91	40.5 (27/66.6)	88.9 (59/66.4)	0.46 (0.29-0.71)
Post hoc subgroups				
Duration of HF				
≥ median 6.4 yr	103	55.1 (39/70.8)	109.3 (83/75.9	0.50 (0.34-0.73)
< median 6.4 yr	103	43.9 (37/84.4)	69.6 (51/73.3)	0.63 (0.41-0.96)
Heart failure hospitalization prior 1 yr				
Yes	108	57.7 (49/84.9)	91.4 (69/75.5)	0.63 (0.44-00.91)
No	98	38.4 (27/70.2)	85.9 (65/75.7)	0.45 (0.28-0.70)
Atrial fibrillation, permanent or persistent				
Yes	52	38.3 (18/47.0)	126.9 (40/31/5)	0.30 (0.17-0.52)
No	154	53.6 (58/108.2)	78.5 (94/119.7)	0.68 (0.49-0.94)
Pulmonary vascular resistance				
≥2 WU	112	68.0 (52/76.5)	88.8 (73/82.2)	0.77 (0.53-1.09)
<2 WU	94	30.5 (24/78.7)	88.5 (61/68.9)	0.34 (0.21-0.55)



Rates are annualized estimates of Heart Failure Events including all-cause death, heart transplantation, left ventricular assist device implantation, all heart failure hospitalizations (HFH) and all worsening heart failure treated as an outpatient with intravenous therapies (WHF). The table contains all prespecified subgroups (except NYHA Class where 96% were NYHA III).

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.

Figure 44: Bootstrap Resampling with Replacement (N=10,000) of LVEF ≤ 40% (HFrEF) Stratum for Nelson-Aalen Comparison of Shunt vs. Control for HF Events (All-Cause Death, HTLV, HFH and WHF Events)



Top, original data. Bottom, log-transformed data. Bootstrapped samples (99.8%) were improved with shunt treatment. Abbreviations: HFH=heart failure hospitalization; HRR=hazard rate ratio at 24 months after randomization; HT/LV=heart transplant/left ventricular assist device; WHF= worsening heart failure treated as an outpatient.

10.7.3 Differential Response in HFpEF vs. HFrEF

A critical observation in this study was the marked difference in treatment response between the HFrEF and HFpEF populations. In RELIEVE-HF, randomization was stratified by LVEF specifically because it was felt by the investigators to be the most likely physiological determinant that could impact the effectiveness of the shunt treatment. Indeed, patients with HFpEF fared worse with shunt therapy. Quantitative and qualitative statistical interaction terms for multiple outcome categories confirmed this fundamentally differential treatment effect and indicate that outcome data should not be pooled between the 2 LVEF strata (Aschengrau & Seage, 2014; Higgins et al., 2024). Moreover, the opposite and worse outcomes in HFpEF patients, also known as crossover interactions, provides an important contrast that strengthens the inference of true therapeutic benefit in HFrEF (Gail & Simon, 1985; Wang et al., 2021). The opposing trends across LVEF strata for all outcomes reduces the likelihood that observed effects in HFrEF are due to chance heterogeneity or unmeasured bias.

Instead, the divergent outcomes may reflect differences in underlying pathophysiology. In HFrEF, elevated left-sided filling pressures due to systolic dysfunction may be effectively alleviated by left atrial decompression, allowing the time needed for reverse remodeling (Eigler et al., 2017; Zile et al., 2025). Cumulative hazard analyses showed that HFH rates began to diverge by approximately 3 months post-randomization, while separation in Terminal Event curves emerged around 12 months. This pattern is consistent with the hypothesis that interatrial shunting improves congestion and HF event burden by preventing further detrimental LV remodeling or promoting reverse remodeling over time. Additionally, HFrEF patients with Terminal Events (all-cause death or HTLV) had a substantially higher rate of HFH and WHF events compared to patients remaining in the trial. This is consistent with observations correlating the number of recurrent HFH episodes and mortality (Huusko et al., 2020; Lindmark et al., 2021; Shah et al., 2017). Conversely, HFpEF is characterized by a complex interplay of diastolic dysfunction, vascular stiffening, chronotropic incompetence, and right heart involvement (Guazzi et al., 2020; Rommel et al., 2018; Sarma et al., 2020; Zile et al., 2004). In this context, left-to-right shunting may offer limited benefit—or even provoke volume overloading of the right heart particularly in patients with latent pulmonary hypertension (Borlaug et al., 2022; Patel et al., 2024; Shah et al., 2022). These physiologic differences may underlie the treatment interaction, underscore the importance of mechanistic targeting in device therapy, and help explain the event specific differential and delayed onset of benefit in HFrEF.

10.7.4 Multiple Recurrent Event Analyses

A variety of recurrent event models including those reported here have been used to examine randomized HF trial datasets including device trials with CRT in MADIT-CRT, implantable hemodynamic monitoring in CHAMPION, GUIDE-HF, LAPTOP-HF and transcatheter edge-to-edge mitral valve repair in COAPT (Abraham et al., 2011; Braga et al., 2018; Claggett et al., 2018; Goldenberg et al., 2011; Gregson et al., 2023;

Lindenfeld et al., 2024; Lindenfeld et al., 2021; Rogers et al., 2014). Recurrent events analyses may increase statistical power relative to time-to-first event models, particularly where there are a substantial number of repeat events (Claggett et al., 2018).

A major strength of this analysis rests in the use of and consistency between multiple recurrent event models, each incorporating different assumptions regarding the timing, dependency, and distribution of repeated events. The Nelson-Aalen estimator, for example, provides a nonparametric assessment of cumulative hazard rates and is useful for visualizing long-term trends, while Poisson and negative binomial models account for event count distributions, especially when adjusting for overdispersion and zero inflation, which may be prevalent confounders with these models. The Andersen-Gill (LWYY) model treats recurrent events as extensions of the Cox model and assumes independence between events, offering a flexible approach for robust error estimation and allowing adjustments for non-proportional hazards. In contrast, the PWP-TT model stratifies events by sequence and time, allowing the hazard for subsequent events to differ from initial ones—a feature particularly relevant in progressive conditions like HF. The AUC model, although assumption free, may be biased in favor of early events, especially when patients have a poor prognosis.

The strength, consistency and convergence of results across these diverse models—both in direction and magnitude—substantially reduces the likelihood that findings are due to Type-I error. This methodological pluralism serves to validate the robustness of the treatment effect, as true signals are more likely to persist across analytical frameworks than false positives (Claggett et al., 2018; Lawlor et al., 2016; Rogers et al., 2014).

Recurrent event models captured the full burden of HF by accounting for the totality of events over time, offering a more comprehensive representation of therapeutic benefit. In contrast, the hierarchical win ratio analysis, which prioritized Terminal Events (death and HTLV) above HFH and WHF, failed to reach statistical significance in HFrEF. This was likely due to the censoring of comparisons once a higher-tier event occurred, effectively discarding meaningful data from patients who experienced frequent HFH or WHF Events. As a result, the win ratio lost statistical power relative to recurrent event models, which incorporate the entirety of events experienced by each patient. These findings highlight a key limitation of the win ratio framework in chronic conditions like HFrEF, where recurrent morbidity represents a substantial component of clinical burden and therapeutic benefit.

Interestingly, the consistent benefits seen for the composite of All Events comprising HF and non-HF-related hospitalizations in HFrEF patients may be hypothesized as shunt treatment reducing comorbid HF, where HF is a secondary cause for hospitalization. For example, there are documented more comorbid hospitalizations in the US than primary HFH (Jackson et al., 2018). Patients hospitalized with comorbid HF are admitted in descending order with primary diagnoses of ischemic heart disease,

pneumonia, COPD, atrial arrhythmias, or stroke, but 69% were hospitalized for other primary etiologies. Whether shunt treatment led to a reduction in comorbid HF associated events in HFrEF patients requires further investigation, but these data make it unlikely that untoward effects of shunting masqueraded as other causes of clinical decompensation requiring hospitalization and would therefore represent potential safety concerns.

10.7.5 Internal Validation and Statistical Robustness

Lower rates of HF Events in the shunt group where consistent across all dichotomous prespecified and post hoc clinical subgroups tested, although only a small number of women were enrolled. Bootstrap resampling and replacement further strengthened the credibility of these findings. In 10,000 randomly sampled comparisons of the enrolled HFrEF population, including many where chance reassignment favored control patients—interatrial shunting, still resulted in reduced hazard of HF Events in 99.8% of replicates. This high level of consistency reduces the likelihood that the observed effects were due to sampling variability or outliers, offering substantial internal validation of the HFrEF results. Additionally, the high event rate in these subpopulations provided sufficient power to detect differences between Shunt and Control in a substantial majority of the subgroups and resamples, further justifying the adequacy of the HFrEF sample size.

10.7.6 Limitations of Recurrent Event Analyses

Several limitations must be acknowledged. First, the recurrent event analyses were conducted post hoc and only some were prespecified in the original trial design. The consistent findings across multiple models, endpoints, and subgroups, however, strengthen the inference reducing uncertainty. Second, recurrent event analyses presented were not adjusted for multiple comparisons, however, the multiple recurrent events models used overlapping data and outcomes are therefore highly correlated or not independent. Finally, long-term durability beyond 24 months, as well as real-world implementation outside of the trial environment, will need to be evaluated in future studies.

10.8 Comparison of REDUCE LAP-HF II to RELIEVE-HF HFpEF Stratum

The two-year findings of a study of another interatrial shunt, performed exclusively in patients with LVEF > 40%, REDUCE LAP-HF II, has been published (Gustafsson et al., 2024). The study had a randomized, double-blind, sham-controlled design. Data were evaluated separately according to responder (N=333) and non-responder (N=265) subgroups described in earlier reports (Borlaug et al., 2022; Shah et al., 2022). These subgroups were not prespecified, nor was their randomization stratified. Rather, the subgroups were derived from examination of a myriad of post hoc subgroups possibilities. Responder patients were defined as having a peak exercise pulmonary vascular resistance (PVR) < 1.74 WU and no pacemaker, while non-responder subgroup patients comprise the remainder where exercise PVR was measurable. The

recent data compare recurrent events outcomes for HF Events defined similarly to the RELIEVE-HF HFH and WHF events.

Table 45 compares the key baseline differences between REDUCE LAP-HF II responders, non-responders, and RELIEVE-HF HFpEF stratum patients. Non-responders had more high-risk features compared to responders including a higher incidence of atrial fibrillation, elevated natriuretic peptide levels (NT-proBNP), reduced RV systolic function (TAPSE), and elevated PVR. RELIEVE-HF HFpEF patients were likely at higher risk for HFH and WHF events due to much higher levels of NT-proBNP and more severe RV systolic dysfunction.

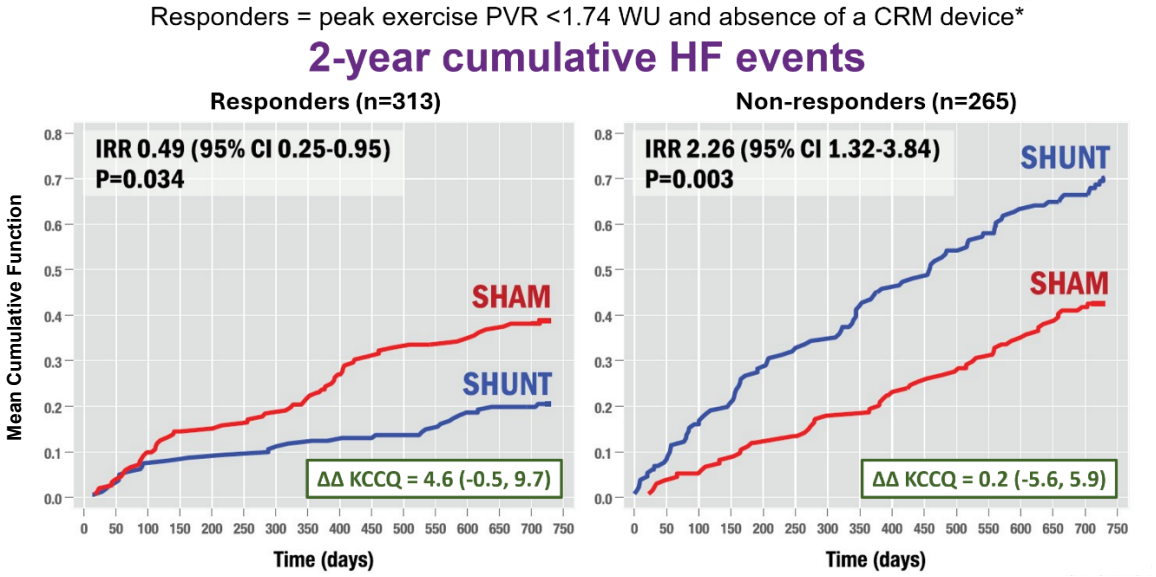
Table 45: Key Baseline Characteristics in Responders and Non-responders in REDUCE LAP-HF II vs RELIEVE-HF HFpEF Cohort

Characteristic	REDUCE LAP-HF II Responders	REDUCE LAP-HF II Non-responders	RELIEVE-HF HFpEF Stratum
Atrial fibrillation	41%	68%	68%
Pacemaker/ICD	0%	43%	40%
NT-pro BNP, pg/ml	299	599	1547
TAPSE, mm	21	20	17
Resting Cardiac index, L/min/m^2	3.0	2.8	2.1
Resting PVR, WU	1.3	1.9	2.1

Average values are medians.
ICD=implantable cardioverter defibrillator; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PVR=pulmonary vascular resistance; TAPSE=Tricuspid annual plane systolic excursion; WU=Wood units.
Source: Patel et al., 2024; Shah ACC Presentation 2024

Figure 25 (from Gustafsson et al., 2024) graphs the mean cumulative function determined by negative binomial regression for HF Events (HFH and WHF) in the REDUCE responder and non-responder subgroups. There are two important finding concerning comparison of REDUCE non-responders to RELIEVE-HF HFpEF stratum. First, the 2-year event rate in sham controls was approximately 0.44, which compares commensurately to the observed hazard rate of 0.64 in the RELIEVE-HF HFpEF stratum, especially considering the RELIEVE-HF HFpEF patients have more high-risk baseline features. Secondly, there was > 2X fold increase of the HF event rate in Shunt-treated non-responders, which was similar to that seen in RELIEVE-HF (see **Section 10.7.2**).

Figure 45: REDUCE LAP-HF II: Responder Analysis



From Gustafsson et al., 2024

*Excluded 5 device group pts in whom a shunt was not implanted and 45 pts with missing exercise PVR data

Finally, the overall findings in the REDUCE LAP-HF II non-responder subgroup are supportive of the results seen in the RELIEVE-HF HFpEF stratum. The differential event rates seen in the Control patients in the two RELIEVE-HF LVEF strata are in line with the studies focusing on HFpEF patients like REDUCE and HFrEF patients with implantable hemodynamic monitor guided therapy (Lindenfeld et al., 2024).