FDA Executive Summary

Prepared for the December 3, 2025, Meeting of the Circulatory System Devices Panel Meeting

Premarket Application (PMA) for

V-Wave® Ventura® Interatrial Shunt System

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1. Introduction

This is FDA's Executive Summary of the original premarket approval (PMA) application from V-Wave for the V-Wave Ventura Interatrial Shunt System for the treatment of NYHA Class III heart failure patients who remain symptomatic despite guideline-directed medical therapy, have a left ventricular ejection fraction 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. This document includes a brief review of heart failure phenotypes and associated standards of care, a description of the device, and a review of the clinical data from the RELIEVE-HF pivotal trial provided in the PMA application.

The V-Wave Ventura Interatrial Shunt System, if it were to be approved, would be the first interatrial shunt device indicated for US patients with heart failure. The PMA is supported by clinical data from the RELIEVE-HF study (Clinicaltrials.gov identifier NCT03499236), which was a blinded, randomized, sham controlled trial.

The Circulatory Systems Devices Panel (the Panel) will be asked to review the totality of the data submitted by V-Wave and provide recommendations regarding whether a reasonable assurance of safety and effectiveness has been demonstrated for the V-Wave Ventura Interatrial Shunt System for its intended use and if the device's benefits outweigh its risks.

2. Background

Approximately 6.7 million Americans and more than 26 million people worldwide have heart failure (HF).[1,2,3] HF rates are increasing; the lifetime risk of HF has increased to 24%, approximately one in four persons will develop HF in their lifetime, and the global prevalence of HF ranges between 1-3%. HF management requires high levels of health care resource utilization.

HF is a complex clinical syndrome with symptoms and signs resulting from structural or functional impairment of ventricular filling or ejection of blood. It is characterized by high mortality and hospitalization rates and a reduced quality of life. Left ventricular ejection fraction (LVEF, the percent of the blood in the left ventricle at end diastole that is ejected during systole) is commonly used to describe HF phenotypes and has frequently been used in clinical trials.

Cardiovascular professional societies including the American Heart Associated (AHA), the American College of Cardiology (ACC), the Heart Failure Society of America (HFSA), and the European Society of Cardiology (ESC) have issued consensus recommendations for HF definition and treatment.[4] The following terminology is used for HF when defined by LVEF:

[1] Ambrosy P, Fonarow GC, Butler J, et al. The Global Health and Economic Burden of Hospitalizations for Heart Failure. Lessons Learned from Hospitalized Heart Failure Registries. J Am Coll Cardiol. 2014;63:1123–1133.
[2] Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics-2014 Update. A Report from the American Heart Association. Circulation 2014,128: DOI: 10.1161/01.cir.0000441139.02102.80.
[3] Butler J, Braunwald E, Gheorghiade M. Recognizing worsening chronic heart failure as an entity and an end point in clinical trials. JAMA. 2014;312(8):789-90.
[4] Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW; ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of

- Heart failure with reduced ejection fraction (HFrEF): LVEF ≤ 40%
- Heart failure with preserved ejection fraction (HFpEF): LVEF ≥ 50%
- Heart failure with mildly reduced ejection fraction (HFmrEF): LVEF = 41% - 49%

HFrEF patients who experience an improvement in LVEF to ≥50% have been classified as heart failure with improved ejection fraction (HFimpEF).

For HFrEF and HFmrEF patients, the Class 1a recommendations (based on strong evidence from multiple high quality randomized controlled trials or meta-analyses) from the AHA-ACC-HFSA and the ESC include:

- Neurohormonal modulators
    - Angiotensin receptor-neprilysin inhibitors (ARNIs) or angiotensin converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) if ARNIs contraindicated
    - Beta-blockers
    - Mineralocorticoid Receptor Antagonists (MRAs)
- Sodium-glucose cotransporter-2 inhibitors (SGLT2) inhibitors
- Loop diuretics for symptom management
- Implantable cardioverter defibrillator (ICD)/cardiac resynchronization therapy (CRT) in eligible patients
- Lifestyle and comorbidity management

For HFpEF patients, the Class 1a recommendations from the AHA-ACC-HFSA and the ESC include:

- SGLT2 inhibitors
- Loop diuretics for symptom management
- Hypertension management
- Atrial fibrillation management (if applicable)
- Lifestyle and comorbidity management

2.1 Pathophysiologic Rationale for Interatrial Shunting

In Lutembacher syndrome,[5] the presence of a congenital atrial septal defect (ASD) in mitral stenosis patients can decompress the left atrium via left atrium-to-right atrium shunting reducing pulmonary congestion symptoms. However, excessive left-to-right shunting across an ASD can lead to right heart chamber dilatation, significant tricuspid regurgitation, and right-sided HF.[6] Following ASD closure, patients with subclinical left ventricular dysfunction can develop pulmonary edema due to loss of left atrial decompression through the interatrial shunt.

Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 May 3;145(18):e895-e1032. doi: 10.1161/CIR.0000000000001063. Epub 2022 Apr 1. Erratum in: Circulation. 2022 May 3;145(18):e1033. doi: 10.1161/CIR.0000000000001073. Erratum in: Circulation. 2022 Sep 27;146(13):e185. doi: 10.1161/CIR.0000000000001097. Erratum in: Circulation. 2023 Apr 4;147(14):e674. doi: 10.1161/CIR.0000000000001142. PMID: 35363499.

[5] Mahajan K, Oliver TI. Lutembacher Syndrome. [Updated 2023 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470307/

[6] Scherlis L, Cowley RA. The Lutembacher syndrome: a physiologic study and case report. Ann Intern Med. 1955; 43: 575–590. https://doi.org/10.7326/0003-4819-43-3-575).

In HF patients, there is usually an increased left atrial to right atrial pressure difference, irrespective of LVEF. Extrapolation from left ventricular flow volume loops suggest that a relatively small reduction in left ventricular volume could lead to a relatively large reduction in left ventricular end diastolic pressure.[7] It has been postulated that creation of an interatrial shunt (IAS) that permits left-to-right shunting could lower left atrial pressure resulting in increased exercise tolerance and a reduction in HF complications (such as decompensated HF episodes and HF-related mortality). The physiology of creating a potentially beneficial interatrial shunt was investigated using theoretical simulations with calculated hemodynamics[8] supplemented with animal and initial human studies[9].

There are still many unanswered questions about interatrial shunting. For example, the optimal interatrial shunt size that produces effective left atrial decompression but does not result in right heart volume overload leading to right heart failure and pulmonary hypertension is not known. Optimal shunt flow rates and cardiac hemodynamic parameters that predict clinical success or failure are unknown. In patients with a congenital ASD, some reports suggest that a pulmonary arterial flow to aortic flow (Qp/Qs) ratio <1.5 is associated with a safe level of interatrial shunting.[10] However, the ASD literature does not address optimal shunt size in HF patients (with or without elevated pulmonary artery pressures). In a study of an interatrial shunt device in HFpEF patients, Borlaug et al. reported that, in the presence of pulmonary vascular disease, an interatrial shunt may cause long term complications even if the Qp/Qs ratio is <1.5.[11]

3. Device Description

The V-Wave Ventura Interatrial Shunt System (Shunt) is a permanent implant designed to shunt blood from the left to right atrium to improve symptoms in patients with advanced chronic heart failure (HF). The Shunt is constructed on an hourglass-shaped, self-expanding Nitinol frame, with expanded polytetrafluoroethylene (ePTFE) encapsulation. The Shunt is shown in Figure 1.

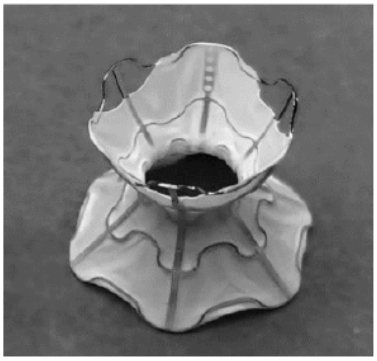


Figure 1: V-Wave Ventura Interatrial Shunt

[7] Burkhoff D, Mirsky I, Suga H. Am J Physiol Heart Circ Physiol 2005; 289: H501–H512
[8] Kaye et al, J Card Failure 2014 20:212-221
[9] Del Trigo 2016; Eigler 2017
[10] Menillo AM, Alahmadi MH, Pearson-Shaver AL. Atrial Septal Defect. [Updated 2025 Jan 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535440/
[11] Borlaug BA et al Circulation (2022) 145:1592-1604

The frame is comprised of six axially aligned bars and five circumferentially aligned sinusoidal struts. It is fully encapsulated in ePTFE except for the three E-shaped nitinol loops where the delivery system engages the Shunt. The internal diameter at the neck is 5.1 mm ± 0.10 mm, and the length of the Shunt is 12 mm. The external diameter at the right atrial end is 11.4 mm ± 0.20 mm and 14.4 mm ± 0.50 mm at the left atrial end. The device was designed to create a left to right shunt with a target Qp/Qs of <1.5.

The Ventura Delivery System (Figure 2 top panel) retains the Shunt, tracks to the target position over a guidewire, and releases the Shunt. The Delivery System includes a delivery catheter and accessory tools. The distal end of the delivery catheter has retractable hooks embedded in the main tip that affix the Shunt to the delivery catheter and allow for controlled disengagement during device deployment. The delivery catheter (Figure 2 bottom panel) proximal end has a handle with a safety lock, a hemostatic valve with a flush port, and a length adjustment knob. The Delivery System is supplied with accessory tools that include a guidewire insertion tool, a length adjustment pin, and tools for crimping the Shunt (pusher, loader, and an empty Ventura cartridge).

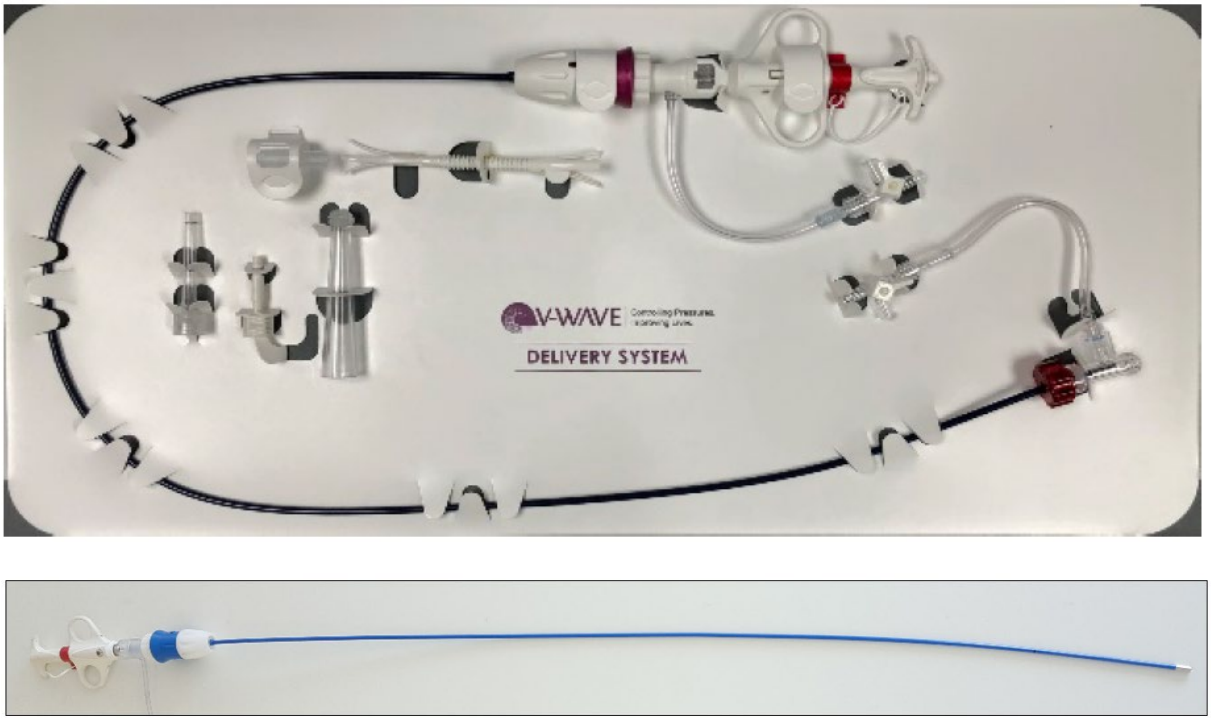


Figure 2: Ventura Delivery System (Top Panel) and Delivery Catheter (Bottom Panel)

Vascular access for the Shunt Delivery System is achieved via percutaneous femoral vein puncture. An interatrial transeptal puncture is performed targeting the center of the fossa ovalis. A guidewire and sheath are inserted, and the Delivery System is advanced across the interatrial septum. The Shunt is implanted by retracting the Delivery System under fluoroscopic guidance creating an IAS (Figure 3). The Delivery System, sheath, and guidewire are then removed from the patient.

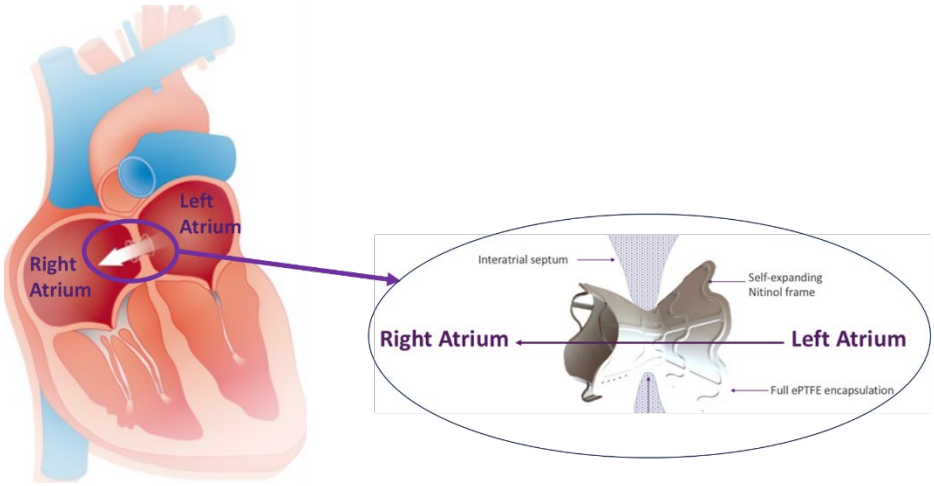


Figure 3: V-Wave Shunt Placement

4. Proposed Indications for Use

The Sponsor's proposed Indications for Use of the Ventura Interatrial Shunt System is as follows:

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

The Panel will be asked to discuss whether the totality of the data indicate that the Shunt demonstrates a reasonable assurance of safety and effectiveness for the proposed indications for use. Additionally, the Panel will be asked to discuss and make recommendations on whether the evidence adequately identifies the intended patient population.

5. Regulatory History

The Shunt received a Breakthrough Device Designation (BDD) under QXXXXXX on August 5, 2019. V-Wave studied their device in the RELIEVE-HF trial (IDE GXXXXXX approved March 2, 2018, Clinicaltrials.gov identifier NCT03499236), the pivotal study evaluating the Shunt. V-Wave filed its PMA on June 3, 2024.

V-Wave submitted a Major Unsolicited Amendment on March 4, 2025 that included complete two year follow-up of RELIEVE-HF trial participants, additional statistical analyses, and additional echocardiographic data providing mechanistic insights. An in-person meeting between the FDA and V-Wave was held on March 12, 2025 to discuss the Amendment and new analyses. Additional information and documentation was submitted via a PMA Amendment on September 4, 2025.

Following review of the PMA, Amendment, and other materials made available to the Agency, FDA referred the PMA to the Circulatory System Devices Panel of the Medical Devices Advisory Committee on August 5, 2025.

5.1 Breakthrough Device Designation

FDA's Breakthrough Devices Program[12] is a voluntary program for selected devices that have the potential to provide more effective treatments or diagnoses of life-threatening or irreversibly debilitating diseases or conditions. This program is intended to provide patients and health care providers with timely access to important new medical devices by accelerating their development, assessment, and regulatory review. It is important to recognize that the statutory requirements for PMA approval of a breakthrough device are the same as a non-breakthrough designated device, that is, a reasonable assurance of safety and effectiveness. FDA "may accept a greater extent of uncertainty of the benefit-risk profile for these devices if appropriate under the circumstances, including that the uncertainty is sufficiently balanced by other factors, such as the probable benefits for patients to have earlier access to the device (e.g., a device that treats a life-threatening disease when no alternative treatments are available) and adequate postmarket controls to support premarket approval." [13]

FDA determined that the Shunt met the Breakthrough Devices Program criteria because it was a novel technology with the *potential* to provide more effective treatment in NYHA Class III and ambulatory Class IV heart failure patients with reduced or preserved left ventricular systolic function.

It is important to note that although the Breakthrough Device Program offers increased interactions with FDA, it does not modify or reduce the statutory requirement for PMA approval.

6. V-Wave Clinical Feasibility Studies Overview

The Canadian Special Access Program (CSAP, single clinical site) and a First-In-Man (FIM, 5 sites in Israel and Spain) shunt study used the first-generation V-Wave Interatrial Shunt System, which contained a valve in the middle of the shunt to prevent backflow from the right to the left atrium. These single arm studies had generally similar patient eligibility criteria, follow-up study schedules and testing, trial conduct, monitoring and oversight procedures. Baseline patient characteristics for the combined CSAP and FIM Shunt are shown in Table 1.

Table 1: Baseline Patient Characteristics for CSAP and FIM Studies

	CSAP + FIM Shunt Patients (n=38)
Demographics	
Age, years	66±9
Male Gender, %	92

[12] For more specifics regarding the Breakthrough Devices Program, please see FDA's guidance available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program.

[13] Breakthrough Devices Program – Guidance for Industry and Food and Drug Administration Staff at 7, 9 (Sept. 15, 2023).

	CSAP + FIM Shunt Patients (n=38)
Body Mass Index, kg/m2	30±6
Medical history	
NYHA class, %	III 97%, IV 3%
Ischemic cardiomyopathy, %	79
Myocardial infarction, %	68
Atrial fibrillation, %	53
Hypertension, %	84
Diabetes, %	68
Chronic Kidney Disease, %	61
Stroke, %	11
Treatment history	
ACE/ARB, %	71
β Blocker, %	89
Mineralocorticoid antagonist, %	68
Loop Diuretic	87
CRT-D or ICD, %	74
CRT, %	39
Laboratory findings	
eGFR, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	54±20
NT-proBNP, pg/ml	2640±2301
Frequency LVEF ≥ 0.40, %	21.1
LVEF HFrEF	26±7
LVEF HFpEF	50±9
6-Minute Walk Distance, m	289±112
Hemodynamics	
Systolic BP, mmHg	116±19
Diastolic BP, mmHg	66±9
Heart Rate, bpm	69±9
Pulmonary wedge pressure, mmHg	21±5
Right atrial pressure, mmHg	8±4
PA systolic pressure, mmHg	44±11
PA mean pressure, mmHg	30±7
Pulmonary vascular resistance, WU	2.8±1.6
Cardiac output,68% vs. L/min	4.4±0.9
Cardiac index, $L/min/m^{-2}$	2.2±0.4

NYHA, New York Heart Association; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; AFIB, atrial fibrillation; ACE/ARB, angiotensin converting enzyme inhibitor-angiotensin receptor blocker; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; PA, pulmonary artery

CSAP and FIM Clinical Results Through 12 Months

- The shunt was successfully implanted in all 38 enrolled patients.
- No cases of shunt repositioning, removal, or replacement.
- No device-related deaths, strokes, TIAs, or thromboembolic events at 12 months follow-up.
- No device migrations, thromboses, or erosions
- Individual serious adverse events (SAEs)

  - 9 cases of acute decompensated heart failure in 7 subjects (18%) through 12 months
  - 2 cardiovascular deaths (5%) through 12 months
  - 3 femoral access site complications: 1 hematoma, 1 pseudoaneurysm, and 1 arteriovenous fistula.
- All SAEs except for one associated with the 12-month right heart catheterization occurred within 9 days after shunt implantation.

CSAP and FIM Transesophageal Echocardiography (TEE) Results

- 36 of the enrolled 38 patients received TEE assessments at 12 and 24 months.
- At 12 months, 18 of 36 (50%) of shunts were patent while 18 of 36 (50.0%) shunts were stenotic/occluded. The two patients with no TEE at one year had shunt flow on transthoracic echo.
- At 24 months, one additional patient was found to be occluded. Therefore, 19 of 36 (52.8%) shunts were occluded at 24 months.
- Patency loss was not associated with device thrombus, thromboembolism, or other adverse clinical events.

Patients with non-stenotic first-generation shunts had sustained improvements in hemodynamics, ejection fraction, and exercise capacity.

The CSAP and FIM feasibility studies utilized a first-generation valved shunt device that was associated with a high rate of shunt stenosis. The sponsor redesigned the device and removed the valve prior to studying the shunt in the RELIEVE-HF study. The CSAP and FIM studies demonstrate limited proof-of-concept and safety data. Insights into potential outcome differences associated with shunt use in HFrEF vs. HFpEF subjects was not provided.

7. RELIEVE-HF – Pivotal Trial Overview

The RELIEVE-HF trial studied the second generation (non-valved) shunt (hereafter referred to as "the Shunt"). The trial enrolled symptomatic HF patients treated with guideline-directed medical therapy (GDMT). The trial consisted of two phases (with study subject eligibility determined by a central eligibility committee):

- Roll-in phase of 97 patients treated with the Shunt. Each investigational site could implant the Shunt in up to 2 roll-in subjects. Roll-in patients were followed and analyzed similarly to the randomized cohort. Roll-in patient outcomes are shown in Appendix 3.
- A 1:1 randomized sham-controlled trial of Shunt treatment vs. a sham procedure in 508 randomized patients
  - Study blinding: Study subjects and study personnel involved in endpoint collection were blinded to treatment group.

7.1 Key Inclusion Criteria

1. Ischemic or non-ischemic cardiomyopathy with either reduced or preserved LV ejection fraction (LVEF) and documented HF for ≥6 months prior to the baseline visit
2. New York Heart Association (NYHA) Class II, Class III or ambulatory Class IV HF
3. Patients treated with GDMT for HF consisting of HF drugs with a Class I indication

a. For HFrEF (LVEF ≤40%) patients: A renin-angiotensin system (RAS) inhibitor [angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI)] plus a beta-blocker (BB) for ≥3 months prior to the baseline visit.
b. For HFrEF (LVEF ≤40%) patients: Other medications recommended for selected populations [e.g., a mineralocorticoid receptor antagonist (MRA) or nitrates/hydralazine used in appropriate patients according to the published guidelines].
c. All patients on stable HF medications for ≥1 month with the exception of diuretics. Stable medication use defined as no more than a 100% increase or 50% decrease in dose within these periods.
d. All patients on appropriate doses of diuretics for volume control.
e. Drug intolerance, contraindications, or lack of indications attested to by the investigator.

4. Patients treated with Class I guideline-recommended cardiac rhythm management device therapy (if indicated) consisting of cardiac resynchronization therapy (CRT), implanted cardioverter-defibrillator (ICD), or a pacemaker for ≥3 months prior to the baseline visit. These therapies could be waived if clinically contraindicated or the patient refused.
5. NYHA Class II patients: Required to meet both 5a **and** 5b criteria.
   NYHA Class III and ambulatory Class IV patients: Required to meet 5a **or** 5b criteria.
   5a. One prior HF hospitalization (HFH) duration >24 hours, emergency room HF visit duration ≥6 hours, or HF clinic acute decompensated HF (ADHF) visit duration ≥6 hours within 12 months of the baseline visit.
      i. If a CRT device was in situ, the HFH required to be ≥1 month after CRT implantation.
      ii. If a mitral valve repair device (e.g. MitraClip) in situ, the HFH required to be ≥1 month after mitral valve repair device implantation.
   5b. If a patient did not have a HFH or ER HF visit within the prior 12 months, a corrected elevated brain natriuretic peptide (BNP) level of ≥300 pg/ml or an N-terminal pro-BNP (NT-proBNP) level of ≥1,500 pg/ml was required ≤3 months prior to the baseline visit while the patient was clinically stable and (if applicable) ≥1 month post-CRT placement or mitral valve repair. (Note: "corrected" refers to a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m^2 in BMI above a reference BMI of 20 kg/m^2.) If the patient was on ARNI, NT-proBNP was to be used exclusively.
6. Able to perform a 6-minute walk test for ≥100 meters and ≤450 meters. The test was performed twice separated by ≥60 minutes between tests. The second test could be performed up to 7 days after the first test. The longer distance was used as the baseline value.
7. Written informed consent and subjects able to comply with the required tests, treatment instructions and follow-up visits

7.2 Key Exclusion Criteria

1. Age <18 years old
2. BMI >45 or <18 kg/m^2
3. Females of childbearing age not on contraceptives or surgically sterile, pregnant, or lactating.
4. Resting systolic blood pressure <90 or >160 mmHg after repeated measurements
5. Baseline echocardiographic evidence of unresolved, non-organized or mobile intracardiac thrombus

6. Severe pulmonary hypertension defined as pulmonary artery (PA) systolic pressure >70 mmHg by echo/Doppler or pulmonary vascular resistance (PVR) >4.0 Wood Units by PA catheter measurement that could not be reduced to ≤4 Wood Units by vasodilator therapy.
7. Right ventricular (RV) dysfunction defined as tricuspid annular plane systolic excursion (TAPSE) <12 mm or RV fractional area change (RVFAC) ≤25% assessed on baseline transthoracic echo (TTE).
8. Left ventricular end-diastolic diameter (LVEDD) >8 cm by baseline TTE.
9. Congenital or iatrogenic ASD, patent foramen ovale (PFO), or anomalous pulmonary venous return with more than trace shunting, or prior surgical or interventional correction of congenital heart disease involving the atrial septum.
10. Untreated moderately severe or severe aortic or mitral stenosis.
11. Untreated severe or greater regurgitant valve lesions, anticipated to require surgical or percutaneous intervention within 12 months.
12. Mitral valve repair device implanted ≤3 months prior to the baseline visit.
13. Untreated coronary stenosis requiring surgical or percutaneous intervention.
14. Acute MI, acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), rhythm management system revision, (not including generator change unless within 1 month of the baseline visit), lead extraction, or cardiac or other major surgery ≤3 months of the baseline visit.
15. Active valvular vegetations, atrial myxoma, hypertrophic cardiomyopathy with significant resting or provoked subaortic gradient, acute myocarditis, pericardial tamponade or large pericardial effusion, constrictive pericarditis, infiltrative cardiomyopathy (including cardiac sarcoidosis, amyloidosis, and hemochromatosis), or congenital heart disease as cause of HF.
16. Stroke, transient ischemic attack (TIA), systemic or pulmonary thromboembolism, or deep vein thrombosis within 6 months of the baseline visit.
17. Prior stroke with permanent neurologic deficit.
18. IVC filter in situ.
19. Transseptal procedure for another indication (e.g. atrial fibrillation ablation, left atrial appendage occlusion, mitral valve repair/replacement) anticipated within 6 months.
20. Bradycardia with heart rate <45 bpm (unless treated with a permanent pacemaker) or uncontrolled tachyarrhythmias, including defibrillation shocks within 30 days of the baseline visit.
21. Intractable HF (consisting of any of the following):
    a) Resting symptoms despite maximal medical therapy (ACC/AHA HF Stage D).
    b) Treatment with IV vasoactive medications (e.g., IV inotropes, IV vasodilators) within the last 30 days.
    c) Cardiac Index <1.5 L/min/m^2.
    d) Ventricular assist device (VAD) in situ.
    e) Listed for cardiac transplantation.
22. Prior cardiac transplantation.
23. HFrEF (LVEF≤40%) patients intolerant to RAS inhibitors (including an ACEI, ARB or ARNI) and intolerant to beta-blockers. Intolerance to one class of medications (RAS inhibitor or beta-blockers) would not exclude the patient.
24. Not eligible for emergency cardiothoracic or vascular surgery in the event of a serious complication during study intervention procedure.
25. Life expectancy <1 year due to non-cardiovascular illness.
26. Coagulopathy or is taking anticoagulants, which cannot be interrupted for the study intervention procedure, contraindicated for post implantation anti-thrombotic medications, or known

hypersensitivity or contraindication to procedural medications which could not be managed medically.
27. Estimated glomerular filtration rate (eGFR) <25 ml/min/1.73 m^2 by the modification of diet in renal disease (MDRD) method, not responsive to diuretics, or receiving dialysis.
28. Hepatic impairment with a liver function tests (transaminases, total bilirubin, or alkaline phosphatase) ≥3 times the upper limit of normal.
29. Severe chronic pulmonary disease requiring daytime home oxygen or chronic oral steroids. Nighttime oxygen therapy and inhaled steroid therapy did not exclude the patient.
30. Active infection requiring antibiotics.
31. Nickel allergy.
32. Patient not appropriate for the study as determined by the investigator or the Eligibility Committee.

7.3 Anatomic and Hemodynamic Exclusion Criteria

Anatomic and hemodynamic exclusion criteria were assessed during cardiac catheterization at the study intervention visit just prior to randomization. These criteria excluded patients: (1) with anatomy or physiology unsuitable for interatrial shunt implantation; or (2) who were clinically and hemodynamically unstable. Patients excluded for anatomic or hemodynamic factors could be considered for repeat screening if the investigator determined the cause of the instability, and the patient returned to stable baseline status.

Anatomic and hemodynamic exclusion criteria:

1. Patient not stable to undergo the intervention.
2. Unable to undergo transesophageal or intracardiac echo (TEE or ICE, respectively).
3. Unable to tolerate or cooperate with general anesthesia or conscious sedation.
4. Anatomical anomaly on TEE or ICE that precluded Shunt implantation:
    a. Fossa ovalis (FO) thickness >6mm in and adjacent to the intended shunt placement target location.
    b. Minimal FO Length <10 mm.
    c. ASD or PFO with greater than trace shunting.
    d. Acute intracardiac thrombus.
    e. Atrial septal aneurysm defined as ≥10 mm phasic septal excursion into either atrium or a sum total excursion of ≥5 mm during the cardiorespiratory cycle, with a base excursion ≥15 mm.
5. Inadequate vascular access for Shunt implantation.
6. Hemodynamic, heart rhythm, or respiratory instability including:
    a. Mean pulmonary artery wedge pressure (PCWP) <7 mmHg, not correctable by IV volume infusion (maximum 1,000 ml normal saline or equivalent).
    b. Mean PCWP >35 mmHg, not correctable by medical therapy (e.g. IV furosemide, IV or sublingual nitroglycerin).
    c. Right atrial pressure (RAP) ≥ left atrial pressure (LAP) or PCWP, when LAP or PCWP ≥7 mmHg.
    d. Cardiac Index (CI) <1.5 liters/min/m^2 after correction of volume depletion with IV fluids (maximum 1,000 ml normal saline or equivalent).

e. Severe pulmonary hypertension defined as PASP >70 mmHg associated with PVR >4.0 Wood Units that could be reduced to PVR ≤4 Wood Units by acute vasodilator therapy.
f. Resting systolic blood pressure <90 or >160 mmHg, not corrected with IV fluids or vasodilators, respectively.
g. Need for IV vasopressors or inotropes. Transient hypotension or bradycardia during anesthesia or catheterization responding promptly to IV fluids or IV vasopressors or chronotropic agents was not an exclusion criterion.
h. Serious arrhythmias such as ventricular fibrillation, ventricular tachycardia, atrial fibrillation/flutter with rapid ventricular response associated with hypotension and requiring cardioversion.
i. Acute respiratory distress or hypoxemia.

7.4 Assessment Schedule

The assessment schedule for RELIEVE-HF patients is shown in Table 2.

Table 2: RELIEVE-HF Assessment Schedule

Visit Assessment	**BASELINE SCREENING**	**FINAL SCREEN-STUDY INTERVENTION Implant or control**	**POST ENROLLMENT PRIOR TO DISCHARGE**	**2 WEEKS (telephone)**	**1, 24 MONTHS (in-clinic)**	**3, 18 MONTHS (in-clinic)**	**6, 12 MONTHS (in-clinic)**	**9, 15, 21 MONTHS (telephone)**	**ANNUAL years 3-5 (in-clinic)**
Informed consent	✓								
Demographics & medical history	✓								
Vital signs, weight, and pulse oximetry	✓[1]	✓[1]	✓[1]		✓	✓	✓		✓
Physical exam	✓	✓	✓		✓	✓	✓		✓
Medications	✓	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]
Na, K, Hgb, HCT, PLTS, WBC, Cr, BUN, AST, ALT, T Bili, Alk phos	✓		✓[3]		✓[3]		✓[3]		
Pregnancy, PT, PTT, INR, Hgb, HCT, Cr, cardiac troponin		✓							
COVID-19 tests [9]					✓				
BNP or NT-proBNP	✓								
12 Lead ECG	✓								
Chest x-ray			✓						
Transthoracic echo (TTE)	✓				✓[4]		✓[4]		✓[4]
Transesophageal or intra cardiac echo (TEE/ICE)		ICE/TEE					TEE[5]		
Right Heart catheterization (RHC)		✓							
NYHA functional class	✓				✓	✓	✓		✓

Visit Assessment	BASELINE SCREENING	FINAL SCREEN-STUDY INTERVENTION Implant or control	POST ENROLLMENT PRIOR TO DISCHARGE	2 WEEKS (telephone)	1, 24 MONTHS (in-clinic)	3, 18 MONTHS (in-clinic)	6, 12 MONTHS (in-clinic)	9, 15, 21 MONTHS (telephone)	ANNUAL years 3-5 (in-clinic)
Patient global assessment					✓	✓	✓		✓
KCCQ, EQ-5D	✓				✓	✓	✓		✓
Cost effectiveness[6]		✓	✓		✓	✓	✓		
6-min walk test (x2)/Borg scale	✓				✓	✓	✓		✓[7]
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓
Worsening HF events treated as an outpatient[10]			✓	✓	✓	✓	✓	✓	✓
COVID-19 history	✓	✓	✓	✓	✓	✓	✓	✓	✓
I/E criteria review	✓	✓							
Case report forms (CRFs)	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient perception of study assignment			✓[8]				✓[8]		
Assure blinding procedures (randomized pts)		✓	✓	✓	✓	✓	✓	✓	

1 Temperature and Pulse oximetry only required at Baseline, Study Intervention and Prior to Discharge
2 Only cardiovascular (including SGLT2s), anticoagulant, and antiplatelet medications assessed during follow-up.
3 Limited to Cr, Hgb and HCT
4 Once unblinded, Shunt patients have TEE if no shunt flow seen on prior TTE
5 Follow-up TEE at 6 and 12 months performed in only Roll-in patients. All patients including the Roll-ins had follow-up TTE at protocol-specified follow-up.
6 US sites only
7 A single 6-min walk test is required during extended follow-up on years 3-5.
8 Patient blinding assessment only performed on randomized patients prior to discharge and at 12-months
9 COVID-19 testing done at the time of unblinding if required.
10 Assessed for randomized patients only

7.5 Randomization and Blinding

In the RELIEVE-HF randomized cohort, patients were randomized in the cath lab 1:1 to either the Shunt treatment group or the sham procedure Control group.

Randomization was stratified by site and left ventricular ejection fraction

- HFrEF: LVEF ≤40% or
- HFpEF: LVEF>40%

as determined by the Echocardiography Core Laboratory on the baseline TTE.

In-lab blinding procedures: Patients were provided headphones with music playing to avoid hearing procedural discussion, and a blindfold or other shielding was used to prevent viewing of monitors. Shunt patients underwent transseptal catheterization and Shunt implantation. Control patients underwent mock transseptal catheterization and mock device placement by the study physician using

a script; subjects otherwise underwent all other study procedures including venous access and right heart catheter placement.

Blinding during follow-up:

- Patients and study personnel involved in endpoint collection remained blinded for 24 months post-procedure or until the last enrolled patient reached 12-month follow-up, whichever occurred earlier.
- Shunt patients received adjunct antiplatelet or anticoagulant medications, and Control patients who were not already on anti-thrombotic medications received matching placebos.
- All patients remained on HF GDMT.

7.6 Crossover

Upon reaching 24 months of follow-up or at study unblinding, patients entered an Open Access phase in which Control patients could cross over and receive a Shunt if they still met eligibility criteria, and the crossover phase of the study was active.

Twenty-two (n=22) Control patients crossed over and all received a Shunt. Summary results are shown in Appendix 4.

7.7 Primary Endpoints

7.7.1 Primary Safety Endpoint

Primary safety endpoint: The proportion of Shunt group patients experiencing device- or procedure-related major adverse cardiovascular or neurological events (MACNE) during the first 30 days after randomization.

- MACNE was a composite of all-cause death, stroke, systemic embolism, need for open cardiac surgery, or major endovascular surgical repair.

The following events were excluded in the MACNE composite endpoint:

- Percutaneous drainage of a pericardial effusion
- Percutaneous catheter snaring and removal of an embolized but uncomplicated Shunt device
- Non-surgical treatment of access site complications.

7.7.2 Primary Effectiveness Endpoint

Primary effectiveness endpoint: The hierarchical composite of the following components:

- All-cause death
- Cardiac transplantation or left ventricular assist device (LVAD) implantation
- HF hospitalization (HFH) that includes ER HF visits duration ≥6 hours
- Worsening HF treated as an outpatient
- Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score of ≥5 points from baseline to 12 months

The primary effectiveness endpoint analysis was performed when the last enrolled patient had been followed for a minimum of 12 months following randomization and included all available data through 24 months of follow-up.

7.8 Secondary Endpoints

Hierarchically tested secondary effectiveness endpoints were as follows:

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

7.9 Technical Success and Device Success Endpoints

Technical success was measured at exit from cath lab and was defined as alive, with successful access, delivery and retrieval of the transcatheter V-Wave delivery system, with deployment and correct positioning of the single intended device and no need for emergency surgery or re-intervention related to either the device or the access procedure.

Device success was measured at 30 days and all post-procedural time points and is defined as alive and stroke free, with original intended device in place and no additional surgical or interventional procedures related to access or the device and intended performance of the device with no device migration, embolization, detachment, fracture, hemolysis or endocarditis, and expected hemodynamic performance including patent device with Qp:QS <1.5, and no detected para-device complications including device leak, erosion, systemic or pulmonary thromboembolism.

7.10 Statistical Analysis Plan

7.10.1 Statistical Analysis Populations

The following RELIEVE-HF study populations were predefined.

7.10.1.1 Intent to Treat (ITT) Population (Primary Analysis Population)

ITT was defined as subjects randomized to the Shunt or Control groups and analyzed according to their randomized assignment regardless of treatment received. The ITT population was the primary analysis cohort.

7.10.1.2 Per Protocol (PP) Population

The PP cohort consisted of randomized subjects who met all inclusion/exclusion criteria, had no major protocol deviations which may have impacted study outcomes, were treated according to

randomization, and had available follow-up data for the endpoint being evaluated. Major protocol deviations leading to PP exclusion were failure to obtain informed consent, randomization or enrollment error, and major inclusion/exclusion criteria violations.

7.10.2 Primary Endpoint Analysis

7.10.2.1 Primary safety endpoint (proportion of Shunt group patients experiencing device-related MACNE during the first 30 days post-randomization)

The primary safety endpoint analysis was tested in all ITT patients randomized to the Shunt group regardless of whether the implantation procedure was successful.

The null (H_0) and alternative (H_1) hypotheses for the primary safety endpoint were as follows:

H_0: R ≥ Performance goal (PG)

H_1: R < PG

where R is the percentage of Shunt group patients experiencing device-related major adverse cardiovascular or neurological events (MACNE) during the first 30-days after randomization.

The estimated true safety endpoint rate was 5%, to which a margin of 6% was added, resulting in a PG = 11%. Assuming a one-sided alpha of 0.025, a sample size of 200 evaluable Shunt patients from the Randomized cohort would achieve an 87% power to detect a difference between the expected safety endpoint rate of 5% and the 11% PG.

7.10.2.2 Primary effectiveness endpoint (hierarchical composite of death; cardiac transplantation or LVAD; HFH; worsening HF treated as an outpatient; and change in KCCQ score of ≥5 points from baseline to 12 months)

The null (H_0) and alternative (H_1) hypotheses for the primary effectiveness endpoint were as follows:

H_0: None of the components is different between the Shunt and Control groups.

H_1: At least one component is different between the Shunt and Control groups.

The null hypothesis is that the components of the composite endpoint are not affected by treatment, and the alternative is that at least one component is favorable to the Shunt group.

The analysis used the Finkelstein and Schoenfeld method. The p-value was calculated, and an unmatched win ratio with 95% confidence intervals was used to measure the ratio of wins in the Shunt group vs. the Control group (see Appendix 1). Assuming a 0.025 one-sided alpha level, simulations indicated that a sample size of 400 patients (200 per treatment group) would achieve a 90% power to detect a sum of ranks greater than zero in the treatment group and reject the null hypothesis.

The assumptions used for event rates and effect sizes for the hierarchical components of the composite primary effectiveness endpoint were stratified between HFrEF and HFpEF subgroups and

are shown in Table 3. It was anticipated that the Shunt would provide benefits for patients of both HF phenotypes (i.e., in both HFrEF and HFpEF subgroup) for all components of the composite endpoint. The largest expected effect sizes favoring the Shunt group was for HFH events in HFpEF subjects.

The trial started with a plan of enrolling approximately 20-25% HFpEF patients and was updated during the trial to enroll 50% HFpEF subjects.

Table 3: Event and Hazard Rate Assumptions Stratified by Treatment Group and HFrEF and HFpEF Subgroups

Type of Event	Reduced Ejection Fraction (HFrEF)			Preserved Ejection Fraction (HFpEF)		
	Control	Shunt	Hazard Ratio	Control	Shunt	Hazard Ratio
Loss to Follow-up	1.7% (0.002927)	1.7% (0.002927)	---	1.7% (0.002927)	1.7% (0.002927)	---
Death	5.1% (0.008742)	4.2% (0.007080)	0.810	3.6% (0.006025)	2.9% (0.004926)	0.818
LVAD/Transplant	1.6% (0.0002620)	1.2% (0.001941)	0.741	0	0	---
HFH1*	27.5% (0.053379)	20.7% (0.038750)	0.726	21.4% (0.040101)	11.5% (0.020399)	0.509
HFH2*	30.1% (0.059793)	22.8% (0.43171)	0.722	23.5% (0.044698)	12.7% (0.022583)	0.505
HFH3+*	32.9% (0.066463)	24.9% (0.047712)	0.718	25.7% (0.049425)	13.8% (0.24796)	0.502
KCCQ	8 (22)	16 (22)	---	11 (26)	22 (26)	---

. *HFH1, 2, 3+ are defined as number of heart failure hospitalizations. That is HFH1 = 1 HFH, HFH2 = 2 HFHs. HFH3+ = 3 or more HFHs.

The trial started with a planned enrollment of 20-25% HFpEF patients and was later updated to enroll 50% HFpEF subjects.

It is important to note that for all components of the composite endpoint, the sponsor expected that event rates would favor the Shunt group in both HFrEF and HFpEF patients (Table 3). For all three heart failure hospitalization (HFH) event types (1, 2, 3+ visits for HFH), it was expected that the Shunt would be particularly favorable in HFpEF with a larger effect size (hazard ratios ≈ 0.5 vs. the Control group) compared to HFrEF patients (hazard ratios ≈ 0.7 vs. the Control group).

7.10.3 Interim analysis

To maintain statistical power, the investigational plan included an adaptive design that allowed sample size increase from 400 randomized patients to a maximum of 1000 patients following a one-time interim analysis. To prevent Type 1 error inflation from the interim analysis, the final Finkelstein-Schoenfeld statistic was derived from data weighted differently before and after the

interim analysis according to the method of Cui L et al.[14] This interim analysis was to be conducted when approximately 50% of the study population had completed a minimum of ≈ 6 months follow-up but no later than 3 months prior to completion of enrollment of the original 400 subjects. The interim analysis, conducted in September 2021, was reviewed by the Data Safety Monitoring Board (DSMB).

The DSMB recommended that the trial continue as planned with no sample size increase, but they noted "limitations in power calculations based upon low event rates at this relatively early stage in the trial." With input from the RELIEVE-HF Executive Committee and concurrence from the DSMB Chair, V-Wave increased enrollment to 500 randomized patients. The increased enrollment was expected to provide additional data to: (1) address limitations in power calculations based upon low event rates due to COVID-19; and (2) increase power for the primary endpoint composite components (particularly recurrent HFH and outpatient worsening HF Events) and for powered secondary endpoints.

7.10.4 Secondary endpoint analysis

The difference between treatment groups was to be hierarchically tested and powered for the secondary effectiveness endpoints in the order specified in Section 7.8 (Secondary Endpoints). Importantly, secondary endpoint testing was to be performed *only if the primary effectiveness endpoint is met*. There were nine additional descriptive safety endpoints and 25 descriptive effectiveness endpoints evaluated. A list of these endpoints is in Appendix 2.

It is important to note that the statistical analysis plan (SAP) states "If the primary effectiveness endpoint was met, then the secondary effectiveness endpoints will be hierarchically tested". In addition, it is a generally accepted statistical principle that formal hypothesis testing of secondary endpoints should not proceed if the primary endpoint fails to reach statistical significance, in order to preserve the overall type I error rate. Therefore, in the absence of a prespecified methodology to control Type 1 error, statistical testing of secondary endpoints without success on the primary effectiveness endpoint may be considered exploratory. As such, the results of such tests may be considered hypothesis-generating.

7.10.5 Subgroup Analysis

The primary safety and effectiveness endpoints were to be evaluated in the following 17 subgroups for the ITT and PP populations:

- Age
- Sex
- BMI
- Diabetes
- Hypertension
- Ischemic vs. non-ischemic cardiomyopathy
- LVEF stratification factor of HFrEF and HFpEF

[14] Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics. 1999 Sep;55(3):853-7. doi: 10.1111/j.0006-341x.1999.00853.x. PMID: 11315017.

- Baseline NYHA (III vs. IV)
- Baseline BNP/NT-proBNP
- Baseline eGFR
- Baseline 6MWT
- Baseline KCCQ score
- Shunt encapsulation process (Shunts manufactured before and after a change in manufacturing of the ePTFE covering)
- US vs. non-US clinical sites
- Prior COVID-19 infection
- Sites stratified by number of enrolled subjects.
- Implanted Shunt patients with patent vs. non-patent Shunts

For each subgroup, the following analyses were performed:

> Primary safety endpoint: MACNE rates at 30 days in each subgroup and compared using a Fisher's Exact test.
>
> Primary effectiveness endpoint: The relative treatment effects within each subgroup were compared using Z-test based on the Finkelstein- Schoenfeld estimates of the test statistic and its variance.

For each subgroup, a test for the difference in the primary safety and effectiveness endpoint rates was used to assess an interaction between treatment effect and the subgroup. Subgroup analyses were intended for descriptive purposes, and no hypothesis tests for subgroup analyses were pre-specified.

It is important to note that the SAP states, "The subgroup analyses [described below] will be performed for descriptive purposes only." The subgroup analyses were not powered for hypothesis testing and did not include methods to control Type 1 error. Therefore, statistical testing of subgroups beyond an interaction test of the primary endpoints may be considered hypothesis generating and should be interpreted with caution.

7.10.6 Subgroup and Post Hoc Analyses

Subgroup and post hoc analyses can provide insights into a medical product's safety and effectiveness and benefit-risk profile, but the results of these analyses should be interpreted with caution.

Clinical interpretation of subgroup analyses, particularly in the absence of acceptable pre-specified methods that control type 1 error, are traditionally deemed hypothesis-generating that need to be conformed in subsequent trials. As noted by Drs. Pocock and Stone[15]:

> "Although it is appropriate to consider subgroup findings in any major trial, for a trial in which the overall result for the primary outcome is neutral or negative, such considerations are often misleading since the potential for harm is often implied for the partner subgroups.

[15] The Primary Outcome Fails - What Next. N Engl J Med 2016; 375: 861-70

> Such qualitative interactions are rarely plausible (unless a strong mechanistic underpinning is present), and the analyses are typically not adjusted for multiple comparisons; even if the findings from statistical tests of interaction are significant, such findings should usually be perceived as useful for generating hypotheses at best. Indeed, we find it hard to think of an example in which an apparent benefit in a subgroup in a trial with a negative outcome has led to a confirmation in a subsequent trial."

The Sponsor anticipated that there *might* be differences in the degree of benefit provided by the shunt in the HFrEF (LVEF ≤40%) and HFpEF (LVEF >40%) groups. In the RELIEVE-HF SAP, subgroup analyses were planned via interaction testing to examine the consistency of the primary endpoints. The subgroup analyses would be performed for descriptive purposes only, and no formal hypothesis testing were planned. Analyses performed after the primary effectiveness endpoint was not met and conducted without prespecified methods to control Type I error results in an unquantifiable Type I error rate raising uncertainty about the validity of the HF phenotype findings.

Figure 4 illustrates how for familywise error rate (FWER), the probability of making at least one Type I error is magnified as the numbers of hypothesis tests increases. For example, testing 6 hypotheses is associated with a FWER of ≈ 25%. This highlights the multiple testing problem, in which conducting multiple independent tests without proper multiplicity correction substantially increases the risk of erroneous conclusions.

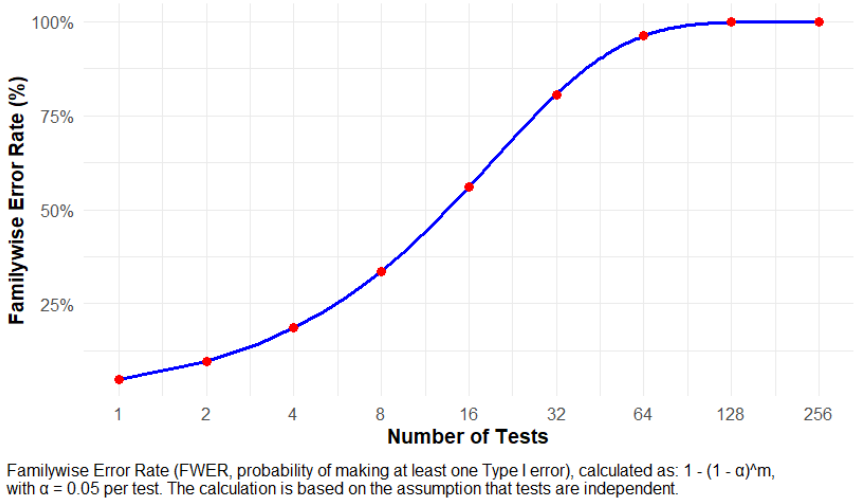


Figure 4: Inflation of Type I Error with Multiple Testing

Relevant Subgroup Analyses in Cardiovascular Clinical Trials

> The PRAISE trials. PRAISE randomized 1153 chronic HF patients with reduced LVEF to amlodipine or placebo.[16] Randomization was stratified by ischemic or nonischemic cardiomyopathy. A benefit for amlodipine did not reach significance, but a subgroup analysis was markedly positive for amlodipine in patients with nonischemic cardiomyopathy

[16] Packer M et al, Effect of amlodipine on morbidity and mortality in severe chronic heart failure, NEJM 1996; 335:1107-14

(mortality reduced by 46%, 95% confidence interval 21-63%, p value < 0.001). The study authors concluded that while this observation was likely a true effect, it should be confirmed in a second trial. The PRAISE-2 trial[17], which randomized 1654 patients with nonischemic cardiomyopathy HF patients to either placebo or amlodipine, showed no benefit of amlodipine.

The TACT trials. The TACT trial[18] randomized patients with a prior myocardial infarction (MI) to chelation therapy or placebo. The primary endpoint (a composite of mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina) was met with a HR of 0.82 (95% CI 0.69 to 0.99), p-value = 0.035. None of the components of the primary endpoint showed statistical significance. However, in the diabetic subgroup, which was prespecified but not a stratified randomized subgroup, the effect size in favor of chelation therapy was large: HR 0.59 (95% CI 0.44 to 0.79), p <0.001.[19] The authors noted that although the subgroup analysis was prespecified, the results must be considered hypothesis-generating, rather than conclusive. The subsequent TACT2 trial randomized *diabetic* patients with a prior MI to chelation therapy or placebo.[20] The primary endpoint (same as the TACT trial) was negative: HR 0.93 (95% CI 0.76 to 1.16), p = 0.53.

The PLATO trial. PLATO[21] compared ticagrelor to clopidogrel in acute coronary syndrome patients. The trial was positive, but the results in US patients were negative, and a question was raised whether results of total population should be applied to the US subgroup. An analysis suggested that the discordant results in US subjects may have been due to a difference in aspirin dosing. The drug was approved. In the case of PLATO, the issue was whether a subgroup analysis could invalidate the positive results of the overall trial, rather than whether a subgroup analysis could lead to approval when the overall results were negative. Also, in PLATO, the same primary endpoint and statistical methods were used for the subgroup as for the overall trial (in contrast to changes in endpoints and statistical methods in the RELIEVE-HF subgroup analyses discussed later in this summary in Section 9).

The REDUCE LAP HF II trial. The randomized REDUCE LAP-HF II trial[22] was intended to be the pivotal trial of an atrial shunt device, with breakthrough device designation, in HFpEF patients. It randomized 626 patients with LVEF ≥40% to a shunt or a sham procedure. The overall results were negative, but a post hoc analysis identified a responder cohort of 313 patients without pulmonary vascular disease and without a pacemaker that appeared to benefit from the device[23] with a win ratio of 1.5 (confidence interval 1.14-2.00, nominal p = 0.004). This subgroup was not prespecified nor stratified. The device is currently being evaluated in a new prospective randomized trial limited to HFpEF patients without

[17] Packer M et al, Effect of Amlodipine on the Survival of Patients With Severe Chronic Heart Failure Due to a Nonischemic Cardiomyopath, JACC HF 2013;1:308-314
[18] Lamas GA, et al. JAMA. 2013;309(12):1241-125
[19] Escolar E, et al. Circ Cardiovasc Qual Outcomes. 2014;7:15-24
[20] Lamas GA, et al. ACC Scientific Sessions 2024
[21] Wallentin L et al, NEJM (2009 361:1045-57
[22] Lancet. 2022 Mar 19;399(10330):1130-1140
[23] Borlaug BA et al Circulation (2022)

pulmonary vascular disease and no cardiac rhythm management device, to confirm the REDUCE LAP-HF II subgroup findings.

The PARAGON-HF trial. The PARADIGM-HF trial showed that sacubitril valsartan was superior to placebo in patients with an LVEF <40%[24]. In the subsequent PARAGON-HF trial[25] (which used the same primary endpoint as PARADIGM-HF), the primary endpoint was missed, but there was a strong trend (p=0.06) toward a benefit of sacubitril valsartan vs placebo. Additionally, there was attenuation of the benefit as LVEF increased, but there was no signal of harm. An important interpretation of the trial results was that there are limitations to applying discrete LVEF thresholds to distinguish the HFrEF subgroups from HFpEF subgroups.

Regarding post hoc analyses, the FDA guidance *Design Considerations for Pivotal Clinical Investigations for Medical Devices* states that "post-hoc analyses can inflate the experiment-wise type I error rate and endanger the scientific validity of an otherwise well-designed and well-conducted study." It's therefore important to adhere to the prespecified SAP in analyzing the strengths and limitations of study evidence.

8. RELIEVE-HF – Pivotal Trial Results

8.1 Subject Accountability

A total of 605 patients at 100 sites were enrolled between October 24, 2018 and October 9, 2022 in the US (n=56), Canada (n=3), Israel (n=10), Europe (n=27), Australia (n=3) and New Zealand (n=1).

- 97 Roll-in patients
- 508 randomized patients
    - 250 assigned to the Shunt group
    - 258 assigned to the sham Control group

Figure 5 shows screening, enrollment, randomization, stratification, and follow-up of patients in the RELIEVE-HF trial.

[24] McMurray JJV et al. NEJM (2014) 371:993-1004
[25] Solomn SD (2019) NEJM 381:1609-1620

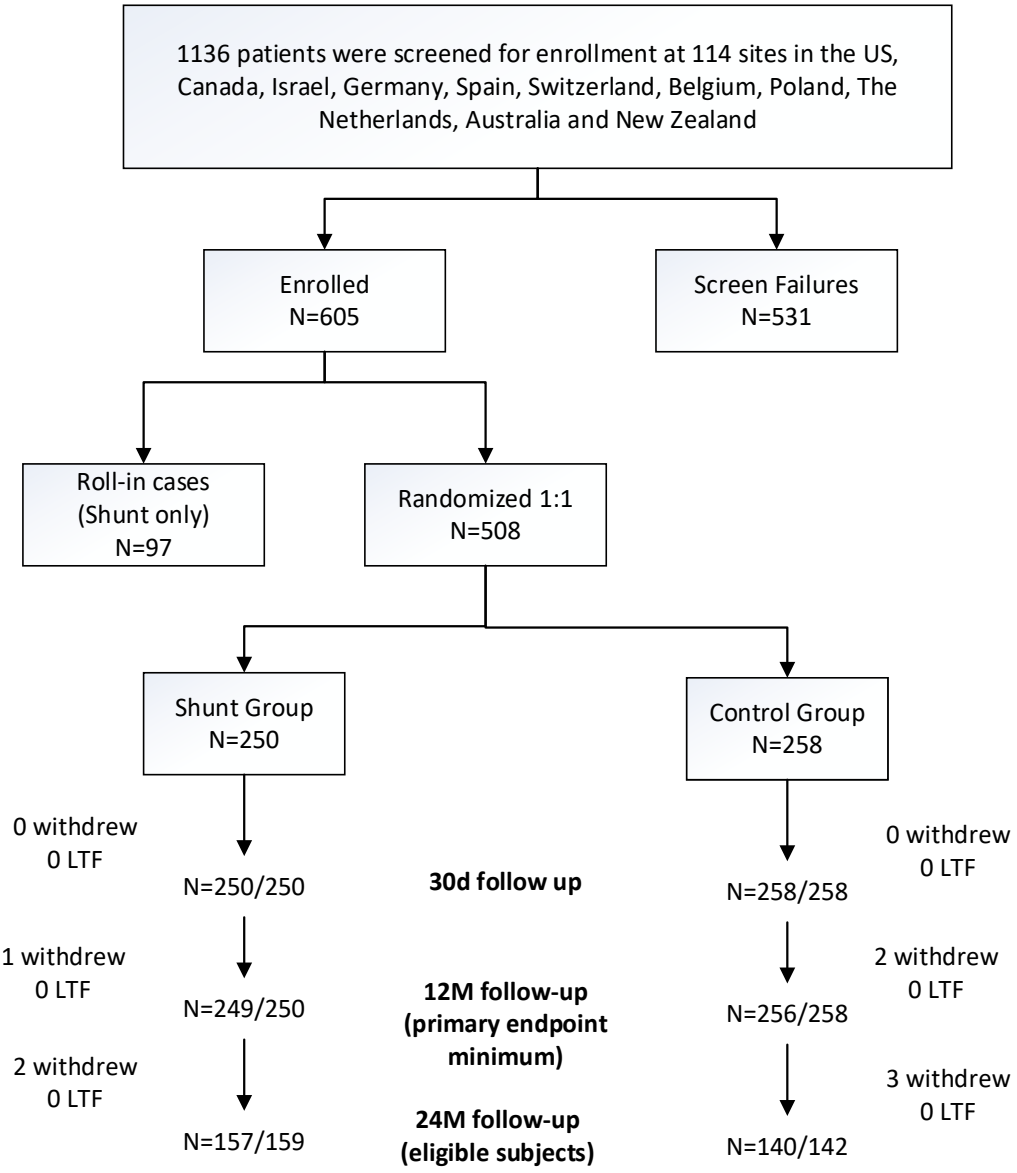


Figure 5: RELIEVE-HF Patient Accountability

Follow-up compliance rates were high, with ≥99% of all randomized subjects completing 12-month follow-up and ≥98% of eligible randomized subjects completing 24-month follow-up.

8.2 Baseline Characteristics – ITT Population

Key demographics and baseline characteristics for the ITT population are shown in Table 4 and were similar between the Shunt and Control groups. The majority of subjects were male (63%) and white (90%). Table 5 shows baseline HF medication and cardiac rhythm devices, and Table 6 shows baseline TTE assessments. Medication use and TTE parameters were consistent with a heart failure patient population. Table 7 shows baseline right heart catheterization data, and Table 8 shows anti-thrombotic treatment at discharge post-Shunt or sham procedure. Subjects who were not already receiving oral anticoagulation and/or dual antiplatelet therapy were treated with dual antiplatelet therapy for 6 months. Baseline clinical characteristics, HF treatment, echo and right heart

catheterization parameters, and discharge anti-thrombotic medications for the Shunt and Control groups were well-matched between treatment groups.

Table 4: Demographics and Baseline Characteristics (ITT Population)

	Shunt 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
HF-hospitalizations 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 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 ± standard deviation or median (interquartile range). CABG denotes coronary artery bypass graft surgery; CRT, cardiac resynchronization therapy; CRT-D, CRT-defibrillator; CRT-P, CRT-pacemaker; eGFR, estimated glomerular filtration rate calculated from the MORD formula; HFH, heart failure hospitalization; ICD, implantable cardiac defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; TIA, transient ischemic attack; PCI, percutaneous coronary intervention; ULN, upper limits of normal

Table 5: Baseline Medications and Electrical Therapies (ITT Population)

	Shunt group (N=250)	Control group (N=258)
Beta-blockers	224 (89.6%)	222 (86.0%)
Renin-angiotensin system inhibitors	176 (70.4%)	185 (71.7%)
-ACEi	32 (12.8%)	38 (14.7%)
-ARB	39 (15.6%)	38 (14.7%)
-ARNi	105 (42.0%)	109 (42.2%)
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

Table 6: Baseline Transthoracic Echocardiography (ITT Population)

	Shunt group (N=250)	Control group (N=258)
Left ventricular end-diastolic volume {biplane), ml	123.3 (87.0, 175.5)	126.0 (96.0, 181.5)
Left ventricular end-systolic volume {biplane), ml	66.3 (37.5, 115.5)	70.0 (40.5, 117.0)
Left ventricular ejection fraction {biplane),%	45.5 ± 15.1	44.4 ± 14.9
Left ventricular ejection fraction {biplane),%	45.4 (33.4, 58.9)	45.3 (33.3, 57.4)
- ≤40% {heart failure with reduced ejection fraction)	101/250 (40.4%)	105/258 (40.7%)
- >40% {heart failure with preserved ejection fraction)	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)
Right ventricular fractional area change, %	37.7 (33.3, 42.9)	37.5 (33.3, 42.9)
Tricuspid annular plane systolic excursion, mm	16.5 (14.0, 20.0)	17.0 (14.0, 19.0)
Pulmonary artery systolic pressure. mmHg	32.0 (24.0, 41.0)	32.0 (25.0, 40.0)
Right ventricular end-diastolic 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%)

Continuous data are median (interquartile range) or mean± standard deviation. Left ventricular ejection fraction data are shown both ways.

Table 7: Right Heart Catheterization Hemodynamic Data (ITT Population)

	Shunt 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

Continuous data were mean ± standard deviat1on.

Table 8: Post Procedure Antiplatelet/Anticoagulant Treatment (ITT Population)

	Shunt group (N=250)	Control group (N=258)
Discharge		
Antiplatelet agents, open label	121 (48.4%)	132 (51.2%)
Antiplatelet agents, study meds*	55 (22.0%)	63 (24.4%)
Chronic oral anticoagulation	158 (63.2%)	150 (58.1%)

*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.

8.3 Study Subject Blinding Assessment

To assess the effectiveness of blinding, patients completed a blinding questionnaire post-procedure, pre-hospital discharge from the enrollment/randomization visit, and at the 12-month visit. All patients were unblinded once the last enrolled subject reached their 12 month follow up visit. The responses to the blinding surveys were used to calculate the Bang's New Blinding Index at both post-procedure and one-year timepoints (Table 9).[26] [27] This analysis indicates that between 2% and 8% of patients correctly guessed their group assignment beyond the play of chance. Blinding appears to have been adequately maintained through one year.

[26] Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. Control Clin Trials. 2004 Apr;25(2):143-56. doi: 10.1016/j.cct.2003.10.016

[27] Poltavskiy E, Nandi R, Wertheim H. Blinding Indexes - Generalized and Unified Framework - a SAS®Macro.. https://www.wuss.arg/ proceedings/2023/WUSS-2023-Paper-102.pdf

Table 9: Blinding Indices at Pre-Discharge and at One Year (ITT Population)

Time of survey	Group	Bang's New Blinding Index	Lower bound 95%CI	Upper bound 95%CI	Interpretation: If confidence interval includes 0, then random guessing
Post-procedure	Shunt	0.056	-0.001	0.113	5.60% guessed Shunt beyond chance
	Control	0.028	-0.084	0.140	2.76% guessed Control beyond chance
One-year	Shunt	0.051	-0.019	0.120	5.05% guessed Shunt beyond chance
	Control	0.078	-0.022	0.177	7.76% guessed Control beyond chance

Assumes 50:50 Shunt vs. Control when no guess made.
https://www.wuss.arg/ proceedings/2023/WUSS-2023-Paper-102.pdf

8.3.1 Technical and Device Success Results

The Ventura Shunt was successfully implanted in all 250 (100%) patients randomized to the Shunt group, and in 1 patient in the Control group due to site error. There were no cases of Shunt migration, embolization, or thrombosis during or after implantation. All patients were discharged from the catheterization laboratory alive, without Major Adverse Cardiovascular or Neurological Events (MACNE).

TEE/ICE Doppler examination of the just implanted Shunts revealed that 96.0% of Shunts had continuous left atrial to right atrial flow and the remaining 4.0% had intermittent bi-directional flow; net Shunt flow averaged 1010 ± 321 mL/min. Net Shunt flow in conjunction with the cardiac output measured during the right heart catheterization was used to estimate the ratio of systemic to pulmonary flow (Qp/Qs), which averaged 1.25 ±0.11.

8.4 Endpoint Results

8.4.1 Primary Safety Endpoint

The primary safety endpoint was the rate of device or procedure related Major Adverse Cardiovascular or Neurological Events (MACNE) at 30 days post-randomization and was evaluated in the 250 Shunt group patients.

As shown in Table 10, no patient experienced a primary safety endpoint event through 30 days. The 0% event rate had an upper 97.5% confidence limit of 1.5%, which was lower than the performance goal of 11% ($p < 0.0001$); therefore, the primary safety endpoint was met. No unanticipated device affects occurred.

Table 10: Primary Safety Endpoint (ITT Population)

		Shunt (N=250)	P-value
Any device-related or procedure-related Major Adverse Cardiovascular or Neurological Events (MACNE)[1] during the first 30-days after randomization[2]	% (n/N)	0.0% (0/250)	<0.0001
All-cause death	% (n/N)	0.0% (0/250)	
Stroke	% (n/N)	0.0% (0/250)	
Systemic embolism	% (n/N)	0.0% (0/250)	

		Shunt (N=250)	P-value
Need for open cardiac surgery	% (n/N)	0.0% (0/250)	
Need for major endovascular surgical repair	% (n/N)	0.0% (0/250)	

1. MACNE: 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.)
2. The proportion of subjects with MACNE events was tested against a performance goal of 11% with an exact binomial test, with a one-sided significance level of 0.025.

There was no device embolization through 2 years. No pericardial effusions occurred in the ITT cohort. One Roll-in patient had a pericardial effusion after transseptal catheterization without hemodynamic compromise or need for pericardiocentesis.

8.4.2 Secondary Safety Endpoints

Additional safety endpoints included bleeding events (BARC type 3 or 5 bleeding and central nervous system (CNS) hemorrhage) and embolic events (stroke, systemic embolization, pulmonary embolization, and device embolization). The results are shown in Table 11. There were two BARC bleeding events (BARC type 3) in the Shunt group within 30 days, and one BARC type 5 event in the control group. BARC Type 3 bleeding is defined as significant bleeding, divided into 3A (moderate, requires transfusion), 3B (major, may need surgery), and 3C (critical, such as intracranial bleeding). BARC Type 5 bleeding is defined as likely fatal bleeding confirmed by imaging or autopsy. For more detailed definitions see Appendix 5.

At 2 years (Table 11), there were 11 cerebrovascular events (7 strokes and 4 transient ischemic attacks), 8 myocardial infarctions, and 2 pulmonary embolisms in the Shunt group. In the control group at 2 years, there were 6 cerebrovascular events (5 strokes which included 1 subarachnoid hemorrhage, and 1 transient ischemic attack) and 13 myocardial infarctions.

Table 11: Additional Safety Endpoints

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

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

In summary, the primary safety endpoint was met. For the secondary safety endpoint, there were numerically more cerebrovascular and pulmonary embolism events, but fewer MI events at 2-years in the Shunt group vs. the Control group. The Panel will be asked to comment on the primary and secondary safety endpoint results.

8.4.3 Primary Effectiveness Endpoint

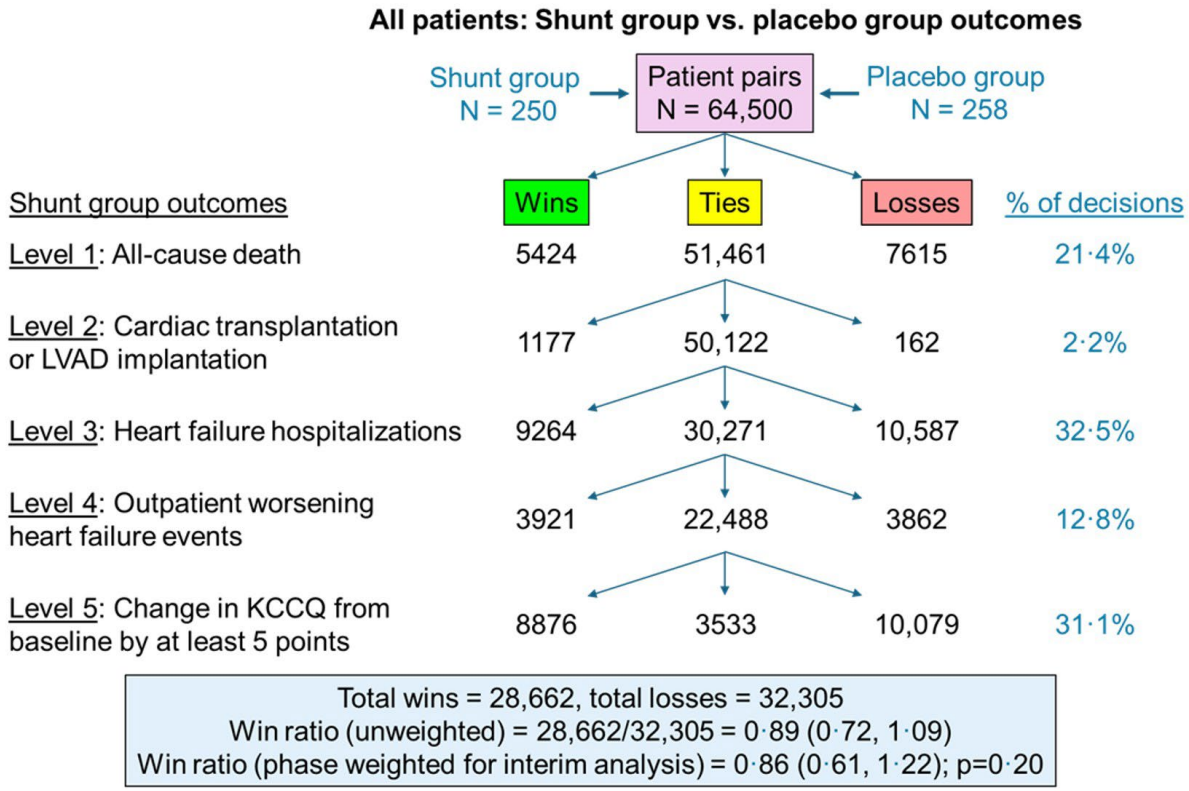
The primary effectiveness endpoint was a hierarchical composite of:

- All-cause death
- Cardiac transplantation or LVAD implantation
- Heart failure hospitalization (HFH)
- Outpatient worsening HF events; and
- KCCQ score change

This hierarchical composite was analyzed by the Finkelstein and Schoenfeld method and by calculating a win ratio.

Win ratio for the Shunt group vs. Control group = 0.86 (95% CI 0.61 to 1.22), p=0.20

The primary effectiveness endpoint was *not* met. The results were similar in the per-protocol population (win ratio of 0.88, 95% CI 0.62 to 1.22). The individual component results of the win ratio analysis are shown in Figure 6.



The numbers of wins, losses, and ties for all pairs of patients at each level of the win ratio hierarchy are shown with 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 unadjusted 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. The proportion of total decisions at each level of the hierarchy (wins or losses at that level divided by the total number of wins plus losses) that contributed to the final win ratio are also shown.

Figure 6: Win Ratio Analysis for the Primary Effectiveness Endpoint (ITT Population)

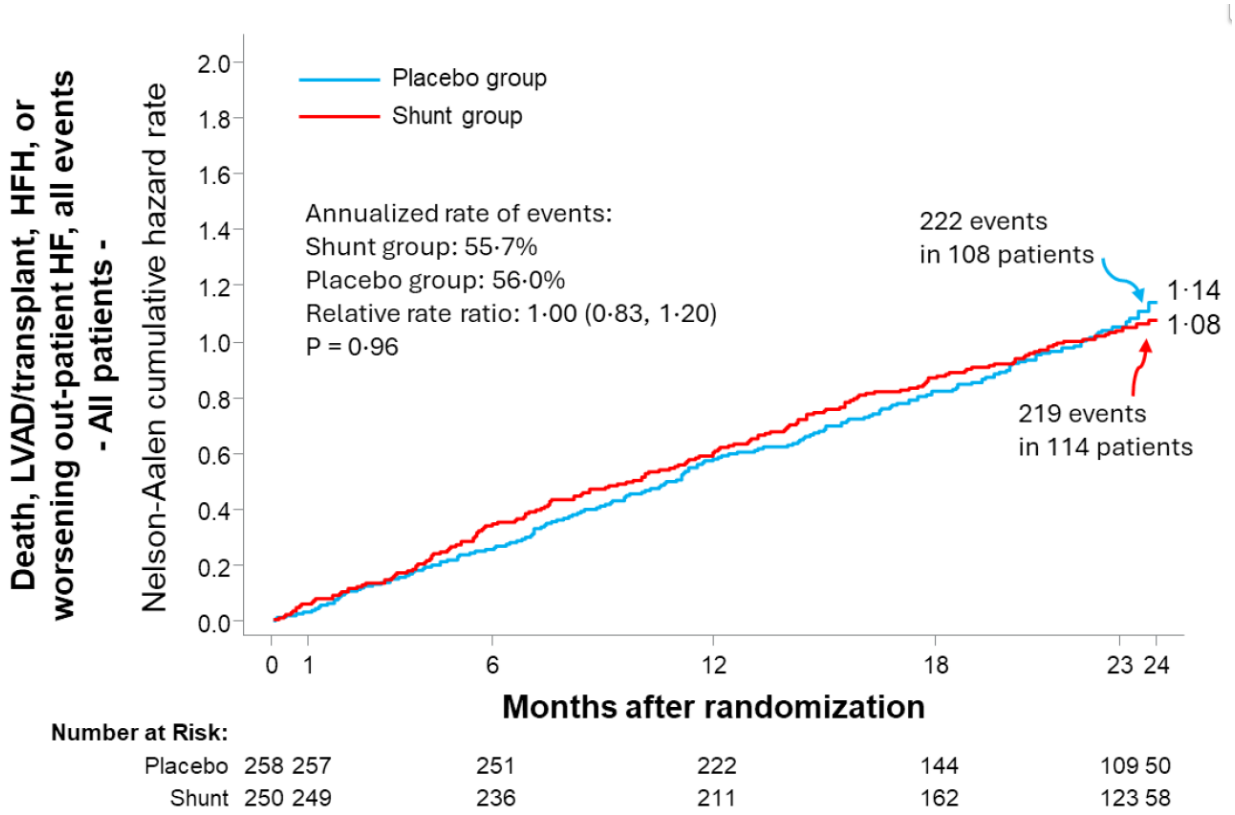
The Panel will be asked to discuss the clinical significance of the negative primary effectiveness results. It is important to remember that the statistical analysis plan specified that if the primary effectiveness endpoint failed, no further hypothesis-driven analyses would be performed.

Event rates for the individual components (except KCCQ score) of the primary effectiveness endpoint are shown in Table 12.

Table 12: Rates of Individual Components of the Primary Effectiveness Endpoint (Except KCCQ)

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

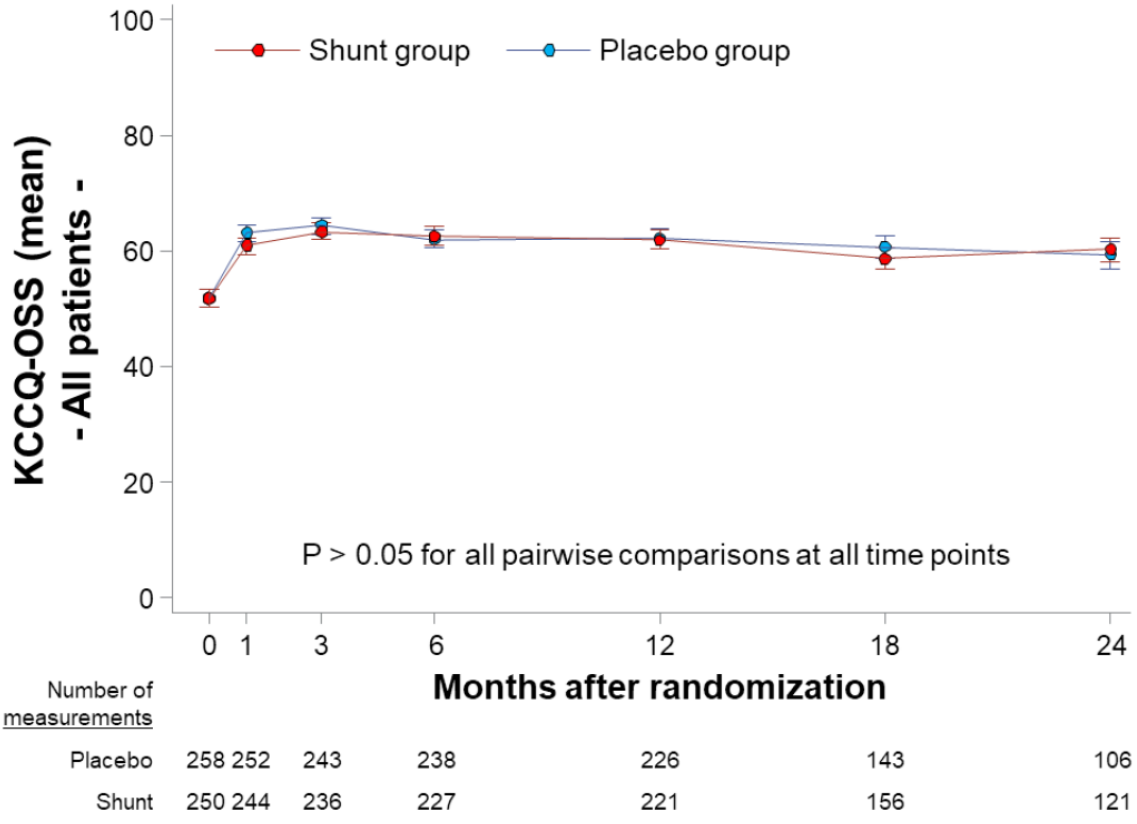
To further illustrate the relative clinical outcomes between the shunt and control groups, a post hoc cumulative event analysis through 2 years of the composite of all-cause death, cardiac transplantation or LVAD implantation, HFH, and outpatient worsening heart failure events (WHF) was conducted (Figure 7). Similar hazard rates were observed for the Shunt group (annualized rate 55.7%) and Control group (56.0%)



The number at the end of each curve is the 2-year hazard rate.

Figure 7: Nelson-Aalen cumulative event analysis of the composite of death, LVAD/transplant, heart failure hospitalization and worsening outpatient heart failure events

KCCQ score change through 2 years are shown in Figure 8. There was a similar increase (approximately 10 points) in KCCQ score in both the Shunt and Control groups at 1 month that was maintained and similar between treatment groups through 2 years.



Data are displayed as mean ± 95% CIs.

Figure 8: KCCQ outcomes over 2 years (ITT population)

In summary, the primary effectiveness endpoint was not met and there was no signal of Shunt benefit in the primary effectiveness endpoint results. Rates for the composite endpoint components of death, cardiac transplantation/LVAD, HFH, and worsening outpatient HF events were generally similar between the Shunt and Control groups, and at all timepoints through 2 years, changes in KCCQ score were similar between the Shunt and Control groups. All-cause death and HFH rates numerically favored the Control group, while cardiac transplantation/LVAD and worsening outpatient HF event rates favored the Shunt group, but between group differences groups were small. The calculations of the individual components and the method of calculating composite rates were not pre-specified. As a result, conclusions regarding statistical significance and the limits of confidence of the results are limited.

8.5 Primary Effectiveness Endpoint Subgroup Analysis by LVEF

In accordance with the SAP, a subgroup analysis of the primary effectiveness endpoint was conducted using Z-test based on the Finkelstein-Schoenfeld estimates of the test statistic and its variance in the HFrEF and HFpEF subgroups. As shown in Figure 9 below, the interaction p-value was 0.0275.

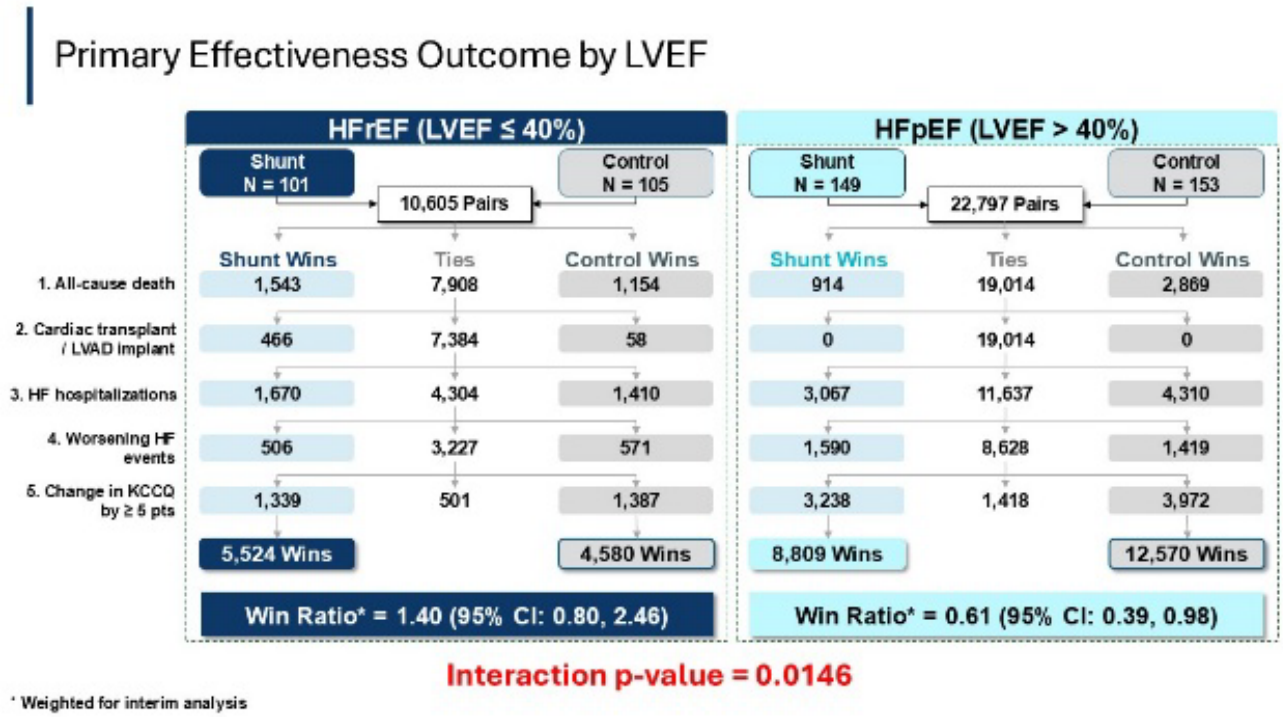


Figure 9: Win Ratio Analysis for HFpEF and HFrEF with Interaction

It is important to note that while prespecified subgroup analysis indicates a nominally significant interaction between LVEF group and the outcome, there was no prespecified hypothesis-driven analysis of any individual subgroup (e.g., the HFrEF subgroup Control vs Shunt patients) per the statistical analysis.

8.6 Post Hoc Analysis of HFrEF and HFpEF subgroups

To further investigate to the outcome of the LVEF subgroup interaction testing, the sponsor conducted additional analyses in the HFrEF and HFpEF subgroups. As shown in Figure 10, of the 508 randomized patients 206 were included in the HFrEF subgroup (101 in the Shunt group and 105 in the Control group) and 302 were included in the HFpEF group (149 in the Shunt group and 153 in the Control group).

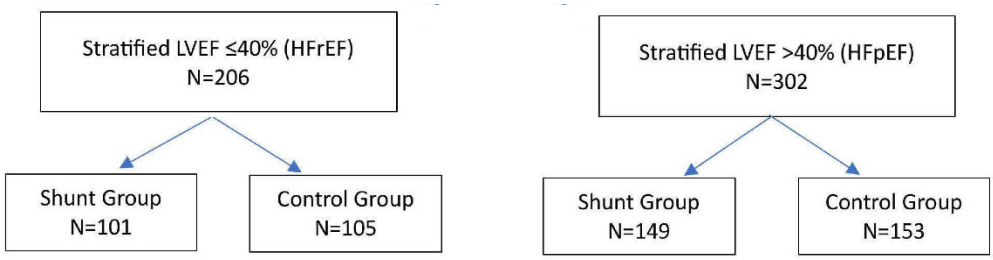


Figure 10: HFrEF and HFpEF Subgroups

It's important to note that the number of randomized patients in each subgroup stratified by LVEF was n=206 for HFrEF (LVEF ≤40%) and n= 302 for HFpEF (LVEF >40%).

9. HFrEF (LVEF ≤40%) Subgroup Analyses

9.1 HFrEF Subgroup Baseline Characteristics

Key demographic and baseline characteristics for the HFrEF subgroup are shown in Table 13 and were similar between the Shunt and Control groups. Over 80% of subjects were male and >90% were Caucasian. There were high rates of hypertension, hyperlipidemia, and coronary artery disease (ischemic cardiomyopathy). Over 94% were NYHA Class III. Median 6MWT distance was longer in the Shunt HFrEF subgroup vs. the Control HFrEF subgroup by a clinically significant distance (32 meters). Other baseline characteristics were generally similar between treatment groups.

Table 13: HFrEF Subgroup Baseline Demographics and Clinical Characteristics

	Shunt group (N = 101)	Control group (N = 105)
Age, years	69.8±11.1	66.5 ± 10.6
Sex, male	84 (83.2%)	84 (80.0%)
Race, Caucasian	91 (90.1%)	93 (88.6%)
Ethnicity, Hispanic	10 (9.9%)	15 (14.3%)
Body mass index, kg/m^2	29.1 ± 5.4	30.4.2 ± 5.7
Duration of heart failure - mos.	97.4 ± 80.5	98.0 ± 82.9
HF-hospitalizations during prior 1yr	0.97±1.11	0.78 ± 0.99
Diabetes mellitus	50 (49.5%)	55 (52.4%)
- Insulin-treated	14 (28.0%)	18 (32.7%)
Hypertension	81 (80.2%)	80 (76.2%)
Hyperlipidemia	80 (79.2%)	75 (71.4%)
Current or previous smoker	61 (60.4%)	60 (57.1%)
Prior stroke or TIA	17 (16.8%)	15 (14.3%)
Chronic obstructive lung disease	18 (17.8%)	20 (19.0%)
Ischemic cardiomyopathy	65 (64.4%)	64 (61.0%)
Non-ischemic cardiomyopathy	36 (35.5%)	41 (39.0%)
At least one HFH in the prior year	55 (54.5%)	53 (50.5%)
Known coronary artery disease	77 (76.2%)	76 (72.4%)
Prior myocardial infarction	58 (57.4%)	60 (57.1%)
Prior PCI	45 (44.6%)	49 (46.7%)
Prior CABG	36 (35.6%)	29 (27.6%)
History of atrial fibrillation or flutter	65 (64.4%)	59 (56.2%)
- Baseline rhythm was afib or flutter	27 (26.7%)	19 (18.1%)
NYHA class - I	0 (0.0%)	0 (0.0%)
- II	4 (4.0%)	6 (5.7%)
- III	97 (96.0%)	99 (94.3%)
- IV	0 (0.0%)	0 (0.0%)
KCCQ summary score	56.0 (35.9, 72.1)	54.2 (39.1, 69.8)
Six-minute walk distance	295 (216, 355)	263 (204, 345)
Troponin I or T >ULN	37/88 (42.0%)	50/98 (51.0%)

	Shunt group (N = 101)	Control group (N = 105)
B-type natriuretic peptide (pg/ml)	301 (203, 751)	319 (155,651)
N-terminal pro-B-type natriuretic peptide (pg/ml)	2231 (1300, 3944)	1867 (954, 3772)
eGFR, ml/min/1.73 m^2	44.5 (37.3, 58.0)	50.4 (39.2, 60.8)
- <60 ml/min/1.73 m^2	76 (75.2%)	74 (70.5%)

Continuous data were mean ± standard deviation or median (interquartile range). CABG denotes coronary artery bypass graft surgery; CRT, cardiac resynchronization therapy; CRT-D, CRT-defibrillator; CRT-P, CRT-pacemaker; eGFR, estimated glomerular filtration rate calculated from the Modification of Diet in Renal Disease (MORD} formula; HFH, heart failure hospitalization; /CD, implantable cardiac defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; TIA, transient ischemic attack; Pct, percutaneous coronary intervention; ULN, upper limits of normal

Table 14 shows baseline HF medication and cardiac rhythm devices, which were well-matched for beta-blockers, renin-angiotensin system inhibitors, mineralocorticoid receptor antagonists, diuretics, and cardiac rhythm devices.

Table 14: HFrEF Subgroup Baseline Medications and Electrical Therapies

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

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

Table 15 shows baseline TTE assessments in the HFrEF subgroup. The mean LVEF was approximately 30% in both treatment groups. Mitral regurgitation was graded as moderate or greater in 24% of Shunt subjects and 18% of Control patients. In the HFrEF subgroup, there were minor differences in multiple measures of RV function favoring the Shunt group, but the impact of these differences on clinical outcomes is uncertain.

Table 15: HFrEF Subgroup Baseline Transthoracic Echocardiography Assessments

	Shunt HFrEF subgroup (N = 101)	Control HFrEF subgroup (N = 105)
Left ventricular end-diastolic volume, ml	188.5 (155.5, 238.0)	187.5 (140.0, 249.5)
Left ventricular end-systolic volume, ml	131.0 (103.5, 167.5)	128.5 (92.5, 184.0)
Left ventricular ejection fraction,%	30.0 ± 6.4	29.2 ± 6.7
Left ventricular ejection fraction (LVEF), %	31.1 (24.9, 35.4)	30.2 (23.8, 34.8)
Left atrial volume, ml	84.5 (65.5, 109.5)	77.5 (61.5, 104.0)
Stroke volume, ml	54.0 (42.0, 67.0)	51.0 (45.0, 62.0)
Stroke volume index, mUm^2	26.9 (21.4, 33.3)	24.7 (21.0, 31.5)
Cardiac output, L/min	3.76 (2.95, 4.66)	3.76 (3.05, 4.66)
Cardiac index, L/min/m^2	1.89 (1.56, 2.30)	1.77 (1.46, 2.28)
Right ventricular fractional area change,%	36.8 (32.0, 41.7)	35.0 (31.6, 40.0)
Tricuspid annular plane systolic excursion, mm	16.0 (13.0, 19.0)	15.0 (14.0, 18.0)
Pulmonary artery systolic pressure, mmHg	29.5 (22.0, 39.0)	32.0 (25.0, 41.0)
Right ventricular end-diastolic area index, cm^2/m^2	10.4 (8.7, 12.4)	10.9 (9.0, 13.5)
Inferior vena cava diameter max, cm	1.6 (1.2, 1.9)	1.6 (1.2, 2.0)
Mitral regurgitation moderate or greater	24 (23.8%)	19 (18.1%)
Tricuspid regurgitation moderate or greater	12/98 (12.2%)	17 (16.2%)

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

Table 16: shows baseline right heart catheterization data. The pulmonary vascular resistance was 2.3 ± 1.3 Wood units in the Shunt group and 2.4 ± 1.4 Wood units in the Control group. In the HFrEF subgroup, RV function in the Shunt group appears to be slightly better than the Control group across several measures. This is based on echo parameters including TAPSE, RVFAC, PA systolic, and tricuspid regurgitation as well as hemodynamic parameters including PA systolic, mean PA, and PCW. The impact of these differences on clinical outcomes is uncertain.

Table 16: HFrEF Subgroup Baseline Right Heart Catheterization Hemodynamic Data

	Shunt HFrEF subgroup (N = 101)	Control HFrEF subgroup (N = 105)
Heart rate, bpm	69.9 ± 12.4	69±10.2
Systolic blood pressure, mmHg	112.9 ± 17.4	111.1 ± 17.1
Diastolic blood pressure, mmHg	65.5 ± 12.3	65.8 ± 10.0
Mean right atrial pressure, mmHg	8.9 ± 4.2	9.3 ± 4.4
Systolic pulmonary artery pressure, mmHg	37.0 ± 10.8	39.6 ± 12.3
Mean pulmonary artery pressure, mmHg	25.6 ± 7.7	27.1 ±8.6
Pulmonary vascular resistance, Wood units	2.3 ± 1.3	2.4 ± 1.4
Pulmonary capillary wedge pressure, mmHg	16.4 ± 6.6	17.2±6.9
Cardiac output, L/min	4.5± 1.4	4.6 ± 1.6
Cardiac index, L/min/m2	2.2 ± 0.6	2.3 ± 0.7

Continuous data are mean ± standard deviation.

Table 17 shows anti-thrombotic treatment at discharge post-Shunt or sham procedure. Rates of anticoagulation and antiplatelet medication use are similar to the overall RELIEVE-HF trial cohort.

Table 17: HFrEF Subgroup Post Procedure Antiplatelet/Anticoagulant Treatment

	Shunt group (N = 101)	Control group (N = 105)
Antiplatelet agents, open label	55 (54.5%)	58 (55.2%)
Antiplatelet agents, study meds*	22 (21.8%)	23 (21.9%)
Chronic oral anticoagulation	64 (63.4%)	58 (55.2%)

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

9.2 HFrEF Subgroup Safety Endpoint Results

Safety endpoint events are shown in Table 18. There was one type 5 BARC bleeding event in the Control group within 30 days. At 2 years, there were 4 cerebrovascular events, 1 myocardial infarction, and 1 pulmonary embolism in the Shunt group. In the Control group, there were 3 cerebrovascular events and 3 myocardial infarctions at 2 years. The HFrEF subgroup safety outcomes were generally similar to those of the overall pivotal trial cohort.

Table 18: HFrEF Subgroup Safety Endpoints Events

	Shunt group (N = 101)	Control group (N = 105)	Relative risk or difference
BARC types 3 or 5 bleeding at 30 days[1]	0 (0.0%)	1 (1.0%)	
Cerebrovascular events at 2 years[1]	4 (4.1%)	3 (3.2%)	1.38 [0.31, 6.15][2]
CNS infarction (stroke)[1]	3 (3.1%)	2 (2.2%)	1.54 [0.26, 9.23][2]
CNS hemorrhage (intracerebral or subarachnoid)[1]**	0 (0.0%)	1 (1.2%)	
Transient ischemic attack[1]	1 (1.0%)	1 (1.0%)	1.04 [0.07, 16.64][2]
Myocardial infarction at 2 years[1]	1 (1.1%)	3 (3.5%)	0.34 [0.04, 3.24][2]
Systemic embolization events at 2 years[1]	0 (0.0%)	0 (0.0%)	
Pulmonary embolization events at 2 years[1]	1 (1.7%)	0 (0.0%)	
Shunt implant embolization at 2 years[1]	0 (0.0%)		

**Does not include 1 additional patient in the control group with an ischemic stroke and hemorrhagic transformation.
1. Event rates were number of events (Kaplan-Meier time-to-first event estimates).
2. Hazard ratio [95% confidence interval].
3. Difference [95% confidence interval], adjusted for baseline value (analysis of covariance).
BARC, Bleeding Academic Research Consortium; CNS, central nervous system

Table 19 and Table 20 show baseline and 12 month medications, and medication changes from baseline to 12 months, respectively. Changes in HF medications occurred for a number of reasons including side effects/intolerance, patient choice, costs, physician prescribing patterns, medication

administration challenges, and clinical changes. Overall, HF medication changes were infrequent and similar between Shunt and Control subjects in the HFrEF subgroup.

Table 19: HFrEF Subgroup Medications at Baseline and 12 months

	Baseline		12 months	
	Shunt group (N = 101)	Control group (N = 105)	Shunt group (N = 101)	Control group (N = 105)
Beta-blockers	99 (98.0%)	101 (96.2%)	92 (100%)	91 (96.8%)
Renin-angiotensin system inhibitors	95 (94.1%)	93 (88.6%)	87 (94.6)	84 (89.4%)
-ACEi	7 (6.9%)	7 (6.7%)	7 (7.6%)	7 (7.4%)
-ARB	8 (7.9%)	7 (6.7%)	6 (6.5%)	3 (3.2%)
-ARNi	80 (79.2%)	79 (75.2%)	74 (80.4%)	74 (78.7%)
Mineralocorticoid receptor antagonists	74 (73.3%)	77 (73.3%)	66 (71.7%)	65 (69.1%)
Sodium-glucose cotransporter-2 inhibitors	48 (47.5%)	56 (53.3%)	59 (64.1%)	56 (59.6%)
Vasodilators	8 (7.9%)	13 (12.4%)	10 (10.9%)	12 (12.8%)
- Long-acting nitrates	7 (6.9%)	11 (10.5%)	9 (9.8%)	8 (8.5%)
- Hydralazine	2 (2.0%)	8 (7.6%)	3 (3.3%)	8 (8.5%)
Diuretics	93 (92.1%)	98 (93.3%)	85 (92.4%)	83 (88.3%)
Antiplatelet agents	51 (50.5%)	52 (49.5%)	49 (53.3%)	49 (52.1%)
Chronic oral anticoagulation	63 (62.4%)	54 (51.4%)	59 (64.1%)	56 (59.6%)

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

Table 20: Summary of Medication Changes

Parameter (Changes in medication at discharge compared to baseline) % (n/N)	**Treatment (N=246)**	**Control (n=252)**	**Overall (N=498)**	**Difference (95% CI)**
Any major changes in the medications	2.0% (5/246)	0.8% (2/252)	1.4% (7/498)	1.2 [-1.1, 4.0]
Decrease dose by >50%	0.4% (1/246)	0.0% (0/252)	0.2% (1/498)	0.4 [-1.1, 2.3]
Increase dose by >100%	0.0% (0/246)	0.0% (0/252)	0.0% (0/498)	N/A
Discontinue	0.8% (2/246)	0.0% (0/252)	0.4% (2/498)	0.8 [-0.7, 3.0]
New drug class started	0.8% (2/246)	0.8% (2/252)	0.8% (4/498)	0.0 [-2.2, 2.2]
ACEi or ARB or ARNi	0.4% (1/246)	0.4% (1/252)	0.4% (2/498)	0.0 [-1.9, 1.9]
Decrease dose by >50%	0.0% (0/246)	0.0% (0/252)	0.0% (0/498)	N/A
Increase dose by >100%	0.0% (0/246)	0.0% (0/252)	0.0% (0/498)	N/A
Discontinue	0.4% (1/246)	0.0% (0/252)	0.2% (1/498)	0.4 [-1.1, 2.3]
New drug class started	0.0% (0/246)	0.4% (1/252)	0.2% (1/498)	-0.4 [-2.2, 1.2]
Beta-blockers	0.4% (1/246)	0.4% (1/252)	0.4% (2/498)	0.0 [-1.9, 1.9]
Decrease dose by >50%	0.0% (0/246)	0.0% (0/252)	0.0% (0/498)	N/A
Increase dose by >100%	0.0% (0/246)	0.0% (0/252)	0.0% (0/498)	N/A
Discontinue	0.0% (0/246)	0.0% (0/252)	0.0% (0/498)	N/A
New drug class started	0.4% (1/246)	0.4% (1/252)	0.4% (2/498)	0.0 [-1.9, 1.9]
MRA	0.4% (1/246)	0.0% (0/252)	0.2% (1/498)	0.4 [-1.1, 2.3]
Decrease dose by >50%	0.0% (0/246)	0.0% (0/252)	0.0% (0/498)	N/A
Increase dose by >100%	0.0% (0/246)	0.0% (0/252)	0.0% (0/498)	N/A
Discontinue	0.0% (0/246)	0.0% (0/252)	0.0% (0/498)	N/A
New drug class started	0.4% (1/246)	0.0% (0/252)	0.2% (1/498)	0.4 [-1.1, 2.3]
Vasodilators	0.8% (2/246)	0.0% (0/252)	0.4% (2/498)	0.8 [-0.7, 3.0]
Decrease dose by >50%	0.4% (1/246)	0.0% (0/252)	0.2% (1/498)	0.4 [-1.1, 2.3]
Increase dose by >100%	0.0% (0/246)	0.0% (0/252)	0.0% (0/498)	N/A
Discontinue	0.4% (1/246)	0.0% (0/252)	0.2% (1/498)	0.4 [-1.1, 2.3]
New drug class started	0.0% (0/246)	0.0% (0/252)	0.0% (0/498)	N/A

ACEi = angiotensin-converting enzyme inhibitors
ARB = angiotensin TT receptor blockers
ARNi = angiotensin receptor-neprilysin inhibitor
MRA = mineralocorticoid receptor antagonist SGLT2 = Sodium-glucose Cotransporter-2
1. Categorical variables are compared between treatment groups by the Chi-square test, and Wald 95% CT is provided for the risk difference.
(*) Fisher's exact p-value and corresponding confidence interval for risk difference are provided when at least one cell has an expected frequency of five or less.

9.3 HFrEF Subgroup Primary Effectiveness Endpoint Outcomes

The primary effectiveness endpoint (hierarchical composite of death, cardiac transplantation or LVAD implantation, HFH, outpatient worsening HF events, and KCCQ) was evaluated in the HFrEF subgroup using the Finkelstein and Schoenfeld method and calculating a win ratio.

The win ratio in favor of the Shunt group did not reach statistical significance in the HFrEF subgroup.

The overall win ratio results and the wins vs. losses for the components of the primary effectiveness endpoint in the HFrEF subgroup are shown in Figure 11.

Win ratio for the Shunt HFrEF subgroup vs. HFrEF Control subgroup = 1.40 (95% CI 0.80 to 2.46)

The overall win ratio results and the wins vs. losses for the components of the primary effectiveness endpoint in the HFrEF subgroup are shown in Figure 11.

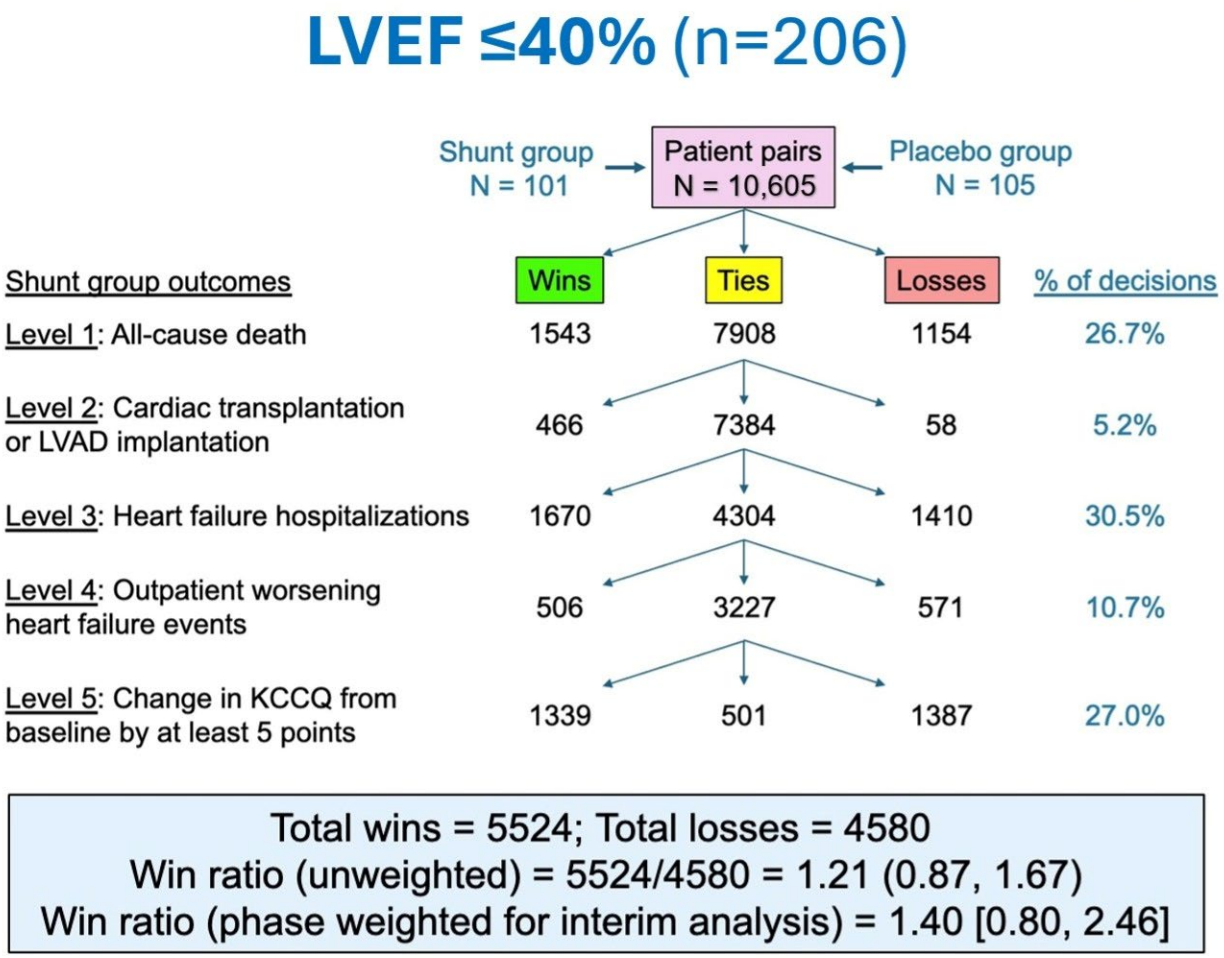


Figure 11: HFrEF Subgroup Primary Effectiveness Endpoint Win Ratio Analysis

Because the win ratio did not capture multiple HF events in patients that exited the trial due to death or transplant/LVAD, further post hoc analyses were conducted to explore the individual components of the primary effectiveness endpoint. Event rates for the individual components of the primary effectiveness endpoint (except KCCQ score change) in the HFrEF subgroup are shown in Table 21 which include recurrent heart failure hospitalizations (HFH) and worsening outpatient heart failure events (WHF). Rates for all events, LVAD/heart transplant, and HFH events favored the Shunt group vs the Control group.

Table 21: HFrEF Subgroup Rates of Individual Components of the Primary Effectiveness Endpoint (Except KCCQ)

	Shunt group (N=101)	Control group (N=108)	RR or HR [95% CI]
All events[1]	76/155.2 (49.0%/year)	134/151.2 (88.6%/year)	0.55 [0.42,0.73] P<0.0001*
All-cause Death[2]	13 (14.3%)	20 (26.8%)	0.63 [0.31,1.26] P=0.19*
LVAD/HT[2]	1 (1.5%)	6 (9.0%)	0.16 [0.02,1.32] P=0.051*
All HFHs[1,3]	41/155.2 (26.4%/year)	78/151.2 (51.6%/year)	0.52 [0.31,0.86] P=0.011*
All out-pt WHFs[1,3]	21/155.2 (13.5%/year)	30/151.2(19.8 %/year)	0.70 [0.39,1.23] P=0.21*

[1]Total no. of events/total no. of patient-years of follow-up (annualized rate) with relative rate ratio {95% CI)
[2]Time-to-first event analysis - n events (Kaplan-Meier estimated rate) with HR {95% CI) from a Cox model (hazard ratio)
[3]HR {95% CI) from a joint frailty model accounting for the competing risk of death
*P-values not adjusted for multiplicity

It was noted that in the HFrEF subgroup, patients who died had a higher rate of HF and WHF events compared to surviving patients in both the Shunt and Control groups (Table 22).

Table 22: HFrEF Subgroup. Comparison of patients that exited the study due to death, heart transplantation (HT), or LVAD implantation (LVAD) vs. alive patients remaining in the trial through the time of unblinding and primary analysis

	if patient died or HT/LVAD	If patient alive	Relative Rate Ratio (95%CI)	P-value[3]
Shunt group[1]	N=14, 10.8 pt-yrs.	N=87; 144.4 pt-yrs.	N/A	
HFH[2]	13 (120.4%/yr)	28 (19.3%/yr)	6.20 (2.95, 12.4)	<.000001
WHF[2]	5 (46.3%/yr)	16 (11.1%/yr)	4.19 (1.20, 11.9)	0.0024
Control Group[1]	N=26; 27.3 pt-yrs.	N=79; 123.8 pt-yrs.	N/A	
HFH[2]	39 (142.8%/yr)	39 (31.5%/yr)	5.22 (3.26, 8.36)	<.000001
WHF[2]	10 (36.6%/yr)	20 (16.2%/yr)	2.61 (1.09, 5.85 0	0.0100

[1]N=number of patients; no of patient-years of follow-up
[2]Total no. of events/total no. of patient-years of follow-up (annualized rate) with relative rate ratio (95% CI)
[3]Chi square P-value

In the HFrEF subgroup, patients who died had an increased rate of heart failure hospitalizations compared to surviving patients. Differences in death and HFH rate differences favoring the Shunt group should be interpreted with caution, as these post hoc analyses were not adjusted for multiplicity to control type 1 error.

9.3.1 HFrEF Subgroup KCCQ Score Analysis

KCCQ score changes through 2 years post-randomization are shown in Figure 12. Similar to the full ITT (HFrEF + HFpEF) cohort, there was a similar increase in KCCQ score in both the HFrEF

subgroup Shunt and Control groups between the index procedure and 1 month. Beyond 1 month, the increased KCCQ score was maintained and similar between treatment groups through 2 years.

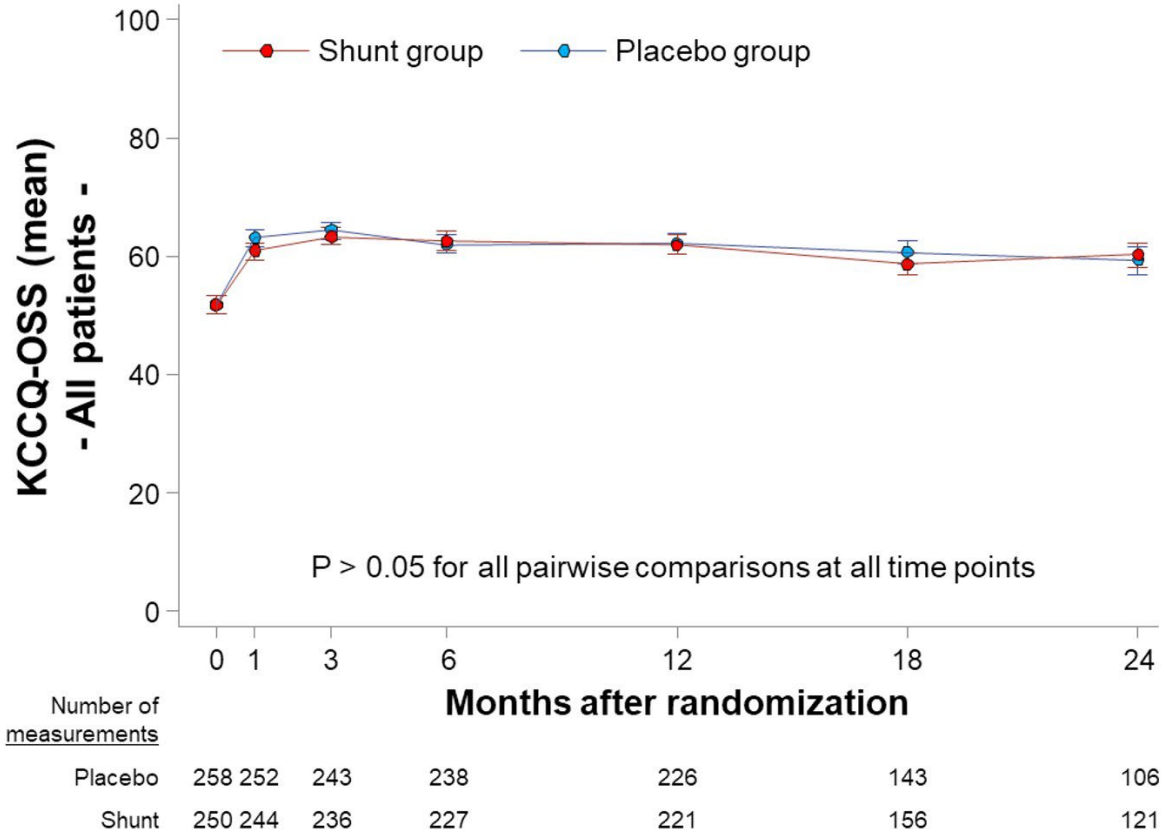


Figure 12: HFrEF Subgroup KCCQ Scores Through 2 Years

It is important to note that in the HFrEF subgroup, Shunt subjects did not experience an improved health status/quality of life compared to Control patients. Both treatment groups experienced an initial increase in KCCQ score, but an effect size difference in favor of the shunt group was absent. Improvements in health status/quality of life is not observed consistently in some HF trials that show benefits for traditional clinical endpoints. However, based on the principle of operation of the Shunt, it was expected that an interatrial shunt that decompresses the left atrium would reduce pulmonary vascular congestion symptoms and improve health status. The unexpected absence of a KCCQ score change difference in favor of the Shunt group vs. the Control group raises uncertainty regarding Shunt benefit in the HFrEF subgroup. The Panel will be asked to comment on the significance of these observations.

9.3.2 Win Ratio Analysis of the hierarchical composite endpoint of death, LVAD/transplant, HFH, and worsening HF treated as an outpatient

Because the analyses in Table 21 above suggested favorable outcomes in the Shunt group compared to the Control group for several of the individual components of the primary endpoint and, as shown in Figure 12, there was no difference in KCCQ between the Shunt and control groups, the sponsor conducted a win ratio analysis of the first four components of the original primary effectiveness endpoint, excluding KCCQ. Figure 13 shows a win ratio analysis of a hierarchical composite endpoint of death, LVAD/transplant, HFH, and worsening HF treated as an outpatient. The win ratio was 1.31 (95% CI 0.87 to 1.97). The p-value (unadjusted for multiplicity) was 0.19. There was no statistically significant difference in the win ratio results between treatment groups in the HFrEF cohort when KCCQ was removed from the primary effectiveness endpoint.

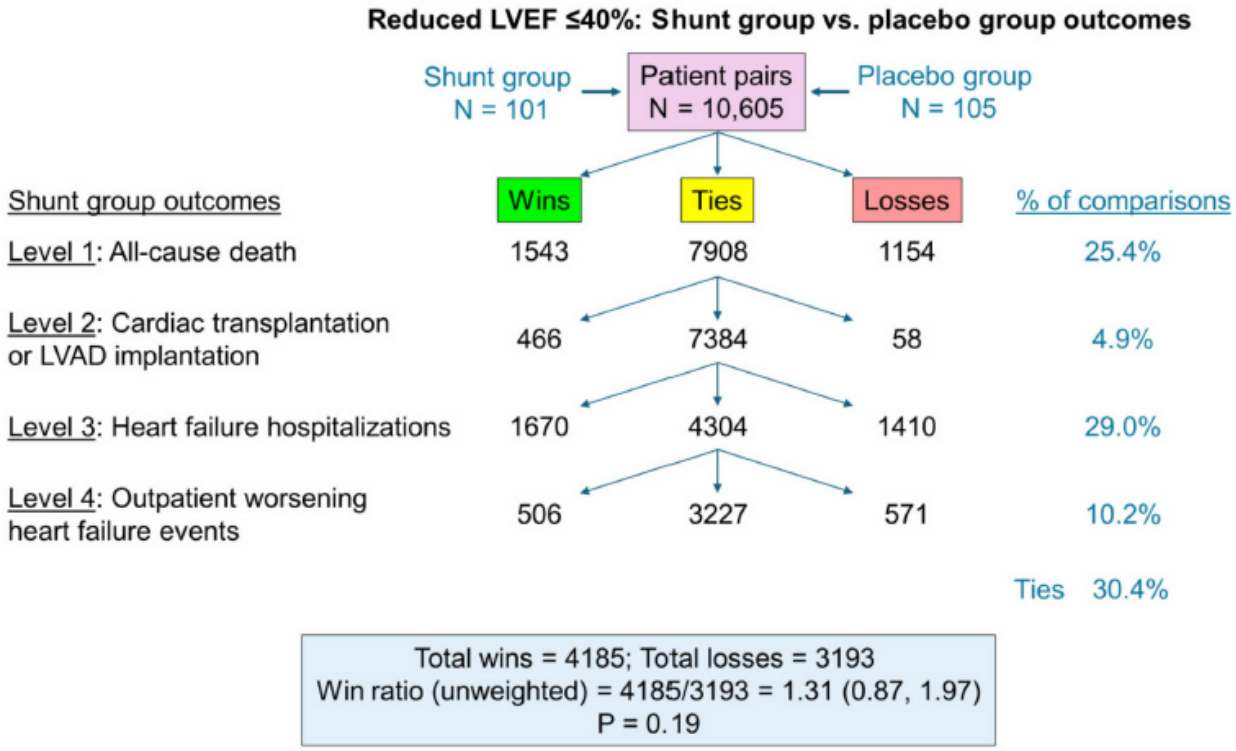


Figure 13: HFrEF Subgroup Win Ratio analysis of Death, LVAD/Transplant, HFH, and Worsening HF Treated as an Outpatient

9.3.3 HFrEF Subgroup Additional Post Hoc Analyses

The Sponsor performed additional post hoc analyses to further evaluate both single and cumulative hazard rates for each component of the primary effectiveness endpoint in the HFrEF subgroup (Table 23). A z-score test was performed to compare the point differences of the hazard rates.

It is noted that the hazard ratio in Table 23 was obtained by taking the ratio of the maximum (final) cumulative hazard values from the Nelson–Aalen estimates for the treatment and control groups, rather than from a Cox proportional hazards model that was pre-specified in the SAP. The confidence interval was computed by simulating random ratios of the treated and control cumulative

hazards and taking the percentiles, rather than using the standard error of a regression coefficient in a Cox model that was pre-specified in the SAP. As such, these results may be interpreted as exploratory and may not correspond to the conventional hazard ratio or confidence intervals derived from the pre-specified approach.

Table 23: HFrEF Subgroup Cumulative Event Analyses

Single and Group Endpoints	Shunt Group	Control Group	Hazard Ratio 95% CI[1]	P-Value Z-Score[1]
Single Events				
Death	0.15	0.31	0.49 (0.20, 1.11)	.077
Heart Transplant/LVAD	0.02	0.09	0.16 (0.00, 1.10)	.083
HFH	0.52	1.13	0.46 (0.29, 0.69)	.00021
Non-HF Hospitalization	0.87	1.15	0.76 (0.53, 1.07)	.11
All-Cause Hospitalization (ACH)	1.39	2.28	0.61 (0.47, 0.79)	.00021
Worsening HF outpatient (WHF)	0.25	0.38	0.64 (0.33, 1.18)	.14
Combined Events				
Death, HT/LV	0.17	0.40	0.42 (0.18, 0.86)	.018
HFH, WHF	0.77	1.51	0.51 (0.35, 0.70)	.000078
Death, HT/LV, HFH	0.69	1.53	0.45 (0.30, 0.63)	.000011
Death, HT/LV, ACH	1.56	2.68	0.58 (0.46, 0.74)	.000015
Death, HT/LV, HFH, WHF	0.93	1.92	0.49 (0.36, 0.65)	.000004
Death, HT/LV, ACH, WHF	1.81	3.07	0.59 (0.47, 0.74)	.000005

[1]Z-score calculated from hazard ratios at 24 months

In evaluating the results of additional post hoc analyses of composite endpoints, which favored the Shunt group, it is important to note that the primary effectiveness endpoint was not met, and the RELIEVE-HF SAP did not include a pre-specified analysis plan to hierarchically test subgroups or secondary endpoints with methods to adjust for multiplicity to control the type 1 error rate. Therefore, these post hoc results should be interpreted with caution and may be considered hypothesis-generating. The Panel will be asked to comment on the significance of these observations.

To provide further support for the potential benefits of the Shunt, the sponsor provided multiple additional statistical models of recurrent events (Table 24). The results of these analysis showed a risk ratio in favor of the Shunt group for each statistical model.

Table 24: All Events: Death, HT/LVAD, All-Cause Hospitalization, and WHF in HFrEF Stratum Patients (Multiple Models)

Model	HR/RR (95% CI)	p-value
Naïve Cox-PH	0.6831 (0.5153,0.9056)	***0.0081***
Cox-PH with frailty	0.6973 (0.4805,1.0118)	0.0577
Cox-PH with robust SE	0.6831 (0.4967,0.9395)	***0.0191***
Anderson-Gill with frailty estimator	0.5659 (0.3435,0.9324)	***0.0254***
Anderson-Gill with robust sandwich variance estimator (LWYY)	0.5520 (0.3592,0.8481)	***0.0067***
Weibull AFT[1]	0.6882 (0.5026,0.9424)	***0.0184***
Log-logistic AFT[2]	1.3062 (0.9431,1.8090)	0.1080
Exact Poisson	0.5526 (0.4114,0.7376)	***0.0000***
Negative binomial	0.5896 (0.3897,0.8920)	***0.0124***
Poisson-over dispersed	0.6295 (0.4103,0.9658)	***0.0341***
Poisson-zero inflated	0.5602 (0.4052,0.7746)	***0.0005***
Poisson-zero inflated and over dispersed	0.5807 (0.3505,0.9620)	***0.0348***
Negative binomial1 with random effect	0.6295 (0.4103,0.9658)	***0.0341***
Negative binomial2 with random effect	0.5896 (0.3897,0.8920)	***0.0124***
Negative binomial1 with random effect-zero inflated	0.6295	
Negative binomial2 with random effect-zero inflated	0.5896 (0.3897, 0.8920)	***0.0124***

AFT: accelerated failure time; HR: hazard ratio; LWYY: Lin-Wei-Yang-Ying; PH: proportional hazards; SE: standard error. Nominal p-values < 0.05 are shown in bold italic font.

1. The Weibull AFT (accelerated time failure) model was reparametrized after fitting to obtain the HR.
2. The Log-Logistic Model interpretation is the time to event multiplier instead of the HR/RR interpretation. Values greater than 1 are consistent with a treatment effect.

Further, the Sponsor conducted a bootstrap analysis to examine how results from the enrolled HFrEF subgroup compared to different samples that might have been selected from this group of patients, if sampling with replacement was performed. A total of 9,999 resamples were taken for each bootstrap analysis. Within each analysis, two statistics were generated: the Nelson-Anderson cumulative Hazard Ratios (HR), and the log of Nelson-Anderson HR. Histograms were examined for bimodality. This analysis was repeated for 3 event sets: HFH alone; HF events inclusive of all-cause death, HT/LVAD, HFH and WHF combined; and for all-cause events inclusive of all-cause death, HT/LVAD, ACH, and WHF combined. Improved events rates associated with Shunt use were observed in all categories examined: HFH event rate (99.3% improvement), HF event rate (99.8% improvement), and all-cause events (99.6% improvement). The sponsor concluded that this bootstrap analysis provides evidence to reject the null hypothesis of no treatment effect in the HFrEF stratum.

In summary, the additional recurrent event analyses were post hoc. While these re-analyses of the same dataset may provide alternative characterizations of the observed HFrEF outcomes, they do not provide independent evidence supporting device effectiveness in the HFrEF subgroup. These re-analyses do not address or reduce the level of risk of type I error.

Overall, while a subgroup analysis of the HFrEF and HFpEF subgroups was pre-specified in the SAP, subsequent analyses of each subgroup were not. The primary effectiveness endpoint was not met in the HFrEF subgroup (with or without KCCQ). While numerous additional analyses exploring individual components of the primary effectiveness endpoint were conducted and some suggest a potential benefit in heart failure hospitalization, none of these analyses were pre-specified.. Therefore, these post hoc results should be interpreted with caution and may be considered hypothesis-generating.

To address concerns raised by FDA regarding control of Type 1 error, the Sponsor conducted post-hoc permutation testing in an attempt to quantify Type 1 error. The analysis involved randomly reassigning treatment labels 10,000 times while keeping all patient data fixed, then executing a full 3-level decision tree (interaction test, primary endpoint testing, and subgroup selection) for each permutation to empirically quantify how often results as extreme as observed would occur by chance. The permutation-based analysis yielded a 2-sided p-value of 0.0746 for the primary effectiveness endpoint demonstrating a Type-I error rate of 3.73% (one-sided) for the entire decision tree. Additionally, a Global Statistical Test showed nominal significance at $p<0.0001$ for the primary and all seven secondary endpoints (KCCQ change from baseline at 12 mo., joint frailty heart failure hospitalization through 24 mo., time to first death, LVAD/transplant, or heart failure hospitalization, time to first death or heart failure hospitalization, Nelson-Aalen cumulative heart failure hospitalization through 24 mo., time to first heart failure hospitalization, win ratio without KCCQ).

In summary, the permutation test similarly fails to address Type I error control, as methods for controlling Type I error must be specified prospectively. This analysis has significant limitations with respect to quantifying Type 1 error and cannot provide assurance of Type 1 error control. Furthermore, the permutation test quantifies error only within a single, post hoc analytic pathway that was neither pre-specified nor aligned with the SAP. The pseudo-decision rule based on which the maximum type 1 error is computed cannot be considered a genuine or proper decision rule since its formulation involves numerical values calculated from data that have already been collected. Consequently, claims of "minimal Type I error inflation" or "well-controlled error" lack statistical validity for confirmatory inference.

9.3.4 HFrEF Subgroup Mortality Analysis

At the time of the primary analysis, there were 13 deaths (14.3%) in the Shunt group vs. 20 deaths (26.8%) in the Control group (unadjusted p-value 0.19). The causes of CEC adjudicated death are shown in Table 25.

Table 25: Cause of Death in the HFrEF Subgroup

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

Importantly, the number of cardiovascular (CV) deaths were similar in HFrEF Shunt and Control subgroups (11 vs. 12, respectively). There was one non-CV death in the Shunt group (neurologic death) and 6 non-CV deaths in the Control group (malignancy 2, infection 2, trauma 1 and pulmonary 1).

A mortality benefit associated with the Shunt was anticipated in the HFrEF subgroup (see statistical assumptions in Table 3). However, the similarity in CV death rates between treatment groups does not support a mortality benefit associated with Shunt use. These results add to the uncertainty of Shunt benefit in HFrEF patients.

10. HFpEF (LVEF >40%) Subgroup Analyses

10.1 HFpEF Subgroup Baseline Characteristics

Key demographic and baseline clinical characteristics for the HFpEF subgroup are shown in Table 26 and were similar between the Shunt and Control groups. Females accounted for 52% of the Shunt group and 48% of the Control group, and 91% were Caucasian. Greater than 85% had hypertension and >95% were NYHA Class III. Median 6-minute walk distance was shorter in the HFpEF Shunt subgroup vs. the HFpEF Control subgroup by a clinically significant difference

(35 meters). Other baseline characteristics were generally similar between treatment groups. The demographics and baseline clinical characteristics of the HFpEF subgroup differed from the HFrEF subgroup in that patients in the HFpEF subgroup were older and more likely to be female.

Table 26: HFpEF Subgroup Baseline Demographic and Clinical Characteristics

	Shunt group (N = 149)	**Control group (N = 153)**
Age, years	74.6 ± 8.6	73.0 ± 9.5
Sex, male	78 (52.3%)	73 (47.7%)
Race, Caucasian	136(91.3%)	139 (90.8%)
Ethnicity, Hispanic	10 (6.7%)	11 (7.2%)
Body mass index, kg/m^2	31.4±6.6	31.8 ± 6.3
Duration of heart failure - mos.	52.3 ±46.8	59.3 ± 58.5
HF-hospitalizations during prior 1 yr	0.68 ± 0.85	0.61 ± 0.79
Diabetes mellitus	74 (49.7%)	70 (45.8%)
- Insulin-treated	35 (47.3%)	30 (42.9%)
Hypertension	128 (85.9%)	136 (88.9%)
Hyperlipidemia	121 (81.2%)	120 (78.4%)
Current or previous smoker	72 (48.3%)	77 (50.3%)
Prior stroke or TIA	26 (17.4%)	33 (21.6%)
Chronic obstructive lung disease	25 (16.8%)	32 (20.9%)
Ischemic cardiomyopathy	49 (32.9%)	56 (36.6%)
Non-ischemic cardiomyopathy	100 (67.1%)	97 (63.4%)
At least one HFH in the prior year	73 (49.0%)	74 (48.4%)
Known coronary artery disease	92(61.7%)	84 (54.9%)
Prior myocardial infarction	46 (30.9%)	43 (28.1%)
Prior PCI	58 (38.9%)	47 (30.7%)
Prior CABG	29 (19.5%)	29 (19.0%)
History of atrial fibrillation or flutter	105 (70.5%)	100 (65.4%)
- Baseline rhythm afib or flutter	49 (32.9%)	45 (29.4%)
NYHA class - I	0 (0.0%)	0 (0.0%)
- II	5 (3.4%)	1 (0.7%)
- III	142 (95.3%)	152 (99.3%)
- IV	2 (1.3%)	0 (0.0%)
KCCQ summary score	49.0 (34.8, 64.3)	47.4 (32.3, 62.8)
Six-minute walk distance	240 (186,316)	275 (193, 321)
Troponin I or T >ULN	42/139 (30.2%)	59/142 (41.5%)
B-type natriuretic peptide (pg/ml)	178 (105, 325)	177.5 (79,391)
N-terminal pro-B-type natriuretic peptide (pg/ml)	1654 (873, 2766)	1454 (779, 2544)

	Shunt group (N = 149)	Control group (N = 153)
eGFR, ml/min/1.73 m^2	46.6 (37.5, 59.8)	47.3 (36.6, 60.1)
- <60 ml/min/1.73 m^2	112 (75.2%)	114/153 (74.5%)

Continuous data are mean ± standard deviation or median (interquartile range). CABG denotes coronary artery bypass graft surgery; CRT, cardiac resynchronization therapy; CRT-D, CRT-defibrillator; CRT-P, CRT-pacemaker; eGFR, estimated glomerular filtration rate calculated from the MDRD formula; HFH, heart failure hospitalization; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; TIA, transient ischemic attack; Pct, percutaneous coronary intervention; ULN, upper limits of normal

Table 27 shows baseline HF medication and electrical therapies. A slightly higher proportion of Control subjects were on mineralocorticoid receptor antagonists. Greater than 91% of subjects were taking diuretics.

Table 27: HFpEF Subgroup Baseline Medications and Electrical Therapies

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

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

Table 28 shows baseline transthoracic echocardiography (TTE) assessments. The mean LVEF as approximately 56% in the Shunt group and 55% in the Control group. There were small right ventricular function differences that favored the Control group, but these are of uncertain clinical significance.

Table 28: HFpEF Subgroup Baseline Transthoracic Echocardiography Assessments

	Shunt group (N = 149)	Control group (N = 153)
Left ventricular end-diastolic volume, ml	97.5 (73.0, 122.0)	106.0 (80.5, 128.5)
Left ventricular end-systolic volume, ml	42.0 (28.0, 61.5)	47.0 (33.0, 64.5)
Left ventricular ejection fraction,%	56.1 ±8.8	54.8 ± 8.7
Left ventricular ejection fraction, %	56.3 (49.4, 62.6)	54.3 (47.6, 62.2)
Left atrial volume, ml	75.3 (62.0, 97.3)	74.3 (58.5, 101.0)
Stroke volume, ml	54.0 (41.0, 66.0)	56.0 (44.0, 69.0)
Stroke volume index, mUm^2	26.5 (22.2, 31.6)	28.6 (22.6, 34.5)
Cardiac output, L/min	3.60 (2.79, 4.48)	3.92 (3.11, 4.73)
Cardiac index, L/min/m^2	1.79 (1.49, 2.10)	1.95 (1.57, 2.32)
Right ventricular fractional area change,%	38.1 (33.3, 42.9)	38.9 (34.8, 45.0)
Tricuspid annular plane systolic excursion, mm	17.0 (15.0, 20.0)	17.0 (15.0, 20.0)
Pulmonary artery systolic pressure, mmHg	34.0 (26.0, 41.0)	32.0 (26.0, 40.0)
Right ventricular end-diastolic area index, cm^2/m^2	9.3 (8.0, 11.3)	9.9 (8.3, 11.3)
Inferior vena cava diameter max, cm	0.7 (0.4, 1.0)	0.7 (0.4, 1.0)
Mitral regurgitation moderate or greater	25 (16.8%)	19 (12.4%)
Tricuspid regurgitation moderate or greater	38 (25.5%)	28/152 (18.4%)

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

Table 29 shows baseline right heart catheterization data. The pulmonary vascular resistance in the Shunt group was 2.4 ± 1.0 Wood units vs. 2.0 ± 1.1 Wood units in the Control group. In the HFpEF subgroup, there were small right ventricular function differences that favored the Control group, but these are of uncertain clinical significance. There was a potentially clinically meaningful higher pulmonary vascular resistance (PVR) in the Shunt group (2.4 ± 1.0 Wood units) vs. the Control group (2.0 ± 1.1 Wood units). An elevated PVR may a predictor of worse prognosis following interatrial shunt creation.[28]

Table 29: HFpEF Subgroup Baseline Right Heart Catheterization Hemodynamic Data

	Shunt group (N = 149)	Control group (N = 153)
Heart rate, bpm	67.4 ± 14.4	67.1 ± 15.0
Systolic blood pressure, mmHg	122.1 ± 18.7	123.9 ± 19.8
Diastolic blood pressure, mmHg	65.3 ± 12.1	65.3 ±11.9
Mean right atrial pressure, mmHg	10.0 ± 4.4	9.1 ± 4.0
Systolic pulmonary artery pressure, mmHg	39.8 ± 10.9	37.3 ± 9.5
Mean pulmonary artery pressure, mmHg	26.3 ± 6.8	24.8 ± 5.9

[28] Borlaug BA et al Circulation (2022) 145:1592-1604

	Shunt group (N = 149)	Control group (N = 153)
Pulmonary vascular resistance, Wood units	2.4 ± 1.0	2.0 ± 1.1
Pulmonary capillary wedge pressure, mmHg	16.5 ± 5.7	16.0±5.4
Cardiac output, L/min	4.5 ± 1.6	4.6 ± 1.4
Cardiac index, L/min/m2	2.3 ± 0.7	2.3 ± 0.7

Continuous data are mean ± standard deviation.

Table 30 shows anti-thrombotic treatment at discharge post-Shunt or sham procedure.

Table 30: HFpEF Subgroup Post Procedure Antiplatelet/Anticoagulant Treatment

	Shunt group (N = 149)	Control group (N = 153)
Antiplatelet agents, open label	66 (44.3%)	74 (48.4%)
Antiplatelet agents, study meds*	33 (22.1%)	40 (26.1%)
Chronic oral anticoagulation	94 (63.1%)	92 (60.1%)

*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.

10.2 HFpEF Subgroup Safety Endpoint Results

Safety endpoint events are shown in Table 31 below. There were two type 3 BARC bleeding events in the Shunt group within 30 days. At 2 years, there were 7 cerebrovascular events, 7 myocardial infarctions, and 1 pulmonary embolism in the Shunt group. In the HFpEF Control group, there were 3 cerebrovascular events and 10 myocardial infarctions at 2 years. At 2-years, the HFpEF Shunt subgroup had numerically more cerebrovascular events and fewer myocardial infarctions vs. the Control group.

Table 31: HFpEF Subgroup Safety Endpoint Events

	Shunt group (N = I49)	Control group (N = I53)	Relative risk or difference
BARC types 3 or 5 bleeding at 30 days[1]	2 (1.3%)	0 (0.0%)	N/A
Cerebrovascular events at 2 years[1]	7 (5.7%)	3 (2.0%)	2.49 [0.64, 9.63][2]
CNS infarction (stroke)[1]	4 (3.3%)	3 (2.0%)	1.42 [0.32, 6.34][2]
CNS hemorrhage (intracerebral or subarachnoid)[1]**	0(0.0%)	0 (0.0%)	N/A
Transient ischemic attack[1]	3 (2.4%)	0 (0.0%)	N/A
Myocardial infarction at 2 years[1]	7 (5.6%)	10.5 (8.5%)	0.73 [0.28, 1.91][2]
Systemic embolization events at 2 years[1]	0 (0.0%)	0 (0.0%)	N/A
Pulmonary embolization events at 2 years[1]	1 (0.7%)	0 (0.0%)	N/A
Shunt implant embolization at 2 years[1]	0 (0.0%)	N/A	N/A

**Does not include 1 additional patient in the control group with an ischemic stroke and hemorrhagic transformation.
1. Event rates were number of events (Kaplan-Meier time-to-first event estimates).
2. Hazard ratio [95% confidence interval].
3. Difference [95% confidence interval], adjusted for baseline value (analysis of covariance).
BARC, Bleeding Academic Research Consortium; CNS, central nervous system

10.3 HFpEF Subgroup Primary Effectiveness Endpoint Outcomes

The primary effectiveness endpoint (hierarchical composite of death, cardiac transplantation or LVAD implantation, HFH, outpatient worsening HF events, and KCCQ.) was evaluated in the HFpEF subgroup using the Finkelstein and Schoenfeld method and calculating a win ratio.

The win ratio results suggest that the Shunt was harmful in the HFpEF subgroup.

Win ratio for the Shunt group vs. Control group = 0.61 (95% CI 0.39 to 0.98)

The overall win ratio results and the wins vs. losses for the components of the primary effectiveness endpoint are shown in Figure 14.

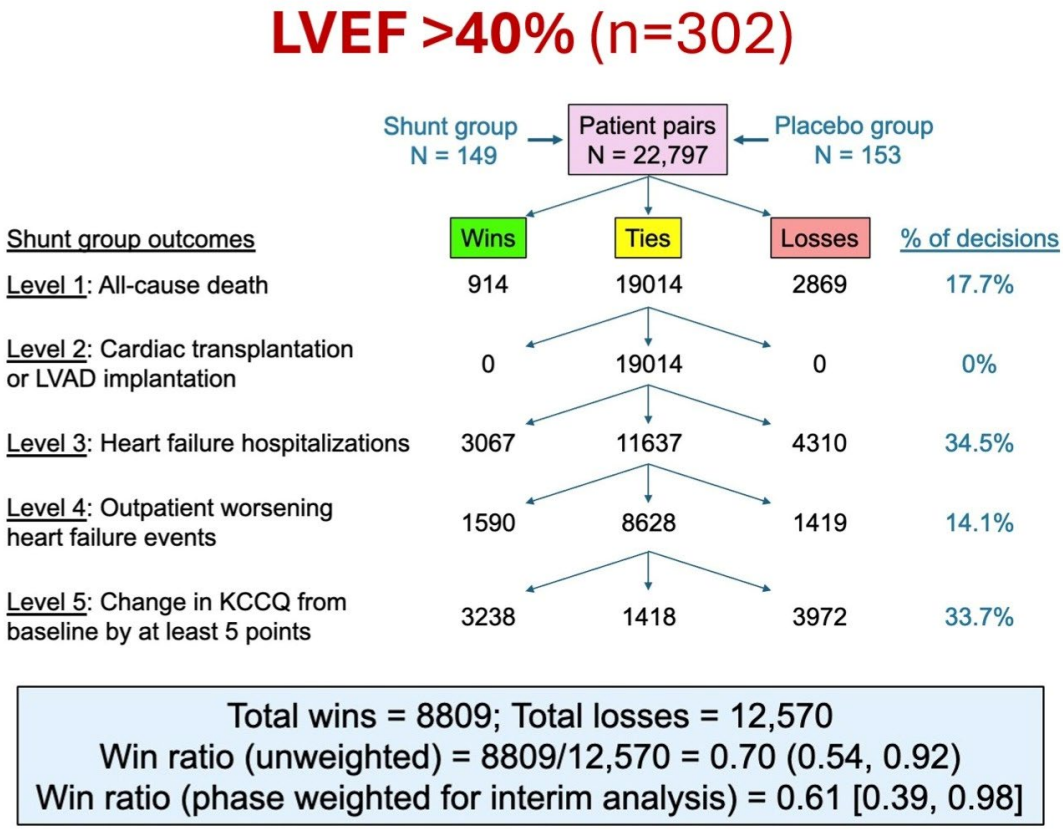


Figure 14: HFpEF Subgroup Primary Effectiveness Win Ratio Analysis

Event rates for the individual components of the primary effectiveness endpoint (except KCCQ score change) through 2 years in the HFpEF subgroup are shown in Table 32. Rates for all events, death, and HFH favored the Control group vs the Shunt group. These analyses were not pre-specified in the SAP. Since p-values were not adjusted to control for type 1 error, statistical significance cannot be confirmed.

Table 32: HFpEF Subgroup Rates of Individual Components of the Primary Effectiveness Endpoint (Except KCCQ) Through 2 Years

	Shunt group (N=149)	Control group (N=153)	RR or HR [95% CI]
All events[1]	143/237.5 (60.2%/year)	88/245.0 (35.9%/year)	1.68 [1.29, 2.19] P=0.0001*
All-cause Death[2]	22 (16.4%)	7 (5.2%)	3.24 [1.38, 7.59] P=0.004*
LVAD/HT[2]	0 (0.0%)	0 (0.0%)	
All HFHs[1,3]	87/237.5 (36.6%/year)	47/245.0 (19.2%/year)	2.05 [1.35, 3.10] P=0.0008*
All out-pt WHFs[1,3]	34/237.5 (14.3%/year)	34/245.0 (13.9%/year)	1.04 [0.64, 1.68] P=0.88*

[1]Total no. of events/total no. of patient-years of follow-up (annualized rate) with relative rate ratio {95% CI)

[2]Time-to-first event analysis - n events (Kaplan-Meier estimated rate) with HR {95% CI) from a Cox model (hazard ratio)

[3]HR{95% CI) from a joint frailty model accounting for the competing risk of death

*P-values not adjusted for multiplicity

In summary, the nominal p-values favoring the Control group (and suggesting Shunt associated harm in HFpEF subjects) for all events, death, and HFH should be interpreted with caution. The primary effectiveness endpoint was not met, and the SAP did not include powered hypotheses for testing subgroups that adjusted for multiplicity and type 1 error control. The panel will be asked to discuss differences in Shunt and Control in HFpEF patients.

10.4 Pathophysiology and Potential Scientific Rationale for Outcome Differences Between HFrEF (LVEF ≤40%) and HFpEF (LVEF >40%) Subgroups

A pre-specified analysis comparing HFrEF and HFpEF subgroups suggested that the Shunt was associated with benefit in HFrEF patients (LVEF ≤40%) and harm in HFpEF subjects (LVEF >40%) with a nominal p-value for interaction (0.0146), which was also reflected in additional post hoc analyses of outcomes in the HFrEF and HFpEF subgroups. These observations contradicted the Sponsor's expectation that the Shunt would benefit HF subjects independent of HF phenotype and that that the Shunt's benefit would be more pronounced benefit in HFpEF patients.

The Sponsor presented a pathophysiologic rationale based on imaging findings in support of a differential effect of the Shunt in HFrEF (benefit with LVEF ≤40%) vs. HFpEF (harm with LVEF >40%) patients.

The Sponsor conducted a post-hoc, exploratory analysis of between group differences in echocardiographic changes at baseline and 12 months.[29] All 508 patients randomized in the RELIEVE-HF study underwent a baseline TTE at a median of 1.1 months prior to randomization. Of these 508, 428 patients underwent a 12-month TTE 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; the remaining 62 patients (62/508/ = 12.2%) were assumed to be missing after randomization. Of 17,272 total measurements (17 measurements x 508 patients x 2 studies), 15,495 (89.7%) were analyzed by the echo core lab without imputation while 1777 (10.3%) parameters were imputed. Echo data at baseline and at 1 year for the HFrEF and HFpEF subgroups are presented in Table 33 and Table 34. These data were compared between the HF phenotype subgroups to identify parameters which differed between the subgroups. The between group differences are shown in Table 35.

Table 33: HFrEF Subgroup Paired Echocardiographic Changes in Cardiac Structure and Function from Baseline to 12 Months

Echocardiographic Data Indexed to Body Surface Area	HFrEF Control (N=105)			HFrEF Shunt (N=101)		
	Baseline	12 Month	12 Month – Baseline Difference	Baseline	12 Month	12 Month – Baseline Difference
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)
LV end-diastolic volume index, ml/m2	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)
LV end-systolic volume index, ml/m2	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)
LV stroke volume index, ml/m2	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)
LV cardiac index, L/min/m2	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)
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)
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)
Left atrial volume index, ml/m2	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)
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)
RV end-diastolic area index, cm2/m2	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)
RV stroke area index, cm2/m2	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)
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)
TAPSE, mm	15.8	15.4	-0.5	16.4	16.8	0.4

[29] Ziles. Mechanistic Basis for Differential Effects of Interatrial Shunt Treatment in HFrEF vs HFpEF: The RELIEVE-HF Trial. J Am Coll Cardiol. 2025;Just Accepted: 29 August 2025

Echocardiographic Data Indexed to Body Surface Area	HFrEF Control (N=105)			HFrEF Shunt (N=101)		
	Baseline	12 Month	12 Month – Baseline Difference	Baseline	12 Month	12 Month – Baseline Difference
	(15.1, 16.5)	(14.6, 16.1)	(-1.3, 0.3)	(15.7, 17.1)	(16.0, 17.6)	(-0.4, 1.3)
Right atrial area index, cm2/m2	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)
Inferior vena cava diameter (max), cm	1.65 (1.53, 1.76)	1.78 (1.66, 1.90)	0.13 (-0.01, 0.28)	1.57 (1.46, 1.69)	1.68 (1.55, 1.81)	0.11 (-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)
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)

Data are least square means (95%, CI). N* is the number of patients with paired 12-month and baseline echocardiographic values after 2-step imputation. Patients without a 12-month echocardiogram who had an adjudicated death due to worsening heart failure or who had cardiac transplantation or were treated with a left ventricular assist device (LVAD) were assigned the worst 12-month values in their group. For all other patients who had missing data due to other reasons (death not due to worsening heart failure or who had cardiac transplantation or were treated with a LVAD) data were assumed to be missing at random (MAR) and multiple imputation by Markov chain Monte Carlo methodology was used. Analysis of covariance (ANCOVA) was performed with a 12-month change relative to adjusted baseline values. Abbreviations: 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.

Table 34: HFpEF Subgroup Paired Echocardiographic Changes in Cardiac Structure and Function from Baseline to 12 Months

Echocardiographic Data Indexed to Body Surface Area	HFpEF Control (N=153)			HFpEF Shunt (N=149)		
	Baseline	12 Month	12 Month – Baseline Difference	Baseline	12 Month	12 Month – Baseline Difference
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)
LV end-diastolic volume index, ml/m2	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)
LV end-systolic volume index, ml/m2	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)
LV stroke volume index, ml/m2	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)
LV cardiac index, L/min/m2	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)
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)
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)
Left atrial volume index, ml/m2	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)
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)

Echocardiographic Data Indexed to Body Surface Area	HFpEF Control (N=153)			HFpEF Shunt (N=149)		
	Baseline	12 Month	12 Month – Baseline Difference	Baseline	12 Month	12 Month – Baseline Difference
RV end-diastolic area index, cm2/m2	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)
RV stroke area index, cm2/m2	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)
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)
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)
Right atrial area index, cm2/m2	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)
Inferior vena cava diameter (max), cm	1.55 (1.47, 1.64)	1.53 (1.44, 1.62)	-0.02 (-0.12, 0.08)	1.63 (1.54, 1.72)	1.80 (1.70, 1.89)	0.17 (0.06, 0.28)
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)
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)

Data are least square means (95%, CI). N* is the number of patients with paired 12-month and baseline echocardiographic values after 2-step imputation. Patients without a 12-month echocardiogram who had an adjudicated death due to worsening heart failure or who had cardiac transplantation or were treated with a left ventricular assist device (LVAD) were assigned the worst 12-month values in their group. For all other patients who had missing data due to other reasons (death not due to worsening heart failure or who had cardiac transplantation or were treated with a LVAD) data were assumed to be missing at random (MAR) and multiple imputation by Markov chain Monte Carlo methodology was used. Analysis of covariance (ANCOVA) was performed with a 12-month change relative to adjusted baseline values. Abbreviations: 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.

Table 35: Between group differences in echocardiographic parameters

Echocardiographic Data *Indexed* to Body Surface Area	HFrEF Shunt vs Control Treatment Difference – HFpEF Shunt vs Control Treatment Difference
Heart rate, bpm	-5.0 (-10.0, -0.1)
LV end-diastolic volume index, ml/m2	-13.3 (-22.8, -3.9)
LV end-systolic volume index, ml/m2	-10.1 (-18.0, -2.3)
LV stroke volume index, ml/m2	-0.5 (-4.0, 3.1)
LV cardiac index, L/min/m2	-0.1 (-0.3, 0.2)
LV ejection fraction, %	2.4 (-1.1, 5.9)
LV global longitudinal strain, %	1.0 (-0.4, 2.5)
Left atrial volume index, ml/m2	-10.6 (-18.0, -3.3)
E/e'	-3.9 (-7.4, -0.4)
RV end-diastolic area index, cm2/m2	-0.9 (-2.3, 0.4)
RV stroke area index, cm2/m2	0.3 (-0.2, 0.8)
RV fractional area change, %	1.2 (-2.1, 4.4)

TAPSE, mm	1.0 (-0.5, 2.5)
Right atrial area index, cm2/m2	-1.5 (-2.7, -0.3)
Inferior vena cava diameter (max), cm	-0.22 (-0.46, 0.03)
PA systolic pressure, mmHg	-6.9 (-14.4, 0.5)
TAPSE / PA systolic pressure, mm/mmHg	0.14 (-0.07, 0.34)

Data are least square means (95%, CI). N* is the number of patients with paired 12-month and baseline echocardiographic values after 2-step imputation. Patients without a 12-month echocardiogram who had an adjudicated death due to worsening heart failure or who had cardiac transplantation or were treated with a left ventricular assist device (LVAD) were assigned the worst 12-month values in their group. For all other patients who had missing data due to other reasons (including death not due to worsening heart failure) data were assumed to be missing at random (MAR) and multiple imputation by Markov chain Monte Carlo methodology was used. Analysis of variance (ANOVA) was performed with a 12-month change relative to adjusted baseline values. A random effect model was performed with the echo value predicted by visit, treatment and the visit by treatment interaction, with a subject level random intercept. Abbreviations: 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.

In the HFrEF subgroup (Table 33), the Shunt group showed a reduced left ventricular end-diastolic volume index (LVEDVi) and end-systolic volume index (LVESVi) from baseline to 12 months and an increase in these parameters in the Control group. The decrease in LVEDVi (-11.9 [-21.3, -2.5] ml/m2) and LVESVi (-8.9 [-17.2, -0.7] ml/m2) vs. the respective Control group suggested shunt-induced LV reverse remodeling in HFrEF. In a meta-analysis of 28 randomized drug studies and 2 cardiac resynchronization studies, reverse LV remodeling was associated with a mortality reduction in HFrEF patients. [30] However, it's important to recognize that in the RELIEVE-HF HFrEF subgroup, the Shunt was not associated with a reduced CV mortality rate. In contrast, HFpEF Shunt patients had no net changes in LVEDVi or LVESVi (consistent with no LV remodeling (Table 34). In both HFrEF and HFpEF subgroups, there was no net change in left ventricular stroke volume index (LVSVi), cardiac index (CI), LVEF or LV global longitudinal strain (GLS), indicating maintenance of LV systolic function after shunt placement (Table 34).

In the HFrEF subgroup, TTE-estimated pulmonary artery systolic pressure (PASP) increased 1.7 mmHg [-3.4, 6.7] at 12 months vs. baseline in the Shunt group compared with an increase of 3.9 mmHg [-0.6, 8.3] in the Control group. In the HFpEF subgroup, TTE-estimated pulmonary PASP increased by 4.0 mmHg [1.4, 6.6] at 12 months follow-up vs. baseline in the Shunt group compared with a decrease of 0.7 mmHg [-3.4, 2.0] in the Control group.

HFpEF Shunt subjects did not have LV remodeling, but had increased RV, RA, and IVC dimensions, and PASP increased (4.0 mmHg [1.4, 6.6]) vs their respective Controls. LV and RV diastolic compliance were lower in HFpEF vs HFrEF at baseline and decreased further after Shunt-placement in HFpEF patients. Based on the differential changes in cardiac structure and function observed by echocardiography in the HFrEF and HFpEF subgroups, the sponsor hypothesizes that differences in both left and right ventricular structure and function and

[30] Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. J Am Coll Cardiol. 2010;56(5):392-406

pulmonary artery pressure provide a plausible mechanism for the differences in clinical outcomes observed in the two HF phenotype subgroups.

In summary, the clinical implications of the echo-based cardiac structure and hemodynamic evaluations are uncertain. These analyses are post-hoc and exploratory, and there are missing data. The clinical significance of numerical differences (considering sample sizes and 95% confidence intervals) among selected cardiac morphologic and hemodynamic parameters between Shunt subjects and respective Control patients across HF phenotypes is unclear. The Panel will be asked to discuss the strengths and limitations of these findings to support potential Shunt-associated benefits and in the HFpEF and HFrEF subgroups.

11. Strengths and Limitations of the Totality of the RELIEVE-HF Trial Data

In evaluating Shunt safety and effectiveness and benefit-risk balance, the following strengths and limitations of the totality of the RELIEVE-HF trial data should be considered:

Strengths

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

Limitations

- The RELIEVE-HF primary effectiveness composite endpoint was not met for the total cohort of enrolled subjects.
- There is uncertainty regarding the HFrEF analysis suggesting clinical benefit.
  - The HFrEF subgroup consisted of 206 randomized subjects.
  - The primary effectiveness endpoint was not met when assessed separately in HFpEF and HFrEF.
  - Benefit was only suggested by changing both the primary endpoint and the statistical methodology.
  - Although comparing the HFrEF and HFpEF subgroups was prespecified, RELIEVE-HF was not powered or pre-specified to test Shunt effectiveness in the two HF phenotypes (LVEF ≤40% vs. >40%).
  - One should exercise caution in drawing conclusions from post hoc subgroup analyses (including additional post hoc endpoints) in the absence prespecified methods in the statistical analysis plan to control type 1 error.
  - No observed mortality benefit associated with Shunt use.
  - No observed health status/quality of life benefit associated with Shunt use, which was anticipated based on the expectation that left atrial decompression would reduce pulmonary vascular congestion symptoms.

- The data suggest a potential benefit in one cohort of patients (HFrEF, LVEF ≤40%) and possible harm in another cohort (HFpEF, LVEF >40%), in which the key difference to guide clinical decision-making in favor of or against Shunt use is LVEF, a continuous variable that: (1) can change over time in response to therapeutic interventions or disease progression or improvement; and (2) is associated with error in the measurement and variability than can result dynamic measurement changes that cross the 40% LVEF threshold. Of note, the absolute intra-patient repeat LVEF measurement variability using the same method within short periods is >7% (in either direction).[31] Further, accurate LVEF measurement is operator-dependent, relies on image quality, and is affected by heart rate and rhythm (e.g., atrial fibrillation). These factors may create challenges in determining a favorable benefit-risk profile in clinical decision making for individual patients.

  The Sponsor provided analyses of the relationship between the baseline LVEF as a continuous measure and the total number of HFHs during follow-up (Figure 15) and all HF events (all cause death, heart transplant/LVAD, heart failure hospitalization, and worsening outpatient heart failure events) (Figure 16).

[31] Packer M. Left Ventricular Ejection Fraction in Heart Failure: Crazy, Stupid Love—and Maybe, Redemption. JAHA 2024; 13: 1-4. DOI: 10.1161/JAHA.124.034642

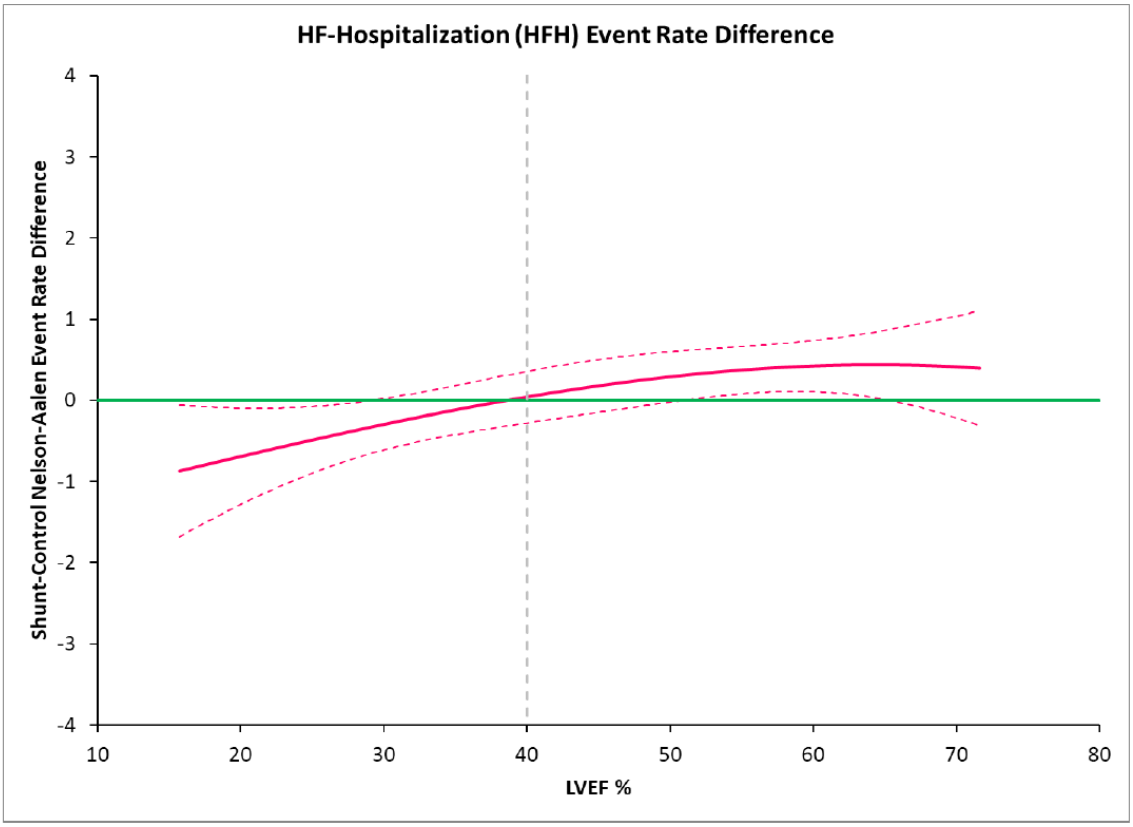


Figure 15: Relationship Between Baseline LVEF as a Continuous Measure and Total Number of HFHs During Follow-up. Differences between Shunt and Control subject event rates for HFHs are plotted across the range of baseline LVEF.[1]

[1]Typical binning values to enable comparison of the groups were by 1 unit of LVEF, but adjacent bins with missing representation were combined so that all bins had at least 2 Shunt and 2 Control values (50 bins). A third-order polynomial curve fit is shown as solid red line.

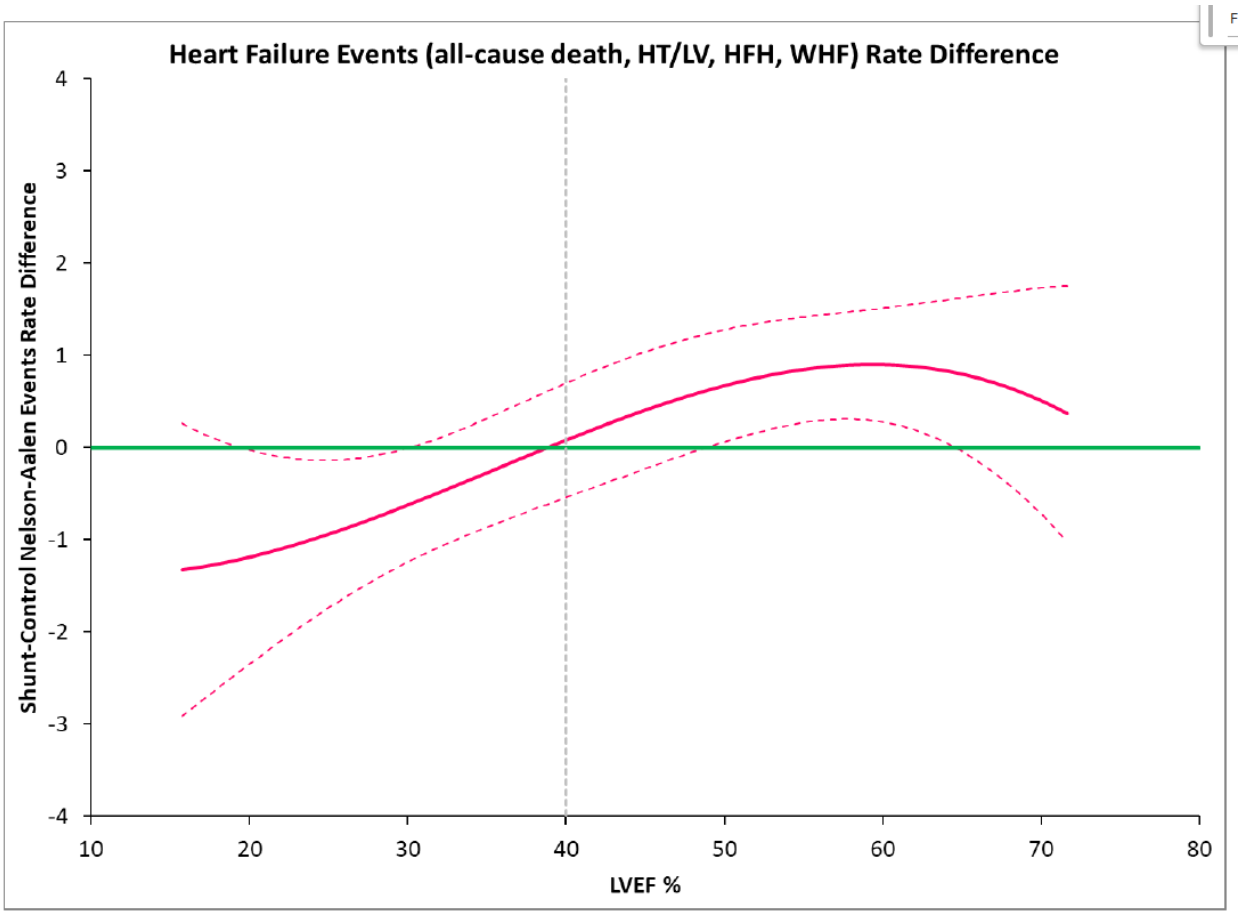


Figure 16: Relationship Between the Baseline LVEF as a Continuous Measure and the Total Number of Adverse Cardiovascular Events During Follow-up. Differences between Shunt and Control subjects event rates for the primary composite effectiveness endpoint (death, heart transplant/LVAD, HFHs, and worsening outpatient HF events) are plotted across the range of baseline LVEF.[1]

[1]Typical binning values to enable comparison of the groups were by 1 unit of LVEF, but adjacent bins with missing representation were combined so that all bins had at least 2 Shunt and 2 Control values (50 bins). A third-order polynomial curve fit is shown.

The solid red lines in Figure 15 and Figure 16 represents the point estimates, and the dotted red lines are 95% CIs. Negative values (below the horizontal green line) favor Shunt subjects and positive values (above the horizontal green line) favor Control subjects. An increasing beneficial effect of Shunt treatment is seen as the LVEF declines. The data suggest that:

- Below an LVEF of approximately 40%, the event rate difference between the Shunt group and the Control group favors the Shunt group (i.e., benefit associated with the Shunt).

- Above an LVEF of approximately 40%, the event rate difference between the Shunt group and the Control group favors the Control group (i.e., harm associated with the Shunt).

However, the 95% CIs around the event rate difference curves show uncertainty regarding the 40% LVEF threshold boundary for defining Shunt-associated benefit vs. harm. In Figure 15, the upper 95% CI curve crosses the green line of unity (consistent with Shunt-associated harm for total HFHs) for LVEFs ≥30%. Similarly, in Figure 16, the upper 95% CI curve crosses the green line of unity (consistent with Shunt-associated harm for the composite of death, heart transplant/LVAD, HFHs, and worsening outpatient HF events) for LVEFs ≥30%. For LVEFs <30%, the upper 95% CI curves run very close to the line of unity of no difference between the Shunt group and the Control group.

The Sponsor also conducted sensitivity analyses using boundaries of LVEF across the HFpEF stratum (LVEF > 40%) for LVEF > 40% to ≤ 47% to support a margin of safety for the LVEF cutoff of ≤ 40% for the HFrEF population. The results of this sensitivity analysis are shown in Table 36 and Table 37, suggest that the Shunt appears to provide a favorable risk ratio for LVEF less than 43%. However, the sample size is small and there are few events, which increases the uncertainty of these results.

Table 36: Poisson HF Event Rates for Patients from the HFpEF Stratum (LVEF>40%) for LVEF from >40% to ≤43%, >40% to ≤ 44%, >40% to ≤ 45%, and >40% to ≤47%

	Patient-Years	**Sample Size**	**Event Count**	**Event Rate (% per Patient-Year)**	**Rate Ratio (95% CI)**
Baseline LVEF > 40% and ≤ 43%					
Shunt Group	26.61	17	8	30.1	0.34 (0.14, 0.76)
Control Group	22.54	15	20	88.7	
Baseline LVEF > 40% and ≤ 44%					
Shunt Group	30.54	20	12	39.3	0.52 (0.25, 1.06)
Control Group	26.58	18	20	75.2	
Baseline LVEF > 40% and ≤ 45%					
Shunt Group	35.73	23	19	53.2	0.83 (0.44, 1.53)
Control Group	35.79	23	23	64.2	
Baseline LVEF > 40% and ≤ 47%					
Shunt Group	43.79	28	22	50.2	0.97 (0.55, 1.70)
Control Group	53.97	35	28	51.9	

CI: confidence interval; HFH: heart failure hospitalizations; HT/LVAD: heart transplant/left ventricular assist device; LVEF: left ventricular ejection fraction; WHF: worsening heart failure. HF events were inclusive of all-cause death, HT/LVAD, all recurrent HFH and WHF as an outpatient.

Table 37: Nelson-Aalen Rate Ratios at 24 Months for HFrEF Patients Plus the Addition of HFpEF Patients to Achieve Upper LVEF Cutoffs of 43%, 44%, and 45%

	NA Rate Ratio (95%CI)
LVEF up to 43%	
HFH	0.43 (0.28, 0.63)
HF events (all-cause death, HT/LVAD, HFH, WHF)	0.47 (0.35, 0.62)
LVEF up to 44%	
HFH	0.46 (0.30, 0.66)
HF events (all-cause death, HT/LVAD, HFH, WHF)	0.49 (0.37, 0.65)
LVEF up to 45%	
HFH	0.48 (0.32, 0.69)
HF events (all-cause death, HT/LVAD, HFH, WHF)	0.54 (0.41, 0.70)

CI: confidence interval; HF: heart failure; HFH: heart failure hospitalization; HT/LVAD: heart transplant/left ventricular assist device; LVEF: left ventricular ejection fraction; NA: Nelson-Aalen; WHF: worsening heart failure.
1. Parametric bootstrap (z-score) p-value at 24 months.

In summary, there are limitations to the HFrEF and HFpEF subgroup effectiveness analyses. The Panel will be asked to comment on the effectiveness outcomes, benefit-risk profile of the device, and patient selection.

12. Proposed Postmarket Study

The Sponsor plans to continue follow-up of all patients implanted with the Shunt in the RELIEVE-HF study through 5 years. Additionally, the Sponsor proposes enrolling a single-arm post-approval study (PAS) that includes a prespecified performance goal, as well as enrollment of all US patients not included in the PAS in a registry to gather real-world data.

13. Conclusions

This FDA executive summary provides background on heart failure and current treatment options, a description of the V-Wave Ventura Shunt device, and a review of the RELIEVE-HF pivotal trial results. Based on the information provided, the Sponsor is requesting that this device be approved and indicated to reduce the risk of hospitalization for heart failure in NYHA Class III heart failure patients who remain symptomatic despite guideline-directed medical therapy,

have a LVEF of ≤ 40%, and who are judged by a Heart Team to be appropriate for Shunt therapy.

The RELIEVE-HF study was a well-executed sham-controlled randomized trial of interatrial shunting in heart failure patients in which randomization was stratified by LVEF. The event rate for the primary safety endpoint of MACNE within 30 days was 0% with an upper 97.5% confidence limit of 1.5%, which met the pre-specified performance goal of 11%. Additional secondary safety endpoints included bleeding events (BARC type 3 or 5 bleeding and central nervous system (CNS) hemorrhage) and embolic events (stroke, systemic embolization, pulmonary embolization, and device embolization).

The primary effectiveness endpoint was a win ratio of the hierarchical composite of all cause death, LVAD/transplant, heart failure hospitalization, worsening heart failure treated as an out-patient, and KCCQ score. The primary effectiveness endpoint was not met; the win ratio was 0.86 with a confidence interval of 0.61 to 1.22 (p=0.20).

A pre-specified subgroup interaction test by LVEF resulted in a nominally significant p-value indicating a difference in primary effectiveness endpoint outcomes by LVEF. Multiple additional post hoc analyses in the HFrEF and HFpEF subgroups were conducted. In the HFrEF subgroup, the primary effectiveness endpoint was not met both with and without the inclusion of KCCQ. A post hoc recurrent rate analysis of components of the primary effectiveness endpoint in the HFrEF (LVEF ≤40%) subgroup, showed that that the Shunt may be associated with a clinical benefit driven by a reduced recurrent HFH rate. However, the following elements of this analysis raise questions regarding potential Shunt benefit including:

- 206 randomized patients in the HFrEF subgroup
- The trial was designed to examine outcomes in all randomized patients and not each LVEF strata,
- Although the subgroup analyses for the LVEF strata (≤40% and >40%) were prespecified, statistical methods to control type 1 error were lacking.
- Shunt implantation was not associated with reduced cardiovascular mortality or an improvement in health status/quality of life as measured by KCCQ.
- Pathophysiology/principle of operation are hypothesis-generating, but the clinical significance remains unclear

Overall, the potentially promising results observed in the HFrEF subgroup may be viewed as hypothesis generating. In addition, a signal of potential harm was associated with Shunt implantation in patients with an LVEF >40%. LVEF measurement can change over time in response to therapeutic interventions or disease progression and is associated with error in the measurement and variability than can result dynamic measurement changes that cross the 40% LVEF threshold. These factors may create challenges in determining a favorable benefit-risk profile in clinical decision making for individual patients.

Because of the public health importance of HF and FDA's desire to bring novel treatments to patients that are safe and effective, we are seeking the Panel's input on the assessment of benefits and risks of this device. FDA is seeking Panel input on the clinical data provided in the PMA as to whether the information provided demonstrates a reasonable assurance of safety and effectiveness as defined in 21 CFR 860.7(d)(l) and (e)(l). The evidence must adequately demonstrate that, with respect to safety, there is an absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use, and that, with respect to effectiveness, in a significant portion of the target population the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

14. Appendix

14.1 Appendix 1 – Win-Ratio Summary

In the win-ratio analysis of the primary endpoint, each patient from the device group was compared with each patient from the control group in the hierarchy of the primary endpoint composite. The pairwise comparison will move to the next hierarchy level (if any left), only when it is a tie at the current hierarchy level. The outcome of each pairwise comparison can be classified into one of the following categories:

1) The V-Wave patient died first.
2) The control patient died first.
3) The V-Wave patient experienced cardiac transplantation or left ventricular assist device (LVAD) implantation first.
4) The control patient experienced cardiac transplantation or left ventricular assist device (LVAD) implantation first.
5) The V-Wave patient experienced HF hospitalization first.
6) The control patient experienced HF hospitalization first.
7) The V-Wave patient experienced worsening HF treated as an outpatient first.
8) The control patient experienced worsening HF treated as an outpatient first.
9) The V-Wave patient, but not the control patient, had an improvement of ≥5 points in KCCQ score from baseline.
10) The control patient, but not the V-Wave patient, had an improvement of ≥5 points in KCCQ score from baseline.
11) None of the above (i.e., a tie).

Let N_1, N_2, N_3, N_4, N_5, N_6, N_7, N_8, N_9, N_{10}, and N_{11} be the number of pairs in categories (1), (2), (3), (4), (5), (6), (7), (8), (9), (10,) and (11) respectively. The total number of "winners" for the device group is: $N_W = N_2 + N_4 + N_6 + N_8 + N_9$, and the total number of "losers" for the device group is: $N_L = N_1 + N_3 + N_5 + N_7 + N_{10}$. The "win ratio" is defined as the total number of "winners" divided by the total number of "losers," i.e., $R_W = N_W/N_L$.

14.2 Appendix 2 – Additional Endpoints

Additional Effectiveness endpoints:

1. NYHA Class (I, II, III, IV) at 12-months
2. Patient Global Assessment (patient self-assessment of current heart failure condition), change from baseline to 1 year
3. Combined all-cause death and all-cause hospitalizations at 12 months
4. All-cause death at 12 months
5. Time to all-cause death
6. Time to cardiovascular death
7. Time to all-cause death, transplant or LVAD
8. Time to cardiovascular death, transplant or LVAD
9. The Nelson-Aalen cumulative distribution functions for the combined occurrences of HFH, LVAD implants, and heart transplant events
10. Days alive free from HFH
11. Outpatient clinic HF visit and/or outpatient intensification of HF therapy
12. Emergency room HF visits
13. HF clinical composite assessment (improved, unchanged, or worsened) as described by Packer comprised of all-cause mortality, HF hospitalization, and changes in NYHA functional class ranking and Patient Global Assessment
14. Comparison of transthoracic echocardiographic parameters as listed in Echocardiography Core Laboratory Manual (including but not limited to heart rate (bpm), interventricular septal thickness (IVSd)(mm), Posterior wall thickness (PWd) (mm), Left Ventricular Systolic Dimension (LVDs) (mm), Time to RV ejection (ms))
15. Loss of shunt flow measured on TTE or TEE
16. Absolute and percentage changes in 6MWT from baseline to 12-months
17. Death: All-cause, cardiovascular (stratified by sudden death, myocardial infarction, pump failure, stroke), non-cardiovascular, and undetermined and relationship to device, study intervention or other cardiovascular procedure
18. Hospitalization: All-cause; HFH, Non-HFH (stratified by cause including if associated with secondary worsening of HF)
19. Change in renal function
20. Medication utilization including type, dose, frequency, and changes
21. Cost and cost-effectiveness
22. Technical success defined as successful delivery and deployment of the Shunt and removal of the delivery catheter
23. Device success - defined as alive and stroke free, with original intended device in place and no additional surgical or interventional procedures related to access or the device and intended performance of the device with no device migration, embolization, detachment, fracture, hemolysis or endocarditis, and expected hemodynamic performance including patent device with Qp:QS <1.5, and no detected para-device complications including device leak, erosion, systemic or pulmonary thromboembolization.

24. Procedural success - defined as device success and no device or procedure related SAEs including life threatening bleeding (>4 units of packed red blood cells), acute kidney injury (stage 2 or 3, including renal replacement therapy), major vascular complications or tamponade requiring intervention, myocardial infarction or coronary ischemia requiring PCI or CABG, severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatment (e.g. ultrafiltration or hemodynamic assist devices including intra-aortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for ≥ 48 hours).
25. Absolute changes in KCCQ score from baseline by 5-point intervals

Additional Safety Endpoints:

1. Major adverse cardiovascular and neurological events (MACNE) and Bleeding Academic Research Consortium (BARC) event types 3 and 5 at 30 days
2. Proportion of Shunt group patients with device-related MACNE at 12 months
3. Incidence of all serious adverse events by type at study duration
4. Incidence of cerebrovascular events at 2 years stratified by CNS infarction, CNS hemorrhage, and TIA and relationship to the device or study procedures (per NeuroARC)
5. Incidence of MI events at 2 years after implantation
6. Incidence of systemic embolization events 2 years after implantation
7. Incidence of pulmonary embolism events at 2 years after implantation
8. Incidence of shunt implant embolization at 2 years
9. Device-related MACNE annually through 5 years

14.3 Appendix 3 – Roll-In Patient Results[32]

Table A1 details baseline patient characteristics for the entire cohort and categorized according to baseline LVEF. Patients were elderly, male, predominantly NYHA Class III with frequent prior HF hospitalizations and a high incidence of comorbidities. GDMT drug utilization was high. LVEF was evenly divided between HFrEF and HFpEF. RV systolic function was moderately reduced and resting hemodynamics were abnormal with elevated filling pressures, reduced cardiac index, and elevated pulmonary vascular resistance. The population was high risk with a median NT-proBNP of 1730 [1076-3518] pg/mL and predicted Meta-Analysis Global Group in Chronic HF risk calculator (MAGGIC)19 and Barcelona Bio-HF risk calculator (BCN BIOHF) 20 1-year mortality rates of 21.1% and 22.0%, respectively.

Table A1. Baseline Patient Characteristics - Roll-in Cohort (open-label)

Characteristic	ALL LVEF	HFrEF (LVEF <40%)	HFpEF (LVEF 240%)	p-value
Number of patients	97	49	48	
Age, yrs.	69.7 ± 11.0	68.9 ± 11.0	70.4 ± 11.1	0.5065
Female	28 (28.9%)	4 (8.2%)	24 (50.0%)	< 0.0001
BMI, kg/m²	31.6 ± 5.6	31.1 ± 5.8	32.0 ± 5.5	0.4138
Duration of HF, yrs.	5.5 ± 5.0	6.6 ± 5.8	4.3 ± 3.7	0.0048
HF Hosp/patient in prior 12 months	1.04 ± 1.22	0.96 ± 1.10	1.13 ± 1.35	0.9755
21 HF Hosp in prior 12 months	56 (57.7%)	28 (57.1%)	28 (58.3%)	1.00
Comorbidities				
Atrial fibrillation	50 (51.5%)	20 (40.8%)	30 (62.5%)	0.0287
Permanent or persistent	26 (26.8%)	11 (22.4%)	15 (31.3%)	0.2702
CKD 2 stage 3a	75 (80.4%)	37 (81.6%)	38 (79.2%)	0.6387
COPD	26 (26.8%)	14 (28.6%)	12 (25.0%)	0.6561
Diabetes	53 (54.6%)	25 (51.0%)	28 (58.3%)	0.4263
Hypertension	83 (85.6%)	40 (81.6%)	43 (89.6%)	0.2672
Hyperlipidemia	74 (77.1%)	36 (75.0%)	38 (79.2%)	0.4874
Ischemic etiology	54 (55.7%)	32 (65.3%)	22 (44.9%)	0.0460
Prior MI	54 (55.7%)	34 (69.4%)	20 (42.6%)	0.0050
Stroke	17 (17.5%)	9 (18.4%)	8 (16.7%)	1.00
Therapies				
ICD	23 (23.7%)	20 (40.8%)	3 (6.3%)	< 0.0001
CRT	24 (24.7%)	21 (42.9%)	3 (6.3%)	< 0.0001
Pacemaker	10 (10.3%)	1 (2.0%)	9 (18.8%)	0.0041
RAS (ACE, ARB, or ARNI)	74 (76.3%)	45 (91.8%)	29 (60.4%)	0.0002
ARNI	35 (36.1%)	29 (59.2%)	6 (12.5%)	< 0.0001
Beta Blocker	82 (84.5%)	47 (95.9%)	35 (72.9%)	0.0010
MRA	58 (59.8%)	35 (71.4%)	23 (47.9%)	0.0152

[32] Rodés-Cabau J, Lindenfeld J, Abraham WT, et al. Interatrial Shunt therapy in advanced heart failure: Outcomes from the open-label cohort of the RELIEVE-HF trial. Eur J Heart Fail. 2024 Apr 1. doi: 10.1002/ejhf.3215. Epub ahead of print.

SGLT2i	15 (15.5%)	11 (22%)	4 (8%)	0.0562
Loop diuretic,	92 (94.8%)	46 (93.9%)	46 (95.8%)	1.00
Loop and Thiazide Diuretic	19 (19.6%)	8 (16.3%)	11 (22.9%)	0.3311
Anticoagulants	34 (35.0%)	17 (34.7%)	17 (35.4%)	1.00
Antiplatelets	33 (34.0%)	18 (36.7%)	15 (31.2%)	0.531
Anti-coagulant/platelet combination	20 (20.6%)	9 (18.4%)	11 (22.9%)	0.474
Lab				
Hgb, gm/dl	12.9 ± 1.9	13.6 ± 2.0	12.3 ± 1.7	0.0006
Creatinine, mg/dl	1.56 ± 0.47	1.63 ± 0.44	1.48 ± 0.49	0.0999
eGFR, ml/min/1.73m^2	42.1 [33.6-55.2]	42.1 [32.9-55.1]	41.7 [35.7-56.5]	0.9742
Echo				
LVEF,%	42.5 ± 16.2	28.2 ± 6.7	57.1 ± 7.5	< 0.0001
RVFAC, %	36.3 ± 6.1	35.0 ± 6.6	37.6 ± 5.4	0.0399
TAPSE, mm	15.8 ± 2.9	15.4 ± 2.8	16.3 ± 2.9	0.0974
Hemodynamics				
HR, bpm	72.4 ± 12.4	74.2 ± 13.0	70.4 ± 11.6	0.1287
BP systolic, mmHg	120.6 ± 16.9	113.0 ± 14.8	128.4 ± 15.4	< 0.0001
RAP, mmHg	11.3 ± 4.6	11.6 ± 4.6	11.0 ± 4.6	0.5258
PAP mean, mmHg	30.3 ± 8.5	31.6 ± 8.7	29.0 ± 8.1	0.1388
PCWP, mmHg	19.6 ± 7.1	20.7 ± 7.6	18.4 ± 6.5	0.1126
LA-RA gradient, mmHg	8.3 ± 5.1	9.1 ± 5.3	7.4 ± 4.8	0.0995
CI, L/min/m^2	2.3 ± 0.8	2.2 ± 0.7	2.3 ± 0.9	0.3917
PVR, Wood units	2.5 ± 1.2	2.5 ± 1.2	2.5 ± 1.3	0.9740
Prognosis				
NYHA Class III, %	94 (96.9%)	48 (98.0%)	46 (95.8%)	0.3672
NYHA Class IV, %	3 (3.1%)	1 (2.0%)	2 (4.2%)	0.3672
KCCQ Overall Summary Score	45.8 ± 21.1	50.9 ± 22.3	40.6 ± 18.7	0.0158
GMWT, m	266 ± 89	287 ± 86	245 ± 88	0.0176
NT-proBNP, pg/ml	1730 [1076-3518]	1730 [1220-3575]	1736 [969-3098]	0.2969
BNP, pg/ml	280 [151-769]	540 [238-1298]	220 [136-317]	0.0652
MAGGIC 1-yr mortality	21.1% ± 11.2%	25.1% ± 12.1%	16.8% ± 8.2%	0.0003
BCN BIO-HF 1-yr mortality	22.0% ± 14.7%	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; HF Hosp = 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.

Table A2 summarizes the procedural outcome measures of MACNE during the first 12 months. Technical, and Device, and Procedural success rates were 99%. A single patient had a pericardial effusion after transseptal catheterization without hemodynamic compromise or need for pericardiocentesis. No Shunt placement was attempted, and the patient was later rescreened and was successfully implanted. Other procedure related SAEs during the first 30 days were seen in 6 (6.2%) patients (including transient atrial fibrillation, hemodynamic instability during anesthesia induction, pneumonia, and 3 vascular access site complications) all of which resolved without sequalae. Procedure duration including invasive echocardiography, vascular access, right heart catheterization, transseptal left atrial access, Shunt placement, repeat echocardiography and sheath removal, averaged a median of 71 [56-90] minutes, without requiring the use of radiographic contrast material.

Device or procedure related MACNE within 30 days was 0%, with an upper 95% confidence limit of 3.73%, which was lower than the PG ($p<0.001$), achieving the Primary Safety Endpoint. Moreover, there were no MACNE from any cause or BARC Type 3 or 5 bleeding during this 1-month period. By 12 months, 15 patients had exited the trial (13 deaths, 1 left ventricular assist device (LVAD) placement, and 1 for withdrawal of consent), but there were no device or procedure related MACNE. There were no strokes, tamponade, thromboembolic or reintervention events. Four late BARC Type 3 bleeding events occurred that were not related to the device or procedure, all in patients on chronic oral anticoagulants.

Table A2. Procedural, 30-Day and 12-Month Safety Outcomes - Roll-in cohort (open-label)

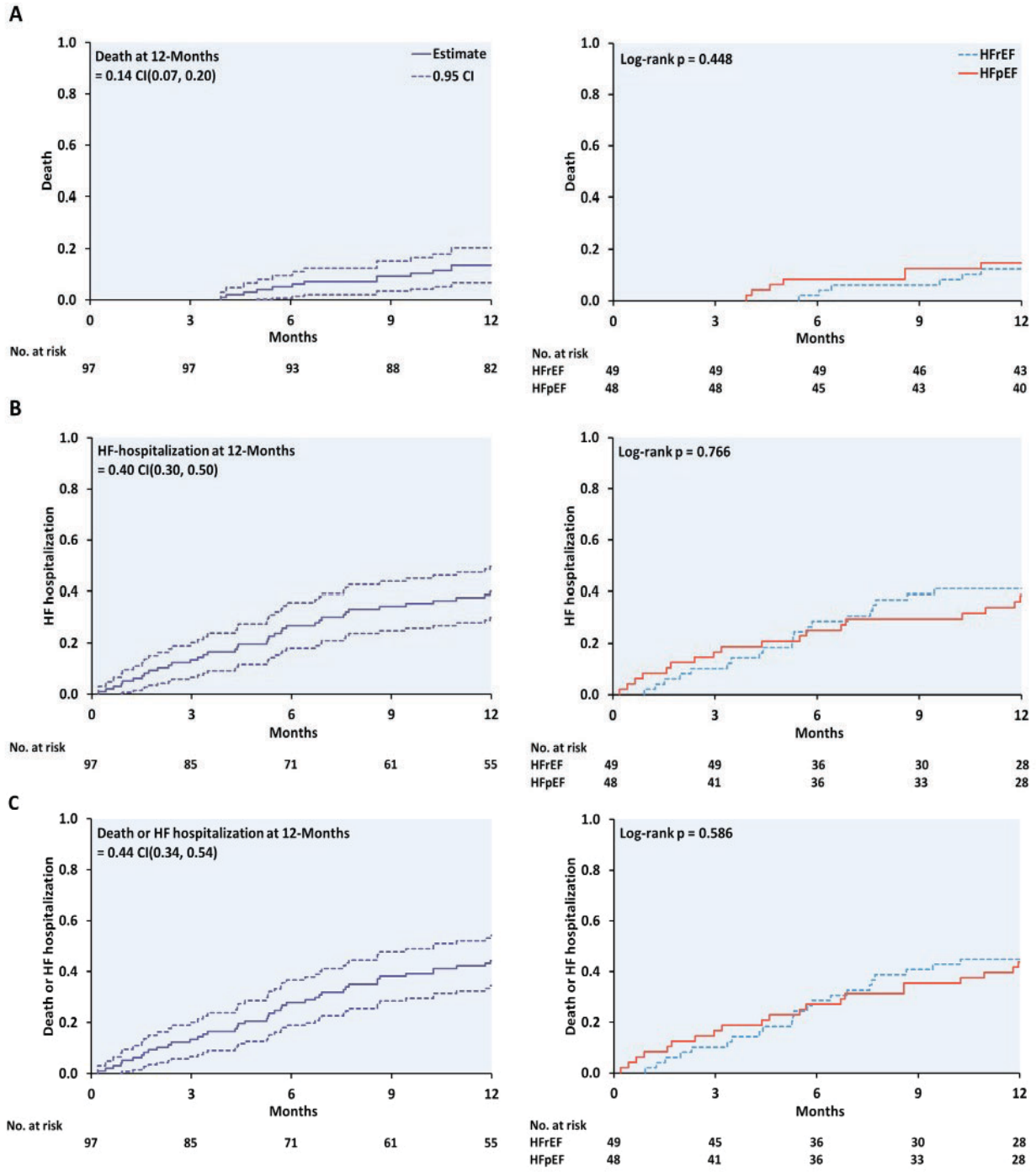
Procedural/in-hospital	**N=97**
Technical Success	96 (98.9%)
Device embolization/dislocation	0 (0%)
Need for a second device	0 (0%)
Procedure duration, min	71 [56-90]
Contrast dose, ml	0 [0-0]
Fluoroscopy time, min	14 [11-20]
Estimated radiation effective dose, mSv	4.9 [2.6-8.2]
Bleeding (BARC) types 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 3G5 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	8 (8.2%)
Non-cardiac	5 (5.2%)
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.

Figure A1 shows Kaplan-Meier estimates of time to death, HF hospitalization, and death or HF hospitalization. Outcomes were similar in the HFrEF and HFpEF groups. All-cause mortality trended lower than predicted by the BCN BIO-HF (p = 0.054) and MAGGIC (p = 0.082) risk scores. Of the 13 deaths, 6 were non-cardiovascular and 7 were of cardiovascular cause. Patients that died or received and LVAD were more likely to be NYHA class IV (20% vs. 0%; p = 0.002), male (93% vs. 67%; p = 0.035), have a prior stroke (40% vs.13%; p = 0.014), not be treated with a neprilysin inhibitor (7% vs. 41%; p = 0.005), and to have a higher rate of HF hospitalizations in the year prior to enrollment (1.7/patient year vs. 0.9/patient year; p=0.010). During the first year 39 patients had one or more HF hospitalizations compared with 56 patients in the year prior to enrollment (p=0.0154). The rate of recurrent HF hospitalizations was reduced from the year prior by 34% (0.71 vs. 1.04 per patient-year; p=0.0043).

Figure A1: Kaplan-Meier estimates: morbidity and mortality - Roll-in cohort (open- label)



Row A: All-cause mortality. Row B: Heart failure hospitalization. Row C: Death or heart failure hospitalization. Left columns display calculated estimates (solid lines) with 95% confidence intervals (dotted lines) for all patients; right column compares calculated estimates for HFrEF (LVEF '540%; blue dashed lines) and HFpEF (LVEF >40%; red lines) subgroups. LVEF = left ventricular ejection fraction

14.4 Appendix 4 – Crossover Patient Results

Control randomized patients were allowed to crossover and be treated with the Shunt once they had completed 24-month follow-up and were unblinded. They needed to meet all the original inclusion / exclusion criteria and be approved by the Central Eligibility Committee. Between February 11, 2022, and August 4, 2023, 22 patients were crossed over and all received a Shunt. There were no cases of device or procedure related MACNE during the first 30-days. Table A3 summarizes currently available results for event rates. On average, patients have less than one year of follow-up.

Table A3. Crossover Patient Early Follow-up Events.

	Reduced LVEF (≤40%)	**Preserved LVEF (>40%)**
N	6	16
Patient years of follow-up	5.6	15.9
Age at Crossover, yrs	70.4 (54.0, 74.2)	77.3 (70.5, 83.7)
Males / Females, N/N	2-Apr	11-May
Events		
Death, all cause	0	3
HT/LV	0	0
HFH	3	5
WHF	0	5
ACH	4	23
HF Event (Death, HT/LV, HFH, WHF), Rate (annualized)	0.54	0.82
All Cause Event (Death, HT/LV, ACH, WHF, Rate (annualized)	0.71	2.08

LVEF, left ventricular ejection fraction; HT/LV, heart transplant or left ventricular assist device; HFH, heart failure hospitalization; WHF, worsening heart failure as outpatient; ACH, all-cause hospitalization.

14.5 Appendix 5 – Bleeding Academic Research Consortium (BARC) Definitions[33]

Type 1: bleeding that is not actionable and does not cause the patient to seek an unscheduled performance of studies, hospitalization, or treatment by a health care professional; it may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional.

Type 2: any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, type 4, or type 5 but does meet at least one of the following criteria: requiring nonsurgical, medical intervention by a health care professional; leading to hospitalization or increased level of care; or prompting evaluation.

Type 3a: overt bleeding plus a hemoglobin drop of 3 to 5 g/dL* (provided the hemoglobin drop is related to bleed); any transfusion with overt bleeding.

Type 3b: overt bleeding plus a hemoglobin drop of 5 g/dL (provided the hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin, and hemorrhoid); bleeding requiring intravenous vasoactive agents.

Type 3c: intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging, or lumbar puncture; intraocular bleed compromising vision.

Type 4: coronary artery bypass grafting-related bleeding; perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of 5 U of whole blood or packed red blood cells within a 48-hour period; chest tube output 2 L within a 24-hour period.

Type 5a: probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious.

Type 5b: definite fatal bleeding; overt bleeding or autopsy, or imaging confirmation.

[33] Wells GA, Elliott J, Kelly S, et al. Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical and Economic Impact of Standard Versus Extended Duration [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 Mar. (CADTH Optimal Use Report, No. 9.2b.) Appendix 10, Bleeding Classification System Definitions. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542934/