Circulation

ORIGINAL RESEARCH ARTICLE

Inhaled Epoprostenol Compared With Nitric Oxide for Right Ventricular Support After Major Cardiac Surgery

Kamrouz Ghadimi, MD, MHS; Jhaymie L. Cappiello, RRT; Mary Cooter Wright, MS; Jerrold H. Levy, MD; Benjamin S. Bryner, MD, MS; Adam D. DeVore, MD, MHS; Jacob N. Schroder, MD; Chetan B. Patel, MD; Sudarshan Rajagopal, MD, PhD; Svati H. Shah, MD, MS, MHS; Carmelo A. Milano, MD; for the INSPIRE-FLO Investigators.

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-blind 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 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 15 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% CI, −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 development of other postoperative secondary outcomes compared with treatment using iNO.

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

Key Words: cardiovascular surgical procedures ■ epoprostenol ■ heart-assist devices ■ heart transplantation ■ hypertension, pulmonary ■ nitric oxide

Circulation
FIRST PROOF ONLY

Downloaded from http://ahajournals.org by on July 5, 2023

Correspondence to: Kamrouz Ghadimi, MD, MHS, Clinical Research Unit, Department of Anesthesiology, Duke University School of Medicine, Box DUMC 3094, Durham, NC 27710. Email kamrouz.ghadimi@duke.edu
This manuscript was sent to Vallerie V. McLaughlin, MD, guest editor, for review by expert referees, editorial decision, and final disposition.
Supplemental Material is available at: https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.122.062464
For Sources of Funding and Disclosures, see page XXX.
© 2023 American Heart Association, Inc.
Circulation is available at www.ahajournals.org/journal/circ

ORIGINAL RESEARCH ARTICLE

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.
- 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 right ventricular failure and other outcomes after major cardiac surgery.

Nonstandard Abbreviations and Acronyms

CMS	Centers for Medicare & Medicaid Services
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
LVAD	left ventricular assist device
OHT	orthotopic heart transplant or transplantation
RV	right ventricle or ventricular
RVAD	right ventricular assist device
RVF	right ventricular failure

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] Although multiple causes are responsible for this devastating complication,[3] right ventricular (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] On 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] Likewise, 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 in 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. Aerosolized prostacyclins, including inhaled epoprostenol (iEPO), were subsequently introduced as alternatives to iNO.[13] It is notable that iNO and iEPO promote precapillary arteriolar smooth-muscle relaxation through activation of 2 distinct biochemical pathways,[14] and the conceptual benefits of modulating individual pathways often determine clinician preference. In addition, 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 pharmacological 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 health care systems,[17] leading to the growing use of iEPO as a

Downloaded from http://ahajournals.org by on July 5, 2023

cost-saving alternative. Thus, we conducted a randomized, double-blind 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 (Inhaled Selective Pulmonary Vasodilators for Advanced Heart Failure Therapies and Lung Transplantation Outcomes; URL: https://www.Clinicaltrials.gov; Unique identifier: NCT03081052; protocol available online) that encompasses 2 separate populations who receive iPVD therapy for different indications and thus have had separate a priori statistical analysis plans with 2 distinct primary outcome measures. Analysis for participants undergoing major cardiac surgery is reported here, whereas a separate analysis in adult lung transplantation has been reported previously.[18] In accordance with the Transparency and Openness Promotion guidelines, the data that support the findings of this current study are available from the corresponding author on reasonable request.

Funding and Oversight

Research-related activities were funded by the 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 the 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

Patients with advanced heart failure, ≥18 years of age, with insurance approval for enrollment were screened for eligibility on 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 9 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 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 on the basis of LVAD type to be implanted: HeartMate II (Thoratec, Pleasanton, CA), HeartMate 3 (Abbott, Abbott Park, IL), or HVAD (Heartware/Medtronic, Framingham, MA). LVAD exchange between any of the LVAD types were grouped together, separate from the primary implant device-type pools (Supplement 1). Within each stratum, participants were assigned to receive either iNO or iEPO at the time of surgery through 1:1 treatment allocation using block sizes of 4. 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-mL syringe solution of either 5% sodium chloride (if randomized to iNO) or 30 000 ng/mL epoprostenol (Veletri, Actelion Pharmaceuticals, South San Francisco, CA). The study respiratory therapist obtained the syringe from the 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 blinding for all participants and clinicians involved in patient care (see Supplement 1). In brief, 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 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, NC) was programmed at 50 $ng \cdot kg^{-1} \cdot min^{-1}$. After surgery, the study therapist accompanied the clinical care team to the ICU to ensure appropriate treatment delivery and masking. In the ICU, a nonstudy 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, MO) and the

Circulation PROOF ONLY

Downloaded from http://ahajournals.org by on July 5, 2023

vibrating-mesh aerosolizer (Aerogen Pro-X, Galway, Ireland) for iEPO delivery were established before trial commencement. After 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. After 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 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. In brief, patients undergo general anesthesia with invasive monitoring and mechanical ventilation in the operating room. Mechanical ventilation is stopped after 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) 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 and 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 INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support), logically modified to include iEPO as an alternate to iNO.[25] In addition, key hemodynamic end points (cardiac index, central venous pressure, pulmonary arterial pressure, mixed venous oxygenation, and inotrope scores) were reported while the patient was 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 incidence and staging were determined by the Kidney Disease Improving Global Outcomes 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, hospital and ICU lengths of stay, 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.

Participants were allowed to re-enroll in the trial if they were scheduled for another surgery >90 days after their first index surgery (ie, primary LVAD recipient scheduled for LVAD exchange or OHT). All relevant components of the analysis accounted for re-enrollments through repeated measures modeling.

All primary and secondary outcomes were hard end points, did not require adjudication by a committee, and were determined based on predefined criteria by the study statistician (M.C.W.), 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 Supplemental Material 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 1 LVAD recipient for every 2 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] Because 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 2 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±SD or median (interquartile range) 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

Circulation
FIRST PROOF—ONLY

Downloaded from http://ahajournals.org by on July 5, 2023

the difference in primary outcome by using the two one-sided test procedure to calculate the point estimate and corresponding 90% CIs for the risk difference between iEPO and iNO. Equivalence would be concluded if the CI of the RVF risk difference between groups was contained within the margin. In addition, we conservatively reported the 95% CI for the risk difference and relative risk 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 backward variable selection based on the 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 2-sided null hypothesis testing to generate effect estimates and corresponding 95% CIs. Binary secondary outcomes were assessed through risk differences and relative risk, whereas continuous secondary outcomes were assessed through Hodges-Lehmann location shift (nonparametric estimator of differences between groups), and mean ratios were 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 was censored at the time of re-enrollment of these participants. Because the time between re-enrollment and the treatment of censoring events in binary-outcome models could affect 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 (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 and 30 days, 90 days, and 1 year after surgery. For hemodynamic end points, daily comparisons of mean±SD and median (interquartile range) 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 end point. 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, of whom 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 before receiving the allocated treatment, we randomly assigned a total of 299 participants to ensure that target sample size for the intention-to-treat analysis was achieved. In particular, 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 who met eligibility criteria at the time of surgery, 120 were allocated to the iEPO group, and 111 were allocated to the iNO group. Fourteen patients were re-enrolled during the trial (8 patients between 90 days and 1 year after the first surgery and 6 patients after 1 year from the first surgery). All patients who 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 (interquartile range) 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. Black patients 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 participants who received iNO, 63 underwent OHT (56.8%), and 48 underwent LVAD implantation (43.2%). Donor characteristics were similar between groups who underwent OHT for all key covariates. Planned operations and key prognostic modifiers were similar between treatment groups to indicate the 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] versus iNO, 90 hours [63–141]; $P=0.16$) and delayed chest closure after surgery (iEPO, 35.8% versus 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%

Downloaded from http://ahajournals.org by on July 5, 2023

Circulation FIRST PROOF ONLY

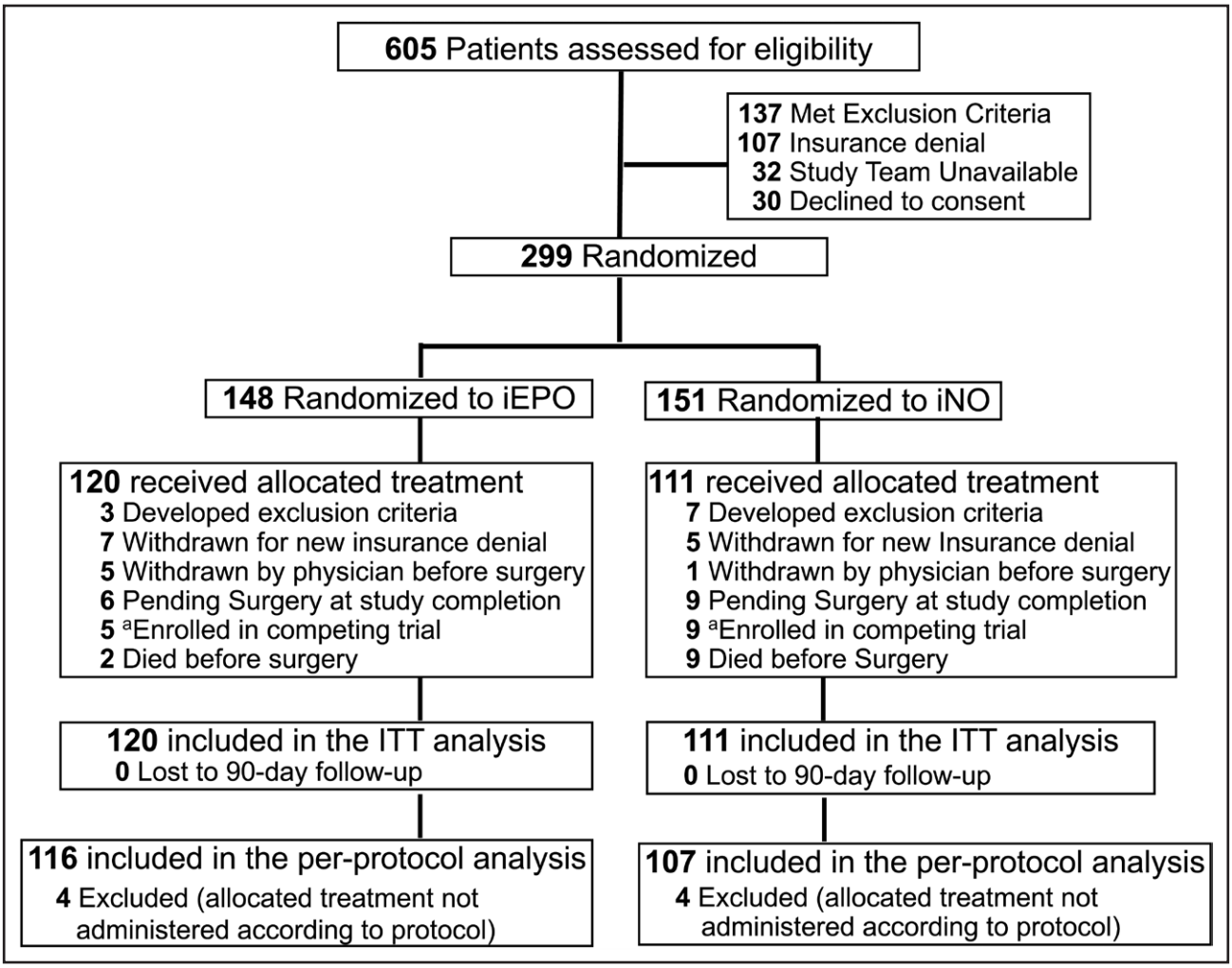


Figure 1. CONSORT diagram.
In all analyses, patients were analyzed according to their randomly assigned group. Participants were excluded from the primary analysis if they were withdrawn, developed exclusion criteria after randomization, or remained on the transplant list but did not receive transplants before the study completed enrollment. Study enrollment was completed after sample size was achieved. None of the participants were lost to 90-day follow-up. *Eligible participants who initially provided consent and were randomly assigned to the INSPIRE-FLO trial (Inhaled Selective Pulmonary Vasodilators for Advanced Heart Failure Therapies and Lung Transplantation Outcomes) were awaiting left ventricular assist device surgery and were found to be eligible for the MOMENTUM-3 trial (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3; NCT02224755; enrollment September 2, 2014, to September 28, 2018; HeartMate III vs HeartMate II LVAS for advanced heart failure) or the TVVAD trial (Treatment of Tricuspid Valve Regurgitation in Patients Undergoing Left Ventricular Assist Device Implantation Study; NCT03775759; enrollment August 22, 2018, and continued after October 2020; tricuspid valve repair vs no repair for moderate or severe tricuspid regurgitation). Because these left ventricular assist device 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 indicates inhaled epoprostenol; iNO, inhaled nitric oxide; and ITT, intention-to-treat.

FIRST PROOF ONLY

Downloaded from http://ahajournals.org by on July 5, 2023

(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 and 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 lengths of stay (Table 2). In addition, there were no significant between-group differences for rates of tracheostomy placement, acute kidney injury development, renal replacement therapy initiation, or mortality at 30 days, 90 days, and 1 year after surgery (Table 2). Furthermore, 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**;** hazard ratio, 2.13 [95% CI, 1.00–4.53]; *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 who died 1 year after surgery showed that death from RVF occurred in only 2 LVAD recipients in the iEPO group

Table 1. Baseline Participant Characteristics

Characteristics	Inhaled epoprostenol (n=120)*	Inhaled nitric oxide (n=111)*
Patient demographics and history		
Age, y	58 [48, 65]	59 [50, 65]
Sex (male), n (%)	85 (70.8)	86 (77.5)
Race, n (%)		
Black	47 (39.2)	44 (39.6)
White	72 (60.0)	66 (59.5)
Other	1 (0.8)	1 (0.8)
Body mass index	28.7 [24.5, 33.0]	29.4 [25.1, 33.1]
New York Heart Association classification (class III/IV), n (%)	85 (70.8)	87 (78.4)
INTERMACS profile, primary LVAD only, n (%)		
INTERMACS 1–3	32 (86.5)	34 (94.4)
INTERMACS 4–7	5 (13.5)	2 (5.6)
Previous CABG or valve surgery, n (%)	30 (25.0)	30 (27.0)
Previous sternotomy, n (%)	57 (47.5)	50 (45.9)
Previous percutaneous coronary intervention, n (%)	35 (29.2)	35 (31.5)
Atrial fibrillation, n (%)	71 (59.2)	62 (55.9)
Cerebrovascular accident / stroke, n (%)	27 (22.5)	13 (11.7)
Inotrope use before surgery, n (%)	40 (33.3)	29 (26.1)
Intra-aortic balloon pump counterpulsation, n (%)	49 (40.8)	53 (47.7)
Peripheral vascular disease, n (%)	12 (10.0)	9 (8.1)
Essential hypertension, n (%)	89 (74.2)	83 (74.8)
Diabetes, n (%)	51 (42.5)	41 (36.9)
Liver disease (noncardiac), n (%)	20 (16.7)	12 (10.8)
Congestive hepatopathy (cardiac-related), n (%)	17 (14.3)	8 (7.2)
Chronic obstructive pulmonary disease, n (%)	23 (19.2)	21 (18.9)
Asthma, n (%)	10 (8.3)	9 (8.1)
Venous thromboembolic disease, n (%)	24 (20.0)	26 (23.4)
Preoperative PH (mean pulmonary arterial pressure >20 mm Hg),† n (%)		
Precapillary PH (PVR ≥3 Wood units, PCWP ≤15 mm Hg)	6 (5.0)	3 (2.7)
Postcapillary PH (PVR <3 Wood units, PCWP >15 mm Hg)	45 (37.5)	45 (40.5)
Pre-/post-capillary PH (PVR ≥3 Wood units, PCWP >15 mm Hg)	42 (35.0)	32 (28.8)
Unknown (missing data)	4 (3.3)	6 (5.4)
Right heart catheterization values before surgery		
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	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]

(*Continued*)

Table 1. Continued

Characteristics	Inhaled epoprostenol (n=120)*	Inhaled nitric oxide (n=111)*
PCWP, mm Hg	23 [16, 27]	22 [16, 30]
Mean pulmonary arterial pressure, 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 ($\times 10^3$ per μL)	202 [155, 246]	175 [137, 225]
International normalized ratio	1.3 [1.1, 1.6]	1.3 [1.2, 1.5]
Activated partial thromboplastin time, s	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 glomerular filtration rate, mL/min	67 [53, 86]	67 [48, 88]
Chronic kidney disease staging by estimated glomerular filtration rate,‡ n (%)		
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), n (%)	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), n (%)	7 (5.8)	12 (10.8)
Class 2 PRA % (among those >0)	45 [9, 63]	49 [11, 52]
Procedural characteristics		
Orthotopic heart transplantation,§ n (%)	68 (56.7)	63 (56.8)
Ischemic cardiomyopathy with LVAD	8 (6.7)	9 (8.1)
Ischemic cardiomyopathy without LVAD	11 (9.2)	11 (9.9)
Nonischemic cardiomyopathy with LVAD	12 (10.0)	11 (9.9)
Nonischemic cardiomyopathy without LVAD	33 (27.5)	29 (26.1)
Other diagnosis	4 (3.3)	3 (2.7)
LVAD implantation,§ n (%)	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,‖ n (%)		
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)

(*Continued*)

Circulation FIRST PROOF-ONLY

Downloaded from http://ahajournals.org by on July 5, 2023

Table 1. Continued

Characteristics	Inhaled epoprostenol (n=120)*	Inhaled nitric oxide (n=111)*
Closure of atrial septal defect or patent foramen ovale	22 (18.3)	16 (14.4)
Cardiopulmonary bypass time, min	176 [139, 220]	182 [128, 212]
Transfusion volume during index surgery, mL#	863 [339, 1733]	700 [220, 1717]
Donor characteristics for orthotopic heart transplant recipients		
Age	32 [27, 38]	32 [27, 41]
Sex donor-recipient mismatch, n (%)	12 (10.0)	12 (10.8)
Race, n (%)		
White	47 (72.3)	47 (74.6)
Black	10 (15.4)	10 (15.9)
Other	8 (12.3)	6 (9.5)
Body mass index donor-recipient % mismatch	5.54 (28.36)	8.08 (22.29)
Cause of death, n (%)		
Anoxia	40 (61.5)	27 (42.9)
Cerebrovascular accident	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, n (%)	13 (20.6)	12 (19.0)
Donor type, n (%)		
Donation after brain death	64 (95.5)	57 (90.5)
Donation after cardiac death	3 (4.5)	6 (9.5)
Donor left ventricular ejection fraction	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%)

INTERMACS indicates Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; OHT, orthotopic heart transplant or transplantation; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; and PRA, panel-reactive antibody.

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

†PH diagnosis may include isolated postcapillary or combined pre- and postcapillary PH.[36]

‡CKD-EPI creatinine 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 Packed red blood cells, fresh frozen plasma, cryoprecipitate, and platelets.

(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 and S9). For hemodynamic end points, 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 of 63) who received iNO (*P*=0.42; Table S10). Although all of these participants experienced RVAD placement, 2 individuals (1 from each treatment group) received extracorporeal membrane oxygenation 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 of 52) who received iEPO and in 43.8% (23 of 52) who received iNO (*P*=0.96; Table S10). Furthermore, RVAD placement occurred in 9.6% (5 of 52) of LVAD recipients who received iEPO and in 10.4% (5 of 48) of those who received iNO (Table S11).

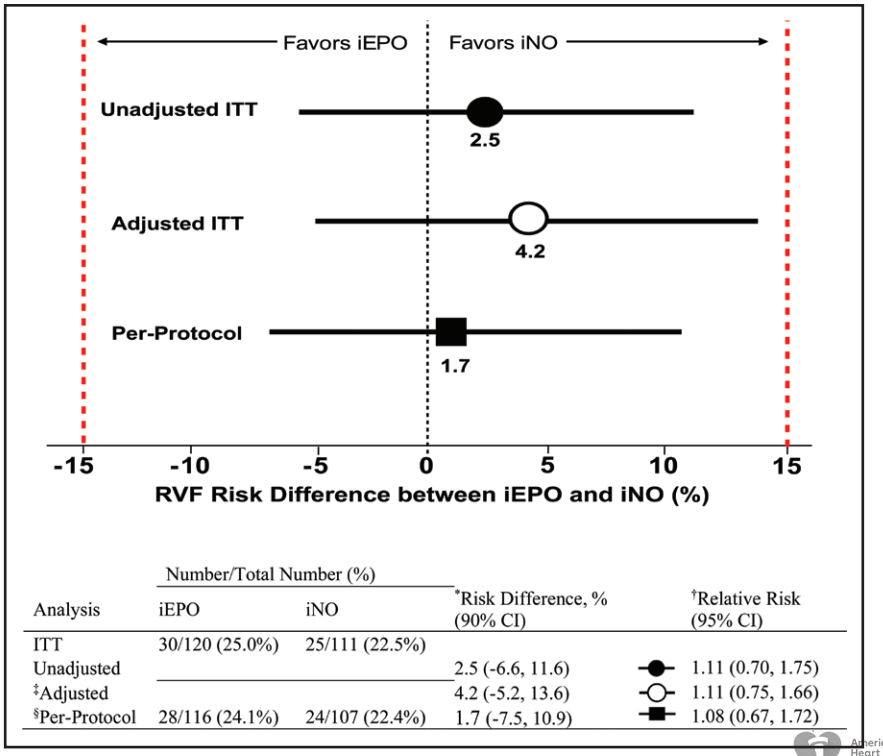
DISCUSSION

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, acute kidney injury development, renal replacement therapy initiation, or mortality 30 days, 90 days, and 1 year after surgery. Moreover, we did not identify important between-group differences in adverse events or hemodynamic end points.

Although iPVD therapy has been recently repurposed in critically ill patients with COVID-19 to potentially improve oxygenation and protect against RVF from hypoxic pulmonary vasoconstriction,[37] iEPO and iNO have been studied for decades, mainly in small trials or observational studies, in patients undergoing cardiac surgery,[38–40] and specifically in OHT[9,34,41–44] and LVAD implantation.[11,29,45,46] 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 blind, 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 time frame 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 (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical

Downloaded from http://ahajournals.org by on July 5, 2023

Circulation FIRST PROOF ONLY



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 procedures using a 2-sided α of 0.05. Setting the α at 0.05 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 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 vs 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 2 patients in the adjusted analysis with the same surgery type (left ventricular assist device or orthotopic heart transplantation) and preoperative platelet count. Number of events and their distribution between the unadjusted and adjusted analyses remained the same. §There were 8 patients (4 per treatment group) for whom the allocated treatment was not weaned per protocol. Seven of these patients underwent orthotopic heart transplantation, and 1 underwent left ventricular assist device implantation. iEPO indicates inhaled epoprostenol; iNO, inhaled nitric oxide; ITT, intention-to-treat; and RVF, right ventricular failure.

American Heart Association.

JOURNAL FIRST PROOF ONLY

Downloaded from http://ahajournals.org by on July 5, 2023

Circulatory Support Therapy with HeartMate 3),[27] precluded co-enrollment; therefore, we predicted an enrollment ratio of 2 participants undergoing OHT to 1 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 what was expected (23.8% observed versus 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, 15 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 8 participants (4 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 Supplemental Appendix) that had been refined and optimized during a 2-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

Table 2. Secondary Outcomes

Outcome	iEPO (n=120)*	iNO (n=111)*	Risk difference, % (90% CI)	Relative risk (95% CI)†	*P* value
Mortality, n (%)					
In-hospital	11 (9.2)	6 (5.4)	3.8 (−3.0 to 10.0)	1.70 (0.65–4.45)	0.28
30 days	7 (5.8)	4 (3.%)	2.2 (−3.0 to 8.0)	1.62 (0.49–5.38)	0.43
90 days	12 (10.0)	5 (4.5)	5.5 (−1.0 to 12.0)	2.22 (0.81–6.10)	0.12
1 y‡	21/117 (17.9)	10/106 (9.4)	8.5 (−0.4 to 17.4)	1.90 (0.94–3.85)	0.07
Acute kidney injury stages 2 or 3§	34 (28.3)	39 (35.1)	−6.8 (−19.0 to 5.0)	0.81 (0.55–1.17)	0.26
Renal replacement therapy	19 (15.8)	22 (19.8)	−4.0 (−14.0 to 6.0)	0.80 (0.46–1.40)	0.43
Discharge on new dialysis	9 (7.5)	7 (6.3)	1.221 (−5.0 to 8.0)	1.19 (0.45–3.11)	0.72
Tracheostomy placement	15 (12.5)	8 (7.2)	5.3 (−2.5 to 12.9)	1.72 (0.76–3.90)	0.20
Duration of mechanical ventilation, Kaplan-Meier estimate, median (95% CI), hǁ	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)**	
Intensive care unit length of stay, days	6 [4, 11]	6 [4, 11]	0 (−1 to 1)	0.94 (0.57–1.56)	0.82
Hospital length of stay, days	17 [11, 28]	16 [12, 30]	1 (−2 to 3)	0.97 (0.73–1.28)	0.83

HL indicates Hodges-Lehman; iEPO, inhaled epoprostenol; iNO, inhaled nitric oxide; and NA, not available.

*Parameters presented as median [Q1, Q3] 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 affected 3 participants in the iEPO group and 5 participants in the iNO group.

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

ǁMeasured 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

**HL nonparametric 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.

Circulation FIRST PROOF ONLY

Downloaded from http://ahajournals.org by on July 5, 2023

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 4 hours to avoid moisture accumulation and increased airway resistance. It remains unclear whether 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 build-up (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. In addition, 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.

It is notable that the intention-to-treat analysis included participants who 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.[47,48] This is because patients could initially present as an outpatient or inpatient, after which the study team would 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 evening before a potential surgery. As a result, 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.[49] 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.[50] 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 postrandomization exclusions developed in relation to our insurance preapproval process. Although we successfully collaborated with CMS to preapprove eligible patients so that their insurance coverage of the hospital stay was not jeopardized by trial enrollment, the

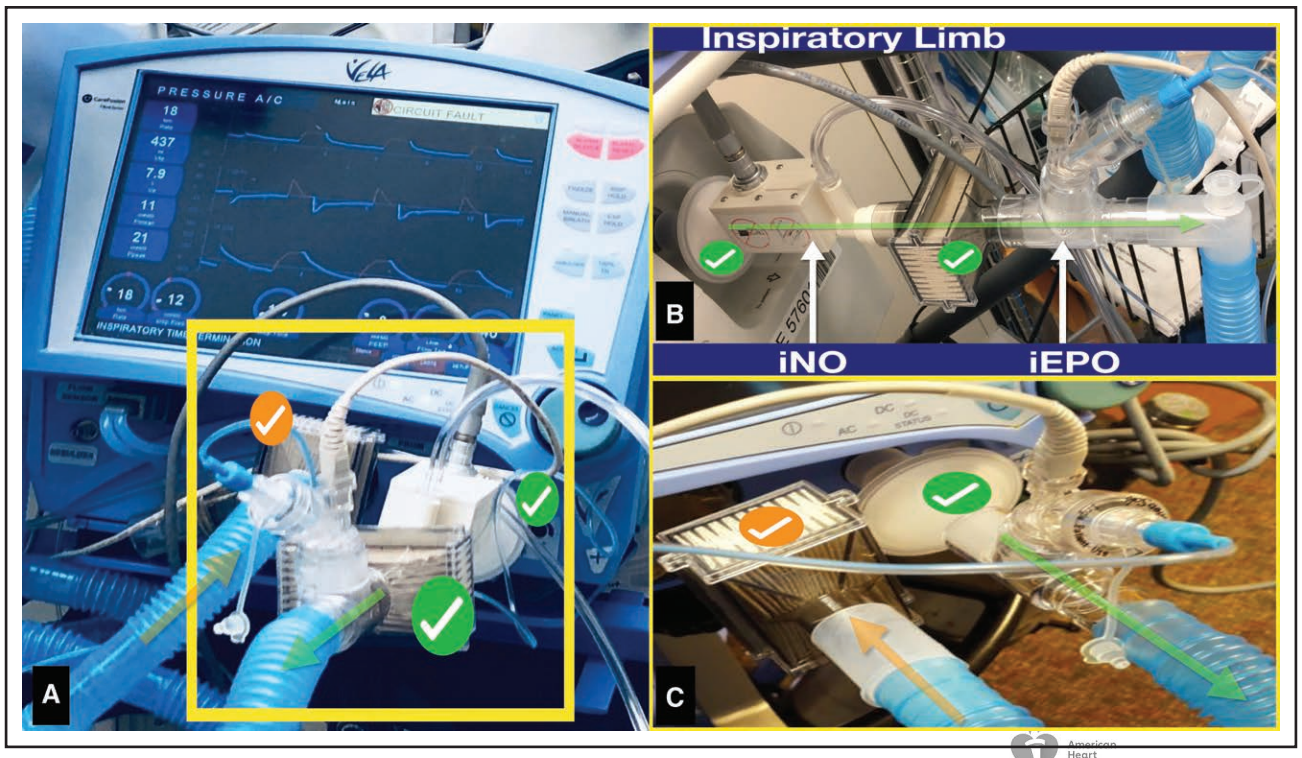


Figure 3. Airway filter placement during mechanical ventilation for both iEPO and iNO delivery.
A, A transport ventilator is displayed, with the inspiratory limb of the circuit-containing filters labeled with green checkmarks and the expiratory limb of the circuit returning to the ventilator containing 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 the inspiratory limb showing a filter placed between the inspiratory port and in-line iNO delivery device and 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. iEPO indicates inhaled epoprostenol; and iNO, inhaled nitric oxide.

Circulation FIRST PROOF ONLY

preapproval requests from eligible patients who were insured by private insurance companies resulted in the denial of 119 potential participants. Of these, 12 were initially approved, consented, and randomly assigned, then denied approval and excluded (Figure 1). Although a classic intention-to-treat analysis would have attenuated differences among these 12 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 randomly assigned, 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.

Although 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% versus 5.4%), 30-day (5.8% versus 3.6%), 90-day (10.0% versus 4.5%), and 1-year (17.9% versus 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 whether circumstances surrounding the cause could be attributed to iPVD assignment and the RVF outcome. Of the 2 patients who died of RVF, both underwent LVAD implantation and received iEPO. One of these patients died within 30 days, was supported preoperatively with venoarterial extracorporeal membrane oxygenation, 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 after 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, for whom infectious causes (7 patients versus 6 patients) and multisystem organ failure (4 patients versus 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

Downloaded from http://ahajournals.org by on July 5, 2023

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. Although 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 who could have experienced increases in pulmonary vascular resistance as a potential cause for postoperative RVF in the cardiac allograft. Although there may be additional causes of RVF after major cardiac surgery that are not managed with iPVD therapy, we found no between-group differences in postoperative RVAD initiation or differences in daily inotrope scores and hemodynamic end points 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 compared with treatment with iNO.

Circulation FIRST PROOF ONLY

ARTICLE INFORMATION

Received September 17, 2022; accepted June 6, 2023.

Affiliations

Department of Anesthesiology, Divisions of Cardiothoracic Anesthesiology and Critical Care Medicine, and the Clinical Research Unit (K.G., M.C.W., J.H.L.), Department of Surgery, Adult Cardiac Surgery Section (J.H.L., B.S.B., J.N.S., C.A.M.), Department of Medicine, Division of Cardiology (A.D.D., C.B.P., S.R., S.H.S.), Duke University School of Medicine, Durham, NC. Department of Respiratory Therapy, Boise State University, ID (J.L.C.).

Acknowledgments

The authors thank the Duke Office of Clinical Research; Duke Patient Revenue Management Organization; US Department of Health & Human Services' Centers for Medicare & Medicaid Services (CMS); the Clinical Research Unit of the Duke Department of Anesthesiology, the Duke Department of Respiratory Care Services, and the Investigational Drug Services Pharmacy and personnel who were responsible for implementation of research-related activities. Please see Supplemental Material for nonauthor collaborators. All authors contributed to the conception/design of the work or acquisition, analysis, or interpretation; the drafting or critical revision of the work; the final approval of the version to be submitted; and agreement to be accountable for all aspects of the work/integrity. Dr Ghadimi and M.C. Wright had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. M.C. Wright conducted and was responsible for data analysis.

Sources of Funding

Duke University Health System ("the funder") was responsible for the funding of research-related activities described in the study protocol. Otherwise, the funder was not involved in the design and conduct of the study; the collection, management, analysis or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit for publication.

Disclosures

Dr Ghadimi received research funding through his institution from the National Institutes of Health (T32 GM 008600), Duke Health, the International Anesthesia Research Society, and Octapharma. J.H. Levy serves on steering committees for Instrumentation Labs, Merck, and Octapharma. Dr Schroder received remuneration as a consultant for Abbott. Dr DeVore received research funding through his institution from the American Heart Association, Biofourmis, Bodyport, Cytokinetics, American Regent, Inc, the National Heart, Lung, and Blood Institute, Novartis, and Story Health; provided consulting services for or received honoraria from Abiomed, AstraZeneca, Cardionomic, InnaMed, LivaNova, Natera, Novartis, Procyrion, Story Health, Vifor, and Zoll; and received nonfinancial support from Abbott for educational and research activities. Dr Rajagopal received research funding through his institution from the American Heart Association, National Institutes of Health, Altavant Sciences, Janssen Pharmaceuticals, and United Therapeutics Corp. Dr Rajagopal provided consulting services for or received honoria from Apie Therapeutics, Altavant Sciences, GossamerBio, Insmed, Janssen Pharmaceuticals, Liquidia Technologies, Polarean, TotalCME, and United Therapeutics Corp. J.L. Cappiello, M.C. Wright, and Drs Bryner, Patel, Shah, and Milano report no disclosures.

Supplemental Material

Tables S1–S11
Figures S1–S7
Supplement 1: trial protocols
Statistical Analysis Plan
List of INSPIRE-FLO Collaborators

REFERENCES

1. Sabatino M, Vitale G, Manfredini V, Masetti M, Borgese L, Maria Raffa G, Loforte A, Martin Suarez S, Falletta C, Marinelli G, et al. Clinical relevance of the International Society for Heart and Lung Transplantation consensus classification of primary graft dysfunction after heart transplantation: epidemiology, risk factors, and outcomes. *J Heart Lung Transplant*. 2017;36:1217–1225. doi: 10.1016/j.healun.2017.02.014
2. Soliman OII, Akin S, Muslem R, Boersma E, Manintveld OC, Krabatsch T, Gummert JF, de By T, Bogers A, Zijlstra F, et al. Derivation and validation of a novel right-sided heart failure model after implantation of continuous flow left ventricular assist devices: the EUROMACS (European Registry for Patients with Mechanical Circulatory Support) right-sided heart failure risk score. *Circulation*. 2018;137:891–906. doi: 10.1161/CIRCULATIONAHA.117.030543
3. Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, Kociol RD, Lewis EF, Mehra MR, Pagani FD, et al; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Cardiovascular Surgery and Anesthesia. Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. *Circulation*. 2018;137:e578–e622. doi: 10.1161/CIR.0000000000000560
4. Bianco JC, Mc Loughlin S, Denault AY, Marenchino RG, Rojas JI, Bonofiglio FC. Heart transplantation in patients >60 years: importance of relative pulmonary hypertension and right ventricular failure on midterm survival. *J Cardiothorac Vasc Anesth*. 2018;32:32–40. doi: 10.1053/j.jvca.2017.09.017
5. Sparrow CT, LaRue SJ, Schilling JD. Intersection of pulmonary hypertension and right ventricular dysfunction in patients on left ventricular assist device support: is there a role for pulmonary vasodilators? *Circ Heart Fail*. 2018;11:e004255. doi: 10.1161/CIRCHEARTFAILURE.117.004255
6. De Santo LS, Romano G, Maiello C, Buonocore M, Cefarelli M, Galdieri N, Nappi G, Amarelli C. Pulmonary artery hypertension in heart transplant recipients: how much is too much? *Eur J Cardiothorac Surg*. 2012;42:864–869; discussion 869. doi: 10.1093/ejcts/ezs102
7. Downing SW, Edmunds LH Jr. Release of vasoactive substances during cardiopulmonary bypass. *Ann Thorac Surg*. 1992;54:1236–1243. doi: 10.1016/0003-4975(92)90113-i
8. Wessel DL, Adatia I, Giglia TM, Thompson JE, Kulik TJ. Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. *Circulation*. 1993;88:2128–2138. doi: 10.1161/01.cir.88.5.2128
9. Chen EP, Bittner HB, Davis RD Jr, Van Trigt P 3rd. Effects of nitric oxide after cardiac transplantation in the setting of recipient pulmonary hypertension. *Ann Thorac Surg*. 1997;63:1546–1555.

Downloaded from http://ahajournals.org by on July 5, 2023

10. Tsukashita M, Takayama H, Takeda K, Han J, Colombo PC, Yuzefpolskaya M, Topkara VK, Garan AR, Mancini DM, Kurlansky PA, et al. Effect of pulmonary vascular resistance before left ventricular assist device implantation on short- and long-term post-transplant survival. *J Thorac Cardiovasc Surg*. 2015;150:1352–60, 1361.e1. doi: 10.1016/j.jtcvs.2015.07.012
11. Houston BA, Kalathiya RJ, Hsu S, Loungani R, Davis ME, Coffin ST, Haglund N, Maltais S, Keebler ME, Leary PJ, et al. Right ventricular afterload sensitivity dramatically increases after left ventricular assist device implantation: a multi-center hemodynamic analysis. *J Heart Lung Transplant*. 2016;35:868–876. doi: 10.1016/j.healun.2016.01.1225
12. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med*. 1993;328:399–405. doi: 10.1056/NEJM199302113280605
13. Hill NS, Roberts KR, Preston IR. Postoperative pulmonary hypertension: etiology and treatment of a dangerous complication. *Respir Care*. 2009;54:958–968. doi: 10.4187/002013209793800439
14. Lai YC, Potoka KC, Champion HC, Mora AL, Gladwin MT. Pulmonary arterial hypertension: the clinical syndrome. *Circ Res*. 2014;115:115–130. doi: 10.1161/CIRCRESAHA.115.301146
15. Rajagopal S, Ruetzler K, Ghadimi K, Horn EM, Kelava M, Kudelko KT, Moreno-Duarte I, Preston IR, Bovino LLR, Smilowitz NR, et al; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, and the Council on Cardiovascular and Stroke Nursing. Evaluation and management of pulmonary hypertension in noncardiac surgery: a scientific statement from the American Heart Association. *Circulation*. 2023;147:1317–1343. doi: 10.1161/CIR.0000000000001136
16. Ichinose F, Zapol WM. Inhaled pulmonary vasodilators in cardiac surgery patients: correct answer is "NO." *Anesth Analg*. 2017;125:375–377. doi: 10.1213/ANE.0000000000002239
17. Rao V, Ghadimi K, Keeyapaj W, Parsons CA, Cheung AT. Inhaled nitric oxide (iNO) and inhaled epoprostenol (iPGI2) use in cardiothoracic surgical patients: is there sufficient evidence for evidence-based recommendations? *J Cardiothorac Vasc Anesth*. 2018;32:1452–1457. doi: 10.1053/j.jvca.2017.12.014
18. Ghadimi K, Cappiello J, Cooter-Wright M, Haney JC, Reynolds JM, Bottiger BA, Klapper JA, Levy JH, Hartwig MG; INSPIRE-FLO Investigators. Inhaled pulmonary vasodilator therapy in adult lung transplant: a randomized clinical trial. *JAMA Surg*. 2022;157:e215856. doi: 10.1001/jamasurg.2021.5856
19. Preston IR, Sagliani KD, Roberts KE, Shah AM, Desouza SA, Howard W, Brennan J, Hill NS. Comparison of acute hemodynamic effects of inhaled nitric oxide and inhaled epoprostenol in patients with pulmonary hypertension. *Pulm Circ*. 2013;3:68–73. doi: 10.4103/2045-8932.109916
20. Rogers JG, Pagani FD, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Boyce SW, Najjar SS, Jeevanandam V, Anderson AS, et al. Intrapericardial left ventricular assist device for advanced heart failure. *N Engl J Med*. 2017;376:451–460. doi: 10.1056/NEJMoa1602954
21. Milano CA, Shah AS, Van Trigt P, Jaggers J, Davis RD, Glower DD, Higginbotham MB, Russell SD, Landolfo KP. Evaluation of early postoperative results after bicaval versus standard cardiac transplantation and review of the literature. *Am Heart J*. 2000;140:717–721. doi: 10.1067/mhj.2000.111105
22. Devore AD, Mentz RJ, Patel CB. Medical management of patients with continuous-flow left ventricular assist devices. *Curr Treat Options Cardiovasc Med*. 2014;16:283–301. doi: 10.1007/s11936-013-0283-0
23. Vega E, Schroder J, Nicoara A. Postoperative management of heart transplantation patients. *Best Pract Res Clin Anaesthesiol*. 2017;31:201–213. doi: 10.1016/j.bpa.2017.06.002
24. Kobashigawa J, Zuckermann A, Macdonald P, Leprince P, Esmailian F, Luu M, Mancini D, Patel J, Razi R, Reichenspurner H, et al; Consensus Conference participants. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. *J Heart Lung Transplant*. 2014;33:327–340. doi: 10.1016/j.healun.2014.02.027
25. INTERMACS. *Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). Appendix A- Adverse Event Definitions*. UAB School of Medicine.
26. Althouse AD, Below JE, Claggett BL, Cox NJ, de Lemos JA, Deo RC, Duval S, Hachamovitch R, Kaul S, Keith SW, et al. Recommendations for statistical reporting in cardiovascular medicine: a special report from the American Heart Association. *Circulation*. 2021;144:e70–e91. doi: 10.1161/CIRCULATIONAHA.121.055393
27. Mehra MR, Naka Y, Uriel N, Goldstein DJ, Cleveland JC Jr, Colombo PC, Walsh MN, Milano CA, Patel CB, Jorde UP, et al; MOMENTUM 3 Investigators. A fully magnetically levitated circulatory pump for advanced heart failure. *N Engl J Med*. 2017;376:440–450. doi: 10.1056/NEJMoa1610426
28. Treatment of tricuspid valve regurgitation in patients undergoing left ventricular assist device implantation (TVVAD). Accessed October 6, 2021. https://clinicaltrials.gov/ct2/show/NCT03775759
29. Potapov E, Meyer D, Swaminathan M, Ramsay M, El Banayosy A, Diehl C, Veynovich B, Gregoric ID, Kukucka M, Gromann TW, et al. Inhaled nitric oxide after left ventricular assist device implantation: a prospective, randomized, double-blind, multicenter, placebo-controlled trial. *J Heart Lung Transplant*. 2011;30:870–878. doi: 10.1016/j.healun.2011.03.005
30. Taghavi S, Jayarajan SN, Komaroff E, Mangi AA. Right ventricular assist device results in worse post-transplant survival. *J Heart Lung Transplant*. 2016;35:236–241. doi: 10.1016/j.healun.2015.10.018
31. Cosio Carmena MD, Gomez Bueno M, Almenar L, Delgado JF, Arizon JM, Gonzalez Vilchez F, Crespo-Leiro MG, Mirabet S, Roig E, Perez Villa F, et al. Primary graft failure after heart transplantation: characteristics in a contemporary cohort and performance of the RADIAL risk score. *J Heart Lung Transplant*. 2013;32:1187–1195. doi: 10.1016/j.healun.2013.08.004
32. Nicoara A, Ruffin D, Cooter M, Patel CB, Thompson A, Schroder JN, Daneshmand MA, Hernandez AF, Rogers JG, Podgoreanu MV, et al. Primary graft dysfunction after heart transplantation: Incidence, trends, and associated risk factors. *Am J Transplant*. 2018;18:1461–1470. doi: 10.1111/ajt.14588
33. Zeigler S, Hill C, Shudo Y, Wang H, Woo YJ, Banerjee D, Ha R. Inhaled epoprostenol is equivalent to inhaled nitric oxide for right ventricular failure following left ventricular assist device placement. *Circulation*. 2016;134:A14454.
34. Ardehali A, Hughes K, Sadeghi A, Esmailian F, Marelli D, Moriguchi J, Hamilton MA, Kobashigawa J, Laks H. Inhaled nitric oxide for pulmonary hypertension after heart transplantation. *Transplantation*. 2001;72:638–641. doi: 10.1097/00007890-200108270-00013
35. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381. doi: 10.1016/j.jbi.2008.08.010
36. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53:1801913. doi: 10.1183/13993003.01913-2018
37. DeGrado JR, Szumita PM, Schuler BR, Dube KM, Lenox J, Kim EY, Weinhouse GL, Massaro AF. Evaluation of the efficacy and safety of inhaled epoprostenol and inhaled nitric oxide for refractory hypoxemia in patients with coronavirus disease 2019. *Crit Care Explor*. 2020;2:e0259. doi: 10.1097/CCE.0000000000000259
38. De Wet CJ, Affleck DG, Jacobsohn E, Avidan MS, Tymkew H, Hill LL, Zanaboni PB, Moazami N, Smith JR. Inhaled prostacyclin is safe, effective, and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery. *J Thorac Cardiovasc Surg*. 2004;127:1058–1067. doi: 10.1016/j.jtcvs.2003.11.035
39. Fattouch K, Sbraga F, Bianco G, Speziale G, Gucciardo M, Sampognaro R, Ruvolo G. Inhaled prostacyclin, nitric oxide, and nitroprusside in pulmonary hypertension after mitral valve replacement. *J Card Surg*. 2005;20:171–176. doi: 10.1111/j.0886-0440.2005.200383w.x
40. Abe S, Ishida K, Masuda M, Ueda H, Kohno H, Matsuura K, Tamura Y, Watanabe M, Matsumiya G. A prospective, randomized study of inhaled prostacyclin versus nitric oxide in patients with residual pulmonary hypertension after pulmonary endarterectomy. *Gen Thorac Cardiovasc Surg*. 2017;65:153–159. doi: 10.1007/s11748-016-0724-2
41. Stobierska-Dzierzek B, Awad H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. *J Am Coll Cardiol*. 2001;38:923–931. doi: 10.1016/s0735-1097(01)01486-3
42. Fattouch K, Sbraga F, Sampognaro R, Bianco G, Gucciardo M, Lavalle C, Vizza CD, Fedele F, Ruvolo G. Treatment of pulmonary hypertension in patients undergoing cardiac surgery with cardiopulmonary bypass: a randomized, prospective, double-blind study. *J Cardiovasc Med (Hagerstown)*. 2006;7:119–123. doi: 10.2459/01.JCM.0000203850.97890.fe
43. Khan TA, Schnickel G, Ross D, Bastani S, Laks H, Esmailian F, Marelli D, Beygui R, Shemin R, Watson L, et al. A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. *J Thorac Cardiovasc Surg*. 2009;138:1417–1424. doi: 10.1016/j.jtcvs.2009.04.063
44. Haraldsson A, Kieler-Jensen N, Nathorst-Westfelt U, Bergh CH, Ricksten SE. Comparison of inhaled nitric oxide and inhaled aerosolized prostacyclin in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance. *Chest*. 1998;114:780–786. doi: 10.1378/chest.114.3.780
45. Baumwol J, Macdonald PS, Keogh AM, Kotlyar E, Spratt P, Jansz P, Hayward CS. Right heart failure and "failure to thrive" after left ventricular

Downloaded from http://ahajournals.org by on July 5, 2023

Circulation FIRST PROOF ONLY

assist device: clinical predictors and outcomes. *J Heart Lung Transplant*. 2011;30:888–895. doi: 10.1016/j.healun.2011.03.006
46. Kukucka M, Potapov E, Stepanenko A, Weller K, Mladenow A, Kuppe H, Habazettl H. Acute impact of left ventricular unloading by left ventricular assist device on the right ventricle geometry and function: effect of nitric oxide inhalation. *J Thorac Cardiovasc Surg*. 2011;141:1009–1014. doi: 10.1016/j.jtcvs.2010.08.010
47. Neuman MD, Feng R, Carson JL, Gaskins LJ, Dillane D, Sessler DI, Sieber F, Magaziner J, Marcantonio ER, Mehta S, et al; REGAIN Investigators. spinal anesthesia or general anesthesia for hip surgery in older adults. *N Engl J Med*. 2021;385:2025–2035. doi: 10.1056/NEJMoa2113514
48. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, Morelli A, Antonelli M, Singer M. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. *JAMA*. 2016;316:1583–1589. doi: 10.1001/jama.2016.11993
49. Matilde Sanchez M, Chen X. Choosing the analysis population in non-inferiority studies: per protocol or intent-to-treat. *Stat Med*. 2006;25:1169–1181. doi: 10.1002/sim.2244
50. Gaudino M, Chikwe J, Bagiella E, Bhatt DL, Doenst T, Fremes SE, Lawton J, Masterson Creber RM, Sade RM, Zwischenberger BA; American Heart Association Council on Cardiovascular Surgery and Anesthesia. American Heart Association Council on Cardiovascular Surgery and Anesthesia. Methodological standards for the design, implementation, and analysis of randomized trials in cardiac surgery: a scientific statement from the American Heart Association. *Circulation*. 2022;145:e129–e142. doi: 10.1161/CIR.0000000000001037

American Heart Association.
Circulation
FIRST PROOF ONLY

Downloaded from http://ahajournals.org by on July 5, 2023