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## Abstract

**Background:** Right ventricular failure (RVF) is a leading driver of morbidity and mortality after major cardiac surgery for advanced heart failure, including orthotopic heart transplantation and left-ventricular assist device implantation. Inhaled pulmonary-selective vasodilators, such as inhaled epoprostenol (iEPO) and nitric oxide (iNO), are essential therapeutics for the prevention and medical management of postoperative RVF. However, there is limited evidence from clinical trials to guide agent selection despite the significant cost considerations of iNO therapy.

**Methods:** In this double-blinded trial, participants were stratified by assigned surgery and key preoperative prognostic features, then randomized to continuously receive either iEPO or iNO beginning at the time of separation from cardiopulmonary bypass with the continuation of treatment into the intensive care unit stay. The primary outcome was the composite RVF rate

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Supplemental Publication Material
Supplemental Tables and Figures
Supplement 1 – trial protocols
Statistical Analysis Plan
List of INSPIRE-FLO Collaborators

after both operations, defined after transplantation by the initiation of mechanical circulatory support for isolated RVF, and defined after left-ventricular assist device implantation by moderate or severe right heart failure according to criteria from the Interagency Registry for Mechanically-Assisted Circulatory Support. An equivalence margin of fifteen percentage-points was prespecified for between-group RVF risk difference. Secondary postoperative outcomes were assessed for treatment differences and included mechanical ventilation duration; hospital and intensive care unit length of stay during the index hospitalization; acute kidney injury development including renal replacement therapy initiation; and mortality at 30-days, 90-days, and 1-year after surgery.

**Results:** Of 231 randomized participants who met eligibility at the time of surgery, 120 received iEPO and 111 received iNO. Primary outcome occurred in 30 participants (25.0%) in the iEPO group and 25 participants (22.5%) in the iNO group, for a risk difference of 2.5 percentage-points (two one-sided test 90% Confidence Interval, −6.6% to 11.6%) in support of equivalence. There were no significant between-group differences for any of the measured postoperative secondary outcomes.

**Conclusions:** Among patients undergoing major cardiac surgery for advanced heart failure, inhaled pulmonary-selective vasodilator treatment using iEPO was associated with similar risks for RVF development and the development of other postoperative secondary outcomes when compared to treatment with iNO.

**Registration:** URL: https://www.ClinicalTrials.gov; Unique identifier: NCT03081052.

**Keywords (MeSH Terms):**

Cardiovascular Surgical Procedures; Nitric Oxide; Pulmonary Hypertension; Epoprostenol; Heart Transplantation; Heart-Assist Devices

## Introduction

Right ventricular failure (RVF) is a key driver of cardiogenic shock and prolonged convalescence after major cardiac surgery, including orthotopic heart transplantation (OHT)[1] and left-ventricular assist device (LVAD) implantation.[2] While multiple etiologies are responsible for this devastating complication,[3] RV afterload represents a critical and modifiable target for improving RV function during the early postoperative period, when subtle increases in RV afterload can lead to major reductions in cardiac output and organ perfusion.[4,5] For the OHT recipient, RV afterload may be elevated due to chronic precapillary pulmonary hypertension[6] or acute pulmonary vasoconstriction that develops during surgery while on cardiopulmonary bypass.[7,8] Upon separation from cardiopulmonary bypass, the clinical team may lower RV afterload by administering inhaled pulmonary-selective vasodilator (iPVD) therapy to augment RV stroke volume from the transplanted heart that was previously accustomed to low RV afterload in the organ donor.[6,9] Lowering RV afterload augments blood flow to the left ventricle to improve systemic cardiac output.[10] Similarly, a newly implanted LVAD will abruptly augment RV preload through mechanical LV unloading. Thus, RV stroke volume synchronization with mechanical LV unloading is essential for early postoperative hemodynamic stability and can be facilitated by intravenous inotropes and iPVD therapy.[11]

Inhaled PVD therapy, a mainstay in the medical management of postoperative RVF, reduces RV afterload without inducing the systemic hypotension that is observed with intravenous vasodilation. Inhaled therapy is initiated in the operating room and continuously delivered after surgery into the intensive care unit (ICU). The prototypical agent has been inhaled nitric oxide (iNO), which was first administered in critically-ill patients with acute respiratory distress syndrome to improve oxygenation,[12] and later adapted to lower RV afterload to help prevent postoperative RVF. Subsequently, aerosolized prostacyclins, including inhaled epoprostenol (iEPO), were introduced as alternatives to iNO.[13] Notably, iNO and iEPO promote precapillary arteriolar smooth-muscle relaxation through activation of two distinct biochemical pathways[14] and the conceptual benefits of modulating individual pathways often determine clinician preference. Additionally, the direct inhalation of these medications into ventilated alveolar units can reduce RV afterload, improve oxygenation, and promote pulmonary endothelial function.[15]

Despite knowledge regarding the acute hemodynamic and pharmacologic properties of these agents, there is a paucity of long-term randomized data regarding iPVD therapy after major cardiac surgery. The dearth of large, parallel-designed, comparative trials between these agents is also due to the challenges of implementing robust research protocols in complex surgical populations.[16]

Economically, iNO pricing has imposed significant financial pressures on multiple, large healthcare systems[17] leading to the growing use of iEPO as a cost-saving alternative. Thus, we conducted a randomized, double-blinded controlled trial funded by our health system to determine whether iEPO and iNO would lead to similar rates of postoperative RVF development and other outcomes after major cardiac surgery.

## Methods

### Design

In this parallel-designed, clinical trial, participants undergoing OHT or LVAD implantation were stratified and randomly assigned to receive either iNO or iEPO. This investigation is registered as part of the INSPIRE-FLO trial (Clinicaltrials.gov identifier: NCT03081052, protocol available online) which encompasses two separate populations that receive iPVD therapy for different indications and thus have had separate *a priori* statistical analysis plans with two distinct primary outcome measures. Analysis for participants undergoing major cardiac surgery is reported here while a separate analysis in adult lung transplantation has been previously reported.[18] In accordance with the Transparency and Openness Promotion (TOP) guidelines, the data that support the findings of this current study are available from the corresponding author upon reasonable request.

### Funding and Oversight

Research-related activities were funded by Duke University Health System. A separate process was initiated to facilitate coverage of medication costs by health insurance providers. Before trial commencement, blanket insurance approval was obtained from the Centers for Medicare & Medicaid Services (CMS) given that most patients undergoing these

operations were historically insured by CMS. After trial commencement, an enrollment request letter was sent to non-CMS insurance providers to seek approval to enroll eligible patients.

Our Institutional Review Board approved this protocol without a data safety monitoring board because both medications were on formulary and could be used as standard-care outside of the study. All participants or their legally authorized representatives provided written informed consent. Predefined adverse events were reviewed quarterly by the principal investigator and research team while blinded to treatment assignment. All events were reported to the Institutional Review Board.

## Participants

Advanced heart failure patients, 18-years and older, with insurance approval for enrollment were screened for eligibility upon listing for OHT or LVAD implantation. Notable exclusions were combined-organ transplantation, refusal of blood products due to personal or religious preference, congenital heart disease, arrhythmogenic RV cardiomyopathy, and RV assist device present before surgery. Primary LVAD recipients enrolled in the trial could be re-enrolled after postoperative day 90 to undergo an LVAD exchange or OHT. Randomization occurred at the time of consent due to the unpredictable timing of these operations, which could occur during evenings, weekends, or holidays. Therefore, the duration from randomization to treatment initiation could be variable. Participants were included in the primary analysis if they did not develop exclusions between randomization and the start of surgery, did not die before surgery, or were not withdrawn from the trial before the start of surgery. Anonymity of participants was observed in all reporting.

## Trial Procedures

We generated nine randomization strata using the scheduled operation and key preoperative clinical features of the participant. If OHT was scheduled, then participants were stratified by advanced heart failure diagnosis (ischemic cardiomyopathy, nonischemic cardiomyopathy, or other) and by the presence or absence of a previous LVAD implantation (that would have to be explanted if it were present, potentially complicating the operation and course). If LVAD implantation was scheduled, then participants were stratified by primary or exchange LVAD implantation. Participants undergoing primary LVAD implantation were randomized based on LVAD type to be implanted: HeartMate II (Thoratec, Pleasanton, California), HeartMate 3 (Abbott, Abbott Park, Illinois), or HVAD (Heartware/Medtronic, Framingham, Massachusetts). LVAD exchange between any of the LVAD types were grouped together, separate from the primary implant device-type pools (see Supplement 1). Within each stratum, participants were assigned to receive either iNO or iEPO at the time of surgery via 1:1 treatment allocation using block sizes of four. Before trial commencement, randomization sequence was generated by nQuery Advisor® v.7 (Statsols, Inc.). Upon notification that a participant would undergo the scheduled operation, the research team contacted the study respiratory therapist and pharmacist. After accessing the password-protected randomization sequence list, the pharmacist prepared a blinded 50-millilter syringe solution of either 5% sodium chloride (if randomized to iNO) or 30,000 nanograms/ml Epoprostenol (Veletri®, Actelion Pharmaceuticals, South San Francisco,

California). The study respiratory therapist obtained the syringe from pharmacy, verbally confirmed the solution identity with the pharmacist, and placed the syringe in a dedicated refrigerator for the trial. Fifteen minutes before separation from the cardiopulmonary bypass machine, a study respiratory therapist initiated the allocated treatment with resumption of mechanical ventilation.

We used an in-line system for masking iEPO and iNO delivery previously described[19] to preserve the blind for all participants and clinicians involved in patient care (see Supplement 1). Briefly, if patients were randomized to receive iNO, the syringe solution of 5% sodium chloride was programmed for continuous aerosolization and the masked iNO device was programmed to continuously deliver 20 parts-per-million (ppm). If patients were randomized to receive iEPO, the syringe solution of epoprostenol was programmed for continuous delivery and the masked iNO device was programmed to 0 ppm. For both epoprostenol and normal saline solutions, the delivery rate displayed on the syringe pump (Medfusion® 3500, Medfusion Inc., Cary, North Carolina) was programmed at 50 ng/kg/min. After surgery, the study therapist accompanied the clinical-care team to the ICU to ensure appropriate treatment delivery and masking. In the ICU, a non-study respiratory therapist then assumed direct patient care while the study therapist remained immediately available to manage treatment delivery. Protocols for iNO delivery (iNOMax®, Mallinkrodt Pharmaceuticals, St.Louis, Missouri) and the vibrating-mesh aerosolizer (Aerogen Pro-X®, Galway, Ireland) for iEPO delivery were established before trial commencement. Once hemodynamic and oxygenation criteria for discontinuation were achieved, the study therapist weaned each treatment by protocol (see Supplement 1).

We masked the allocated treatment in the electronic record (Maestro-Care®, Epic-Systems, Madison, WI) using a separate clinical documentation platform developed for this study. All research team members with database access were blinded to treatment assignment. Following study completion, an independent statistician created a blinded-treatment assignment code for use during analysis, and the study statistician remained blinded to the assignment until all analyses up to 90-day outcomes were completed.

## Standardized Care for LVAD and OHT Recipients

We have previously described the standardized surgical[20,21] and medical treatment[22,23] for LVAD and OHT recipients at our institution. Relevant protocols for mechanical ventilation and iPVD therapy are included in Supplement 1. Briefly, patients undergo general anesthesia with invasive monitoring and mechanical ventilation in the operating room. Mechanical ventilation is stopped once cardiopulmonary bypass is initiated, to evacuate blood from the heart chambers and to oxygenate and ventilate the patient's cardiac output. Separation from bypass occurs using a combination of transesophageal echocardiography, inotropes, vasopressors, iPVD therapy and mechanical ventilation. After cardiopulmonary bypass, the perioperative team provides additional intravascular volume resuscitation or blood product transfusion according to patient-centered goals.

## Outcomes

The primary outcome was the composite rate of RVF development after both operations. After OHT, the primary outcome was defined by placement of a mechanical circulatory support device for isolated RVF (RV assist device, RVAD, or venoarterial extracorporeal membrane oxygenation, ECMO) within 30-days after surgery.[24] Given the indication for using iPVD therapy, we modified the classic RVF definition after OHT to not exclude precapillary pulmonary hypertension (pulmonary vascular resistance ≥ 3 Wood units, pulmonary capillary wedge pressure < 15 mm Hg) as a cause for RVF in the cardiac allograft. For LVAD implantation, RVF was defined by moderate or severe right-heart failure criteria according to the Interagency Registry for Mechanically-Assisted Circulatory Support (INTERMACS), logically modified to include iEPO as an alternate to iNO.[25] In addition, key hemodynamic endpoints (cardiac index, central venous pressure, pulmonary arterial pressure, mixed venous oxygenation, inotrope scores) were reported while receiving the allocated treatment.

Secondary outcomes included duration of mechanical ventilation measured from ICU arrival to endotracheal extubation or time of tracheostomy placement for those who were not liberated from mechanical ventilation. Acute kidney injury (AKI) incidence and staging were determined by the Kidney Disease-Improving Global Outcomes (KDIGO) criteria modified to use changes in serum creatinine only through postoperative day 10 (see Supplement 1). Other secondary outcomes included initiation of renal replacement therapy (RRT), hospital and ICU lengths-of-stay (LOS), and mortality within 30-days, 90-days, and 1-year after surgery. While blinded to treatment group, the study team reviewed the electronic health record and recorded the perioperative course and cause of death for each patient who died within 1-year after surgery.

Notably, participants were allowed to re-enroll in the trial if they were scheduled for another surgery greater than 90-days after their first index surgery (i.e., primary LVAD recipient scheduled for LVAD exchange or OHT). All relevant components of the analysis accounted for re-enrollments via repeated measures modeling.

All primary and secondary outcomes were hard endpoints, did not require adjudication by a committee, and were determined based on pre-defined criteria by the study statistician (MCW) who was blinded to treatment assignments for all outcomes assessed up to 90-days.

## Statistical Analysis

Details regarding the statistical analysis plan are provided in the supplement and prepared according to journal guidelines.[26] We designed the study for equivalence between iEPO and iNO groups around the primary outcome measure. Using annual operations at our institution for enrollment potential, we anticipated enrolling one LVAD recipient for every two OHT recipients. One factor accounted for in this enrollment ratio was the presence of competing LVAD trials, which did not permit co-enrollment but could provide direct benefits to LVAD recipients during the primary enrollment period of our study.[27,28] Given the higher expected primary outcome rate in LVAD recipients (20%) using pooled estimates from previous LVAD trials[20,27,29] compared with OHT recipients (7%) using pooled estimates from large

observational studies,[30–32] we incorporated this ratio into the sample size determination to arrive at the expected composite primary outcome rate of 11.3% for the iNO group. The expected rate was calculated based on a weighted average of the expected rate within the OHT and LVAD subgroups and the enrollment rates. We prespecified an equivalence margin of 15%, which was derived by using primary outcome rates from previous studies in cardiac surgery that compared iNO with placebo or iNO with iEPO.[29,33,34] As primary outcome assessment was performed during the index hospitalization, sample size was calculated without expected loss to follow-up. We used a *Z*-test with unpooled variance to determine sample size based on equivalence tests for the difference between two proportions (PASS 2020 v20.0.3, power analysis and sample size calculation). Thus, we determined that 224 participants allocated 1:1 to receive either iNO or iEPO would be sufficient to establish equivalence for the prespecified margin with at least 80% power. The α-value was set at 0.05 significance level for all comparisons.

An intention-to-treat analysis was planned for the primary and secondary outcomes, supplemented by per-protocol analysis for the primary outcome. Baseline characteristics for each treatment group were reported as mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables and as count (percentage) for categorical variables. Summaries were used to assess randomization performance and protocol adherence. Using the intention-to-treat and per-protocol populations, we assessed the difference in primary outcome by using the two one-sided test (TOST) procedure to calculate the point estimate and corresponding 90% confidence intervals (CI) for the risk difference between iEPO and iNO. Equivalence would be concluded if the CI of the RVF risk difference between groups were contained within the margin. In addition, we conservatively reported the 95% CI for the risk difference, and relative risk, RR, estimates (95% CI) for RVF development if treated with iEPO compared with iNO. We conducted generalized linear mixed models with a log link and a random intercept term to account for patient re-enrollment in the cohort. A planned adjusted analysis of the intent-to-treat population was performed using surgery type and other baseline covariates found to be out-of-balance between groups ($P<0.15$). Thus, a stepwise, multivariable regression model for RVF using backwards variable selection based on quasi-information criterion (a corollary to Akaike Information Criterion but for generalized repeated measured models) was developed to adjust the treatment difference for these potential confounders.

Secondary outcomes were assessed through 1-year after surgery for treatment differences under typical two-sided null hypothesis-testing to generate effect estimates and corresponding 95% CI. Binary secondary outcomes were assessed via risk differences and RR, while continuous secondary outcomes were assessed via Hodges-Lehmann location shift (nonparametric estimator of differences between groups) and mean ratios estimated from generalized linear mixed models with a log link and random intercept term. Repeated measures analysis was performed to account for re-enrollment. In the event that participants were re-enrolled beyond 90-days but before reaching the 1-year mark after the first index surgery, follow-up for all 1-year outcomes associated with the first surgery were censored at the time of re-enrollment in these participants. As the time between re-enrollment and the treatment of censoring events in binary-outcome models could impact results, we performed a sensitivity analysis for the 1-year mortality outcome using a survival

analysis method called the Andersen Gill (counting-process) model with robust sandwich variance estimator to account for re-enrollments and censoring events. Kaplan-Meier point estimates (95% CI) and hazard ratios, HR, (95% CI) were used to determine differences in mechanical ventilation duration censored for postoperative tracheostomy placement. An additional harms analysis was performed for predefined adverse events and summarized for in-hospital, 30-days, 90-days, and 1-year after surgery. For hemodynamic endpoints, daily comparisons of mean (SD) and median (IQR) values (using t-tests and Wilcoxon rank-sum tests, respectively) were displayed through the upper quartile of treatment duration for each group. Based on the assumption that randomization would balance baseline covariates between treatment groups and that similar clinical criteria would be used for treatment discontinuation, we expected a similar number of participants in each treatment group per day to contribute data for each hemodynamic endpoint. Finally, subanalysis of primary outcome and RV mechanical support stratified by surgery type was performed given the known association of poor outcomes after these operations related to RV mechanical support.[2,30]

Study data were collected and managed using research electronic data capture (REDCap).[35] Analyses were performed using SAS version 9.4 (SAS Institute) and R version 3.6 (R Foundation).

## Results

### Population and Intervention

From May 4, 2017 to September 5, 2020, 605 patients were screened for eligibility. Of these, 306 did not meet eligibility criteria during screening, where 137 patients (44.8%) met exclusion criteria and 169 (55.2%) were eligible but not enrolled for other reasons (Figure 1). Due to changes in eligibility criteria prior to receiving the allocated treatment, we randomized a total of 299 participants to ensure target sample size for the intention-to-treat analysis was achieved. Specifically, 68 patients developed changes to eligibility after randomization before they could receive the allocated treatment (10 developed exclusion criteria, 18 were withdrawn for clinical deterioration or new insurance denial, 14 were withdrawn after subsequent enrollment in LVAD trials that could provide direct benefits but that did not allow co-enrollment with INSPIRE-FLO,[27,28] 15 were awaiting transplantation at study completion, and 11 died before surgery). Of 231 participants that met eligibility criteria at the time of surgery, 120 were allocated to the iEPO group and 111 to the iNO group. Fourteen patients were re-enrolled during the trial (eight patients between 90-days and 1-year from the first surgery and six patients after 1-year from the first surgery). All patients that were re-enrolled met their 90-day follow-up before re-enrollment. None of these patients were re-enrolled more than once. Final 1-year follow-up was performed on September 5, 2021.

Baseline characteristics in the intention-to-treat population are shown in Table 1. The median (IQR) age was 58 years (48–65) in the iEPO group and 59 years (50–65) in the iNO group. Women comprised 29.2% of the iEPO group and 22.5% of the iNO group. African-Americans comprised 39.2% of the iEPO group and 39.6% of the iNO group. Of all participants receiving iEPO, 68 underwent OHT (56.7%) and 52 underwent

LVAD implantation (43.3%). Of those that received iNO, 63 participants underwent OHT (56.8%) and 48 underwent LVAD implantation (43.2%). Donor characteristics were similar between groups that underwent OHT for all key covariates. Planned operations and key prognostic modifiers were similar between treatment groups to indicate success of the stratified randomization. In addition, no difference was found between treatment groups for the duration between randomization and treatment initiation (iEPO, 2 days [1, 9] versus iNO, 3 days [1, 15], $P$=0.34). After randomized treatment initiation, median duration of treatment (iEPO, 78 hours [50–123] vs. iNO, 90 hours [63–141]; $P$=0.16) and delayed chest closure after surgery (iEPO, 35.8% vs. iNO, 32.4%; $P$=0.59) were also similar between groups.

## Outcomes

In the unadjusted intention-to-treat analysis, the composite rate of RVF after major cardiac surgery was 25.0% (n=30) in the iEPO group and 22.5% (n=25) in the iNO group for an absolute risk difference of 2.5 percentage-points (90% CI, −6.6 to 11.2; $P$=0.012 in support of equivalence)(Figure 2). The results of the per-protocol analysis and adjusted intention-to-treat analysis (Tables S1, S2) confirmed the results of the primary analysis (Figure 2).

For secondary outcomes, no significant between-group differences were seen for the median duration of mechanical ventilation (Figure S1, Table 2) or ICU and hospital LOS (Table 2). Additionally, there were no significant between-group differences for rates of tracheostomy placement, AKI development, RRT initiation, or mortality at 30-days, 90-days, and 1-year after surgery (Table 2). Further, we did not find a significant between-group difference in mortality through 1-year when performing the time-to-event sensitivity analysis that accounted for re-enrolled participants (Table S3, HR 2.13, 95% CI, 1.00 to 4.53; $P$=0.051). At 1-year, no important differences were seen in predefined adverse events (Table S4). Mortality review (Tables S5–S7) of 31 patients that died in 1-year after surgery showed that death from RVF occurred in only two LVAD recipients in the iEPO group (Table S7). Patients who had died in both groups displayed a complicated perioperative course with other causes of death including infection, multisystem organ failure, transplant rejection, pulmonary embolism, or stroke (Tables S8–S9). For hemodynamic endpoints, no important differences were seen between treatment groups through postoperative day 6, when the majority of participants had completed the allocated treatment (Figures S2–S7).

**Primary outcome by Surgery Type—**For the intention-to-treat population, primary outcome occurred in 10.3% (7/68) of OHT recipients who received iEPO and in 6.4% (4/63) who received iNO ($P$=0.42)(Table S10). While all of these participants experienced RVAD placement, two individuals (one from each treatment group) received ECMO initially and then were converted to RVAD (Table S11). For LVAD recipients, the primary outcome in the intention-to-treat population occurred in 44.2% (23/52) who received iEPO and in 43.8% (23/52) who received iNO ($P$=0.96)(Table S10). Furthermore, RVAD placement occurred in 9.6% (5/52) of LVAD recipients who received iEPO and in 10.4% (5/48) of those who received iNO(Table S11).

## Discussion

In this prospective randomized controlled trial of adult patients undergoing major cardiac surgery, we found the risk difference between groups to be 2.5% and sufficient evidence to demonstrate that iNO and iEPO treatments were similar for RVF development after major cardiac surgery. No significant between-group differences were observed in duration of mechanical ventilation, ICU and hospital lengths-of-stay, tracheostomy placement, AKI development, RRT initiation, or mortality at 30-days, 90-days, and 1-year after surgery. Moreover, we did not identify important between-group differences in adverse events or hemodynamic endpoints.

While iPVD therapy has been recently repurposed in critically-ill COVID-19 patients to potentially improve oxygenation and protect against RVF from hypoxic pulmonary vasoconstriction,[36] iEPO and iNO have been studied for decades, mainly in small trials or observational studies, in patients undergoing cardiac surgery,[37–39] and specifically in OHT[9,34,40–43] and LVAD implantation.[11,29,44,45] The results of these smaller, negative studies have been compelling and have generated the necessary foundation for the current study. To our knowledge, this current study is the largest blinded, randomized controlled trial addressing whether iEPO is a clinically-equivalent medication to iNO after major cardiac surgery using RVF and other important postoperative outcomes. RVF is an important outcome that could be diagnosed within an established timeframe after these operations. We evaluated the composite rate of RVF development in both operations given the indication for use in our practice for each population. During the design of this trial, actively enrolling LVAD trials, including MOMENTUM-3,[27] precluded co-enrollment. Therefore, we predicted an enrollment ratio of two participants undergoing OHT-to-one participant undergoing LVAD implantation (2 OHT:1 LVAD). However, the observed enrollment of LVAD recipients was higher than expected (4 OHT:3 LVAD). Because the rate of RVF after LVAD was higher than after OHT, the composite rate of RVF was more than twice expected (23.8% observed vs. 11.3% expected).

Equivalence testing was chosen beyond noninferiority as both iPVD medications are commonly used for mitigating the pulmonary hypertensive contribution to RVF after major cardiac surgery. The choice of prespecified margin of equivalence was based on an acceptable potential loss of efficacy with iNO use in exchange for cost-saving gains with iEPO. In addition, fifteen percentage-points remained below the risk difference between placebo and active control, given the best available evidence.

Conducting a randomized, controlled trial blinded to clinicians and participants in this critically-ill, surgical population is incredibly difficult, as we and others have previously outlined.[16,17] Although one of the most important of these challenges is likely protocol adherence, our unadjusted intention-to-treat and per-protocol populations differed by only eight participants (four per group). This high rate of protocol-adherence occurred despite masking the allocated treatments and was facilitated by implementation of protocols for iEPO and iNO delivery (see supplemenatary appendix) that had been refined and optimized over a two-year period leading up to trial commencement. These protocols, including

criteria for discontinuation, were likely contributory to the similar durations of iPVD therapy between treatment groups.

One key component of protocolization was related to filter management within the airway circuit of the ventilator (Figure 3). Adopted from the iEPO administration protocol, a hygroscopic filter was placed in between the expiratory limb of the airway circuit and the expiratory port of the ventilator just before the expiratory valve for all participants. Our institutional practice is to exchange this filter every four hours to avoid moisture accumulation and increased airway resistance. It remains unclear if the extended-stability Veletri® solution demonstrates enough reduced adhesive properties, compared with epoprostenol solutions using the glycine moiety, to avoid using an expiratory-limb filter. That said, moisture buildup (independent of medication properties) within the expiratory limb if left unchecked without a hygroscopic filter could also lead to “sticking” of the expiratory valve, potentially leading to lethal airway pressurization. Therefore, it remains prudent to maintain a competent hygroscopic filter in the expiratory limb. Additionally, we routinely remove the heat and moisture exchange filter that is otherwise situated between the circuit and endotracheal tube to avoid moisture accumulation through either aerosolized saline or epoprostenol that could increase airway resistance.

Notably, the intention-to-treat analysis included participants that had not developed exclusions by the time of surgery. Given the acute nature of these operations, randomization occurred at the time of consent as previously performed in perioperative and ICU comparative effectiveness trials.[46,47] This is because patients could initially present as an outpatient or inpatient, where the study team would then be alerted and have a narrow window to approach an eligible patient. Thus, this potential participant may not return to the heart failure cardiology clinic or hospital until the eve of a potential surgery. Consequently, the intention-to-treat analysis was modified to be pragmatic and to include all participants who had received the allocated treatment as opposed to analyzing all participants as randomized, whereby the effect size would be diluted with participants who did not receive the randomized treatment.[48] The use of a modified intention-to-treat analysis is supported by a recent guideline statement from the American Heart Association for noninferiority trial design in cardiac surgery.[49] This analytical approach is supported in our trial because patients would have received iNO or iEPO whether or not they were enrolled in the trial, and the choice of iPVD agent would have been at the discretion of the perioperative care team rather than the trial randomization process. Another unique source of post-randomization exclusions developed in relation to our insurance pre-approval process. While we successfully collaborated with CMS to pre-approve eligible patients so that their insurance coverage of the hospital stay was not jeopardized by trial enrollment, the pre-approval requests from eligible patients who were insured by private insurance companies resulted in the denial of 119 potential participants. Of these, twelve were initially approved, consented, and randomized, then denied approval and excluded (Figure 1). Although a classic intention-to-treat analysis would have attenuated differences among these twelve patients in the primary analysis, it would not have accounted for the possibility that these patients would not have been treated with the iPVD as randomized but rather determined by the care team with high potential for cross-over to the other treatment arm.

Thus, our approach also reduced the cross-over potential and avoided artificially decreasing the between-group risk difference.

While the mortality signal in our study was not statistically significant ($P>0.05$), participants who received iEPO consistently demonstrated a higher rate of mortality than iNO at in-hospital (9.2% vs. 5.4%), 30-days (5.8% vs. 3.6%), 90-days (10.0% vs. 4.5%), and 1-year (17.9% vs. 9.4%) intervals. Despite performing a sensitivity analysis for the 1-year mortality outcome to account for re-enrolled participants, the mortality signal remained insignificant between treatment groups. Thus, to better characterize this signal, we reviewed all deaths at each interval after the index operation to delineate if circumstances surrounding the cause could be attributed to iPVD assignment and the RVF outcome. Of the two that died from RVF, both underwent LVAD implantation and received iEPO. One of these patients died within 30-days, was supported preoperative with venoarterial ECMO, and required an aortic valve replacement at the time of surgery; defining a highly complicated clinical course. The other participant experienced RVF between 90-days and 1-year of surgery; not early after surgery. Additional review of perioperative courses and causes of death did not suggest a difference between the iEPO and iNO groups, where infectious causes (7 patients vs. 6 patients) and multisystem organ failure (4 patients vs. 3 patients) were the most common. Although the sample size may not have been large enough to find important differences, these findings suggest that mortality was more likely due to various manifestations of critical illness after surgery than iPVD assignment.

### Limitations

Our study has several limitations. First, the funding mechanism for this trial was unique and restricted to our single academic medical center without the ability to broaden to a multicenter investigation. Second, the adjustment model for the intention-to-treat analysis was not prespecified with specific variables. Instead, a stepwise, data-driven approach was used to identify significant modifiers of the primary outcome. While this approach did not account for all sources of confounding, it was part of an *a priori* statistical analysis plan and served to account for the most significant confounders that could have biased results. Third, both LVAD and OHT recipients are at high risk for postoperative RVF due to multifocal causes, which are poorly disambiguated by currently established RVF definitions. For both treatment groups, we modified RVF criteria in OHT recipients to include participants that could have experienced increases in pulmonary vascular resistance as a potential cause for postoperative RVF in the cardiac allograft. While there may be additional causes of RVF after major cardiac surgery that are not manage with iPVD therapy, we found no between-group differences in postoperative RVAD initiation or differences in daily inotrope scores and hemodynamic endpoints while the majority of patients received their randomized treatment, suggesting that these additional causes of RVF were most likely balanced between treatment groups.

## Conclusions

Among patients undergoing major cardiac surgery, inhaled pulmonary-selective vasodilator therapy using iEPO was associated with similar risks for RVF development and the

development of other postoperative secondary outcomes when compared to treatment with iNO.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Non-standard Abbreviations and Acronyms

| | |
|---|---|
| **AKI** | Acute kidney injury |
| **CMS** | Centers for Medicare and Medicaid Services |

| | |
|---|---|
| **ECMO** | Extracorporeal membrane oxygenation |
| **ICU** | Intensive care unit |
| **iEPO** | Inhaled epoprostenol |
| **iNO** | Inhaled nitric oxide |
| **INSPIRE-FLO study** | Inhaled selective pulmonary vasodilators for advanced heart failure therapies and lung transplantation outcomes |
| **INTERMACS** | Interagency registry for mechanically-assisted Circulatory Support |
| **iPVD** | Inhaled pulmonary-selective vasodilator |
| **KDIGO** | Kidney disease-improving global outcomes |
| **LOS** | Length of stay |
| **LVAD** | Left ventricular assist device |
| **OHT** | Orthotopic heart transplant or transplantation |
| **PH** | Pulmonary hypertension |
| **PPM** | Parts-per-million |
| **RRT** | Renal replacement therapy |
| **RV** | Right ventricle or ventricular |
| **RVAD** | Right ventricular assist device |
| **RVF** | Right ventricular failure |
| **TOST** | Two one-sided test |

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## Clinical Perspective

**What is New ?**

- In a double-blind, parallel-design, randomized controlled trial of 231 adult patients undergoing major cardiac surgery, inhaled pulmonary-selective vasodilator treatment with either inhaled epoprostenol or nitric oxide was associated with similar risks for the development of acute postoperative right ventricular failure (RVF).
- No statistical differences were seen between groups for secondary outcomes after surgery, including mechanical ventilation duration, hospital and intensive care unit length of stay for the index hospitalization, acute kidney injury development, renal replacement therapy initiation, or mortality at 30-days, 90-days, and 1-year after treatment.

**What Are the Clinical Implications ?**

- High-grade evidence supports inhaled epoprostenol as similar to nitric oxide for the management of acute postoperative RVF and other outcomes after major cardiac surgery.

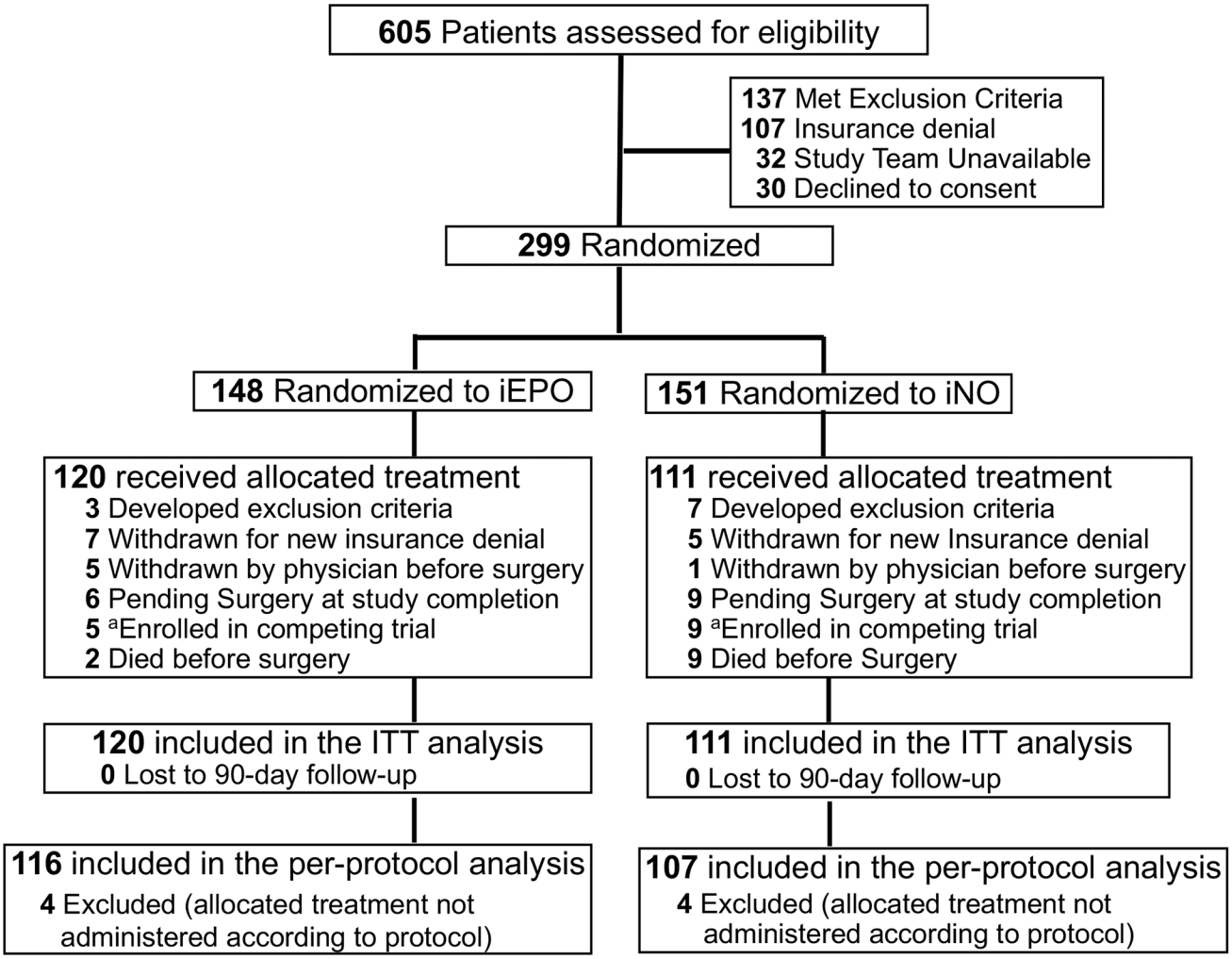
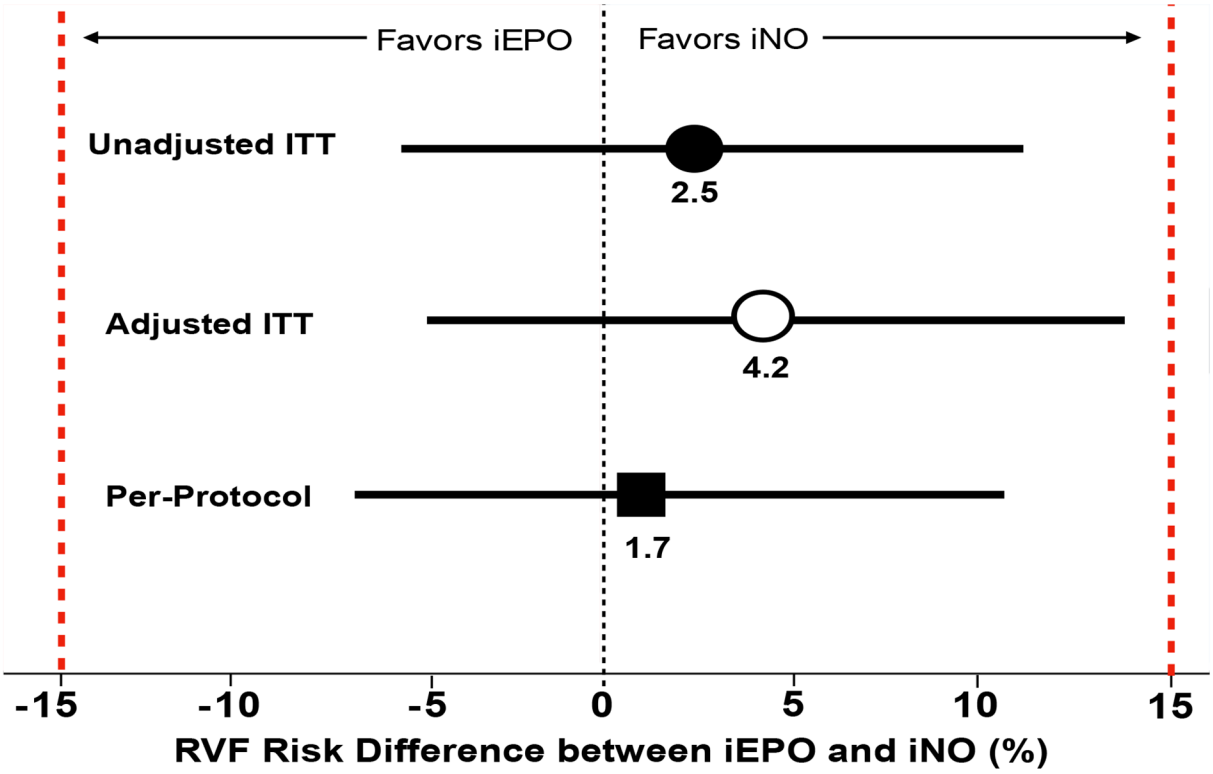



**Figure 1. CONSORT diagram.**

In all analyses, patients were analyzed according to their randomized group. Participants were excluded from the primary analysis if they were withdrawn, developed exclusion criteria after randomization, or remained on the transplant list but were not transplanted before the study completed enrollment. Study enrollment was completed once sample-size was achieved. None of the participants were lost to 90-day follow-up.

*Eligible participants who were initially consented and randomized to INSPIRE-FLO, were awaiting LVAD surgery and found to be eligible for MOMENTUM-3 (NCT02224755, enrollment: September 2, 2014 - September 28, 2018, HeartMate III vs. HeartMate II LVAS for advance heart failure) or TVVAD (NCT03775759, start enrollment: August 22, 2018 and continued after October 2020, tricuspid valve repair vs no repair for moderate or severe tricuspid regurgitation) trials. As these LVAD recipients could potentially benefit from these surgical interventions, they were allowed to enroll in those other trials and were excluded from INSPIRE-FLO due to co-enrollment restrictions.

iEPO, Inhaled epoprostenol; iNO, inhaled nitric oxide; ITT, Intention-to-treat.




| Analysis | Number/Total Number (%) iEPO | iNO | *Risk Difference, % (90% CI) | †Relative Risk (95% CI) |
|---|---|---|---|---|
| ITT | 30/120 (25.0%) | 25/111 (22.5%) | | |
| Unadjusted | | | 2.5 (-6.6, 11.6) | 1.11 (0.70, 1.75) |
| ‡Adjusted | | | 4.2 (-5.2, 13.6) | 1.11 (0.75, 1.66) |
| §Per-Protocol | 28/116 (24.1%) | 24/107 (22.4%) | 1.7 (-7.5, 10.9) | 1.08 (0.67, 1.72) |

**Figure 2. Risk Differences in RVF Development between iNO and iEPO Treatment Groups.**

To determine the presence of clinical equivalence between iNO and iEPO, a lower and upper bounds of −15% and +15% was prespecified (red lines).

*Risk difference is the absolute difference for equivalence and is determined by the two one-sided test procedure using two-sided α of 0.05. Setting α at .05 and testing the upper and lower bounds separately, equivalence is confirmed if both test results are significant. This procedure is then transformed into a single confidence interval, CI, by 1 − 2α (hence, 90% CI). A more conservative 95% CI (1 − α) was used for the unadjusted ITT (−8.3% to 13.3%), adjusted ITT (−7.0% to 15.4%), and per-protocol (−9.2% to 12.6%) analyses.

†Relative risk, RR, is the risk of developing RVF if treated with iEPO compared with iNO

‡Multivariable logistic regression adjusted for operation (Left ventricular assist device implantation versus orthotopic heart transplantation) and preoperative platelet count. Risk difference and RR are derived from the multivariable logistic regression model. Differences between adjusted and unadjusted risk difference and RR were due to the difference in

comparing two patients in the adjusted analysis with the same surgery type (LVAD or OHT) and preoperative platelet count. Number of events and their distribution between the unadjusted and adjusted analyses remained the same.

§There were eight patients (four per treatment group) for whom the allocated treatment was not weaned per-protocol. Seven of these patients underwent orthotopic heart transplantation and one underwent LVAD implantation.

ITT, Intention-to-treat; RVF, Right ventricular failure.

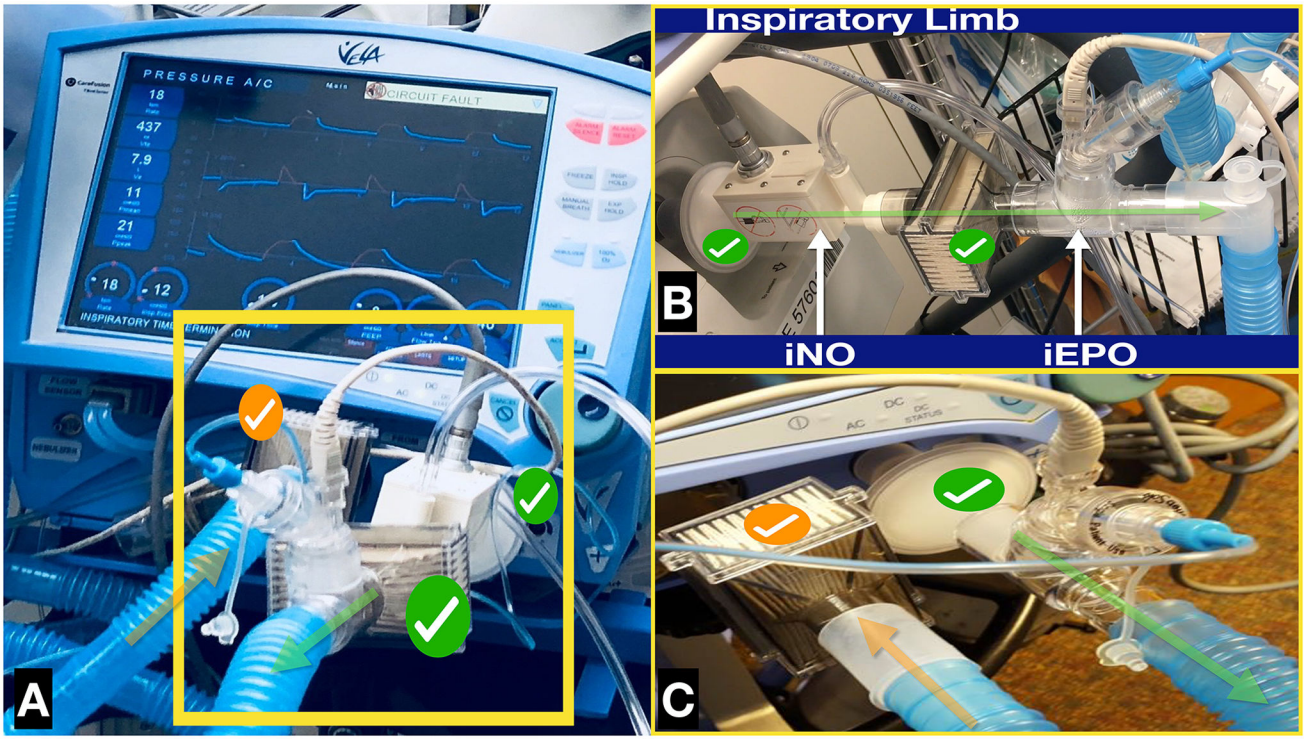



**Figure 3. Airway filter placement during mechanical ventilation for both iEPO and iNO delivery.**

**A**. A transport ventilator is displayed, with inspiratory limb of circuit containing filters labeled with green checkmarks and the expiratory limb of the circuit returning to the ventilator containing a single filter labeled with an orange checkmark. This filter placement paradigm was applied to ventilators in the operating room, for transport, and in the intensive care unit.

**B**. The intensive care unit ventilator is displayed, with inspiratory limb showing a filter placed between the inspiratory port and in-line iNO delivery device as well as one placed between the in-line iNO and iEPO delivery devices. **C**. Adopted from the iEPO delivery protocol (see Supplement 1), filters between the ventilator and the inspiratory and expiratory limbs of the ventilator circuit are displayed.

**Table 1.**

Baseline Participant Characteristics

| | iEPO (N=120)* | iNO (N=111)* |
|---|---|---|
| **Patient Demographics and History** | | |
| Age, years | 58 [48, 65] | 59 [50, 65] |
| Sex (Male) | 85 (70.8%) | 86 (77.5%) |
| Race | | |
| African American | 47 (39.2%) | 44 (39.6%) |
| Caucasian/ White | 72 (60.0%) | 66 (59.5%) |
| Other | 1 (0.8%) | 1 (0.8%) |
| BMI | 28.7 [24.5, 33.0] | 29.4 [25.1, 33.1] |
| NYHA classification (class III/IV) | 85 (70.8%) | 87 (78.4%) |
| INTERMACS profile, Primary LVAD only | | |
| INTERMACS 1–3 | 32 (86.5%) | 34 (94.4%) |
| INTERMACS 4–7 | 5 (13.5%) | 2 (5.6%) |
| Previous CABG or Valve surgery | 30 (25.0%) | 30 (27.0%) |
| Previous Sternotomy | 57 (47.5%) | 50 (45.9%) |
| Previous Percutaneous Coronary Intervention | 35 (29.2%) | 35 (31.5%) |
| Atrial Fibrillation | 71 (59.2%) | 62 (55.9%) |
| CVA/Stroke | 27 (22.5%) | 13 (11.7%) |
| Inotrope use before surgery | 40 (33.3%) | 29 (26.1%) |
| IABP Counterpulsation | 49 (40.8%) | 53 (47.7%) |
| Peripheral vascular disease | 12 (10.0%) | 9 (8.1%) |
| Essential Hypertension | 89 (74.2%) | 83 (74.8%) |
| Diabetes Mellitus | 51 (42.5%) | 41 (36.9%) |
| Liver disease (non-cardiac) | 20 (16.7%) | 12 (10.8%) |
| Congestive hepatopathy (cardiac-related) | 17 (14.3%) | 8 (7.2%) |
| COPD | 23 (19.2%) | 21 (18.9%) |
| Asthma | 10 (8.3%) | 9 (8.1%) |
| Venous Thromboembolic Disease | 24 (20.0%) | 26 (23.4%) |
| †Preoperative PH (mPAP>20 mm Hg) | | |
| Pre-capillary PH (PVR ≥3 WU, PCWP ≤15 mm Hg) | 6 (5.0%) | 3 (2.7%) |
| Post-capillary PH (PVR <3 WU, PCWP >15 mmHg) | 45 (37.5%) | 45 (40.5%) |
| Pre-/Post-capillary PH (PVR ≥3 WU, PCWP >15 mmHg) | 42 (35.0%) | 32 (28.8%) |
| Unknown (missing data) | 4 (3.3%) | 6 (5.4%) |
| **Right Heart Catheterization Values Before Surgery** | | |
| Cardiac Index (L/min/m$^2$) | 2.0 [1.7, 2.4] | 2.0 [1.6, 2.5] |
| Right atrial pressure (mm Hg) | 10 [7, 14] | 12 [7, 17] |
| PVR (Wood unit) | 2.7 [1.8, 3.8] | 2.4 [1.5, 3.6] |

| | iEPO (N=120)* | iNO (N=111)* |
|---|---|---|
| PCWP (mm Hg) | 23 [16, 27] | 22 [16, 30] |
| Mean PAP (mm Hg) | 30 [25, 36] | 30 [23, 38] |
| **Preoperative Laboratory Values** | | |
| Hemoglobin (g/dL) | 11.6 [9.9, 12.9] | 11.7 [10.1, 12.8] |
| Platelet Count (× $10^3$ per μL) | 202 [155, 246] | 175 [137, 225] |
| International Normalized Ratio (INR) | 1.3 [1.1, 1.6] | 1.3 [1.2, 1.5] |
| Activated Partial Thromboplastin Time (aPTT) (seconds) | 54.7 [35.6, 71.8] | 59.3 [38.1, 69.4] |
| Serum Creatinine (mg/dL) | 1.2 [1.0, 1.5] | 1.2 [1.0, 1.6] |
| Estimated GFR, eGFR (ml/min) | 67 [53, 86] | 67 [48, 88] |
| ‡Chronic Kidney Disease staging by eGFR | | |
| Stage 1 | 25 (20.8%) | 26 (23.4%) |
| Stage 2 | 52 (43.3%) | 40 (36.0%) |
| Stage 3 | 38 (31.7%) | 40 (36.0%) |
| Stage 4 | 4 (3.3%) | 5 (4.5%) |
| Stage 5 | 1 (0.8%) | 0 (0.0%) |
| Class 1 PRA > 0 (OHT recipients only) | 14 (11.7%) | 13 (11.7%) |
| Class 1 PRA % (among those >0) | 16 [6, 26] | 20 [9, 54] |
| Class 2 PRA > 0 (OHT Recipients only) | 7 (5.8%) | 12 (10.8%) |
| Class 2 PRA % (among those > 0) | 45 [9, 63] | 49 [11, 52] |
| **Procedural Characteristics** | | |
| §Orthotopic Heart Transplantation | 68 (56.7%) | 63 (56.8%) |
| Ischemic CM with LVAD | 8 (6.7%) | 9 (8.1%) |
| Ischemic CM without LVAD | 11 (9.2%) | 11 (9.9%) |
| NICM with LVAD | 12 (10.0%) | 11 (9.9%) |
| NICM without LVAD | 33 (27.5%) | 29 (26.1%) |
| Other diagnosis | 4 (3.3%) | 3 (2.7%) |
| §LVAD Implantation | 52 (43.3%) | 48 (43.2%) |
| HeartMate 3 | 29 (24.2%) | 28 (25.2%) |
| HeartWare | 8 (6.7%) | 6 (5.4%) |
| HeartMate 2 | 0 (0.0%) | 2 (1.8%) |
| LVAD Exchange | 15 (12.5%) | 12 (10.8%) |
| ‖Additional Cardiac Operations | | |
| Tricuspid valve repair or replacement | 8 (6.7%) | 8 (7.2%) |
| Mitral valve repair or replacement | 1 (0.8%) | 1 (0.9%) |
| Aortic valve replacement or Park stitch | 7 (5.8%) | 5 (4.5%) |
| Closure of ASD or PFO | 22 (18.3%) | 16 (14.4%) |
| CPB time (minutes) | 176 [139, 220] | 182 [128, 212] |
| #Transfusion Volume during index surgery (mL) | 863 [339, 1733] | 700 [220, 1717] |

| | iEPO (N=120)* | iNO (N=111)* |
|---|---|---|
| **Donor Characteristics for Orthotopic Heart Transplant recipients** | | |
| Age | 32 [27, 38] | 32 [27, 41] |
| Sex donor-recipient mismatch | 12 (10.0%) | 12 (10.8%) |
| Race | | |
| Caucasian/White | 47 (72.3%) | 47 (74.6%) |
| African American/Black | 10 (15.4%) | 10 (15.9%) |
| Other | 8 (12.3%) | 6 (9.5%) |
| BMI donor-recipient % mismatch | 5.54 (28.36) | 8.08 (22.29) |
| Cause of Death | | |
| Anoxia | 40 (61.5%) | 27 (42.9%) |
| CVA | 5 (7.7%) | 11 (17.5%) |
| Head Trauma | 19 (29.2%) | 24 (38.1%) |
| Other | 1 (1.5%) | 1 (1.6%) |
| Donor cigarette use > 20 pack years | 13 (20.6%) | 12 (19.0%) |
| Donor type | | |
| Donation after brain death | 64 (95.5%) | 57 (90.5%) |
| Donation after cardiac death | 3 (4.5%) | 6 (9.5%) |
| Donor LVEF | 60 [55, 65] | 60 [55, 65] |
| Cold ischemia time (minutes) | 162 [93, 198] | 170 [97, 202] |
| Use of TransMedics Organ Care System Heart™ | 20 (29.4%) | 18 (28.6%) |

*Parameters presented as median [Q1, Q3], mean (SD), or N (%)

†PH diagnosis may include isolated postcapillary or combined pre and postcapillary PH[50]

‡CKD Epi Cr equation

§Randomization strata provided according to operation and diagnosis for surgery. Other diagnosis indicates advanced heart failure that could not be otherwise categorized (repeat OHT without previous acute allograft rejection, n=2; cardiac amyloidosis, n=1; cardiac sarcoidosis, n=1; hypertrophic obstructive cardiomyopathy, n=2; restrictive cardiomyopathy, n=1).

‖Additional operations mainly performed in LVAD implantation.

#Includes all allogeneic units of PRBC, FFP, cryoprecipitate, and platelets.

Abbreviations: ASD, Atrial septal defect; BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; CPB; Cardiopulmonary bypass; CVA, Cerebrovascular accident; Fresh frozen plasma, FFP; GFR, glomerular filtration rate; IABP, Intra-aortic balloon pump; LVEF, Left ventricular ejection fraction; OHT, Orthotopic heart transplant or transplantation; OCS, Organ care system; PAP, pulmonary arterial pressure; PCWP, Pulmonary capillary wedge pressure; PFO, Patent foramen ovale; PRBC, Packed red blood cell; PVR, pulmonary vascular resistance; PRA, panel-reactive antibody.

**Table 2.**

Secondary Outcomes

| Outcome | iEPO (N=120)* | iNO (N=111)* | RD, % (90% CI) | †RR(95% CI) | *P* value |
|---|---|---|---|---|---|
| Mortality | | | | | |
| In-Hospital | 11 (9.2%) | 6 (5.4%) | 3.8 (−3.0, 10.0) | 1.70 (0.65, 4.45) | 0.28 |
| 30-day | 7 (5.8%) | 4 (3.6%) | 2.2 (−3.0, 8.0) | 1.62 (0.49, 5.38) | 0.43 |
| 90-day | 12 (10.0%) | 5 (4.5%) | 5.5 (−1.0, 12.0) | 2.22 (0.81, 6.10) | 0.12 |
| ‡1-year | 21/117 (17.9%) | 10/106 (9.4%) | 8.5 (−0.4, 17.4) | 1.90 (0.94, 3.85) | 0.07 |
| §AKI stages 2 or 3 | 34 (28.3%) | 39 (35.1%) | −6.8 (−19.0, 5.0) | 0.81 (0.55, 1.17) | 0.26 |
| Renal Replacement Therapy | 19 (15.8%) | 22 (19.8%) | −4.0 (−14.0, 6.0) | 0.80 (0.46, 1.40) | 0.43 |
| Discharge on New Dialysis | 9 (7.5%) | 7 (6.3%) | 1.221 (−5.0, 8.0) | 1.19 (0.45, 3.11) | 0.72 |
| Tracheostomy Placement | 15 (12.5%) | 8 (7.2%) | 5.3 (−2.5, 12.9) | 1.72 (0.76, 3.90) | 0.20 |
| ‖Duration of mechanical ventilation, Kaplan-Meier estimate, median (95%CI), hours | 26.1 [18.0, 37.1] | 26.3 [19.5, 34.4] | NA | NA | 0.64[f] |
| | | | ****HL Location Shift (95% CI)** | **Mean Ratio (95% CI)** | |
| ICU LOS (days) | 6 [4, 11] | 6 [4, 11] | 0 (−1, 1) | 0.94 (0.57, 1.56) | 0.82 |
| Hospital LOS (days) | 17 [11, 28] | 16 [12, 30] | 1 (−2, 3) | 0.97 (0.73, 1.28) | 0.83 |

*Parameters presented as median [Q1, Q3], mean (SD), or N (%)

†Relative Risk (with *P* values) of developing the outcome if participants receive iEPO compared with iNO.

‡For participants who re-enrolled between 90-days and 1-year after the initial index surgery, only the events that occurred after the second index surgery were included in 1-year mortality rates. This approach impacted 3 participants in the iEPO group and 5 participants in the iNO group.

§Acute Kidney Injury grading by Kidney Disease Improving Global Outcomes.

‖Measured for those who received postoperative tracheostomy, time to extubation was censored at the time of tracheostomy placement to avoid underestimating the distribution of time to end of mechanical ventilation.

#Log-rank *P* value

**Hodges-Lehmann (HL) non-parametric difference estimator was used to provide an estimate of effect size between groups (similar to a standardized difference) given the non-Gaussian distribution. The *p*-values arise from the traditional Wilcoxon tests and the HL estimator is simply used to estimate magnitude of difference.

AKI, Acute kidney injury; CI, Confidence interval; h, hours; K-M, Kaplan-Meier; LOS, Length-of-stay, RD, Risk difference; RR, Relative risk.