Table 1. Clinical trials of iNO in adult cardiac surgery.

CITATION	STUDY DESIGN	N	SETTING	COMPARISON	MEASURES	PRIMARY RESULTS	SAFETY
Schmid E et al.[19]	Randomized cross-over	14	severe pulmonary hypertension (PH) after cardiac surgery	iNO (40 ppm), IV prostaglandin E1 (PGE1), IV nitroglycerin (NTG)	Pulmonary vascular resistance (PVR), cardiac index (CI), right ventricular ejection fraction (RVEF)	With iNO, IV PGE1, IV NTG all decreased PVR and increased CI. PGE1 increased RVEF, while NTG had no effect on CI and RV performance.	Median methemoglobin (metHB) levels significantly increased from 0.64% to 1.06% with iNO. Maximal metHB was 1.55%. NO_2 levels of 2.4 ppm (95% CI: 1.8, 4.2) were detected. In one patient peak NO_2 was 6.4 ppm. No adverse effects due to iNO were observed.
Solina AR. et al. [20]	Randomized	45	cardiac surgery with PH	40 ppm iNO vs 20 ppm iNO	heart rate (HR), RVEF, PVR, requirement for pressors	iNO (20 or 40ppm) had lower HR, higher RVEF and lower vasopressor requirement vs IV milrinone, given at separation from CPB	No adverse events, serious adverse events or deaths were noted
Solina AR. et al. [21]	Randomized	62	cardiac surg with PH	INO doses vs milrinone	HR, mean arterial pressure (MAP), PVR, peripheral VR (periphVR), CI, RVEF	iNO was associated with significant reductions in PVR in all groups. iNO at 10, 20, 30, 40 ppm showed no difference in PVR response between doses and vs milrinone	No adverse events, serious adverse events or deaths were noted
Gianetti J . et al. [22]	Randomized	29	Aortic valve replacement + CABG surgery	iNO or no	Creatine kinase, creatine kinase MB fraction (CKMB), troponin, brain natriuretic peptide (BNP), P-selectin	iNO 20ppm can blunt release of markers of myocardial injury, antagonize LV dysfunction after CPB vs placebo	No adverse events documented in either group
Fattouch K, et al. [23]	Double-blind, Randomized	58	Mitral valve surgery	iNO, inhaled prostacyclin (i-PGi2), nitroprusside (NTP)	PAP, PulmVR, transpulmonary gradient, cardiac output (CO)	iNO as effective in treating PH as i-PGI2. Both inhaled treatments superior to NTP.	One patient died in surgery due to right ventricular failure (RVF) (randomized to, but did not get iNO); 1 patient needed a biventricular assist device because of RVF; 2 patients had massive bleeding requiring re-exploration; 2 patients died of multi-organ failure (groups for these patients not stated).

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Fattouch K, et al. [24]	Double-blind, Randomized	58	Mitral valve surgery	iNO, i-PGi2, NTP	Weaning time off CPB, intubation time, ICU time, RV function by echocardiogram	Inhaled treatments superior in time to weaning, intubation time and ICU stay ($p<0.05$)	Two deaths occurred, 1 in the control group from uncontrolled bleeding and 1 in the iNO group died from RVF
Winterhalter M et al. [25]	Randomized	46	Cardiac surgery	PH during weaning from CPB; iNO vs iloprost	HR, MAP, PAP, central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP)	iNO and iloprost both reduced PAP and PVR immediately after weaning from CPB. Iloprost gave > reductions in PVR and mPAP and > increase in CO.	No major side effects observed
Fernandes JL et al. [26]	Randomized	29	Mitral valve surgery	iNO (a10 ppm), O_2	Hemodynamic data, the use of vasoactive drugs, duration of stay, and short-term complications.	After 24 and 48 hours, iNO had a significantly greater increase in CI vs O_2. PVR was significantly reduced with iNO vs O_2 at 48 hours. The iNO group used fewer systemic vasoactive drugs and had a shorter ICU stay. Postop use of iNO and oral sildenafil results in an additive favorable effect on MPAP and PVRI, without systemic hypotension and V/Q mismatch.	There were fewer predefined complications in the iNO group 29% vs 60%.
Matamis D et al**.** [27]	Randomized	20	Valve surgery	iNO (10ppm), sildenafil	Hemodynamic data MPAP, PVRI, systemic vascular resistance index (SVRI)	iNO significantly reduced MPAP, PVRI. Sildenafil decreased MPAP, PVRI, and SVRI and PaO_2/ FiO_2 ratio. In both groups, coadministration of the 2 drugs further reduced MPAP, pulmonary artery occlusive pressure, SVRI, and PVRI. Hypoxemia after sildenafil improved after the coadministration of iNO, and PaO_2/FiO_2 returned to values near baseline.	Not reported

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Lei C, [28]	Randomized	244	elective, multiple valve replacement surgery, mostly due to rheumatic fever	iNO (80 ppm) through CPB circuit during surgery, then iNO for 24h post-op, compared with nitrogen gas	Incidence of AKI within 7 days of surgery; secondary outcomes: develop-ment of stage 3 CKD, loss of 25% of eGFR compared with baseline, and MAKE (composite outcome of loss of 25% of eGFR from baseline, end-stage renal disease requiring a continuous renal replacement therapy, and mortality) at 30 days, 90 days, and 1 year after ICU admission.	Significantly fewer patients in the iNO group developed AKI within 7 days of surgery compared with the control group (intention-to-treat analysis: 50% vs. 64%; RR, 0.78; 95% CI, 0.62–0.97; P = 0.014; 50% vs. 63%; RR, 0.78; 95% CI, 0.62–0.99; P = 0.022. In addition, transition to stage 3 CKD, and MAKE at 30 days, 90 days, and 1 year.	iNO dose was never reduced for safety concerns. Continuous measurement of NO_2 was always <1 ppm in all patients with iNO treatment. Plasma Met-Hb significantly increased from baseline to the end of CPB with iNO; significantly higher at the end of CPB (P< 0.001), 0 hours (P<0.001), 6 hours (P<0.001), and 24 hours after ICU admission (P<0.001) compared with the control group. The highest value of Met-Hb measured in the iNO group was 9.3%, and no patient exceeded 10% Met-Hb at any time. There were no AEs, complications, or other organ dysfunction associated with the use of iNO.
Kamenshchikov N et al. [29]	Randomized	96	Cardiac surgery requiring CPB in patients with moderate risk of renal complications	NO (40 ppm) through bypass circuit for the entirety of CPB period, vs usual care	Incidence of AKI, urine output during CPB, urinary neutrophil gelatinase-associated lipocalin level, concentrations of NO metabolites, concentrations of proinflammatory and anti-inflammatory mediators, free plasma hemoglobin	NO was associated with a significant decrease in AKI incidence (20.8% vs 41.6%; RR, 0.5; 95%, CI, 0.26-0.95; P = 0.023), and among NO patients, a higher median UOP during CPB and lower median urinary neutrophil gelatinase-associated lipocalin level at 4 hours after surgery. Levels of pro- and anti-inflammatory mediators and free plasma hemoglobin did not differ between the 2 groups.	No adverse events or organ dysfunctions were associated with NO administration. Postop complications were similar in the 2 groups.

AE=adverse events, BP=blood pressure, CABG=coronary artery bypass grafting. I=cardiac index, CO=cardiac output, CPB= cardiopulmonary bypass, CVP=central venous pressure, FiO_2=fraction of inspired oxygen; HR=heart rate, iNO=inhaled nitric oxide, i-PGi2=inhaled prostacyclin, LAP=left atrial pressure, MAP=mean arterial pressure, metHB=methemoglobin, MPAP=mean pulmonary arterial pressure, NO_2-nitrrogen dioxide, NTP=nitroprusside, PCWP= pulmonary capillary wedge pressure, PH=pulmonary hypertension, PGE1=IV prostaglandin E1, ppm=parts per million, PVR=pulmonary vascular resistance, PVRI= pulmonary vascular resistance index, RVEF=right ventricular ejection fraction, SVRI=systemic vascular resistance index, UOP=urinary output, V/Q=ventilation/perfusion