Supplemental Material

Inter-Atrial Shunt Treatment for Heart Failure: The randomized RELIEVE-HF trial

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Table S1. RELIEVE-HF trial organization and participating centers

Principal investigators: Stefan D. Anker, Department of Cardiology, Charité Campus Virchow-Klinikum, Berlin, Germany; JoAnn Lindenfeld, Vanderbilt Heart and Vascular Institute, Nashville, TN; Josep Rodés-Cabau, Institut Universitaire de Cardiologie et de Pneumologie de Quebec (IUCPQ) - Universite´ Laval, Quebec, Canada; Gregg W. Stone, The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY.

Executive Committee: Stefan D. Anker, JoAnn Lindenfeld, Josep Rodés-Cabau, Gregg W. Stone, Michael Zile, Saibal Kar, John Gorcsan, Rich Holcomb, William T. Abraham.

Steering Committee: Executive Committee plus Maria Rosa Costanzo, Antoni Bayes-Genis, Jeroen Bax, Alan Bank, Stefan Verheye, Ariel Roguin, Gerasimos Filippatos, Stephan von Bardeleben, Raj Makkar, Tom McRae, Wayne Batchelor, Frank Ruschitzka, Berkert Pieske.

Central Eligibility Committee: Heart Failure Specialists: Michael Zile (moderator), JoAnn Lindenfeld, Jeroen Bax, Alan Bank, Maria Rosa Costanzo; Interventionalists: Gregg W. Stone, Josep Rodes-Cabau, Ariel Roguin, Stefan Verheye.

Echocardiographic Core Laboratory: Penn State Health-Milton S. Hershey Medical Center, Hershey, PA: Michael P. Pfeiffer (director), John P. Boehmer and John Gorcsan, January 26, 2021- current; Washington University, St. Louis MO: John Gorcsan (director), February 24, 2018- January 26, 2021.

Clinical Endpoints Committee (CEC): The Cardiovascular Research Foundation, New York City, NY; Marrick Kukin (chair), David Engel, Evelyn M. Horn, Steven Marx, John R. Teerlink, Jesse Weinberger, Shing-Chiu Wong.

Data Safety Monitoring Board (DSMB): The Cardiovascular Research Foundation, New York City, NY; Bernard Gersh, MD (chair), Brian Whisenant, MD, Gary Michael Felker, MD, Uri

Elkayam, MD (Start date May 12, 2021), Javed Butler (June 19, 2018- February 19, 2021), Tim Collier, MSC (biostatistician), Thomas McAndrew, PhD (biostatistician).

Data management: The Cardiovascular Research Foundation, New York, NY; Ovidiu Dressler (director).

Biostatistics and data analysis: The Cardiovascular Research Foundation, New York, NY; Yiran Zhang (manager).

Site management and data monitoring: V-Wave, Agoura Hills, CA and Caesarea, IL, Cheryl Calhoun, Debbie Deutsch, Merav Hareli, Olivia Mishall, Margaret Sanborn, Beverly Walker; BioClever 2005 SL, Barcelona, Spain; Creative Consulting Solutions, Nashville, TN; Francois CRMG LLC, Stone Mountain GA; IQVIA (formerly Genae Associates NV), Antwerp, Belgium; JC Clinical Consulting, Scottsdale, AZ; Noblewell Sp. z o.o. Warsaw, Poland; Pacific Clinical Research Group, Sydney NSW, Australia; Sanderson Clinical Consulting, Hudson, Quebec, Canada; Synco Research Solutions, LLC, Las Vegas, NV; TFS HealthScience (formerly GCP Clinical Studies Ltd), Kfar Saba Israel.

Sponsor and funding: V-Wave LTD, Caesarea, Israel.

Participating countries (with total enrollment in the randomized trial and roll-in registry), hospitals and principal investigators (PI):

United States (250 randomized, 59 roll-in): Rochester General Hospital, Rochester, NY, Elizabeth Lee (Scott Feitell end date 02 Nov 2021); Medical University of South Carolina (MUSC), Charleston, SC: Sheldon Litwin; Lindner Center for Research and Education at The Christ Hospital, Cincinnati, OH: Eugene Chung Scripps Memorial Hospital, La Jolla, CA: Matthew Price; UPMC - Pinnacle Health Cardiovascular Institute; Harrisburg, PA: Hemal Gada (Co-PI), Roberto Hodara (Co-PI); Austin Heart, Austin, Texas: Kunjan Bhatt, Roger Gammon;

Keck Medical Center of University of Southern California, Michael, Fong, David Shavelle; Los Robles Regional Medical Center, Thousand Oaks, CA, Saibal Kar; University of California, San Francisco, CA, Liviu Klein; Kaiser Permanente – San Francisco Hospital, San Francisco, CA: Alicia Romero; Mission Hospital, Ashville, NC: Vinay Thohan; Memorial Hermann-University of Texas, Houston, TX: Sachin Kumar; The Ohio State University Wexner Medical Center, Columbus, OH: Garrie Haas; Arizona Heart Rhythm Center, Phoenix, AZ: Vijay Swarup; Minneapolis Heart Institute Foundation, Minneapolis, MN: Alan Bank; North Carolina Heart & Vascular Research, Raleigh, NC: Elizabeth Volz, Christopher Chien; Rush University Medical Center, Chicago, IL: Fareed Collado, Clifford Kavinsky; Sentara Norfolk General Hospital, Norfolk, VA: Amit Badiye, David Baran; University of Miami, Miami, FL: Luanda Grazette, Mauricio; University of Utah Hospital, Salt Lake City, UT: Kevin Shah; Cedars-Sinai Medical Center, Los Angeles, CA: Michelle Hamilton (Co-PI), Raj Makar (Co-PI); Centennial Medical Center, Nashville, TN: Tom McRae; Memorial Jacksonville Hospital, Jacksonville, FL: Sumant Lamba; Methodist Healthcare System of San Antonio; San Antonio, TX: Daniel Donovan; Nebraska Heart Hospital, Lincoln, NE: Steven Krueger; Abrazo Arizona Heart Hospital, Phoenix, AZ: Timothy Byrne; Morton Plant Mease Health Care, Clearwater, FL: Leslie Miller; First Coast Cardiovascular Institute, Jacksonville, FL: Youssef Al-Saghir; Lundquist Institute (Harbor-UCLA) Medical Center, Torrance, CA: Robin Chand; Memorial Health Services, Long Beach, CA: David Shavelle; St. Elizabeth Healthcare, Edgewood KY: Saeb Khoury; South Denver Cardiology, Littleton, CO: Ira Dauber; University of Virginia, Charlottesville, VA: Sula Mazimba; Valley Health, Ridgewood, NJ: Suneet Mittal; Advocate Illinois Masonic Medical Center, Chicago, IL: Steven Driver; CHRISTUS Trinity Mother Frances Health System, Tyler, TX: Stanislav Weiner; The Cleveland Clinic Foundation, Cleveland, OH: Samir Kapadia; Memorial Healthcare System, Hollywood, FL, Priyanka Gosain; Piedmont Hospital Atlanta, Atlanta, GA: Rajeev Singh; Texas Heart Institute, Houston, TX: Zvonimir Krejcer; Vanderbilt Heart and Vascular Institute, Nashville, TN: Lynn Punnoose; Wake Med, Raleigh, NC: Stuart Russell; Weill Cornell Medical

College, The New York Presbyterian, New York, NY: Maria Karas; Atlanta VA Health System; Atlanta, GA: Gautam Kumar; Baylor College of Medicine (Houston), Houston, TX: Ajith Nair; Baylor Scott and White, Temple, TX: Robert Widmer; Chippenham and Johnston Willis Hospital, Richmond, VA: Ramesh Kundur; Dignity Health - Mercy Gilbert Medical Center, Gilbert, AZ: Nabil Dib; Northeast Georgia Medical Center; Gainesville, GA: Ugochukwu Egolum; Northwell Health - Lenox Hill Hospital, NY, NY: Miguel Alvarez Villela; Penn State Health, Milton S. Hershey Medical Center, Hershey, PA, John Boehmer; St. Francis Hospital, Roslyn, NY: George Petrossian; Stanford University Hospital and Clinics, Stanford, CA: Jeffrey Teuteberg; Summa Health, Akron, OH: Peter Bittenbender.

Spain (74 randomized, 9 roll-in): Hospital Clinico Universitario de Valencia, Valencia: Julio Núñez; Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona: Antoni Bayes- Genis; Hospital Clinico Universitario de Valladolid, Valladolid: Ignacio Amat Santos; Hospital Clinic of Barcelona, Barcelona: Ana Garcia; Hospital Universitario Puerta de Hierro, Majadahonda, Madrid: Maria del Trigo; Hospital de la Santa Creu I Sant Pau, Barcelona: Sònia Pérez Mirabet; Hospital Clinico San Carlos, Madrid: Luis Nombela Franco University Hospital Virgen de la Arrixaca, El Palmar, Murcia: Domingo Pascual Figal.

Israel (55 randomized, 12 roll-in): Sourasky Medical Center – Ichilov, Tel-Aviv: Michal Laufer Perl; Shamir Medical Center, Be'er Ya'akov: Gil Moravsky; Hadassah Medical Center, Jerusalem: Israel Gotsman; The Baruch Padeh Medical Center, Tiberias: Wadi Kinany; Kaplan Medical Center, Rehovot: Sorel Goland; Sheba Medical Center at Tel Ha'shomer, Ramat Gan: Dov Freimark; Shaare Zedek Medical Center, Jerusalem: Tal Hasin; Rambam Medical Center, Haifa: Oren Caspi; University Hospital Samson Assuta Ashdod, Ashdod: Eli Lev; Soroka University Medical Center, Be'er Sheva: Hilmi Alnsasra.

Germany (32 randomized, 6 roll-in): Kath Marien Krankenhaus, Hamburg: Dimitry Schewel; Sana-Klinikum Hospital, Remscheid: Burkhard Sievers; Vivantes Clinic in Friedrichs Hain, Berlin: Stephan Kische; Charite University Hospital, Berlin: Mohammad Sherif; Heart Center Leipzig, Leipzig: Karl Fengler; University of Leipzig, Leipzig: Rolf Wachter; Vivantes Hospital Am Urban, Berlin: Ince Hüseyin; Ludwig Maximilian University, München; Jörg Hausleiter; University Medicine Mainz, Mainz: Ralf Stephan Von Bardeleben; University Hospital of Rostock, Rostock, Ince Hüseyin (Primary Regulatory site for Germany EC).

Canada (35 randomized, 0 roll-in): Institut Universitaire de Cardiologie et de Pneumologie de Quebec (IUCPQ) - Universite´ Laval, Quebec, Quebec: Josep Rodes-Cabau Montreal Heart Institute, Montreal, Quebec: Reda Ibrahim; University Health Network - Toronto General Hospital, Toronto, Ontario: Eric Horlick.

Poland (22 randomized, 5 roll-in): Institute of Heart Diseases, University Clinical Hospital Jan Mikulicz-Radecki, Wroclaw: Adam Kołodziej; The 4th Military Hospital in Wroclaw, Wroclaw: Bartosz Krakowiak; Institute of Cardiology, Warsaw: Adam Witkowski; Upper Silesian Medical Center, Medical University of Katowice, Katowice: Wojciech Wojakowski.

Belgium (17 randomized, 2 roll-in): ZNA Middelheim Hospital, Antwerpen: Edgard Prihadi; AZ Sint-Jan Brugge, Bruges: Jan Van Der Heyden.

Netherlands (8 randomized, 2 roll-in): Academic Medical Center, Amsterdam: Robbert de Winter; Erasmus Medical Center, Rotterdam: Nicholas Van Mieghem; St. Antonius Hospital, Nieuwegein: Martijn Post.

Australia (7 randomized, 1 roll-in): The Prince Charles Hospital, Chermside, QLD: Scott McKenzie, Yee Weng Wong; Flinders Medical Centre, Bedford Park, SA: Carmine DePasquale.

Epworth Healthcare, Richmond, VIC: Tony Walton; St Vincent's Hospital Melbourne, Fitzroy, VIC: Robert Whitbourn (Primary Regulatory site for Australia HREC).

Switzerland (4 randomized, 1 roll-in): University Hospital Inselspital Bern, Bern: Lukas Hunziker; University Hospital Zurich, Zurich: Frank Ruschitzka.

New Zealand (4 randomized, 0 roll-in): Christchurch Hospital, Christchurch: Richard Troughton.

Table S2. Patient inclusion and exclusion criteria

All patients were screened for eligibility in a 3-stage process. After preliminary screening by the site, de-identified patient information including echocardiographic core lab data was reviewed by an independent eligibility committee to confirm that all inclusion and exclusion criteria were met, especially as regards treatment with maximally tolerated guideline directed medical therapy. Patients who were approved by the eligibility committee then underwent right cardiac catheterization and transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE) to assess whether final disqualifying hemodynamic or anatomic exclusion criteria were absent. Patients free from each of these criteria were then immediately randomized.

INCLUSION CRITERIA

All must be present.

1. Ischemic or non-ischemic cardiomyopathy with either reduced or preserved left ventricular ejection fraction and documented heart failure for at least 6 months from baseline visit.
2. NYHA class II, Class III, or ambulatory Class IV heart failure
   NYHA class II patients must also meet both criteria 2a) AND 2b) below. NYHA class III and ambulatory Class IV must meet criteria 2a) OR 2b) below.
   a) At least one (1) prior heart failure hospitalization (HFH) with duration >24 hours or emergency room heart failure visit with duration ≥6 hours, or clinic visit with for acute decompensated heart failure with duration ≥6 hours, within 12 months from baseline visit.
      i) If a CRT device was previously implanted, the HFH must be ≥ 1 month after CRT implantation.
      ii) If a mitral valve repair device (e.g. MitraClip) was previously implanted, the HFH must be ≥ 1 month after the mitral valve repair.
   b) Corrected elevated brain natriuretic peptide (BNP) level of at least 300 pg/ml or an N-terminal pro-BNP (NT-proBNP) level of at least 1,500 pg/ml, according to local measurement, within 3 months of the baseline visit during a clinically stable period and at least 1 month after implantation of a CRT or mitral valve repair device. (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 patient is on ARNI, NT-proBNP must be used exclusively.

3. Is receiving maximally tolerated doses of guideline directed medical therapy (GDMT) for heart failure with a class I indication per societal guidelines, with no intention to make changes during the study follow-up period:
    a) Patients with reduced LVEF (≤40%): An inhibitor of the renin-angiotensin system (RAS inhibitor), including an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) or angiotensin receptor/neprilysin inhibitor (ARNI) and a beta-blocker (BB), for at least 3 months prior to the baseline visit.
    b) Patients with reduced LVEF (≤40%): Other medications recommended for selected populations, e.g., mineralocorticoid receptor antagonist (MRA) or nitrates/hydralazine should be used in appropriate patients, according to the published guidelines.
    c) All patients: Patient has been on stable heart failure medications as determined by the investigator, for at least 1 month, with the exception of diuretic therapy. Stable is defined as no more than a 100% increase or 50% decrease in dose within these periods.
    d) All patients: Drug intolerance, contraindications, or lack of indications must be attested to by the investigator. Patients should be on appropriate doses of diuretics as required for volume control.
4. Has been treated with class I recommended cardiac rhythm management device therapy, cardiac resynchronization therapy (CRT), and implanted cardioverter-defibrillator (ICD), or a pacemaker (each as indicated) for at least 3 months prior to the baseline visit. These criteria may be waived by the eligibility criteria if a patient is clinically contraindicated for these therapies, cannot afford them, or refuses them and will not receive them during the study follow-up period as attested to by the investigator.
5. Able to perform the 6-minute walk test with a distance ≥100 meters and ≤450 meters. The test will be performed twice separated by a minimum of 60 minutes between tests. The second test may be performed up to 7 days after the first test, if needed. The higher reading will be used as the baseline value.
6. Provide written informed consent for study participation and be willing and able to comply with the required tests, treatment instructions and follow-up visits.

EXCLUSION CRITERIA (prior to right heart catheterization and TEE or ICE)

All must be absent)

1. Age <18 years old.

2. BMI <18 or >45 kg/m^2.
3. Females of childbearing age who are not on contraceptives or surgically sterile, or pregnant or lactating mothers.
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 systolic pressure (PASP) >70 mmHg by echo/Doppler (or pulmonary vascular resistance (PVR) >4.0 Wood Units by PA catheter measurement that cannot be reduced to ≤4 Wood Units by vasodilator therapy).
7. RV dysfunction defined as TAPSE <12 mm or RVFAC ≤25% as assessed on baseline transthoracic echocardiography (TTE).
8. Left ventricular end-diastolic diameter (LVEDD) >8 cm as assessed on baseline TTE.
9. Atrial septal defect (congenital or iatrogenic), patent foramen ovale, or anomalous pulmonary venous return, with more than trace shunting on color Doppler or intravenous saline contrast (bubble study) or prior surgical or interventional correction of congenital heart disease involving the atrial septum (including placement of a PFO or ASD closure device but excluding closure by suture only).
10. Untreated moderately severe or severe aortic or mitral stenosis.
11. Untreated severe or greater regurgitant valve lesion(s), which are anticipated to require surgical or percutaneous intervention within 12 months.
12. Mitral valve repair device (e.g. MitraClip) implanted within 3 months prior to the baseline visit.
13. Untreated coronary artery stenosis which requires surgical or percutaneous intervention.
14. Acute myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, rhythm management system revision (other than generator change), lead extraction, or cardiac or other major surgery within 3 months of the baseline visit, or rhythm management system generator change within 1 month of the baseline visit.
15. Known active valvular vegetations, atrial myxoma, hypertrophic cardiomyopathy with significant resting or provoked subaortic gradient, acute myocarditis, tamponade, or large pericardial effusion, constrictive pericarditis, infiltrative cardiomyopathy (including cardiac sarcoidosis, amyloidosis, and hemochromatosis), or congenital heart disease, as cause of heart failure.

16. Stroke, transient ischemic attack, systemic or pulmonary thromboembolism, or deep vein thrombosis within 6 months of the baseline visit, or any prior stroke with permanent neurologic deficit, or the presence of an existing inferior vena cava filter.
17. Transseptal procedure for another indication (e.g. atrial fibrillation ablation, left atrial appendage occlusion, mitral valve repair or replacement) anticipated within 6 months.
18. Bradycardia with heart rate <45 bpm (unless treated with a permanent pacemaker) or uncontrolled tachyarrhythmias. This includes defibrillation shocks reported by the patient within 30 days of the baseline visit.
19. Intractable heart failure with:
    a) Resting symptoms despite maximal medical therapy (ACC/AHA HF Stage D).
    b) Treatment with intravenous vasoactive medications (e.g., inotropes, vasodilators) within the last 30 days.
    c) Cardiac index <1.5 L/min/m^2.
    d) Treated with a ventricular assist device.
    e) Listed for cardiac transplantation.
20. Prior cardiac transplantation.
21. Patients with heart failure with reduced ejection fraction (HFrEF, defined as LVEF ≤40%) who are intolerant to a RAS inhibitor including all of ACEI, ARB or ARNI, and intolerant to beta-blocker therapy.
22. Not eligible for emergency cardiothoracic or vascular surgery in the event of cardiac perforation or other serious complication during study intervention procedure.
23. Life expectancy <1 year due to non-cardiovascular illness.
24. Coagulopathy or is taking anticoagulation therapy which cannot be interrupted for the study intervention procedure or has contraindications for all of the study mandated post implantation anticoagulation / antiplatelet regimens or known hypersensitivity, or contraindication to procedural medications which cannot be adequately managed medically.
25. Estimated glomerular filtration rate (eGFR) <25 ml/min/1.73 m^2 by the MDRD method, or not responsive to diuretics, or is receiving dialysis.
26. Hepatic impairment with a documented liver function test result (transaminases, total bilirubin, or alkaline phosphatase) ≥3 times upper limit of normal.
27. Severe chronic pulmonary disease requiring daytime home oxygen or chronic oral steroid therapy (Note: nighttime oxygen therapy and inhaled steroid therapy are acceptable).
28. Active infection requiring parenteral or oral antibiotics.
29. Known allergy to nickel.

30. Any condition that may interfere with compliance of all protocol procedures, such as active drug addiction, active alcohol abuse, or psychiatric hospital admission for psychosis within the prior year.
31. Currently participating in a clinical trial of any investigational drug or device that has not reached its primary endpoint, or any study that may interfere with the procedures or endpoints of this trial. Participation in an observational study or registry with market approved drugs or devices would not exclude a patient from participation in this trial.
32. Patient is otherwise not appropriate for the study as determined by the investigator or the Eligibility Committee, for which the reasons must be documented.
33. Patient belongs to a vulnerable population per investigator's judgment or patient has any kind of disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures.

FINAL EXCLUSION CRITERIA (after right heart catheterization and TEE or ICE just prior to randomization)

1. Change in clinical status between baseline screening and study intervention visit such that the patient is not stable to undergo the intervention procedure.
2. Females with a positive pregnancy test on laboratory testing.
3. Unable to undergo TEE or ICE.
4. Unable to tolerate or cooperate with general anesthesia or conscious sedation.
5. Anatomical anomaly on TEE or ICE that precludes implantation of the shunt across the fossa ovalis (FO) of the interatrial septum including:
    a) Minimal FO thickness >6 mm.
    b) Minimal FO length <10 mm.
    c) ASD or PFO with more than a trace amount of shunting.
    d) Intracardiac thrombus felt to be acute and not present on prior exams.
    e) Atrial septal aneurysm defined as ≥10 mm of phasic septal excursion into either atrium or a sum total excursion of ≥15 mm during the cardiorespiratory cycle, with a base of ≥15 mm.
6. Inadequate vascular access for implantation of the shunt. Femoral venous or inferior vena cava access for transseptal catheterization are not patent as demonstrated by failure to pass a Swan-Ganz or ICE catheter from the right or left femoral vein to the right atrium.

7. Hemodynamic, heart rhythm, or respiratory instability at time of cardiac catheterization including:
    a) Mean PCWP <7 mmHg, not correctable by intravenous volume infusion (maximum 1,000 ml normal saline or equivalent).
    b) Mean PCWP >35 mmHg, not correctable by medical therapy (e.g. intravenous furosemide or intravenous or sublingual nitroglycerin).
    c) Right atrial pressure (RAP) ≥ left atrial pressure (LAP or PCWP) when LAP (PCWP) is ≥7 mmHg.
    d) Cardiac index (CI) <1.5 liters/min/m^2 after correction of volume depletion with intravenous 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 cannot be reduced to PVR ≤4 Wood Units by acute vasodilator therapy.
    f) Resting systolic blood pressure <90 or >160 mmHg, not corrected with intravenous fluid administration or vasodilators, respectively.
    g) Need for intravenous infusions of vasopressor or inotropic medication. Transient hypotension or bradycardia during anesthesia or catheterization, manifest as a vagal or similar acute episode or dehydration, responding promptly to intravenous fluid boluses or intravenous push vasopressors or chronotropic agents is not an exclusion criterion.
    h) Malignant 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.
8. Patient is otherwise not appropriate for study as determined by the Investigator.

Table S3. The Ventura inter-atrial shunt and implant procedure

The V-Wave® Ventura® Interatrial Shunt System consists of the Ventura® Inter-atrial Shunt (Figure S1a), the Ventura® Delivery System (Figure S1b) and an introducer sheath. The Ventura shunt is a permanent inter-atrial implant, designed to treat symptomatic heart failure by shunting blood across the inter-atrial septum. The Ventura shunt is delivered percutaneously and implanted across the fossa ovalis, with the left and right cone of the hourglass shaped device protruding into the left and right atria respectively.

The Shunt implant procedure is performed under conscious sedation or general anesthesia, depending on hospital standard practice. Fluoroscopic and echocardiographic guidance is used during the procedure to visualize the device and to assess cardiac anatomy. Radiocontrast administration is not required. Femoral venous access is obtained. Following hemodynamic and anatomical confirmation that no disqualifying conditions are present (see Appendix full inclusion and exclusion criteria) by right heart catheterization (RHC) and transesophageal (TEE) or intracardiac echo (ICE), respectively, the inter-atrial septum is crossed near the middle of the fossa ovalis using standard techniques. The transseptal system is exchanged for the system introducer sheath and guidewire. The Ventura delivery system is inserted and advanced through the introducer sheath. Prior to full insertion of the delivery system, the position of the introducer sheath tip in the mid-left atrium is confirmed by echocardiography. The left atrial cone of the Ventura shunt is deployed when the delivery system is fully inserted into the introducer sheath (Figure S2a.). The introducer sheath and delivery system are retracted as a unit until the Ventura shunt contacts the atrial septum without back-tenting (Figure S2b). Using the controls on the delivery system, the shunt is released, and the delivery system is retracted into the introducer sheath. The introducer sheath and delivery system are retracted as a unit to deploy the right atrial cone of the shunt (Figure S2c). Following removal of the guidewire, echocardiography and color flow Doppler are used to evaluate the shunt position and flow characteristics.

A loading dose of clopidogrel (≥300 mg) and/or aspirin (325 mg) may be used at clinician discretion per standard of care for transseptal procedure. If a loading dose is to be given, it can be administered either pre or immediately post implant procedure. During the shunt implant, patients are anticoagulated with unfractionated heparin to a target ACT of ≥250 seconds. Post-procedure chronic anticoagulation is established with either: 1) daily clopidogrel (75 mg) and aspirin (81 mg) for at least 6 months at clinician discretion; or 2) if the patient has another indication for chronic oral anticoagulation (warfarin or a direct-acting oral anticoagulant), these

agents are administered, in which case aspirin and clopidogrel use are not recommended but are allowed if otherwise indicated for other conditions.

Table S4. Patient blinding questionnaire

PATIENT BLINDING PERCEPTION ASSESSMENT	
Do you think you know randomization assignment? (**If Yes, answer the following questions**)	☐ Yes ☐ No
What treatment assignment do you think you received?	☐ Received the Study Device (Shunt) ☐ Did not receive the study device (Shunt)
Are you certain of the treatment assignment?	☐ Yes ☐ No
Why do you think you know?	☐ I overheard a conversation during the procedure ☐ I was told by the doctor who did the procedure ☐ I was told by another person in the procedure room ☐ I was told by another person in the hospital before discharge ☐ I overheard the doctor/staff who did the procedure talking to someone else ☐ I was told by a family member/friend who was told ☐ I beleive so becasue I am feeling better ☐ I believe so because I am not feeling better ☐ Other
Other, specify	

Table S5. Baseline and follow-up schedule of activities

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 and medical history	✓								
Vital signs, including 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 (T, I or C)		✓							
COVID-19 serological tests [9]					✓				
BNP or NT-proBNP	✓								
12-lead ECG	✓								
Chest X-ray			✓						
Transthoracic echo (TTE)	✓				✓[4]		✓[4]		✓[4]
Transesophageal or intracardiac echo (TEE/ICE)		TEE/ ICE					TEE[5]		
Right heart catheterization (RHC)		✓							
NYHA functional class	✓				✓	✓	✓		✓
Patient global assessment					✓	✓	✓		✓
KCCQ, EQ-5D assessments	✓				✓	✓	✓		✓
Cost-effectiveness[6]		✓	✓		✓	✓	✓		
6-minute walk test (x2) / Borg scale	✓				✓	✓	✓		✓[7]
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓
Worsening heart failure events treated as an outpatient[10]			✓	✓	✓	✓	✓	✓	✓
COVID-19 history	✓	✓	✓	✓	✓	✓	✓	✓	✓
I/E criteria review	✓	✓							

Complete case report forms (CRFs)	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient perception of study assignment			✓[8]				✓[8]		
Assure blinding procedures[10]		✓	✓	✓	✓	✓	✓	✓	

1. Temperature and pulse oximetry only required at baseline, study intervention and prior to discharge.
2. Only cardiovascular, anticoagulant, and antiplatelet therapy medications need be collected during follow-up. SGLT2 inhibitor use will also be collected.
3. Limited to creatinine, hemoglobin and hematocrit.
4. Once unblinded, shunted patients will undergo TEE if no shunt flow is seen on a prior TTE.
5. Follow-up TEE at 6 and 12 months will be performed in roll-in patients only. All patients (including roll-in patients) will have follow-up TTE at the protocol specified follow-up intervals.
6. US sites only.
7. A single 6-minute walk test is required during extended follow-up at years 3-5.
8. Patient blinding assessment should be done on randomized patients and prior to discharge and at 12-month follow-up only.
9. COVID-19 serological testing done at the time of unblinding, if required.
10. Assessed for randomized patients only (not roll-in patients).

Table S6. Primary and secondary endpoints

Primary safety endpoint (powered)

The percentage of treatment group patients experiencing any device-related or procedure-related Major Adverse Cardiovascular or Neurological Events (MACNE) during the first 30-days after randomization, compared to a pre-specified performance goal. MACNE is defined as all-cause death, stroke, systemic embolism, need for open cardiac surgery or major endovascular surgical repair. Specifically, 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 are excluded from the definition of MACNE.

Primary effectiveness endpoint (powered)

The hierarchical composite ranking of all-cause death, heart transplantation (HT) or left ventricular assist device (LVAD) implantation, recurrent heart failure hospitalizations (HFH, including emergency room heart failure Visits with duration ≥6 hours), recurrent worsening outpatient heart failure events (including emergency room heart failure visits with duration <6 hours), and change in KCCQ overall score of at least 5 points, comparing treatment and control groups.

Secondary effectiveness endpoints, powered and hierarchically-tested if the primary effectiveness endpoint is passed

If the primary effectiveness endpoint is met, the difference between study groups will be hierarchically tested for the following secondary effectiveness endpoints in the following order:

- KCCQ change from baseline to 12 months
- Rate of heart failure hospitalization adjusted for all-cause mortality
- Time to first all-cause death, HT/LVAD or HFH
- Time to first all-cause death or HFH
- Cumulative HFHs
- Time to first HFH
- The hierarchical composite of all-cause death, HT/LVAD, HFH and worsening outpatient heart failure events (i.e. the clinical components of the primary effectiveness endpoint, but without KCCQ)
- 6MWT changes from baseline to 12 months

Secondary effectiveness endpoints (non-powered)

- NYHA class
- Patient Global Assessment
- Combined all-cause death and all-cause hospitalizations
- All-cause death
- Time to all-cause death
- Time to cardiovascular death
- Time to all-cause death, HT or LVAD
- Time to cardiovascular death, HT or LVAD
- The Nelson-Aalen cumulative distribution functions for the combined occurrences of HFH, HT, and LVAD events
- Days alive free from heart failure hospitalization
- Outpatient clinic HF visit and /or intensification of HF therapy
- Emergency room HF visits
- Heart failure clinical composite assessment (improved, unchanged, or worsened) as described by Packer comprised of all-cause mortality, HFH, and changes in NYHA functional class ranking and Patient Global Assessment
- Comparison of transthoracic echocardiographic parameters as listed in echocardiography core laboratory manual
- Incidence of loss of shunt flow as measured on TTE and/or TEE
- Absolute and percentage changes in 6MWT
- Death: All-cause; cardiovascular cause (with breakdown by cause, e.g. sudden death, myocardial infarction, pump failure, stroke); non-cardiovascular cause; undetermined cause; and relationship to device, study intervention or other cardiovascular procedure
- Hospitalization: All-cause; HFH, non-HFH (with breakdown for cause including if associated with secondary worsening of HF)
- Change in renal function
- Medication utilization including type, dose, frequency, and changes
- Cost and cost-effectiveness data
- Technical success
- Device success
- Procedural success
- Absolute changes in KCCQ from baseline by intervals of 5 points

Secondary safety endpoints (non-powered)

- Device-related or procedure-related MACNE and Bleeding Academic Research Consortium (BARC) types 3 and 5 bleeding at 30 days
- Percentage of treatment group patients with device-related or procedure-related MACNE at 12 months
- Incidence of all serious adverse events by type at study duration
- Incidence of cerebrovascular events at study duration with sub-classification of CNS infarction, CNS hemorrhage, and TIA and their relationship to device or study procedures (per NeuroARC)
- Incidence of MI events at study duration after implantation
- Incidence of systemic embolization events at study duration after implantation
- Incidence of pulmonary embolism events at study duration after implantation
- Incidence of shunt implant embolization at study duration
- Device-related MACNE annually through 5 years

Table S7. Endpoint definitions

Major adverse cardiovascular or neurological events (MACNE): The composite of device-related or procedure-related all-cause death, stroke, systemic embolism, need for open cardiac surgery or major endovascular surgical repair.

Hospitalizations:

All-cause hospitalization: Defined as an admission to an acute care facility, inpatient unit, observation unit or emergency room, or some combination thereof, for at least 24 hours. Excludes hospitalizations planned for pre-existing conditions (elective admissions) unless there is worsening in the baseline clinical condition prior to the planned admission. Overnight stays at nursing home facilities, physical rehabilitation or extended care facilities, including hospice, do not meet the definition of hospitalization. hospitalizations will be adjudicated by the clinical events committee as heart failure hospitalization, other cardiovascular hospitalization, or non-cardiovascular hospitalization.

Heart failure hospitalization: Meets the definition of all-cause hospitalization above and the primary reason for admission is acute decompensated heart failure (ADHF) meeting the following criteria:

1) Patient has one or more symptoms of ADHF such as worsening or new onset of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, reduced exercise capacity and/or lower extremity/abdominal swelling;

AND

2) Patient has one or more signs or laboratory evidence of ADHF such as: rapid weight gain, pulmonary edema or rales, elevated jugular venous pressure, radiological signs of pulmonary congestion or increased pulmonary venous pressure, increasing peripheral edema or ascites, S3 gallop, hepatojugular reflux, and/or elevated BNP or NT pro-BNP above most recent baseline, right heart catheterization within 24 hours of admission showing elevated PCWP or low cardiac index;

AND

3) Admission results in the initiation of intravenous heart failure therapies such as diuretics, vasodilators, inotropes, or mechanical or surgical intervention (e.g., ultrafiltration, intra-aortic balloon pump, mechanical assistance) or the intensification of these therapies or at least

doubling of the oral diuretic dose with the clear intent of promoting increased diuresis for the treatment of ADHF;

AND

4) No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

For a HFH event, the diagnosis of HF must be the primary disease process accounting for the above signs and symptoms. All hospitalizations where the primary reason for admission is other than ADHF, if accompanied by worsening HF or subsequently complicated by ADHF, do not meet the criteria for HFH. Outpatient intensification of heart failure therapy whether managed in a heart failure clinic, other clinic setting, or done remotely, does not meet the definition of HFH. Admissions for HT or LVAD implantation and MitraClip procedures will also, by definition, be considered a HFH.

Other (non-heart failure-related) cardiovascular hospitalization: Meets the definition of all-cause hospitalization for conditions such as coronary artery disease, acute coronary syndromes, hypertension, cardiac arrhythmias, pericardial effusion, atherosclerosis, peripheral vascular disease, pulmonary embolisms, stroke and aortic dissection but not classified as a HFH.

Non-cardiovascular hospitalization: Meets the definition of all-cause hospitalization for conditions but does not meet the definition of HFH or other cardiovascular hospitalization.

Emergency room heart failure visit: Admission to an emergency room for <24 hours, where the primary reason for admission is ADHF, otherwise meeting all the same criteria defined for HFH when the patient is not transferred to an inpatient unit or observation unit but is discharged home.

Worsening heart failure event treated as an out-patient without hospitalization (includes ER visit with duration <6 hours): Standardized definition from Heart Failure Collaboratory Academic Research Consortium (HFC-ARC). Broadly characterized as unscheduled outpatient medical contact associated with changes in heart failure therapy and requires:

• Documented new or worsening symptoms due to heart failure

• Objective evidence of new or worsening heart failure

• Treatment specifically for worsening heart failure:

- Significant augmentation in oral diuretic therapy (including at least a doubling of loop diuretic dose, initiation of loop diuretic therapy, initiation of combination diuretic therapy)
- Initiation of intravenous diuretic (even a single dose)
- Initiation of an intravenous vasoactive agent (catecholamine, phosphodieaterase-3 inhibitor, other vasopressor, vasodilator)
- Mechanical fluid removal (ultrafiltration, hemofiltration, initiation of dialysis for what is felt to be a primary cardiac rather than renal cause)

• Documented response to treatment

Outpatient intensification of heart failure therapy: Requires that the patient has worsening symptoms, signs or laboratory evidence of worsening heart failure and the dose of diuretics was increased and sustained for a month, or intravenous treatment given for HF, or a new drug was added for the treatment of worsening HF. This event category excludes patients meeting the definition of Outpatient Clinic Heart Failure Visit.

Heart failure endpoint qualifying events: All hospitalizations and emergency room visits lasting at least 6 hours as well as worsening HF event treated as an outpatient (including ER HF visits with duration of <6 hours) as defined will be adjudicated by the CEC to determine if they qualify as heart failure endpoint events for inclusion in the primary effectiveness endpoint analysis.

Technical success: Measured at exit from cath lab and is 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 additional emergency surgery or reintervention related to either the device or the access procedure.

Device success: Measured at 30 days and all post-procedural intervals 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 thrombo-embolization.

Procedural success: Measured at 30 days and is 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 intraaortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for ≥48 hours).

Neurological events: Classified according to Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative (NeuroARC). Events. Clinical assessment will include a neurological consultation, assessment of the National Institutes of Health Stroke Scale, and assessment of neurological deficits and cognitive function according to institutional standards. Patients experiencing a neurological event will have an MRI or a head CT (if MRI is contraindicated) and will undergo transesophageal echocardiography (TEE) to evaluate cardiac origin, device patency and involvement in their neurological event.

Type 1 - Overt CNS Injury (Stroke): Acutely symptomatic brain or spinal cord injury

Type 1.a - Ischemic stroke: Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that:

- Persists for ≥24 h or until death, with pathology or neuroimaging evidence that demonstrates either: a) CNS infarction in the corresponding vascular territory (with or without hemorrhage); or b) Absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected;

OR

- Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. Note: When CNS infarction

location does not match the transient symptoms, the event would be classified as covert CNS infarction (Type 2a) and a TIA (Type 3a), but not as an ischemic stroke. Signs and symptoms consistent with stroke typically include an acute onset of 1 of the following: focal weakness and/or numbness; impaired language production or comprehension; homonymous hemianopia or quadrantanopsia; diplopia; altitudinal monocular blindness; hemispatial neglect; dysarthria; vertigo; or ataxia.

Subtype 1.a.H - Ischemic stroke with hemorrhagic conversion: Ischemic stroke includes hemorrhagic conversions. These should be subclassified as Class A or B when ischemic stroke is the primary mechanism and pathology or neuroimaging confirms a hemorrhagic conversion.

Class A: Petechial hemorrhage: Petechiae or confluent petechiae within the infraction or its margins, but without a space-occupying effect

Class B: Confluent hemorrhage: Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect

Type 1.b - Symptomatic intracerebral hemorrhage: Rapidly developing neurological signs or symptoms (focal or global) caused by an intraparenchymal, hemorrhage intraventricular, spinal cord, or retinal collection of blood, not caused by trauma

Type 1.c - Symptomatic subarachnoid hemorrhage: Rapidly developing neurological signs or symptoms (focal or global) and/or headache caused by bleeding into hemorrhage the subarachnoid space, not caused by trauma

Type 1.d - Stroke, not otherwise specified: An episode of acute focal neurological signs or symptoms and/or headache presumed to be caused by CNS ischemia or CNS hemorrhage, persisting ≥ 24 h or until death, but without sufficient evidence to be classified (i.e., no neuroimaging performed)

Type 1.e - Symptomatic hypoxic-ischemic injury: Nonfocal (global) neurological signs or symptoms due to diffuse brain, spinal cord, or retinal cell death (confirmed by pathology or neuroimaging) in a nonvascular distribution, attributable to hypotension and/or hypoxia

<u>Type 3 – Neurologic dysfunction (acutely symptomatic) without CNS injury</u>

Type 3.a – TIA: Transient focal neurological signs or symptoms (lasting <24 h) presumed to be due to focal brain, spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging)

Type 3.b - Delirium without CNS injury: Transient non-focal (global) neurological signs or symptoms (variable duration) without evidence of cell death by neuroimaging or pathology

Pulmonary embolism: Requires confirmation by high probability V/Q scan, angiography, CT pulmonary angiography with or without acute onset of dyspnea, pleuritic chest pain, hypoxia or hemodynamic dysfunction.

Access and vascular complications

1. Major access site vascular complications:
   - Aortic dissection or aortic rupture; or
   - Access site-related arterial or venous injury (dissection, stenosis, ischemia arterial, or venous thrombosis including pulmonary emboli, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect), irreversible nerve injury, or compartment syndrome resulting in death; hemodynamic compromise; life-threatening, extensive, or major bleeding (see bleeding scale); visceral ischemia; or neurological impairment; or
   - Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage; or
   - Unplanned endovascular or surgical interventions resulting in death; life-threatening, extensive, or major bleeding; visceral ischemia; or neurological impairment.

2. Minor access site vascular complications:
   - Access site arterial or venous injury (dissection, stenosis, arterial, or venous thrombosis including pulmonary emboli, ischemia, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect) not resulting in death, life-threatening, extensive, or major bleeding, visceral ischemia, or neurological impairment; or

- Distal embolization treated with embolectomy and/or thrombectomy not resulting in amputation or irreversible end-organ damage; or
- Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication or vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)

3. Cardiac structural complications due to access-related issues:
   - Major cardiac structural complications, including: cardiac perforation (including left ventricle, left atrium, coronary sinus, right atrium and right ventricle) or pseudoaneurysm resulting in death, life-threatening bleeding, hemodynamic compromise, or tamponade, or requiring unplanned surgical or percutaneous intervention
   - Minor cardiac structural complications, including: cardiac perforation (including left ventricle, left atrium, coronary sinus, right atrium and right ventricle) or pseudoaneurysm not meeting major criteria

Table S8. Finkelstein-Schoenfeld and win ratio methodology with interim analysis

The primary effectiveness endpoint will be evaluated with a sum of ranks (TShunt) test statistic in the Shunt group using the method of Finkelstein and Schoenfeld, based on adjudicated endpoint events when last enrolled patients has minimum 12-month follow-up since randomization. In addition, the unmatched win-ratio approach will be used to evaluate the primary effectiveness endpoint. In addition, the unmatched win-ratio approach will be used to evaluate the primary effectiveness endpoint. The win ratio will be calculated as the total number of shunt arm patient wins divided by the number of Shunt arm loses (win ratio) and 95% confidence interval after all the pairwise comparisons. All subjects have a scheduled minimum follow-up period of 12 months, and all data collected through 24 months of follow-up will be included in the final analyses.

The null hypothesis of this test is that the components of the composite endpoint are not affected by treatment, and the alternative is that at least one demonstrates improvement in favor of the intervention. The Finkelstein-Schoenfeld statistic is evaluated by comparing every subject i to every other subject j in the dataset and assigning a rank Uij in accordance with the following hierarchical ranking algorithm across the total evaluable study population (Shunt and Control groups).

1. Death (all-cause)
2. Heart transplant or LVAD implant
3. HF hospitalizations (including qualifying ER visits ≥6 hours)
4. Worsening heart failure treated as an outpatient (including ER HF visits < 6 hours)
5. KCCQ Overall Score (KCCQ measured as absolute point change from baseline), with at least a 5-point difference viewed as significant

At each level, the following comparisons will be done:

1. Death

First, an attempt is made to compare the two subjects based on their Death event.

a. If subject i died and subject j did not die, we check whether subject j was followed at least as long as the death time of subject i, in which case Uij = -1. But if subject j was followed for less than the death time of subject i, the ranking cannot be based on Death events and we proceed to ranking based on LVAD/Transplant events.

b. If the opposite is true, where subject j died and subject i survived at least as long as the death time of subject j, Uij = 1. But if subject i was followed for less than the death time of subject j, the ranking cannot be based on Death events and we proceed to ranking based on LVAD/Transplant events.

c. In case both subjects have a Death event, where subject i died at least 7 days after subject j, Uij = 1. If the opposite is true and subject j died at least 7 days after subject i, Uij = -1. If both subjects died within 7 days of each other, the ranking can not be assigned based on Death events and we proceed to ranking based on LVAD/Transplant events.

2. LVAD/Transplant events:

In cases where the two subjects cannot be compared and ranked based on their Death events, LVAD/Transplant events are used next to compare them and assign ranks. The comparison and ranking of two subjects based on LVAD/Transplant events is exactly the same as for Death events.

a. If subject i had an LVAD/Transplant event and subject j did not, we check whether subject j was followed at least as long as the time that the LVAD/Transplant event occurred for subject i, in which case Uij = -1. But if subject j was followed for less than the LVAD/Transplant time of subject i, the ranking cannot be based on LVAD/Transplant events and we proceed to ranking based on HF hospitalization events.

b. If the opposite is true, where subject j had an LVAD/Transplant event and subject i did not, we check whether subject i was followed at least as long as the time that the LVAD/Transplant event occurred for subject j, in which case Uij = 1. But if subject i was followed for less than the LVAD/Transplant time of subject j, the ranking cannot be based on LVAD/Transplant events and we proceed to ranking based on HF hospitalization events.

c. In cases where both subjects have had the LVAD/Transplant event, if subject i had the LVAD/Transplant event at least 7 days after subject j, then Uij = 1, or if subject j had the LVAD/Transplant event at least 7 days after subject i, then assign Uij = -1. If both subjects had the LVAD/Transplant event within 7 days interval, the ranking cannot be assigned based on LVAD/Transplant event and we proceed to ranking based on HF hospitalization events.

3. Heart Failure Hospitalization (HFH):

In cases where the two subjects cannot be compared and ranked based on their Death or LVAD/Transplant events, HFH events are used next to compare them and assign ranks.

a. The two subjects are first compared on the basis of the number of HFH events, where the subject with the fewer HFH events has the better rank. This comparison is made over the time period of the subject with the shorter follow-up time.

b. In case the two subjects have the same number of HFH events, the first HFH times are compared and if subject i 's first HFH event time is 7 days earlier than that of subject j, we assign Uij = -1. If the opposite is true so that subject j's first HFH event time is 7 days earlier than that of subject i, we assign Uij = 1.

c. When both subjects have the same number of HFH events and the first HFH event times for the two subjects are within a 7-day interval, ranking cannot be assigned based on HFH event times and we proceed with the investigation of their worsening heart failure events .

d. In all other cases where the two subjects cannot be compared (such as if one subject has been followed without any events for less time than the first HFH time of the other) we proceed with the investigation of their worsening heart failure events.

4. Worsening Heart Failure Events without Hospitalization or Qualifying ER Visit:

If the HFH level of the hierarchical ranking is reached and ranking between subjects cannot be assigned, then the numbers of Worsening Events will be compared between subjects. The subject with fewer Worsening Events, over the longest time period in common between two subjects, will have the better rank. If the subjects have the same number of Worsening Events, then the ranking procedure will proceed to Step 5.

5. KCCQ Overall Score:

If xi is subject to i's change from baseline and xj is subject to j's change from baseline in KCCQ overall score, then:

a) If xi – xj ≥ 5, Uij = 1

b) If xi – xj ≤ -5, Uij = -1

c) Otherwise, Uij =0

Blinded research staff will perform in-clinic follow-up visits at 1, 3, 6, 12, 18, and 24 months, including the evaluation of KCCQ (Protocol, Section 6.3.2). For purposes of hierarchical ranking, the last KCCQ values for the longest follow-up interval in common between two subjects being compared will be used, consistent with the hierarchical ranking procedure for other primary endpoint components.

Test Statistic

Suppose m subjects are randomized to the Shunt arm, n subjects are randomized to the control arm, and N = m + n is the total sample size. In the RELIEVE-HF trial, m=n. Each subject will be assigned a score $U_i = \sum_{i=1(j\neq i)}^{N} U_{ij}$ based on the above algorithm. Let Di = 1 if subject i is randomized to receive the VWAVE shunt device, the F-S statistic can be written as $T = \sum_{i=1}^{N} D_i U_i$.

The statistic T is asymptotically normal with mean E(T) =2mn(θ – ½) , where θ is the probability that a random subject i in the treatment group has a better outcome than a random subject j in the control group. The null hypothesis of no treatment effect with respect to death, LVAD, HFH or KCCQ is thus equivalent to H0: θ = ½. Under H0 the variance of T is var(T) $= \frac{mn}{N(N-1)} \sum_{i=1}^{N} U_i^2$ (Equation 1), which reduced in the absence of ties to var(T) $= \frac{mn(N+1)}{3}$ (Equation 2).

As is generally the case for normal statistics derived from independent multinomial distributions, under local alternatives (values of θ approaching ½) one may use the null variance to standardize the distribution of T. When source data are available, we shall compute the variance of T by Equation 1. Otherwise we shall use Equation 2 to estimate the variance of T.

For clarification, heart transplant and LVAD implant are considered terminal endpoints from an effectiveness analysis standpoint and will be censored for HF hospitalizations and KCCQ after the date of admission that results in heart transplant or LVAD placement. The hypothesis will be tested by comparing the test statistic $(T_{Shunt} / \sqrt{var(T)})$ to the normal distribution, with a one-sided significance level of 0.025.

In additional to the F-S statistics, the effect size for primary effectiveness endpoint will be calculated as $R_W = \frac{N_W}{N_L}$ where NW equals the number of Shunt wins and NL _equals the number of Shunt losses. The standard error is estimated by assuming the estimated standard error (s) will match the theoretical standard error z. That is, $\frac{\log(R_W)}{s} = z$. We can solve this equation to compute the standard error as s=log(RW)/z, the standardized normal deviates. An approximate 95% confidence intervals will be estimated by adding and subtracting s x 1.96 to log(RW) and exponentiating both results.

The WIN ratio (RW) the end of the trial will be estimated in a manner analogous to that of the FS statistic for the primary effectiveness endpoint described above. The effect size will use the same pre-specified weights for combing (RW) in the two phases (interim and post-interim analysis cohorts, as described below), with the sum of estimated variances used to construct the associated estimate of the 95% confidence interval.

Interim Analysis

A single, midpoint interim analysis with adaptive sample size re-estimation is planned at the point when approximately 50% of the study population have completed approximately a minimum of 6 months of follow-up, but no later than 3 months prior to completion of enrollment of the original 400 subjects. This interim analysis would consider only data collected for the composite primary effectiveness endpoint and be based on validation of the original planning assumptions for the components of the endpoint. The interim analysis would be performed by an independent third party, who would communicate results only to the study DSMB, who will make a recommendation to the sponsor about possible changes to the study sample size.

The interim analysis will be limited to data collected in an identified study cohort (e.g., the first 200 evaluable subjects). Using the analysis method specified for evaluation of the primary effectiveness endpoint (Finkelstein-Schoenfeld), the unconditional power to meet the endpoint at the conclusion of the study will be re-estimated. At that time a decision will be taken to possibly increase the sample size. This decision will utilize maximum likelihood estimates of the design parameters displayed in Table 2. The sample size of the trial will be re-computed by assuming that the updated maximum likelihood estimates are the true design parameters. To be specific, the entire trial will be redesigned with these updated design parameters so as to obtain the new sample size required to achieve 90% power. If the new sample size is less than 400, the trial will proceed as planned initially, with 400 subjects. If, however, the new sample size is greater than 400, the sample size will be increased appropriately, up to a maximum of 1000 subjects. Sequential design by Cui, Huang and Wang (Modification of Sample Size in Group Sequential Trials, Biometrics, 55: 853-857, 1999) will be used to combine the separable results during the first phase (prior to interim analysis) and the second phase (post-interim analysis) to control the type I error.

Let m and n denote the pre-specified sample sizes for the experimental and control groups, respectively. (Here, for example, m = n = 200 for the original total sample size of 400.) Suppose the pre-specified plan is to use the data from the first m1 subjects in the experimental group and the first n1 subjects in the control group for the interim analysis. Let m2 = m - m1 and n2 = n - n1 denote the pre-specified incremental sample sizes for the second stage in the absence of a sample size increase. (Here m1 = n1 = m2 = n2 = 100). If the sample size is increased at the interim analysis, let m* and n* be the new total sample sizes for the experimental and control groups. Let T1 denote the F-S statistic for the (m1; n1) subjects in the first cohort evaluated at the time of the final analysis. Similarly let T2 denote the F-S statistic for the (m2; n2) subjects in the second cohort if there is no sample size change and T*2 denote the F-S statistic for the (m*2 , n*2) subjects in the second cohort if the sample size is increased. The CHW statistic is a weighted sum of the two incremental F-S statistics of the form:

$$Tchw = \begin{cases} w1\left(\frac{T1}{\sqrt{var\,(T1)}}\right) + w2\left(\frac{T2}{\sqrt{var\,(T2)}}\right) \\ w1\left(\frac{T1}{\sqrt{var\,(T1)}}\right) + w2\left(\frac{T^{*}2}{\sqrt{var\,(T^{*}2)}}\right) \end{cases}$$

Where the bottom equation corresponds to test statistics when there is sample size re-assessment and weights are pre-specified as: $w1 = \sqrt{\frac{m1+n1}{m+n}}$ and $w2 = \sqrt{\frac{m2+n2}{m+n}}$

The weights w1 and w2 remain the same whether the sample sizes are increased from (m; n) to (m*; n*). This is necessary in order to prevent inflation of the type-1 error, as shown originally by Cui, Hung and Wang (1999). The null hypothesis of no treatment effect can be rejected at the one-sided level-of significance if Tchw ≥ zα. In the absence of same size re-assessment, Tchw is asymptotically equivalent to the F-S statistic T evaluated from the complete dataset of m subjects on the experimental arm and n subjects on the control arm as defined by $T = \sum_{i=1}^{N} D_i U_i$ without any weighting.

Note: Because of COVID-19 issues, it is expected that the adaptive sample size re-estimation will increase the needed sample size beyond the original 400 subjects. In response, the pre-specified weights will be based on a total sample size of 600 subjects (the original upper limit after adaptive re-estimation, since revised to a maximum of 1000). The pre-specified weights, as required by the Cui, Huang and Wang method, used during the interim analysis and in the final analysis for the study will be $w1 = (200/600)^{1/2}$ and $w2 = (400/600)^{1/2}$ for the two stages, instead of equal weighting.

The following guidelines are provided to the DSMB for making a recommendation (zone and associated recommended action to be taken) based on the estimated unconditional power:

Interim Analysis Results	**DSMB Recommendation**
P400 ≥ 90%	Zone 1: Continue trial with no expansion
P400 < 90% and P1000 ≥ 90%, or P1000 ≥ 50% and P1000 – P400 ≥ 10%	Zone 2: Expand trial by 1-600 subjects to increase power, up to 90% design target
P400 > 20% and none of the above conditions apply	Zone 3: Continue trial with no expansion (futility for expansion)
P400 ≤ 20%	Zone 4: Consider early termination for trial (futility for treatment effect)
Definitions: P400/P1000 – statistical power associated with 400/1000 evaluable subjects	

In making their recommendation, the DSMB will not reveal specific details of the FS component event rates or estimated power achieved and will also consider all available safety information collected to date.

Table S9. Baseline medications, all patients, by randomized treatment

	Shunt group (N=250)	Placebo group (N=258)
Beta-blockers	224 (89.6%)	222 (86.0%)
Renin-angiotensin system inhibitors, any	176 (70.4%)	185 (71.7%)
- ACEi	32 (12.8%)	38 (14.7%)
- ARB	39 (15.6%)	38 (14.7%)
- ARNi	105 (42.0%)	109 (42.2%)
Mineralocorticoid receptor antagonists	145 (58.0%)	174 (67.4%)
Sodium-glucose cotransporter-2 inhibitors	93 (37.2%)	113 (43.8%)
Vasodilators	33 (13.2%)	34 (13.2%)
- Long-acting nitrates	29 (11.6%)	25 (9.7%)
- Hydralazine	10 (4.0%)	20 (7.8%)
Diuretics	230 (92.0%)	239 (92.6%)
Antiplatelet agents	106 (42.4%)	111 (43.0%)
Chronic oral anticoagulation	152 (60.8%)	141 (54.7%)

ACEi denotes angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNi, angiotensin receptor-neprilysin inhibitor.

Table S10. Baseline transthoracic echocardiography, all patients, by randomized treatment

	Shunt group (N=250)	Placebo 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 cava 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 S11. Baseline right heart catheterization, all patients, by randomized treatment

	Shunt group (N=250)	Placebo group (N=258)
Heart rate, bpm	67.0 (60.0, 75.0)	68.0 (60.0, 77.0)
Systolic blood pressure, mmHg	116.0 (104.0, 133.0)	115.0 (103.0, 134.0)
Diastolic blood pressure, mmHg	64.0 (57.0, 73.0)	65.0 (59.0, 73.0)
Mean right atrial pressure, mmHg	9.0 (6.0, 12.0)	9.0 (6.0, 11.0)
Systolic pulmonary artery pressure, mmHg	37.0 (30.0, 45.0)	37.0 (31.0, 44.0)
Mean pulmonary artery pressure, mmHg	25.0 (21.0, 31.0)	25.0 (20.0, 30.0)
Pulmonary vascular resistance, Wood units	2.1 (1.5, 3.1)	2.0 (1.4, 2.8)
Pulmonary capillary wedge pressure, mmHg	15.5 (12.0, 20.0)	16.0 (12.0, 21.0)
Cardiac output, L/min	4.2 (3.4, 5.3)	4.3 (3.6, 5.3)
Cardiac index, L/min/m^2	2.1 (1.8, 2.6)	2.2 (1.8, 2.6)

Continuous data are shown as median (interquartile range).

Table S12. Procedural details, all patients, by randomized treatment

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

*Due to site error (mis-interpretation of the randomization code). Continuous data are median (interquartile range).

Table S13. Medications at discharge and during follow-up, all patients, by randomized treatment

	Shunt group (N=250)	Placebo group (N=258)	Difference [95% CI]
Discharge			
Beta-blockers	225 (90.0%)	223 (86.4%)	3.6 [-2.0, 9.2]
Renin-angiotensin system inhibitors, any	175 (70.0%)	186 (72.1%)	-2.1 [-10.0, 5.8]
- ACEi	31 (12.4%)	39 (15.1%)	-2.7 [-8.7, 3.3]
- ARB	39 (15.6%)	38 (14.7%)	0.9 [-5.4, 7.1]
- ARNi	105 (42.0%)	109 (42.2%)	-0.2 [-8.8, 8.3]
Mineralocorticoid receptor antagonists	146 (58.4%)	174 (67.4%)	-9.0 [-17.4, -0.7]
Sodium-glucose cotransporter-2 inhibitors	96 (38.4%)	114 (44.2%)	-5.8 [-14.3, 2.8]
Vasodilators	32 (12.8%)	34 (13.2%)	-0.4 [-6.2, 5.5]
- Long-acting nitrates	28 (11.2%)	25 (9.7%)	1.5 [-3.8, 6.8]
- Hydralazine	10 (4.0%)	20 (7.8%)	-3.8 [-7.8, 0.3]
Diuretics	235 (94.0%)	241 (93.4%)	0.6 [-3.6, 4.8]
Antiplatelet agents, open-label	121 (48.4%)	132 (51.2%)	-2.8 [-11.5, 5.9]
Antiplatelet agents, study medications*	55 (22.0%)	63 (24.4%)	-2.4 [-9.8, 4.9]
Chronic oral anticoagulation	158 (63.2%)	150 (58.1%)	5.1 [-3.4, 13.5]
1 year	N=229	N=242	
Beta-blockers	206 (90.0%)	209 (86.4%)	3.6 [-2.2, 9.4]
Renin-angiotensin system inhibitors, any	160 (69.9%)	172 (71.1%)	-1.2 [-9.4, 7.0]
- ACEi	27 (11.8%)	33 (13.6%)	-1.8 [-7.9, 4.2]
- ARB	33 (14.4%)	31 (12.8%)	1.6 [-4.6, 7.8]
- ARNi	100 (43.7%)	108 (44.6%)	-1.0 [-9.9, 8.0]
Mineralocorticoid receptor antagonists	138 (60.3%)	160 (66.1%)	-5.9 [-14.6, 2.8]
Sodium-glucose cotransporter-2 inhibitors	120 (52.4%)	127 (52.5%)	-0.1 [-9.1, 8.9]
Vasodilators	35 (15.3%)	32 (13.2%)	2.1 [-4.3, 8.4]
- Long-acting nitrates	30 (13.1%)	22 (9.1%)	4.0 [-1.7, 9.7]
- Hydralazine	11 (4.8%)	18 (7.4%)	-2.6 [-6.9, 1.7]
Diuretics	214 (93.4%)	218 (90.1%)	3.4 [-1.6, 8.3]
Antiplatelet agents, open-label	102 (44.5%)	120 (49.6%)	-5.0 [-14.1, 4.0]
Chronic oral anticoagulation	148 (64.6%)	145 (59.9%)	4.7 [-4.0, 13.5]

*Open-label aspirin for 2 years and clopidogrel (75 mg per day or a matching placebo), unless the patient was otherwise taking open-label aspirin and a platelet $P2Y_{12}$ receptor inhibitor or chronic oral anticoagulation.
ACEi denotes angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers;
ARNi, angiotensin receptor-neprilysin inhibitor.

Table S14. Results of the blinding questionnaires

Post-procedure pre-discharge	**All patients**	**Shunt group**	**Placebo group**
Eligible randomized patients	n=508	n=250	n=258
Blinding questionnaire completed	504 (99.2%)	250 (100.0%)	254 (98.4%)
1. Patient does not know or suspect the treatment assignment	410 (81.3%)	204 (81.6%)	206 (81.1%)
2. Patient is “certain” of treatment assignment	30 (5.6%)	11 (4.4%)	19 (7.5%)
- Believes received placebo procedure	5 (1.0%)	3 (1.2%)	2 (0.8%)
- Believes received the shunt	25 (5.0%)	8 (3.2%)	17 (6.7%)
Reason for possible unblinding			
- Due to change in symptoms	18 (3.6%)	8 (3.2%)	10 (3.9%)
- For "other" reasons	11 (2.2%)	2 (0.8%)	9 (3.5%)
- Patient-reported possible unblinding event	1 (0.2%)	1 (0.4%)	0 (0.0%)
3. Patient suspects but is uncertain of treatment assignment	64 (12.7%)	35 (14.0%)	29 (11.4%)
- Believes received placebo procedure	14 (2.8%)	6 (2.4%)	8 (3.1%)
- Believes received the shunt	50 (9.9%)	29 (11.6%)	21 (8.3%)
Reason for possible unblinding			
- Due to change in symptoms	30 (5.6%)	14 (5.6%)	16 (6.3%)
- For "other" reasons	32 (6.3%)	20 (8.0%)	12 (4.7%)
- Patient-reported possible unblinding event	2 (0.4%)	1 (0.4%)	1 (0.4%)
4. Patient is certain of or suspects the treatment assignment	94 (18.7%)	46 (18.4%)	48 (18.9%)
- Believes received placebo procedure	19 (3.8%)	9 (3.6%)	10 (3.9%)
- Believes received the shunt	75 (14.9%)	37 (14.8%)	38 (15.0%)
Reason for possible unblinding			
- Due to change in symptoms	48 (9.5%)	22 (8.8%)	26 (10.2%)
- For "other" reasons	43 (8.5%)	22 (8.8%)	21 (8.3%)
- Patient-reported possible unblinding event	3 (0.6%)	2 (0.8%)	1 (0.4%)
5. Successful blinding (either patient was unaware of their treatment or their belief was incorrect)	457 (90.7%)	213 (85.2%)	244 (96.1%)
6. Successful blinding (no unblinding event was reported)	501 (99.4%)	248 (99.2%)	253 (99.6%)
At one-year	**All patients**	**Shunt group**	**Placebo group**
Eligible randomized patients	n=463	n=227	n=235
Blinding questionnaire completed	447 (96.6%)	222 (99.8%)	225 (95.7%)
1. Patient does not know or suspect the treatment assignment	261 (58.4%)	130 (58.6%)	131 (58.2%)
2. Patient is “certain” of treatment assignment	99 (22.1%)	47 (21.2%)	52 (23.1%)
- Believes received placebo procedure	35 (7.8%)	10 (4.5%)	25 (11.1%)
- Believes received the shunt	64 (14.3%)	37 16.7%)	27 (12.0%)
Reason for possible unblinding			
- Due to change in symptoms	78 (17.4%)	32 (14.4%)	46 (20.4%)
- For "other" reasons	8 (1.8%)	5 (2.3%)	3(1.3%)
- Patient-reported possible unblinding event	13 (2.9%)	10 (4.5%)	3 (1.3%)
3. Patient suspects but is uncertain of treatment assignment	87 (19.5%)	44 (19.8%)	43 (19.1%)
- Believes received placebo procedure	37 (8.3%)	14 (6.3%)	23 (10.2%)
- Believes received the shunt	50 (11.2%)	30 (13.5%)	20 (8.9%)
Reason for possible unblinding			
- Due to change in symptoms	74 (16.6%)	37 (16.7%)	37 (16.4%)
- For "other" reasons	11 (2.5%)	7 (3.2%)	4 (1.8%)
- Patient-reported possible unblinding event	2 (0.5%)	0 (0.0%)	2 (0.9%)
4. Patient is certain of or suspects the randomization treatment	186 (41.6%)	92 (41.4%)	94 (41.8%)
- Believes received placebo procedure	72 (16.1%)	25 (11.3%)	47 (20.9%)
- Believes received the shunt	114 (25.5%)	67 (30.2%)	47 (20.9%)
Reason for possible unblinding			
- Due to change in symptoms	152 (34.0%)	69 (31.1%)	83 (36.9%)
- For "other" reasons	19 (4.3%)	12 (5.4%)	7 (3.1%)
- Patient-reported possible unblinding event	15 (3.4%)	10 (4.5%)	5 (2.2%)
5. Successful blinding (either patient was unaware of their treatment or their belief was incorrect)	334 (74.7%)	156 (70.3%)	178 (79.1%)
6. Successful blinding (no unblinding event was reported)	432 (96.6%)	212 (95.5%)	220 (97.8%)

Table S15. Additional pre-specified secondary safety and effectiveness outcomes, all patients, by randomized treatment

	Shunt group (N=250)	Placebo 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%)	-	-	-
Secondary effectiveness endpoints:				
Technical success at exit from the cath lab	250 (100%)	-	-	-
Device success at 30 days	247 (98.8%)[††]	-	-	-
Procedural success at 30 days	239 (95.6%)[††]	-	-	-
All-cause death and all HFHs through 2 years – no. of events/total no. of patient-yr (annualized rate)	163/392.7 (41.3%)	152/396.1 (38.3%)	1.08 (0.86, 1.34)[3]	0.52
All-cause death or HFH, time-to-first through 2 years[1]	90 (38.8%)	80 (33.9%)	1.18 [0.87, 1.59][2]	0.29
Cardiovascular death or cardiac transplantation or LVAD, time-to-first through 2 years[1]	24 (11.0%)	22 (11.2%)	1.11 [0.62, 1.98][2]	0.73
All-cause death or all hospitalization, time-to-first through 2 years[1]	138 (61.3%)	126 (55.3%)	0.99 [0.74, 1.31][2]	0.92
Cardiovascular hospitalization, time-to-first through 2 years[1]	55 (27.7%)	45 (22.0%)	1.26 [0.85, 1.86][2]	0.25
Non-cardiovascular hospitalization, time-to-first through 2 years[1]	92 (42.2%)	95 (43.4%)	0.99 [0.74, 1.31][2]	0.92
Days alive and free from HFH through 2 years	547.5 [306,717]	486.5 [357, 710]	0 [-10, 19][4]	0.70
NYHA class at 1 year	N=218	N=225		
I	12 (5.5%)	13 (5.8%)	-0.3 [-4.6, 4.0][5]	0.90
II	101 (46.3%)	97 (43.1%)	3.2 [-6.0, 12.5][5]	0.50
III	101 (46.3%)	111 (49.3%)	-3.0 [-12.3, 6.3][5]	0.53
IV	4 (1.8%)	4 (1.8%)	0.1 [-2.9, 3.1][5]	1.00
Patient global assessment, change from baseline to 1 year	N=220	N=226		0.97[6]
Improved	73 (33.2%)	73 (32.3%)	0.9 [-7.8, 9.6][5]	
Unchanged	131 (59.5%)	137 (60.6%)	-1.1 [-10.2, 8.0][5]	
Worsened	16 (7.3%)	16 (7.1%)	0.2 [-4.6, 5.0][5]	

HF clinical composite assessment, change from baseline to 1 year‡	N=249	N=256		0.76[6]
Improved	133 (53.4%)	145 (56.6%)	-3.2 [-11.9, 5.4][5]	
Unchanged	24 (9.6%)	24 (9.4%)	0.3 [-4.9, 5.4][5]	
Worsened	92 (36.9%)	87 (34.0%)	3.0 [-5.4, 11.3][5]	
Change in 6MWD from baseline through 1 year, meters	3.7 ± 72.6	8.3 ± 82.8	-4.9 [-20.3, 10.5][7]	0.53
Presence of shunt flow at 1 year	140/140 (100%)‡‡	-	-	-
Change in creatinine clearance from baseline to 1 year (mL/min/1.73m^2)¶	-2.9 ± 11.5	0.8 ± 29.6	-3.7 [-8.0, 0.5][7]	0.09

*MACNE is device-related or procedure-related.

**The 7 strokes in patients who were treated with the shunt were classified by the clinical events committee as being due to cerebrovascular disease (n=3), embolic due to atrial fibrillation (n=2) and undetermined (n=2). The 5 strokes in patients who were treated with a placebo-procedure were classified by the clinical events committee as being due to cerebrovascular disease (n=1), embolic due to atrial fibrillation (n=2), subarachnoid hemorrhage (n=1) and undetermined (n=1). Only one stroke occurred within 30 days of randomization, that being in the placebo-procedure group.

†Does not include 1 additional patient in the placebo group with an ischemic stroke and hemorrhagic transformation.

††Device success and procedure success were adjudicated by the clinical events committee according to the definitions on pages 25 and 26 of the appendix. The adjudicated causes for failure of device success within 30 days in three patients were as follows: One patient developed a procedure-related minor pericardial effusion not requiring treatment on the day of the procedure; one patient developed COVID-19-related pneumonia and had a pulmonary embolism on day 18 post-procedure – this event was also adjudicated as procedure-related; and one patient developed severe gastroenteritis, a serosanguineous pericardial effusion, multiorgan failure and died on day 16 post-procedure – this event was adjudicated to not be device-related or procedure-related. The adjudicated causes for failure of procedural success within 30 days in three patients were as follows: procedure-related device failure occurred in the two patients above; 9 additional patients had other events adjudicated as definitely or probably related to the procedure that met the definition of procedural failure - three patients had vascular access site complications including bleeding; two patients had ventricular tachycardia (one during right heart catheterization, the other torsade de pointes); one patient had a suspected air embolism during the procedure; one patient developed transient hypotension; one patient developed epistaxis at the end of the procedure; and one patient developed acute kidney injury.

‡All-cause mortality, HF hospitalization, and changes in NYHA functional class ranking and Patient Global Assessment.

‡‡The denominator is patients in whom the shunt could be visualized (n=140). A total of 209 shunt group patients had a transthoracic echocardiogram at 12 months, among whom the shunt could not be visualized in 69 patients and thus patency was not assessed.

¶Calculated from the Modification of Diet in Renal Disease (MDRD) formula.

1. Event rates are number of events (Kaplan-Meier time-to-first event estimates).
2. Hazard ratio [95% confidence interval].
3. Relative rate ratio [95% confidence interval] of the two annualized rates.
4. Median difference [interquartile range].
5. Difference [95% confidence interval].
6. Cochran-Mantel-Haenszel test used to compare the ordered response.
7. Difference [95% confidence interval], adjusted for baseline value (analysis of covariance).

Note: All P values should be considered hypothesis generating.

6MWD denotes six-minute walk distance; BARC, Bleeding Academic Research Consortium; CNS, central nervous system; HF, heart failure; HFH, heart failure hospitalization; MACNE, device-related or procedure-related major adverse cardiovascular or neurologic events; NYHA, New York Heart Association.

Table S16. Adjudicated causes of death within 2 years, all patients, by randomized treatment

	Shunt group (N=250)	Placebo group (N=258)	Hazard ratio [95% CI]
All-cause death	35 (15.6%)	27 (13.7%)	1.31 [0.79, 2.16]
Cardiovascular death	23 (10.4%)	16 (8.0%)	1.47 [0.77, 2.78]
Due to heart failure	13 (6.3%)	8 (4.8%)	1.63 [0.68, 3.94]
Due to acute myocardial infarction	0 (0.0%)	1 (0.4%)	-
Due to sudden cardiac death	8 (3.6%)	6 (2.7%)	1.38 [0.48, 3.99]
Due to stroke	1 (0.4%)	0 (0.0%)	-
Due to cardiovascular hemorrhage	0 (0.0%)	1 (0.4%)	-
Due to cardiovascular procedures	0 (0.0%)	0 (0.0%)	-
Due to other cardiovascular cause	1 (0.4%)	0 (0.0%)	-
Non-cardiovascular death	10 (5.0%)	9 (5.1%)	1.09 [0.44, 2.69]
Renal	0 (0.0%)	0 (0.0%)	-
Pulmonary	0 (0.0%)	1 (0.5%)	-
Gastrointestinal	1 (0.4%)	0 (0.0%)	-
Hepatobiliary	0 (0.0%)	0 (0.0%)	-
Pancreatic	0 (0.0%)	0 (0.0%)	-
Infection	6 (3.1%)	5 (3.2%)	1.16 [0.35, 3.81]
Inflammatory	0 (0.0%)	0 (0.0%)	-
Hemorrhage (non-cardiovascular)	0 (0.0%)	0 (0.0%)	-
Non-cardiovascular procedure or surgery	0 (0.0%)	0 (0.0%)	-
Trauma	0 (0.0%)	1 (0.6%)	-
Suicide	0 (0.0%)	0 (0.0%)	-
Non-prescription drug reaction or overdose	0 (0.0%)	0 (0.0%)	-
Prescription drug reaction or overdose	0 (0.0%)	0 (0.0%)	-
Neurologic (non-cardiovascular)	1 (0.5%)	0 (0.0%)	-
Malignancy	1 (0.4%)	2 (1.0%)	0.52 [0.05, 5.72]
Other non-cardiovascular cause	1 (0.6%)	0 (0.0%)	-
Undetermined cause of death	2 (0.8%)	2 (1.1%)	1.01 [0.14, 7.14]

Event rates are number of events (Kaplan-Meier estimated percentages).

Table S17. One-year transthoracic echocardiography, all patients, by randomized treatment

	Shunt group (N=209)	Placebo group (N=222)	Difference	P value
Left ventricular end-diastolic volume (biplane), mL	115.0 (78.0, 167.0)	128.5 (86.5, 170.5)	-6.3 [-17.5, 5.0][1]	0.27
Left ventricular end-systolic volume (biplane), mL	55.0 (32.0, 109.0)	62.5 (38.0, 104.0)	-3.3 [-11.0, 4.5][1]	0.43
Left ventricular ejection fraction (biplane), %	48.1 (34.3, 59.0) 46.7 ± 14.6	47.3 (36.0, 58.2) 46.6 ± 14.5	0.04 [-2.8, 2.8][2]	0.99
Left atrial volume (biplane), mL	79.5 (62.0, 96.0)	74.5 (57.5, 95.26)	3.8 [-1.5, 9.0][1]	0.17
Stroke volume, mL	51.0 (40.0, 64.5)	53.0 (42.0, 66.0)	-2.5 [-6.0, 1.0][1]	0.14
Stroke volume index, mL/m^2	25.7 (20.1, 31.6)	26.8 (21.2, 32.5)	-1.0 [-2.6, 0.6][1]	0.23
Cardiac output, L/min	3.44 (2.66, 4.36)	3.67 (2.86, 4.58)	-0.26 [-0.51, -0.15][1]	0.0384
Cardiac index, L/min/m^2	1.71 (1.37, 2.14)	1.89 (1.48, 2.21)	-0.11 [-0.22, 0.00][1]	0.0447
Right ventricular fractional area change, %	38.9 (35.0, 42.9)	37.5 (33.3, 42.9)	0.9 [-0.4, 2.2][1]	0.19
Tricuspid annular plane systolic excursion, mm	17.0 (14.0, 20.0)	16.0 (14.0, 20.0)	0.5 [0.0, 1.0][1]	0.17
Pulmonary artery systolic pressure, mmHg	35.0 (27.0, 44.0)	31.0 (24.0, 39.0)	3.5 [1.0, 6.0][1]	0.0083
Right ventricular end-diastolic area index, cm^2/m^2	10.2 (8.9, 12.9)	9.6 (7.8, 11.9)	0.8 [0.2, 1.3][1]	0.0178
Inferior vena cava diameter max, cm	1.8 (1.3, 2.1)	1.6 (1.2, 1.9)	0.2 [0.0, 0.3][1]	0.0078
Mitral regurgitation moderate or greater	23 (11.0%)	23 (10.4%)	0.6 [-5.2, 6.5][2]	0.82
Tricuspid regurgitation moderate or greater	33 (15.8%)	24/218 (11.0%)	4.8 [-1.7, 11.2][2]	0.15

Continuous data are median (interquartile range) or mean ± standard deviation. Left ventricular ejection fraction data are shown both ways.
1. Median difference [interquartile range].
2. Difference [95% confidence interval].
Note: All P values should be considered hypothesis generating.

Table S18. Baseline characteristics in patients with reduced and preserved ejection fraction

	Heart failure with reduced ejection fraction (≤40%) (N=206)	Heart failure with preserved ejection fraction (>40%) (N=302)	P value
LVEF, % (core laboratory read)	30.2 (23.4, 34.7)	55.8 (47.6, 62.3)	<0.0001
Age, years	70.0 (62.0, 76.0)	75.0 (68.0, 80.0)	<0.0001
Sex*, male	168 (81.6%)	151 (50.0%)	<0.0001
Sex*, female	38 (18.4%)	151 (50.0%)	<0.0001
Race, White	184 (89.3%)	275 (91.1%)	0.36
Ethnicity, Hispanic	25 (12.1%)	21 (7.0%)	0.046
Body mass index, kg/m^2	29.7 (25.5, 33.1)	30.9 (26.6, 37.1)	0.002
Diabetes mellitus	105 (51.0%)	144 (47.7%)	0.47
- Insulin-treated	32 (15.5%)	65 (21.5%)	0.09
Hypertension	161 (78.2%)	264 (87.4%)	0.006
Hyperlipidemia	155 (75.2%)	241 (79.8%)	0.22
Current or previous smoker	121 (58.7%)	149 (49.3%)	0.04
Prior stroke or transient ischemic attack	32 (15.5%)	59 (19.5%)	0.25
Chronic obstructive lung disease	38 (18.4%)	57 (18.9%)	0.90
Ischemic cardiomyopathy	129 (62.6%)	105 (34.8%)	<0.0001
Non-ischemic cardiomyopathy	77 (37.4%)	197 (65.2%)	<0.0001
At least one HFH in the prior year	108 (52.4%)	147 (48.7%)	0.41
Known coronary artery disease	153 (74.3%)	176 (58.3%)	0.0002
Prior myocardial infarction	118 (57.3%)	89 (29.5%)	<0.0001
Prior PCI	94 (45.6%)	105 (34.8%)	0.01
Prior CABG	65 (31.6%)	58 (19.2%)	0.001
History of atrial fibrillation or flutter	124 (60.2%)	205 (67.9%)	0.07
ICD	98 (47.6%)	29 (9.3%)	<0.0001
CRT-D	86 (41.7%)	26 (8.6%)	<0.0001
CRT-P	6 (2.9%)	11 (3.6%)	0.65
Pacemaker	9 (4.4%)	55 (18.2%)	<0.0001
NYHA class	9 (47.6%)	28 (9.3%)	0.09
- I	0 (0.0%)	0 (0.0%)	
- II	10 (4.9%)	6 (2.0%)	
- III	196 (95.1%)	294 (97.4%)	
- IV	0 (0.0%)	2 (0.7%)	

KCCQ summary score	55.2 (38.5, 72.1)	48.4 (33.1, 63.5)	0.002
Six-minute walk distance	280.3 (212.0, 350.0)	254.8 (187.4, 318.2)	0.003
Troponin I or T >ULN	87 (46.8%)	101 (35.9%)	0.002
B-type natriuretic peptide (pg/mL)	319.0 (196.0, 687.0)	177.5 (93.5, 366.0)	0.002
N-terminal pro-B-type natriuretic peptide (pg/mL)	2162.0 (1069.0, 3840.3)	1547.0 (816.0, 2700.0)	0.0003
eGFR, mL/min/1.73 m^2	47.1 (37.6, 60.4)	47.3 (37.0, 60.1)	0.80
- <60 mL/min/1.73 m^2	150 (72.8%)	226 (74.8%)	0.61

*Determined as biologic sex at birth. Continuous data are shown as 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 (MDRD) formula; HFH, heart failure hospitalization; ICD, implantable cardiac defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; ULN, upper limits of normal.

Table S19. Baseline medications in patients with reduced and preserved ejection fraction

	Heart failure with reduced ejection fraction (≤40%) (N=206)	Heart failure with preserved ejection fraction (>40%) (N=302)	P value
Beta-blockers	200 (97.1%)	247 (81.8%)	<0.0001
Renin-angiotensin system inhibitors, any	188 (91.3%)	173 (57.3%)	<0.0001
- ACEi	14 (6.8%)	56 (18.5%)	0.0002
- ARB	15 (7.3%)	62 (20.5%)	<0.0001
- ARNi	159 (77.2%)	55 (18.2%)	<0.0001
Mineralocorticoid receptor antagonists	151 (73.3%)	168 (55.6%)	<0.0001
Sodium-glucose cotransporter-2 inhibitors	104 (50.5%)	102 (33.8%)	0.0002
Vasodilators	21 (10.2%)	46 (15.2%)	0.10
- Long-acting nitrates	18 (8.7%)	36 (11.9%)	0.25
- Hydralazine	10 (4.9%)	20 (6.6%)	0.41
Diuretics	191 (92.7%)	278 (92.1%)	0.78
Antiplatelet agents	103 (50.0%)	114 (37.7%)	0.006
Chronic oral anticoagulation	122 (69.2%)	186 (61.6%)	0.59

ACEi denotes angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNi = angiotensin receptor-neprilysin inhibitor.

Table S20. Baseline characteristics in patients with reduced and preserved ejection fraction by randomized treatment

	Heart failure with reduced ejection fraction (≤40%)		Heart failure with preserved ejection fraction (>40%)	
	Shunt group (N=101)	**Placebo group (N=105)**	**Shunt group (N=149)**	**Placebo group (N=153)**
Age, years	72.0 (64.0, 78.0)	68.0 (59.0, 73.0)	75.0 (70.0, 81.0)	74.0 (68.0, 80.0)
Sex*, male	84 (83.2%)	84 (80.0%)	78 (52.3%)	73 (47.7%)
Sex*, female	17 (16.8%)	21 (20.0%)	71 (47.7%)	80 (52.3%)
Race, White	91 (90.1%)	93 (88.6%)	136 (91.3%)	139 (90.8%)
Ethnicity, Hispanic	10 (9.9%)	15 (14.3%)	10 (6.7%)	11 (7.2%)
Body mass index, kg/m^2	29.3 (25.5, 32.6)	29.8 (25.6, 33.9)	31.6 (25.7, 36.0)	30.9 (27.1, 37.1)
Diabetes mellitus	50 (49.5%)	55 (52.4%)	74 (49.7%)	70 (45.8%)
- Insulin-treated	14 (28.0%)	18 (32.7%)	35 (47.3%)	30 (42.9%)
Hypertension	81 (80.2%)	80 (76.2%)	128 (85.9%)	136 (88.9%)
Hyperlipidemia	80 (79.2%)	75 (71.4%)	121 (81.2%)	120 (78.4%)
Current or previous smoker	61 (60.4%)	60 (57.1%)	72 (48.3%)	77 (50.3%)
Prior stroke or transient ischemic attack	17 (16.8%)	15 (14.3%)	26 (17.4%)	33 (21.6%)
Chronic obstructive lung disease	18 (17.8%)	20 (19.0%)	25 (16.8%)	32 (20.9%)
Ischemic cardiomyopathy	65 (64.4%)	64 (61.0%)	49 (32.9%)	56 (36.6%)
Non-ischemic cardiomyopathy	36 (35.5%)	41 (39.0%)	100 (67.1%)	97 (63.4%)
At least one HFH in the prior year	55 (54.5%)	53 (50.5%)	73 (49.0%)	74 (48.4%)
Known coronary artery disease	77 (76.2%)	76 (72.4%)	92 (61.7%)	84 (54.9%)
Prior myocardial infarction	58 (57.4%)	60 (57.1%)	46 (30.9%)	43 (28.1%)
Prior PCI	45 (44.6%)	49 (46.7%)	58 (38.9%)	47 (30.7%)
Prior CABG	36 (35.6%)	29 (27.6%)	29 (19.5%)	29 (19.0%)
History of atrial fibrillation or flutter	65 (64.4%)	59 (56.2%)	105 (70.5%)	100 (65.4%)
- Baseline rhythm is atrial fibrillation or flutter	27 (26.7%)	19 (18.1%)	49 (32.9%)	45 (29.4%)
ICD or CRT-D	89 (88.1%)	95 (90.5%)	26 (17.4%)	28 (18.3%)
CRT-D or CRT-P	49 (48.5%)	43 (41.0%)	21 (14.1%)	16 (10.5%)
NYHA class				
- I	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- II	4 (4.0%)	6 (5.7%)	5 (3.4%)	1 (0.7%)
- III	97 (96.0%)	99 (94.3%)	142 (95.3%)	152 (99.3%)
- IV	0 (0.0%)	0 (0.0%)	2 (1.3%)	0 (0.0%)

KCCQ summary score	56.0 (35.9, 72.1)	54.2 (39.1, 69.8)	49.0 (34.8, 64.3)	47.4 (32.3, 62.8)
Six-minute walk distance	295.0 (216.0, 355.1)	262.5 (204.0, 344.5)	240.0 (185.5, 315.8)	275.0 (192.5, 321.0)
Troponin I or T >ULN	37/88 (42.0%)	50/98 (51.0%)	42/139 (30.2%)	59/142 (41.5%)
B-type natriuretic peptide (pg/mL)	301.0 (203.0, 750.5)	319.0 (155.2, 651.0)	177.5 (104.5, 325.0)	177.5 (79.0, 391.0)
N-terminal pro-B-type natriuretic peptide (pg/mL)	2230.5 (1300.0, 3944.0)	1867.0 (954.0, 3772.0)	1653.8 (873.0, 2766.4)	1454.0 (779.0, 2544.0)
eGFR, mL/min/1.73 m^2	44.5 (37.3, 58.0)	50.4 (39.2, 60.8)	46.6 (37.5, 59.8)	47.3 (36.6, 60.1)
- <60 mL/min/1.73 m^2	76 (75.2%)	74 (70.5%)	112 (75.2%)	114/153 (74.5%)

*Determined as biologic sex at birth. Continuous data are shown as 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 (MDRD) formula; HFH, heart failure hospitalization; ICD, implantable cardiac defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; ULN, upper limits of normal.

Table S21. Baseline medications in patients with reduced and preserved ejection fraction by randomized treatment

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

ACEi denotes angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNi = angiotensin receptor-neprilysin inhibitor.

Table S22. Baseline transthoracic echocardiography in patients with reduced and preserved ejection fraction by randomized treatment

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

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

Table S23. Baseline right heart catheterization in patients with reduced and preserved ejection fraction by randomized treatment

	Heart failure with reduced ejection fraction (≤40%)		Heart failure with preserved ejection fraction (>40%)	
	Shunt group (N= 101)	Placebo group (N= 105)	Shunt group (N=149)	Placebo group (N=153)
Heart rate, bpm	69.0 (60.0, 77.0)	70.0 (62.0, 77.5)	64.0 (58.0, 75.0)	65.0 (58.0, 76.0)
Systolic blood pressure, mmHg	109.0 (99.0, 123.0)	106.0 (98.0, 121.0)	119.0 (108.5, 136.0)	122.0 (109.5, 140.5)
Diastolic blood pressure, mmHg	63.0 (57.0, 73.0)	65.0 (59.0, 73.0)	64.0 (56.0, 72.5)	64.5 (57.5, 73.0)
Mean right atrial pressure, mmHg	9.0 (6.0, 11.0)	9.0 (6.0, 11.0)	10.0 (7.0, 13.0)	9.0 (6.0, 11.0)
Systolic pulmonary artery pressure, mmHg	35.0 (29.0, 45.0)	40.0 (32.0, 47.0)	39.0 (31.0, 46.0)	36.0 (31.0, 43.0)
Mean pulmonary artery pressure, mmHg	24.0 (20.0, 31.0)	26.0 (22.0, 32.0)	26.0 (21.0, 31.0)	25.0 (20.0, 29.0)
Pulmonary vascular resistance, Wood units	2.1 (1.3, 3.1)	2.0 (1.6, 3.3)	2.2 (1.6, 3.2)	2.0 (1.2, 2.5)
Pulmonary capillary wedge pressure, mmHg	15.0 (12.0, 19.0)	16.0 (12.0, 21.0)	16.0 (12.0, 20.0)	15.0 (12.0, 19.0)
Cardiac output, L/min	4.1 (3.4, 5.1)	4.2 (3.6, 5.2)	4.3 (3.3, 5.3)	4.5 (3.5, 5.3)
Cardiac index, L/min/m^2	2.0 (1.8, 2.6)	2.1 (1.8, 2.4)	2.1 (1.8, 2.6)	2.2 (1.9, 2.7)

Continuous data are shown as median (interquartile range).

Table S24. Procedural details in patients with reduced and preserved ejection fraction by randomized treatment

	Heart failure with reduced ejection fraction (≤40%)		Heart failure with preserved ejection fraction (>40%)	
	Shunt group (N=101)	Placebo group (N=105)	Shunt group (N=149)	Placebo group (N=153)
Procedure duration, minutes	74 (62, 92)	43 (30, 55)	82 (56, 102)	43 (31, 55)
Fluoroscopy time, minutes	14 (10, 20)	4 (2, 7)	14 (10, 21)	4 (2, 7)
Contrast administered, mL	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Heparin administered, units	8000 (7000, 11,000)	-	9000 (6294, 12,000)	-
Activated clotting time, seconds	298 (240, 346)	-	285 (248, 337)	-
Shunt implant attempt	101 (100%)	1/1 (100%)*	149 (100%)	-
Shunt implanted successfully	101 (100%)	1/1 (100%)	149 (100%)	-
Hospital duration post procedure, days	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)

*Due to site error (mis-interpretation of the randomization code). Continuous data are shown as median (interquartile range).

Table S25. Medications at discharge and during follow-up in patients with reduced and preserved ejection fraction by randomized treatment

	Heart failure with reduced ejection fraction (≤40%)		Heart failure with preserved ejection fraction (>40%)	
	Shunt group (N=101)	**Placebo group (N=105)**	**Shunt group (N=149)**	**Placebo group (N=153)**
Discharge				
Beta-blockers	100 (99.0%)	102 (97.1%)	125 (83.9%)	121 (79.1%)
Renin-angiotensin system inhibitors, any	95 (94.1%)	93 (88.6%)	80 (53.7%)	93 (60.8%)
- ACEi	7 (6.9%)	7 (6.7%)	24 (16.1%)	32 (20.9%)
- ARB	8 (7.9%)	7 (6.7%)	31 (20.8%)	31 (20.3%)
- ARNi	80 (79.2%)	79 (75.2%)	25 (16.8%)	30 (19.6%)
Mineralocorticoid receptor antagonists	74 (73.3%)	77 (73.3%)	72 (48.3%)	97 (63.4%)
Sodium-glucose cotransporter-2 inhibitors	49 (48.5%)	56 (53.3%)	47 (31.5%)	58 (37.9%)
Vasodilators	8 (7.9 %)	13 (12.4%)	24 (16.1%)	21 (13.7%)
- Long-acting nitrates	7 (6.9%)	11 (10.5%)	21 (14.1%)	14 (9.2%)
- Hydralazine	2 (2.0%)	8 (7.6%)	8 (5.4%)	12 (7.8%)
Diuretics	95 (94.1%)	97 (92.4%)	140 (94.0%)	144 (94.1%)
Antiplatelet agents, open-label	55 (54.5%)	58 (55.2%)	66 (44.3%)	74 (48.4%)
Antiplatelet agents, study medications*	22 (21.8%)	23 (21.9%)	33 (22.1%)	40 (26.1%)
Chronic oral anticoagulation	64 (63.4%)	58 (55.2%)	94 (63.1%)	92 (60.1%)
1 year	N=92	N=94	N=137	N=148
Beta-blockers	92 (100.0%)	91 (96.8%)	114 (83.2%)	118 (79.7%)
Renin-angiotensin system inhibitors, any	87 (94.6%)	83 (88.3%)	73 (53.3%)	89 (60.1%)
- ACEi	7 (7.6%)	7 (7.4%)	20 (14.6%)	26 (17.6%)

- ARB	6 (6.5%)	3 (3.2%)	27 (19.7%)	28 (18.9%)
- ARNi	74 (80.4%)	73 (77.7%)	26 (19.0%)	35 (23.6%)
Mineralocorticoid receptor antagonists	67 (72.8%)	65 (69.1%)	71 (51.8%)	95 (64.2%)
Sodium-glucose cotransporter-2 inhibitors	59 (64.1%)	54 (57.4%)	61 (44.5%)	73 (49.3%)
Vasodilators	10 (10.9%)	11 (11.7%)	25 (18.2%)	21 (14.2%)
- Long-acting nitrates	9 (9.8%)	8 (8.5%)	21 (15.3%)	14 (9.5%)
- Hydralazine	3 (3.3%)	7 (7.4%)	8 (5.8%)	11 (7.4%)
Diuretics	85 (92.4%)	83 (88.3%)	129 (94.2%)	135 (91.2%)
Antiplatelet agents, open-label	49 (53.3%)	49 (52.1%)	53 (38.7%)	71 (48.0%)
Chronic oral anticoagulation	59 (64.1%)	56 (59.6%)	89 (65.0%)	89 (60.1%)

*Aspirin and clopidogrel (one or both), unless the patient is otherwise taking open-label aspirin and a platelet $P2Y_{12}$ receptor inhibitor. ACEi denotes angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNi = angiotensin receptor-neprilysin inhibitor.

Table S26. Additional pre-specified secondary safety and effectiveness outcomes in patients with reduced and preserved ejection fraction by randomized treatment

	Heart failure with reduced ejection fraction (≤40%)			Heart failure with preserved ejection fraction (>40%)		
	Shunt group (N=101)	**Placebo group (N=105)**	**Relative risk or difference**	**Shunt group (N=149)**	**Placebo group (N=153)**	**Relative risk or difference**
Secondary safety endpoints:						
MACNE* or BARC types 3 or 5 bleeding at 30 days[1]	0 (0.0%)	-	-	2 (1.3%)	-	-
BARC types 3 or 5 bleeding at 30 days[1]	0 (0.0%)	1 (1.0%)	-	2 (1.3%)	0 (0.0%)	-
MACNE* at 1 year[1]	0 (0.0%)	-	-	0 (0.0%)	-	-
MACNE* at 2 years[1]	0 (0.0%)	-	-	0 (0.0%)	-	-
Cerebrovascular events at 2 years, any[1]	4 (4.1%)	3 (3.2%)	1.38 [0.31, 6.15][2]	7 (5.7%)	3 (2.0%)	2.49 [0.64, 9.63][2]
CNS infarction (stroke)[1]	3 (3.1%)	2 (2.2%)	1.54 [0.26, 9.23][2]	4 (3.3%)	3 (2.0%)	1.42 [0.32, 6.34][2]
CNS hemorrhage (intracerebral or subarachnoid)[1]**	0 (0.0%)	1 (1.2%)	-	0 (0.0%)	0 (0.0%)	-
Transient ischemic attack[1]	1 (1.0%)	1 (1.0%)	1.04 [0.07, 16.64][2]	3 (2.4%)	0 (0.0%)	-
Myocardial infarction at 2 years[1]	1 (1.1%)	3 (3.5%)	0.34 [0.04, 3.24][2]	7 (5.6%)	10 (8.5%)	0.73 [0.28, 1.91][2]
Systemic embolization events at 2 years[1]	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Pulmonary embolization events at 2 years[1]	1 (1.7%)	0 (0.0%)	-	1 (0.7%)	0 (0.0%)	-
Shunt implant embolization at 2 years[1]	0 (0.0%)	-	-	0 (0.0%)	-	-
Secondary effectiveness endpoints:						
Technical success at exit from the cath lab	101 (100.0%)	-	-	149 (100%)	-	-
Device success at 30 days	101 (100.0%)	-	-	146 (98.0%)	-	-
Procedural success at 30 days	99 (98.0%)	-	-	140 (94.0%)	-	-
All-cause death and all HFHs through 2 years – no. of events/total no. of patient-yr (annualized rate)	54/155.2 (34.8 %)	98/151.2 (64.8%)	0.53 [0.38, 0.75][3]	109/237.5 (45.9%)	54/245.0 (22.0%)	2.08 [1.50, 2.88][3]

All-cause death or HFH, time-to-first through 2 years[1]	34 (35.9%)	45 (49.5%)	0.72 [0.46, 1.13][2]	56 (40.5%)	35 (24.0%)	1.76 [1.15, 2.69][2]
Cardiovascular death or cardiac transplantation or LVAD, time-to-first through 2 years[1]	12 (13.6%)	18 (24.0%)	0.65 [0.31, 1.36][2]	12 (9.2%)	4 (2.6%)	3.13 [1.01, 9.70][2]
All-cause death or all hospitalization, time-to-first through 2 years[1]	47 (52.0%)	52 (59.7%)	0.87 [0.59, 1.29][2]	91 (67.0%)	74 (52.6%)	1.29 [0.95, 1.76][2]
Cardiovascular hospitalization, time-to-first through 2 years[1]	20 (24.9%)	20 (24.2%)	0.98 [0.53, 1.83][2]	35 (29.6%)	25 (20.6%)	1.49 [0.89, 2.50][2]
Non-cardiovascular hospitalization, time-to-first through 2 years[1]	27 (30.5%)	36 (47.2%)	0.70 [0.43, 1.16][2]	65 (49.5%)	59 (42.1%)	1.17 [0.82, 1.66][2]
Days alive and free from HFH through 2 years	516 [316, 717]	402 [268, 669]	28 [-3, 118][4]	572 [278, 714]	523 [368, 716]	-3 [-37,9][4]
NYHA class at 1 year	N=90	N=86		N=128	N=139	
I	6 (6.7%)	8 (9.3%)	-2.6 [-10.7, 5.4][5]	6 (4.7%)	5 (3.6%)	1.1 [-3.7, 5.9][5]
II	51 (56.7%)	39 (45.3%)	11.3 [-3.4, 26.0][5]	50 (39.1%)	58 (41.7%)	-2.7 [-14.4, 9.1][5]
III	32 (35.6%)	37 (43.0%)	-7.5 [-21.9, 6.9][5]	69 (53.9%)	74 (53.2%)	0.7 [-11.3, 12.6][5]
IV	1 (1.1%)	2 (2.3%)	-1.2 [-7.3, 4.1][5]	3 (2.3%)	2 (1.4%)	0.9 [-3.1, 5.5][5]
Patient global assessment, change from baseline to 1 year	N=90	N=86		N=130	N=140	
Improved	31 (34.4%)	36 (41.9%)	-7.4 [-21.7, 6.9][5]	42 (32.3%)	37 (26.4%)	5.9 [-5.0, 16.7][5]
Unchanged	55 (61.1%)	44 (51.2%)	9.9 [-4.6, 24.5][5]	76 (58.5%)	93 (66.4%)	-8.0 [-19.5, 3.6][5]
Worsened	4 (4.4%)	6 (7.0%)	-2.5 [-10.9, 5.2][5]	12 (9.2%)	10 (7.1%)	2.1 [-4.5, 8.6][5]
HF clinical composite assessment from baseline to 1 year†	N=101	N=105		N=149	N=153	
Improved	58 (57.4%)	55 (52.4%)	5.0 [-8.5, 18.6][5]	75 (50.3%)	91 (59.5%)	-9.1 [-20.3, 2.0][5]
Unchanged	8 (7.9%)	10 (9.5%)	-1.6 [-9.3, 6.1][5]	17 (11.4%)	14 (9.2%)	2.3 [-4.6, 9.1][5]
Worsened	35 (34.7%)	40 (38.1%)	-3.4 [-16.6, 9.7][5]	57 (38.3%)	48 (31.4%)	6.9 [-3.8, 17.6][5]
Change in 6MWD from baseline through 1 year, meters	3.1 ± 67.8	24.1 ± 81.2	-20.7 [-44.3, 3.0][6]	4.1 ± 76.3	-1.1 ± 82.6	3.6 [-16.6, 23.8][6]
Presence of shunt flow at 1 year	56/56 (100%)††	-	-	84/84 (100%)††	-	-
Change in creatinine clearance from baseline to 1 year (mL/min/1.73m^2)‡	-3.3 ± 10.7	-0.6 ± 11.9	-2.5 [-5.8, 0.7][6]	-2.7 ± 12.1	1.6 ± 36.6	-4.3 [-11.2, 2.6][6]

*MACNE is device-related or procedure-related.

**Does not include 1 additional patient in the placebo group with an ischemic stroke and hemorrhagic transformation.

†All-cause mortality, HF hospitalization, and changes in NYHA functional class ranking and Patient Global Assessment.
††The denominator is patients in whom the shunt could be visualized (n=140). A total of 209 shunt group patients had a transthoracic echocardiogram at 12 months, among whom the shunt could not be visualized in 69 patients and thus patency was not assessed.
‡Calculated from the Modification of Diet in Renal Disease (MDRD) formula.
1. Event rates are number of events (Kaplan-Meier time-to-first event estimates).
2. Hazard ratio [95% confidence interval].
3. Relative rate ratio [95% confidence interval] of the two annualized rates.
4. Median difference [interquartile range].
5. Difference [95% confidence interval].
6. Difference [95% confidence interval], adjusted for baseline value (analysis of covariance).
6MWD denotes six-minute walk distance; BARC, Bleeding Academic Research Consortium; CNS, central nervous system; HF, heart failure; HFH, heart failure hospitalization; MACNE, device-related or procedure-related major adverse cardiovascular or neurologic events; NYHA, New York Heart Association.

Table S27. Adjudicated causes of death within 2 years in patients with reduced and preserved ejection fraction by randomized treatment

	Heart failure with reduced ejection fraction (≤40%)			Heart failure with preserved ejection fraction (>40%)		
	Shunt group (N=101)	Placebo group (N=105)	Hazard ratio [95% CI]	Shunt group (N=149)	Placebo group (N=153)	Hazard ratio [95% CI]
All-cause death	13 (14.3%)	20 (26.8%)	0.63 [0.31, 1.26]	22 (16.4%)	7 (5.2%)	3.24 [1.38, 7.59]
Cardiovascular death	11 (12.2%)	12 (16.4%)	0.91 [0.40, 2.05]	12 (9.2%)	4 (2.6%)	3.13 [1.01, 9.70]
Due to heart failure	5 (6.5%)	8 (12.1%)	0.61 [0.20, 1.85]	8 (6.3%)	0 (0%)	-
Due to acute myocardial infarction	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	1 (0.7%)	-
Due to sudden cardiac death	4 (4.1%)	3 (4.0%)	1.34 [0.30, 6.00]	4 (3.1%)	3 (2.0%)	1.40 [0.31, 6.26]
Due to stroke	1 (1.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Due to cardiovascular hemorrhage	0 (0.0%)	1 (1.0%)	-	0 (0.0%)	0 (0.0%)	-
Due to cardiovascular procedures	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Due to other cardiovascular cause	1 (1.1%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Non-cardiovascular death	1 (1.3%)	6 (9.6%)	0.15 [0.02, 1.26]	9 (7.3%)	3 (2.6%)	3.04 [0.82, 11.23]
Renal	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Pulmonary	0 (0.0%)	1 (1.3%)	-	0 (0.0%)	0 (0.0%)	-
Gastrointestinal	0 (0.0%)	0 (0.0%)	-	1 (0.7%)	0 (0.0%)	-
Hepatobiliary	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Pancreatic	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Infection	0 (0.0%)	2 (2.6%)	-	6 (5.1%)	3 (2.6%)	2.03 [0.51, 8.13]
Inflammatory	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Hemorrhage (non-cardiovascular)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Non-cardiovascular procedure or surgery	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Trauma	0 (0.0%)	1 (1.6%)	-	0 (0.0%)	0 (0.0%)	-
Suicide	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Non-prescription drug reaction or overdose	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Prescription drug reaction or overdose	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Neurologic (non-cardiovascular)	1 (1.3%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Malignancy	0 (0.0%)	2 (2.5%)	-	1 (0.7%)	0 (0.0%)	-
Other non-cardiovascular cause	0 (0.0%)	0 (0.0%)	-	1 (1.0%)	0 (0.0%)	-
Undetermined cause of death	1 (1.0%)	2 (3.1%)	0.47 [0.04, 5.23]	1 (0.7%)	0 (0.0%)	-

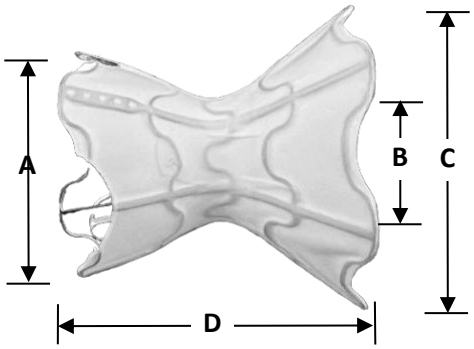
Event rates are number of events (Kaplan-Meier estimated percentages).

Table S28. One-year transthoracic echocardiography in patients with reduced and preserved ejection fraction by randomized treatment

	Heart failure with reduced ejection fraction (≤40%)			Heart failure with preserved ejection fraction (>40%)		
	Shunt group (N=86)	**Placebo group (N=84)**	**Difference [95% CI]**	**Shunt group (N=124)**	**Placebo group (N=138)**	**Difference [95% CI]**
Left ventricular end-diastolic volume (biplane), mL	177.0 (144.0, 225.0)	176.0 (139.0, 230.5)	-0.8 [-21.0, 19.5][1]	89.0 (68.0, 113.5)	98.0 (74.5, 136.3)	-10.3 [-19.5, -1.0][1]
Left ventricular end-systolic volume (biplane), mL	118.5 (91.0, 163.0)	120.5 (88.5, 165.5)	-1.8 [-18.5, 15.0][1]	37.5 (26.5, 52.3)	43.5 (28.0, 62.8)	-4.8 [-10.0, 0.5][1]
Left ventricular ejection fraction (biplane), %	32.4 (25.5, 39.1) 32.9 ± 8.9	29.5 (25.3, 39.1) 32.0 ± 9.0	0.9 [-2.0, 3.7][2]	57.6 (50.1, 63.0) 56.2 ± 9.1	56.6 (48.8, 61.9) 55.2 ± 9.3	0.8 [-1.4, 3.1][2]
Left atrial volume (biplane), mL	84.5 (61.5, 108.5)	80.5 (57.5, 102.5)	3.5 [-6.5, 13.5][1]	77.8 (63.0, 91.5)	71.0 (57.5, 91.5)	3.8 [-2.5, 10.0][1]
Stroke volume, mL	54.0 (43.0, 70.0)	56.0 (41.0, 65.0)	1.0 [-5.0, 7.0][1]	49.0 (37.0, 60.0)	52.0 (42.0, 67.0)	-5.0 [-9.0, -1.0][1]
Stroke volume index, mL/m^2	28.4 (20.7, 34.0)	25.8 (19.7, 32.3)	1.2 [-1.5, 3.9][1]	24.3 (19.9, 29.0)	27.0 (21.7, 32.7)	-2.3 [-4.3, -0.4][1]
Cardiac output, L/min	3.74 (2.94, 4.74)	3.91 (2.85, 4.78)	0.11 [-0.54, 0.33][1]	3.34 (2.60, 3.92)	3.61 (2.88, 4.52)	-0.37 [-0.67, -0.07][1]
Cardiac index, L/min/m^2	1.89 (1.38, 2.28)	1.94 (1.39, 2.26)	0.01 [-0.21, 0.18,][1]	1.65 (1.34, 1.93)	1.84 (1.50, 2.18)	-0.18 [-0.30. -0.06][1]
Right ventricular fractional area change, %	37.5 (34.5, 42.9)	35.9 (30.4, 40.0)	2.2 [0.0, 4.4][1]	40.0 (35.3, 43.8)	39.5 (35.3, 43.8)	0.4 [-1.2, 1.9][1]
Tricuspid annular plane systolic excursion, mm	17.0 (14.0, 19.0)	15.0 (13.0, 19.0)	1.0 [0.0, 2.0][1]	18.0 (14.0, 21.0)	17.0 (15.0, 20.0)	0.0 [-1.0, 1.0][1]
Pulmonary artery systolic pressure. mmHg	30.0 (23.0, 41.5)	32.0 (23.0, 40.0)	-0.5 [-5.0, 4.0][1]	37.0 (31.0, 44.0)	31.0 (24.0, 37.0)	6.0 [3.0, 9.0][1]
Right ventricular end-diastolic area index, cm^2/m^2	10.2 (8.8, 13.4)	10.2 (7.9, 12.2)	0.6 [-0.4, 1.6][1]	10.2 (9.0, 12.6)	9.5 (7.8, 11.7)	0.9 [0.2, 1.5][1]
Inferior vena cava diameter max, cm	1.7 (1.2, 2.0)	1.6 (1.2, 2.0)	0.0 [-0.2, 0.2][1]	1.8 (1.4, 2.2)	1.5 (1.2, 1.9)	0.3 [0.1, 0.4][1]
Mitral regurgitation moderate or greater	12/86 (14.0%)	8/84 (9.5%)	4.4 [-5.2, 14.1][2]	11/123 (8.9%)	15/138 (10.9%)	-1.9 [-9.2, 5.3][2]
Tricuspid regurgitation moderate or greater	7/86 (8.1%)	8/81 (9.9%)	-1.7 [-10.4, 7.0][2]	26/123 (21.1%)	16/137 (11.7%)	9.5 [0.5, 18.5][2]

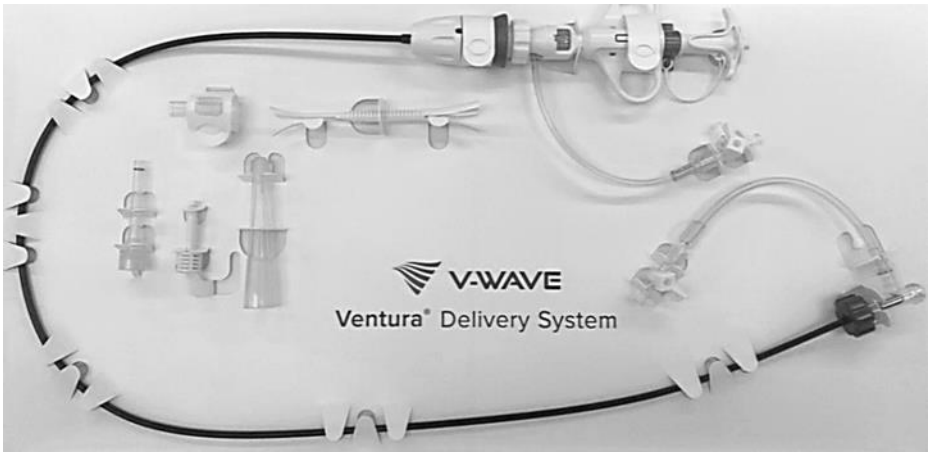
Continuous data are median (interquartile range) or mean ± standard deviation. Left ventricular ejection fraction data are shown both ways.
1. Median difference [interquartile range]; 2. Difference [95% confidence interval].

Figure S1. The Ventura inter-atrial shunt device



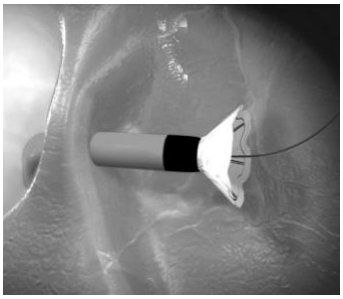
A. Right atrial cone – 11 mm
B. Waist – 5 mm
C. Left atrial cone – 14 mm
D. Length – 12 mm

Ventura Interatrial Shunt

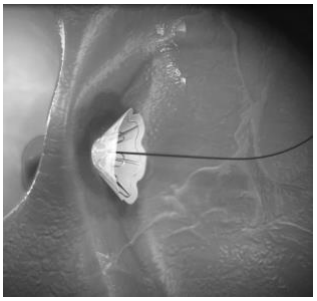


Ventura delivery system

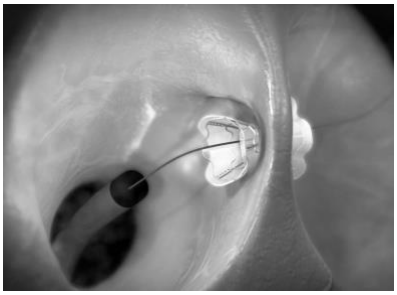
Figure S2. Ventura shunt deployment



a. The left atrial cone is deployed in the left atrium



b. The left atrial cone is retracted against the inter-atrial septum



c. The right atrial cone is deployed and the delivery system is withdrawn

Figure S3. CONSORT diagram of patient flow in the RELIEVE-HF trial

The intention-to-treat population consists of all subjects analyzed in their originally assigned groups as randomized (250 patients assigned to the shunt group and 258 to the placebo-procedure group), regardless of the treatment actually received. The per-protocol population consists of all randomized subjects who met all initial and exclusion criteria and had no major pre-specified protocol deviations. Four patients in the shunt group were excluded from the per-protocol population for the following reasons: inclusion/exclusion criteria not met (n=2) and randomization or enrollment error (n=2). Six patients in the placebo-procedure group were excluded from the per-protocol population for the following reasons: inclusion/exclusion criteria not met (n=3), randomization or enrollment error (n=3), and informed consent issue (n=1).

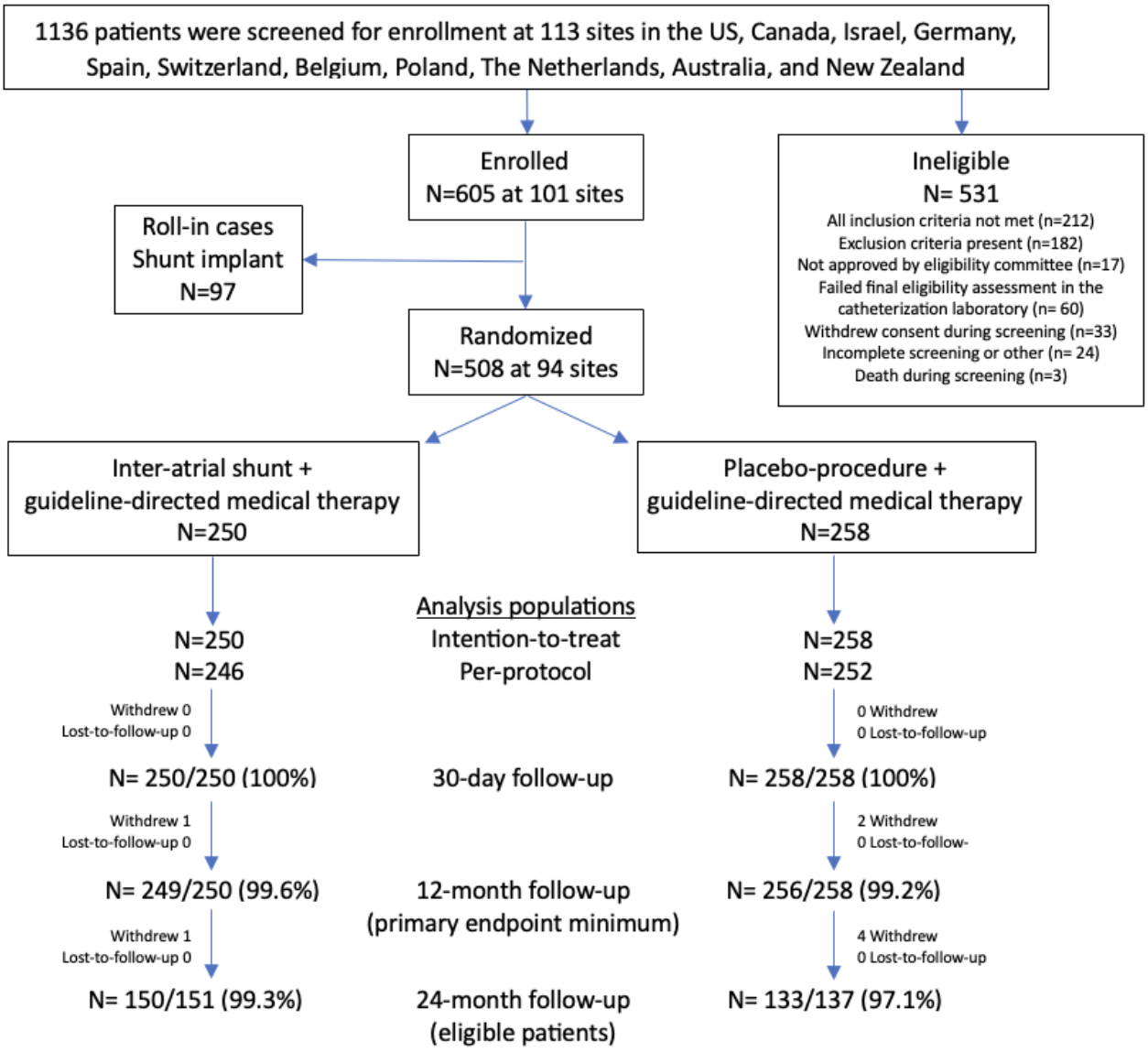


Figure S4. Win ratio analysis for the primary hierarchical composite effectiveness outcome in the full intention-to-treat population

The numbers of wins, losses and ties for all pairs of patients at each level of the win ratio hierarchy are shown, as well as the method for calculation of the win ratio (number of wins in the shunt group divided by number of ties in the shunt group). The 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. *Cui L, Hung HMJ, Wang S-J. Modification of sample size in group sequential clinical trials. Biometrics 1999;55:853-857.

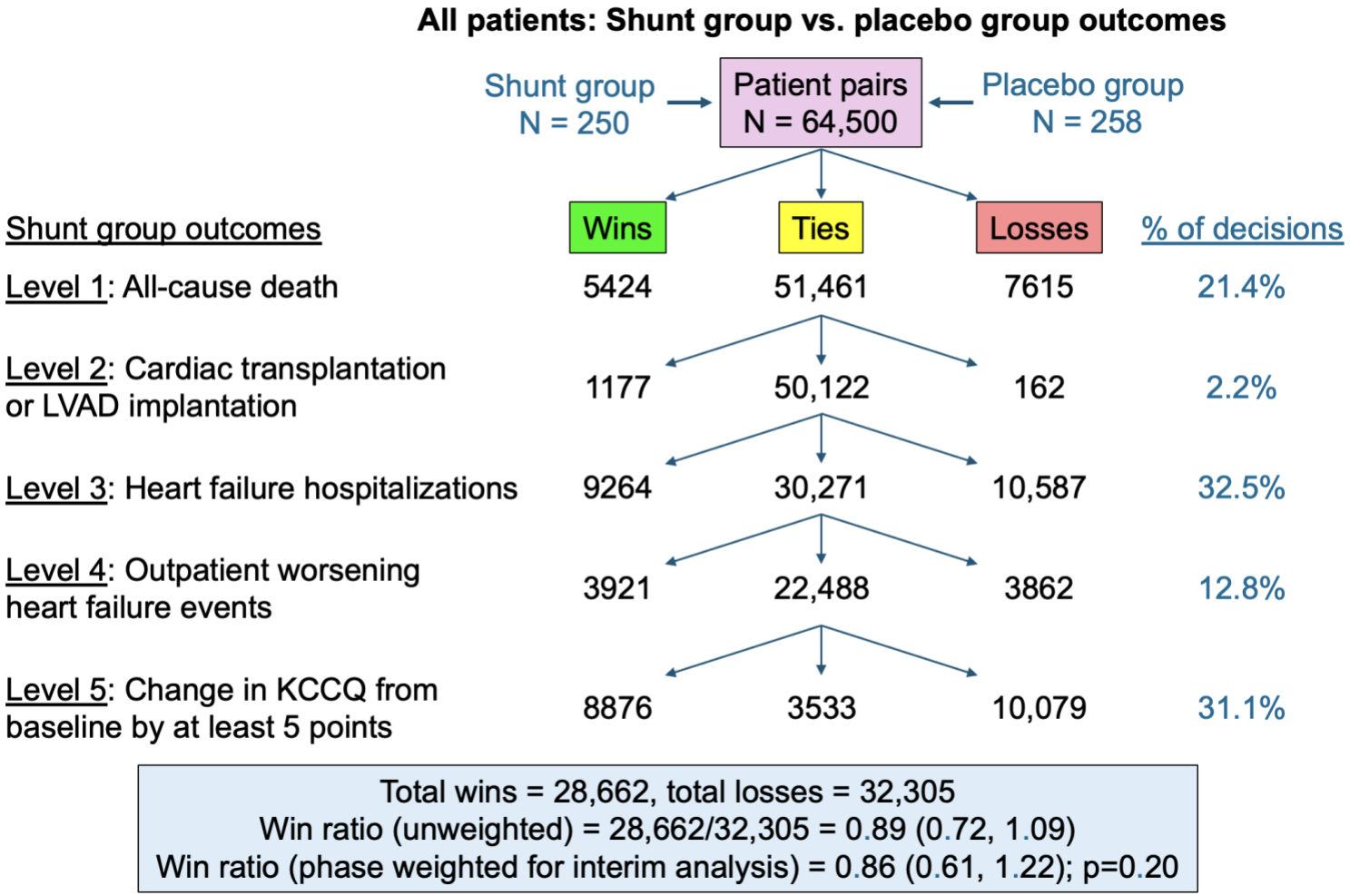


Figure S5. Win ratio analysis for the primary hierarchical composite effectiveness outcome in patients with reduced (≤40%) LVEF

The numbers of wins, losses and ties for all pairs of patients at each level of the win ratio hierarchy are shown, as well as the method for calculation of the win ratio (number of wins in the shunt group divided by number of ties in the shunt group). The 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. LVEF denotes left ventricular ejection fraction. *Cui L, Hung HMJ, Wang S-J. Modification of sample size in group sequential clinical trials. Biometrics 1999;55:853-857.

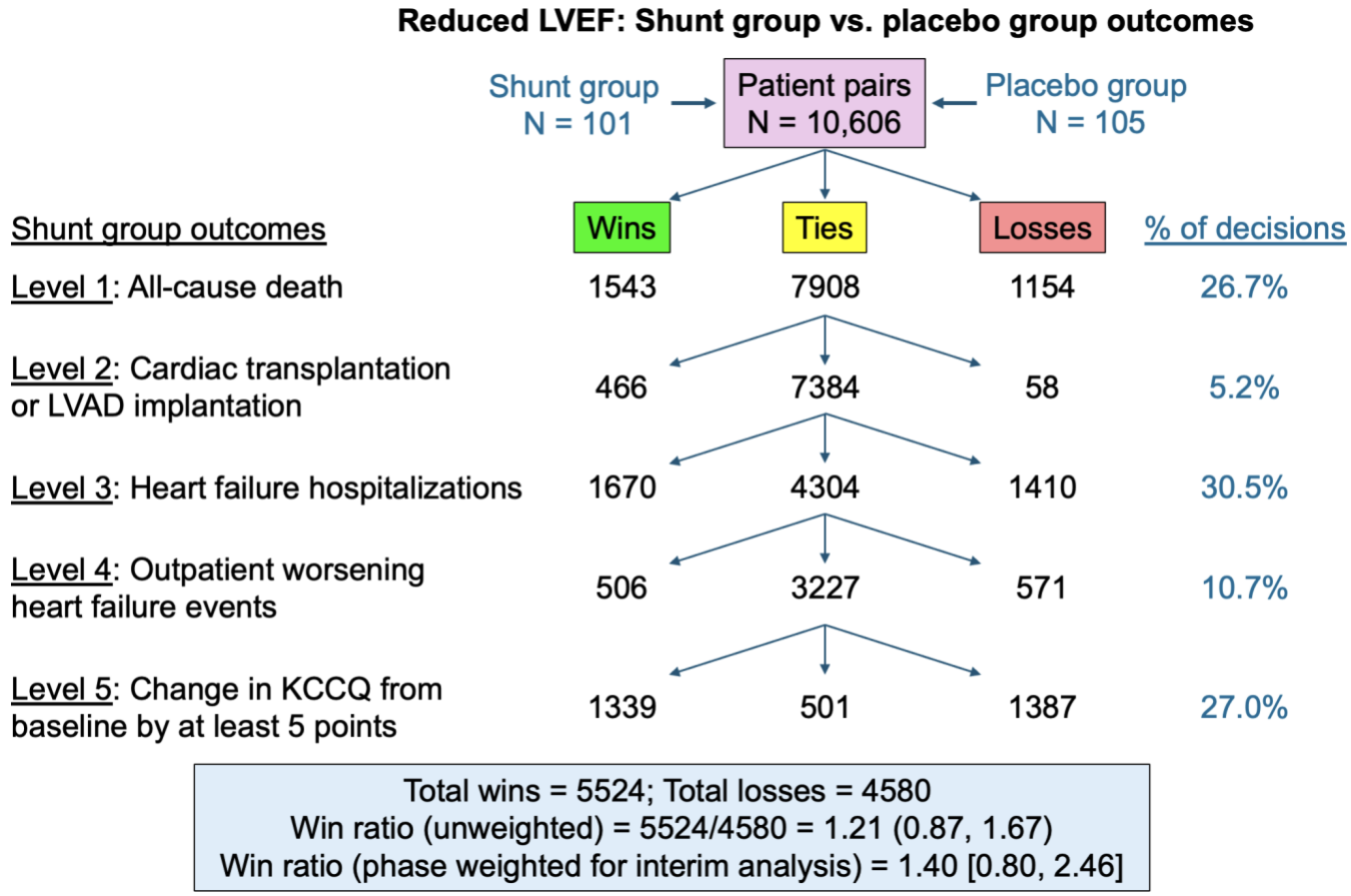


Figure S6. Win ratio analysis for the primary hierarchical composite effectiveness outcome in patients with preserved (>40%) LVEF

The numbers of wins, losses and ties for all pairs of patients at each level of the win ratio hierarchy are shown, as well as the method for calculation of the win ratio (number of wins in the shunt group divided by number of ties in the shunt group). The 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. LVEF denotes left ventricular ejection fraction. *Cui L, Hung HMJ, Wang S-J. Modification of sample size in group sequential clinical trials. Biometrics 1999;55:853-857.

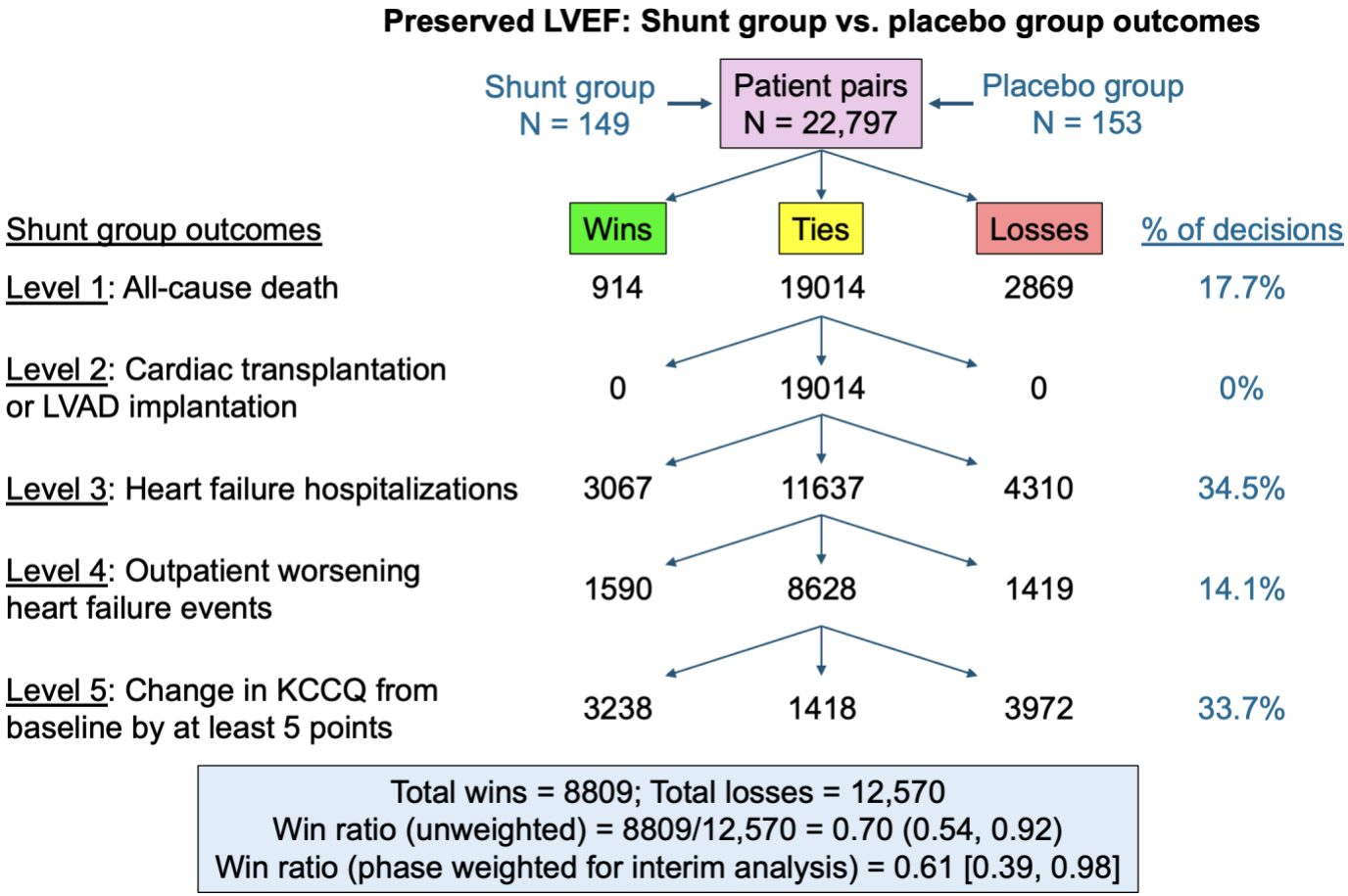


Figure S7. Relationship between the baseline ejection fraction as a continuous measure and the total number of adverse cardiovascular events during follow-up

Differences between Shunt and Placebo (Control) subjects in the number of events per patient per year of follow-up for the four clinical event components of the primary composite effectiveness outcome (death, heart transplant/LVAD, heart failure hospitalizations and worsening outpatient heart failure visits) are plotted across the range of baseline LVEF. 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 a lest 2 Shunt and 2 Placebo values (50 bins). A third-order polynomial curve fit is shown as a solid red line and the dashed red lines indicate 95% CIs. Negative values favor Shunt subjects while positive values favor Placebo subjects. Solid red line represents the point estimate and the dotted red lines represent the 95% confidence intervals. An increasing beneficial effect of shunt treatment is seen as the LVEF declines. Above an LVEF of ~38-40%, the effect of shunt treatment shifts from benefit to harm. However, the point estimate declines above an LVEF of ~60-65%, suggesting less harm with shunt treatment in patients with very high LVEF. However, the confidence intervals are increasingly wide in this range, reflecting the fact that few patients with very high LVEF were randomized. Thus, further study is warranted to determine whether a “falling limb” in this relationship exists, especially given the lack of a mechanistic underpinning for this observation in patients with preserved LVEF. LVAD denotes left ventricular assist device. LVEF denotes left ventricular ejection fraction.

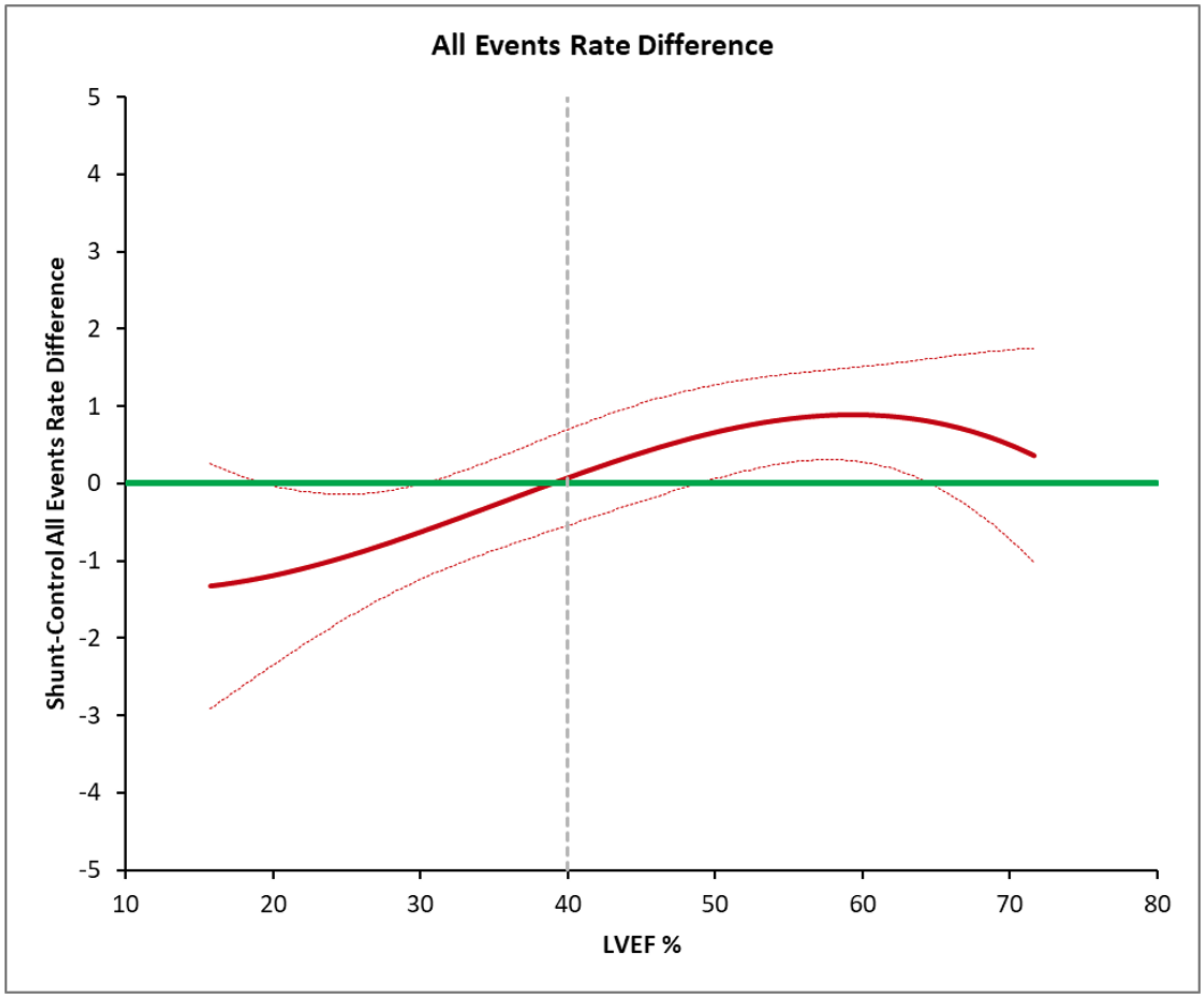


Figure S8. Relationship between the baseline ejection fraction as a continuous measure and the total number of heart failure hospitalizations during follow-up

Differences between Shunt and Placebo (Control) subjects in the number of events per patient per year of follow-up for heart failure hospitalization are plotted across the range of baseline LVEF. 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 a lest 2 Shunt and 2 Placebo values (50 bins). A third-order polynomial curve fit is shown as solid red line and dashed red lines indicate 95% CIs. Negative values favor Shunt subjects while positive values favor Placebo subjects. Solid red line represents the point estimate and the dotted red lines represent the 95% confidence intervals. An increasing beneficial effect of shunt treatment is seen as the LVEF declines. Above an LVEF of ~38-40%, the effect of shunt treatment shifts from benefit to harm. HFH denotes heart failure hospitalization. LVEF denotes left ventricular ejection fraction.

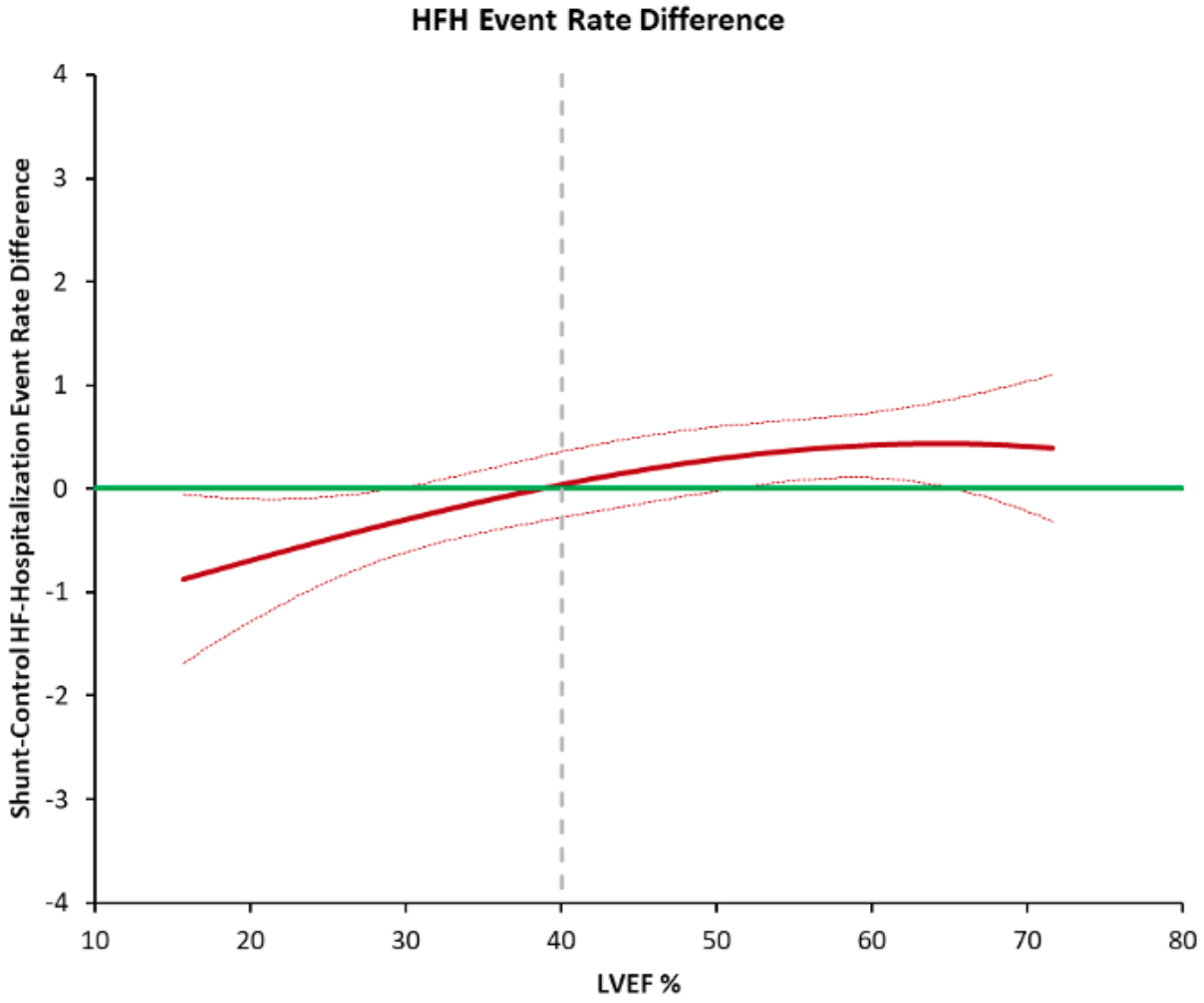


Figure S9. **Echocardiography-based diastolic pressure vs volume compliance analysis**

Mean left atrial volume index (LAVI, a surrogate of diastolic filling pressure)[1] was plotted against mean left ventricular end-diastolic volume index (LVEDVI) in patients with HFrEF (LVEF ≤40%, in dark blue at baseline; in red at 12 months after shunt) and in patients with HFpEF (LVEF >40%, in light blue at baseline; in orange at 12 months after shunt). At baseline, the end-diastolic pressure–volume (EDPV) coordinate was shifted to the left in HFpEF compared with HFrEF indicating lower compliance (increased stiffness) of the LV in HFpEF. In HFrEF patients at 12 months, the shunt resulted in the EDPV coordinate moving down in a compliant fashion. In HFpEF patients the shunt resulted in the EDPV coordinate moving leftward in a non-compliant fashion. The grey curves represent conceptualized relationships between LVEDVI and LAVI from prior experimental observations.[2]

References

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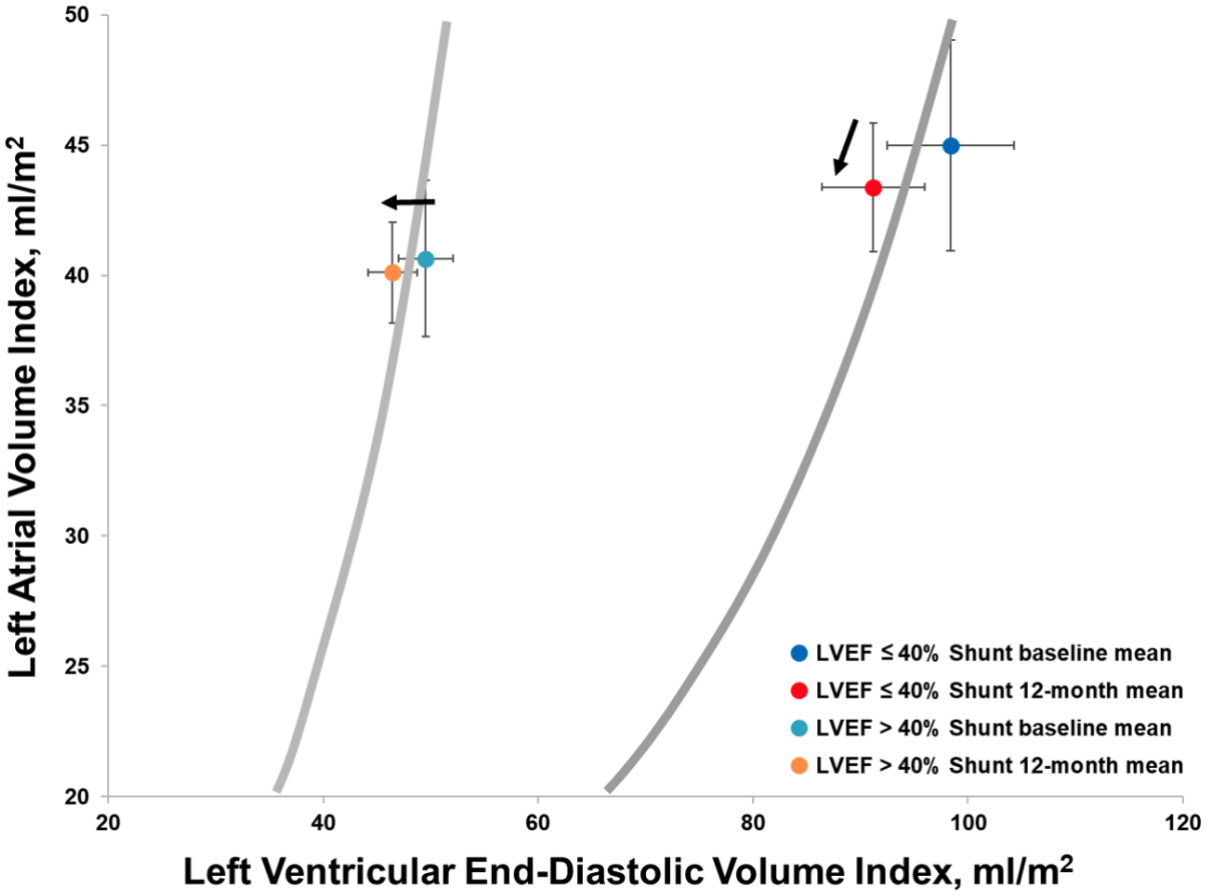

Figure S10. **Echocardiography-based Frank-Starling systolic function analysis**

Mean cardiac index (CI) was plotted against mean left ventricular end-diastolic volume index (LVEDVI, a measure of preload) in patients with HFrEF (EF ≤40%, in dark blue at baseline; in red at 12 months after shunt) and in patients with HFpEF (EF >40%, in light blue at baseline; in orange at 12 months after shunt). In HFrEF patients at 12 months, the shunt resulted in the CI vs LVEDVI relationship moving above (off) the baseline Starling curve (representing improved cardiac performance) vs. in HFpEF patients where the shunt resulted in the CI vs LVEDVI relationship moving down the baseline Starling curve. The grey curves represent conceptualized relationships between LVEDVI and CI from prior experimental observations.[1,2]

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