Review article

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Comparison of inhaled iloprost and nitric oxide in the management of pulmonary hypertension post-cardiac surgery: A systematic literature review of randomized clinical trials

David Marintua Raja Silalahi[1], Philia Setiawan[1], Fajar Perdhana[1], Teuku Husain[1], Yos Kowara[1]

Abstract

***Background*: Pulmonary hypertension (PH) is a critical complication of cardiac surgery, particularly in patients undergoing pulmonary endarterectomy (PEA), heart transplantation, and lung transplantation. Inhaled iloprost and nitric oxide (NO) are widely used as pulmonary vasodilators; however, their comparative efficacy and safety are unclear.**

***Objectives*: This systematic literature review aimed to compare the effectiveness and safety of inhaled iloprost and NO in managing PH after cardiac surgery, focusing on hemodynamic improvements and adverse effects.**

***Methods*: A systematic search was conducted for randomized controlled trials (RCTs), randomized crossover studies, and open-label trials published until April 2025. Five relevant studies were included, encompassing 115 patients with various forms of post-cardiac surgery-related PH. The primary outcomes included reductions in mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR). In contrast, the secondary outcomes included hemodynamic parameters, oxygenation, incidence of pulmonary hypertensive crises (PHTC), and adverse events.**

***Results*: Both inhaled iloprost and NO effectively reduced mPAP and PVR across all studies, with no significant differences in the overall efficacy between the two treatments. However, iloprost demonstrated superior effects in improving cardiac output and reducing PVR compared with those of NO. Both therapies were associated with a significant reduction in PHTC and improvement in hemodynamic and oxygenation parameters. Iloprost also exhibited a better safety profile with fewer systemic side effects, such as thrombocytopenia. The studies revealed that the incidence of adverse effects was generally low for both treatments, and no major complications were reported in either group.**

***Conclusion*: Inhaled iloprost provides superior hemodynamic improvements compared with NO, particularly in reducing PVR and increasing cardiac output. Both treatments were safe and effective in managing post-cardiac surgery PH. Iloprost may offer a better alternative to NO, especially for long-term management, given its sustained effects and fewer systemic side effects. Future studies should focus on larger multicenter trials to validate these findings and explore long-term outcomes.**

Keywords: Pulmonary hypertension, inhaled iloprost, inhaled nitric oxide, cardiac surgery.

[1] Department of Anesthesiology and Reanimation, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia

Address for correspondence:
Fajar Perdhana
Jl. Dharmahusada No. 2, Surabaya, Indonesia
Email: dr.fajarperdhana@gmail.com
ORCID ID: 0000-0002-9204-0039

Introduction

Perioperative pulmonary arterial hypertension (PAH) is frequently observed during thoracic surgery involving cardiopulmonary bypass (CPB). Patients often present with pre-existing conditions, such as left ventricular dysfunction or valvular disease, which increase their susceptibility to perioperative PAH. (1) PAH increases afterload on the right ventricle, potentially leading to right ventricular dysfunction during cardiac surgery. (2) It serves as

a critical prognostic indicator and is associated with elevated morbidity and mortality. (3–6) Reducing pulmonary artery pressure (PAP) and enhancing right ventricular function are imperative for safe weaning from CPB. Pathophysiological factors include left ventricular dysfunction and valvular disease, which manifest both preoperatively and postoperatively. The contributing factors include systemic inflammatory response, pulmonary reperfusion syndrome, and blood transfusions. Extracorporeal circulation during CPB induces pulmonary damage via cytokine release and ischemia-reperfusion injury. The administration of protamine after CPB provokes pulmonary vasoconstriction. Additionally, hypoxia, hypercarbia, pulmonary embolism, and mitral prosthesis mismatch also contribute to PAH. (1)

To treat low blood pressure, it is important to closely monitor the patient, administer fluids, and use drugs such as norepinephrine that constrict blood vessels. Another option is the use of inhaled drugs that widen blood vessels in the lungs to avoid low blood pressure in other parts of the body. Inhaled nitric oxide (NO) is a common choice, and recent research has shown that inhaled prostacyclin analogs may help improve blood flow in the lungs during heart surgery; however, their effectiveness remains unclear. (7–9) There is no global consensus on whether inhaled or intravenous drugs are superior for managing high blood pressure in the lungs during heart surgery with a heart-lung machine. (10–12) In these surgeries, intravenous drugs are used to manage high lung blood pressure, but they can cause low blood pressure throughout the body because they widen many blood vessels. (13–15)

In 2017, a study was conducted to evaluate the treatment of pulmonary hypertension (PH) during cardiac surgery. This study had several limitations, including a limited number of trials and a primary focus on mortality rates and intensive care unit duration. It did not assess blood flow and oxygen levels, nor did it analyze different patient groups separately. (16) Notably, no study has examined changes in blood flow following the initiation of treatment, despite its significance. We conducted a study to assess the efficacy and safety of inhaled and injected medications for managing PH during cardiac surgery with CPB. Our focus was on changes in blood flow during the surgical procedure.

Method

This systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The study protocol is publicly available on the Open Science Framework (OSF).

Eligibility criteria

We included randomized controlled trials (RCTs) evaluating the efficacy and safety of various treatment approaches for PAH in patients undergoing cardiac surgery with CPB. Published and unpublished articles, conference abstracts, and letters were also considered. No restrictions were imposed based on language or country of origin, and studies were included irrespective of year of publication or follow-up duration. However, we excluded cluster-randomized, quasi-experimental, and quasi-randomized trials from our analysis.

Participants

We included studies involving patients undergoing chest surgery with CPB, without restrictions on sex, race, or geographic location. The reviewed studies assessed treatment outcomes in various clinical settings, including operating rooms, intensive care units (ICU), and other healthcare settings. Studies from non-RCT subjects were excluded. This study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the number CRD42051078969.

Interventions and comparators

In the intervention group, the following inhaled vasodilators were administered: NO, prostacyclin analogs (epoprostenol, iloprost, and treprostinil), and phosphodiesterase inhibitors (milrinone, oxone, and levosimendan). The inhalation dose was determined on an individual basis and administered during both the intraoperative and postoperative periods. The following intravenous vasodilators were included in the comparator group: prostacyclin analogs (epoprostenol, iloprost, treprostinil, and selexipag), nitroglycerin, nitroprusside, phosphodiesterase inhibitors (e.g., milrinone, enoximone, levosimendan, olprinone, amrinone, tadalafil, and sildenafil), and dobutamine. The intravenous therapy dose was individualized and administered both intraoperatively and postoperatively.

Outcomes of interest

The primary outcomes were perioperative PAH, defined as a mean pulmonary artery pressure (mPAP) ≥20 mmHg, measured using methods such as a pulmonary artery catheter (PAC), transesophageal echocardiography (TEE), transthoracic echocardiography (TTE), or other devices, and low perioperative systemic vascular resistance (SVR), defined as SVR≤900 dyne s.cm^{-5}, with measurements obtained using PAC, TEE, TTE, or hemodynamic monitoring

systems (e.g., FloTrac™, and LiDCO^{TM}). Secondary outcomes included hemodynamic parameters, such as systemic arterial pressure (systolic, diastolic, and mean), PAP (systolic, diastolic, and mean), pulmonary vascular resistance (PVR), and cardiac index during the first 30 min of treatment; oxygenation parameters, particularly mixed venous oxygen saturation (SvO2) during the first 30 min of treatment; and adverse events, including any side effects or complications related to the treatment, as defined in the original studies. In cases where multiple drugs and dosages were used in both the inhalation and intravenous groups, they were combined for analysis according to the Cochrane Handbook guidelines.

Information sources and selection

We conducted a comprehensive search across multiple databases, including MEDLINE via PubMed, Embase via ProQuest, CENTRAL, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP). The search covered all records available from the inception of each database until April 2025 using the following keywords: "inhaled iloprost," "inhaled nitric oxide," "pulmonary hypertension," "cardiac surgery," "postcardiac surgery pulmonary hypertension," "hemodynamic improvement," "pulmonary vascular resistance," "mean pulmonary artery pressure," "randomized controlled trial," and "safety." We used the PICO framework to guide our search strategy, with the following elements: P (population), patients with pulmonary hypertension following cardiac surgery (e.g., pulmonary endarterectomy, heart or lung transplantation); I (intervention), inhaled iloprost; C (comparison), inhaled NO; O (outcome), hemodynamic improvements (reduction in mPAP and pulmonary vascular resistance), oxygenation, incidence of pulmonary hypertensive crises, and adverse events.

The search was performed using Boolean operators (AND, OR) to combine terms and refine results. We applied filters to include only RCTs, randomized crossover studies, and open-label trials published in English. Additionally, we reviewed the reference lists of the identified studies, relevant international clinical guidelines, and articles cited in the key references.

The search was conducted independently by the author and one of the four reviewers, in accordance with a double-blind review policy. After screening the titles and abstracts, we selected studies for full-text review. Disagreements were resolved through discussion, with a third reviewer acting as an arbitrator when necessary.

Data collection

Data extraction was performed independently by author A and one of the four reviewers (concealed in accordance with the double-blind policy) using a standardized form. A pre-checked form was applied to ten randomly selected articles. The form included information on the study design, participant population, interventions, outcomes, study setting (single- or multicenter), follow-up time, and funding sources. Any disagreements in data extraction were resolved through discussion, and if necessary, a third reviewer acted as an adjudicator. Missing information was obtained from the original authors when required. Studies from which such information could not be retrieved were excluded from the analyses.

Result

Overview of literature search

A comprehensive search of databases, including MEDLINE via PubMed, Embase via ProQuest, CENTRAL, ClinicalTrials.gov, and WHO-ICTRP, identified 900 records by April 2025. After duplicate removal, we excluded 860 irrelevant records. Full-text assessment of the remaining 40 articles resulted in the exclusion of 35 articles that were not RCTs, crossover, or open-label trials; did not address post-cardiac surgery PH; lacked direct comparison of inhaled iloprost versus NO; had unreported outcomes; or were duplicates. Consequently, five studies were included in the systematic review, encompassing 115 patients and evaluating hemodynamic improvements and safety.

A systematic review of the five included studies comparing inhaled iloprost and NO for the management of PH after cardiac surgery revealed several important findings across the studies, focusing on efficacy, safety, and hemodynamic effects. Both iloprost and NO reduced the mPAP and PVR. However, iloprost consistently outperformed NO in these key parameters, particularly in studies involving adult patients undergoing pulmonary endarterectomy (PEA) and heart-lung transplants (Abe et al., 2017; Khan et al., 2009; Winterhalter et al., 2008)

Across all studies, the primary outcomes showed a significant reduction in mPAP and PVR with both inhaled therapies. Winterhalter et al. (2008) found that iloprost led to a more substantial decrease in both mPAP and PVR than NO, along with a greater improvement in cardiac output (CO) (Winterhalter 2008). This finding suggests that iloprost may be more effective than NO in improving right ventricular function, especially in postoperative settings where PH is common.

When examining secondary outcomes, both iloprost and NO improved oxygenation parameters and the cardiac index (CI); however, no significant differences were observed between the two therapies in SvO2 or other oxygenation parameters. Additionally, studies assessing pulmonary hypertensive crises (PHTC) found that while both treatments reduced the frequency of PHTCs, no significant difference in the incidence or severity of PHTCs was observed between the two treatments. This finding aligns with the results of Khan et al. (2009) and Loukanov et al. (2011), who found that both treatments were effective in preventing crises (Khan et al., 2009; Kirbas et al., 2012).

In terms of safety, both iloprost and NO were well tolerated, with minimal adverse events reported. The most common side effects were thrombocytopenia and mild systemic hypotension; however, these were not directly linked to the inhaled agents (Kirbas et al., 2012; Winterhalter et al., 2008). Notably, no major adverse events, such as severe methemoglobinemia or excessive bleeding, were reported, which is particularly significant in clinical practice where safety concerns are paramount. Furthermore, iloprost had a slightly lower incidence of adverse effects than NO, particularly regarding systemic vasodilatory effects.

In summary, both inhaled iloprost and NO demonstrated clinical efficacy in treating PH after cardiac surgery, improving hemodynamic parameters and oxygenation. However, iloprost was more effective than NO in reducing mPAP and PVR, with sustained improvements in CO and fewer systemic side effects. Despite the positive results of iloprost, NO remains the standard treatment in many clinical settings owing to its established use, clinical guidelines, and availability. These findings highlight the potential of iloprost as a viable alternative to NO for managing PH, especially in settings where long-term inhalation therapy is necessary (Abe et al., 2017; Khan et al., 2009; Kirbas et al., 2012; Winterhalter et al., 2008). **Table 1** summarizes all the key findings related to iloprost.

Table 2 compares five significant studies on the efficacy and safety of inhaled iloprost and NO for treating PH after cardiac surgery. These studies included diverse patients, including adults undergoing PEA, heart-lung transplantation, and children and infants with congenital heart defects. Each study assessed critical outcomes, such as mPAP, PVR, hemodynamic parameters, side effects, and clinical outcomes.

Risk of bias

The risk of bias across the five included studies was assessed using the Cochrane Risk of Bias tool for randomized controlled trials. All studies exhibited a high risk of bias in blinding of participants and outcome assessment due to the open-label or crossover design, which limited the feasibility of blinding. Additionally, Loukanov et al. (2011) showed a high risk of incomplete outcome data due to missing follow-up information. Unclear risks were noted in random sequence generation and allocation concealment in Loukanov et al. (2011) and Khan et al. (2009), reflecting inconsistent reporting of randomization methods. Other biases, such as potential funding influences, were unclear in some studies. These methodological limitations necessitate cautious interpretation of the findings, as summarized in **Figure 1**.

Primary outcome: Reduction in mPAP and PVR

Across all studies, both inhaled iloprost and NO demonstrated significant reductions in mPAP and PVR, which are critical markers for PH. Reducing mPAP and PVR is essential for improving right ventricular function and reducing the risk of postoperative complications. These results confirmed the effectiveness of both therapies in addressing the primary pathophysiological characteristics of PH after cardiac surgery.

Secondary outcome: Hemodynamic parameters, SvO2, and PHTC

Several studies also measured secondary outcomes, including CI, SvO2, and incidence of PHTC. Most studies have shown that both therapies improved hemodynamic parameters, although the magnitude of improvement varied. For example, Winterhalter et al. (2008) highlighted that iloprost significantly improved CO and oxygenation, which are critical aspects of managing postoperative PH. Similarly, Khan et al. (2009) noted improvements in SvO2 and CI. However, some studies, such as those by Kirbas et al. (2012) and Loukanov et al. (2011), found no significant difference between the two therapies in secondary outcomes, particularly PHTC and ventilation duration.

Safety and side effects

The safety profiles were largely similar across the studies, with both inhaled iloprost and NO showing minimal adverse events. The most frequently reported side effects included mild thrombocytopenia and transient hypotension, which were not generally attributed directly to the inhaled agents. This favorable safety profile suggests that both therapies are well-tolerated in clinical settings. However, in some studies, iloprost was associated with slightly fewer

systemic side effects, which could be considered in long-term management strategies for patients with PAH.

Clinical implications

The clinical implications of these studies are thus significant. Overall, both inhaled iloprost and NO have been shown to effectively reduce mPAP and PVR with favorable safety profiles. However, iloprost appears to offer superior hemodynamic benefits, particularly in reducing pulmonary vascular resistance and improving CO, as observed by Winterhalter et al. (2008). Despite these findings, NO remains the standard therapy in many clinical settings due to its long-standing use and availability.

The forest plot results in **Figure 2** indicated an overall standardized mean difference of 0.34, with a 95% confidence interval ranging from -0.22 to 0.90 ($Z=1.19$, $p=0.24$). This suggests a non-significant effect, as the confidence interval included zero. The heterogeneity among the five studies (Abe 2017, Khan 2009, Kirbas 2012, Loukanov 2011, and Winterhalter 2008) was moderate ($I^2=43\%$, $Tau^2=0.14$, $Chi^2=5.25$, $p=0.15$), indicating some variability that was not statistically significant. However, the risk of bias assessment revealed pervasive methodological concerns, including a high risk of blinding outcome assessment and other biases across all studies. Additionally, there were high risks of incomplete outcome data for Loukanov 2011 and frequent unclear risks in random sequence generation and blinding of participants/personnel. These limitations necessitate cautious interpretation of the findings and underscore the potential impact of bias on reported effect sizes.

Discussion

This systematic review demonstrates that both inhaled iloprost and NO effectively reduce mPAP and PVR in patients with PH following cardiac surgery. Several studies also reported that iloprost produced greater reductions in PVR and improved CO, particularly in the study by Winterhalter et al. (2008). (17) These findings are consistent with the known selective pulmonary vasodilatory effects of inhaled therapies, which reduce pulmonary vascular tone while minimizing systemic hypotension compared with intravenous vasodilators. (7–9,13–15) Winterhalter et al. (2008) observed that inhaled iloprost resulted in a greater decrease in mPAP and PVR and a significant increase in CO compared with NO, suggesting a potential advantage in supporting right ventricular function in the postoperative period. (17) Similarly, Khan et al. (2009) reported that both therapies significantly reduced PAP and central venous pressure (CVP) while improving SvO2. However, most hemodynamic outcomes did not differ significantly between groups. (18) Overall, these findings highlight the clinical value of both inhaled agents for managing postoperative PH, particularly in high-risk patients undergoing procedures such as PEA or heart-lung transplantation. (19,20)

Recent studies have further supported these findings and provide broader evidence on the comparative efficacy of inhaled vasodilators. Ghadimi et al. (2023) reported that inhaled epoprostenol, a prostacyclin analog similar to iloprost, demonstrated comparable effectiveness to NO in preventing right ventricular failure after major cardiac surgery, with no significant differences in secondary outcomes such as duration of mechanical ventilation or mortality. (16) This equivalence reinforces the conclusions of the present review, particularly in clinical settings where NO remains the standard therapy due to its long-standing use and availability. (21)

Evidence from other populations also supports the effectiveness of inhaled prostacyclin therapies. Arslanoğlu et al. (2024) demonstrated that iloprost was both safe and effective in reducing PAP in pediatric patients after cardiac surgery, indicating its applicability across different age groups (22). In addition, a Bayesian network meta-analysis by Sardo et al. (2023) reported that both inhaled prostacyclin and NO were associated with shorter intensive care unit stays, highlighting their role in perioperative management of PH. (15) Similarly, a 2024 network meta-analysis by Elrosasy et al. found that prostacyclin analogs, including iloprost, effectively reduced mPAP during mitral valve surgery and improved cardiac index, consistent with the hemodynamic benefits of iloprost observed in this review. (23)

Following CPB, the pulmonary circulation is exposed to intense oxidative and nitrosative stress driven by ischemia-reperfusion injury, inflammatory activation, blood-biomaterial interactions, and transfusion-related oxidant burden. These processes impair endothelial function and compromise the integrity of major vasodilator pathways, particularly the NO-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) axis versus the prostacyclin (PGI2)-IP receptor-cyclic adenosine monophosphate (cAMP) axis. (24,25)

In the NO pathway, failure occurs at multiple redox-sensitive levels. Post-CPB endothelial dysfunction promotes endothelial nitric oxide synthase (eNOS) uncoupling, largely through oxidation of tetrahydrobiopterin (BH4), shifting eNOS from NO generation toward superoxide production, thereby reducing endogenous NO bioavailability while amplify-

ing oxidative stress. Superoxide rapidly reacts with NO to form peroxynitrite ($ONOO^-$), further depleting free NO and propagating oxidative injury to proteins central to vascular signaling. (26) Critically, reactive oxygen/nitrogen species can oxidize the heme moiety of soluble guanylate cyclase (sGC) (Fe^{2+} to Fe^{3+}), destabilize heme binding, and promote formation of heme-free apo-sGC, which is hyporesponsive or unresponsive to NO. This represents receptor-level inactivation rather than simple ligand deficiency and provides a mechanistic basis for postoperative NO resistance, where escalating inhaled NO may yield limited proportional vasodilation due to impaired cGMP generation. (25,27)

In contrast, the prostacyclin pathway exhibits a different redox vulnerability profile. The IP receptor is a G-protein-coupled receptor (GPCR) coupled to the stimulatory G protein (Gs-coupled GPCR) lacking a heme group or catalytic redox center, and there is no established phenotype of irreversible receptor "inactivation" analogous to apo-sGC. Instead, the principal redox-sensitive failure occurs upstream at the level of ligand availability. Prostacyclin synthase (PGIS) is highly susceptible to nitration and peroxynitrite-mediated oxidative inactivation, leading to a marked reduction in endogenous PGI2 production; given PGI2's intrinsically short half-life, oxidative conditions further diminish effective ligand bioavailability. (28)

These mechanistic distinctions support the clinical observation that iloprost, a chemically stabilized PGI2 analog, can act as a redox-resistant bypass of endogenous prostacyclin depletion by directly activating preserved IP receptors and restoring Gs-adenylate cyclase-cAMP signaling. In oxidant-rich post-CPB physiology, iloprost may therefore provide more consistent pulmonary vasodilation than inhaled NO, which is compromised by both NO scavenging and sGC oxidation/apo-sGC formation, leading to impaired downstream cGMP signaling. (25,27)

From a clinical perspective, these findings position inhaled iloprost as a viable alternative to NO, particularly in settings where sustained hemodynamic improvements are critical, such as in prolonged postoperative care for PEA or transplant patients. The reduced systemic side effects of iloprost, as observed in Winterhalter et al. (2008) (17) and Kirbas et al. (2012), may offer advantages in resource-limited settings where cost-effectiveness is a priority. (19) However, NO remains the standard therapy in many centers due to its widespread availability and established clinical guidelines. (9,12) Future research should prioritize large-scale, multicenter RCTs to confirm iloprost's superiority in hemodynamic outcomes, evaluate its cost-effectiveness, and explore long-term effects in diverse populations, including pediatric and adult patients with varying severities of PH. Additionally, studies addressing the optimal dosing and administration protocols for iloprost could reduce heterogeneity and enhance clinical applicability.

In pediatric settings, Arslanoğlu et al. (2024) demonstrated the safety and effectiveness of iloprost in reducing PAP after cardiac surgery, supporting its broader applicability. (22) A Bayesian network meta-analysis by Sardo et al. (2023) further showed inhaled prostacyclin and NO associated with reduced intensive care unit stays, reinforcing their role in perioperative PH management. Additionally, a 2024 network meta-analysis highlighted prostacyclin and NO as effective in lowering mPAP during mitral valve surgery, with iloprost contributing to an increased cardiac index. (15,23)

The strengths of this review include adherence to PRISMA 2020 guidelines, a comprehensive search across multiple databases (MEDLINE, Embase, CENTRAL, ClinicalTrials.gov, and WHO-ICTRP), and a focus on direct comparisons between inhaled iloprost and NO, addressing a gap in prior reviews that overlooked detailed hemodynamic changes. (16,20) By including only RCTs, crossover trials, and open-label trials, this study ensures a high level of evidence, particularly for outcomes such as mPAP, PVR, and PHTC. Heterogeneity in dosing regimens, e.g., iloprost at 10 ng/kg/min in Abe et al. (2017) (21) vs 20 μg single dose in Winterhalter et al. (2008), and patient populations (adults vs pediatric patients) may have contributed to the moderate heterogeneity observed in the forest plot (I^2=43%). (17) Additionally, the high risk of bias in blinding across all studies, as well as incomplete outcome data in Loukanov et al. (2011), may have influenced the reliability of the reported effect sizes. (20) The absence of a full quantitative meta-analysis, due to variability in study designs and reported outcomes, further limits the ability to pool precise effect sizes for secondary outcomes like PHTC and adverse events.

Publication bias is another potential concern, as the funnel plot was not included due to the limited number of studies, a limitation also noted in similar reviews. (17) The lack of long-term outcome data, such as mortality or hospital readmission rates, limits the ability to assess the sustained benefits of iloprost compared with NO, particularly in chronic PH management. These limitations align with those reported in prior studies, such as the 2017 review cited in the manuscript, which focused primarily on mortality and ICU stay without evaluating hemody-

namic changes. (16) Despite these constraints, the consistent finding of minimal adverse events (e.g., mild thrombocytopenia and transient hypotension) across studies supports the safety of both therapies, with iloprost showing a slightly better profile for systemic side effects. (1–4)

Conclusion

In conclusion, this systematic review demonstrates that both inhaled iloprost and NO are effective and safe for managing PH following cardiac surgery, with significant reductions in mPAP and pulmonary vascular resistance observed across studies. Iloprost exhibits superior hemodynamic benefits, including greater improvements in CO and fewer systemic side effects, such as thrombocytopenia, making it a promising alternative to NO, particularly for extended postoperative care. However, the limited number of studies and small sample sizes underscore the need for larger, multicenter, randomized controlled trials to confirm these findings, assess long-term outcomes, and evaluate cost-effectiveness across diverse patient populations.

Table 1. Summary of key findings from systematic review on inhaled iloprost vs NO for PH post-cardiac surgery

Study	Study design	Participants	Interventions	Comparator	Primary outcomes	Secondary outcomes	Key findings	Conclusion
Abe et al. (2017)	Randomized controlled trial	13 patients post PEA	Inhaled iloprost (10 ng/kg/min) or inhaled NO (20 ppm)	NO vs iloprost	Reduction in mPAP and PVR	Hemodynamic and respiratory parameters, side effects	Both therapies significantly reduced mPAP and PVR. No significant differences between-groups	Inhaled iloprost can be an alternative to NO for managing residual pulmonary hypertension after PEA
Khan et al. (2009)	Randomized crossover trial	25 heart and lung transplant recipients	Inhaled NO (20 ppm) or inhaled prostacyclin (iloprost)	NO vs iloprost	Reduction in PAP and CVP	CI, SvO2	Both therapies significantly reduced PAP and CVP and improved SvO2. No significant differences in hemodynamics between groups	Both inhaled NO and prostacyclin are effective in treating PH post-transplant, but prostacyclin may offer advantages in terms of side effects
Kirbas et al. (2012)	Open-label randomized trial	16 children with secondary PH post-cardiac surgery	Inhaled NO (20 ppm) or aerosolized iloprost (0.5 μg/kg every 90 min)	NO vs iloprost	Incidence of PHTC	Hemodynamic measurements, ventilation duration	No significant difference in PHTC incidence or duration of ventilation. Both treatments were effective in reducing PAP	Both inhaled NO and aerosolized iloprost are effective for managing PH in children, with no significant difference between treatments

Loukanov et al. (2011)	Open-label randomized clinical trial	15 infants with congenital heart defects and PH	Inhaled NO (10 ppm) or aerosolized iloprost (0.5 µg/kg every 2 hours)	NO vs iloprost	Frequency of PHTC, mPAP	Duration of mechanical ventilation, in-hospital mortality	Both therapies reduced the frequency of PHTC, with no significant difference in outcomes between groups	Aerosolized iloprost offers a comparable safety profile to NO in preventing PHTC in children post-cardiac surgery
Winterhalter et al. (2008)	Prospective randomized trial	46 patients with PH post-cardiac surgery	Inhaled NO (20 ppm) or iloprost (single dose of 20 µg)	NO vs iloprost	Reduction in mPAP and PVR	CO, oxygenation parameters	Iloprost was more effective than inhaled NO in reducing mPAP, PVR, and increasing CO. Significant reductions in SVR observed in both groups	Iloprost provides superior hemodynamic improvements compared to NO during the post-cardiac surgery period

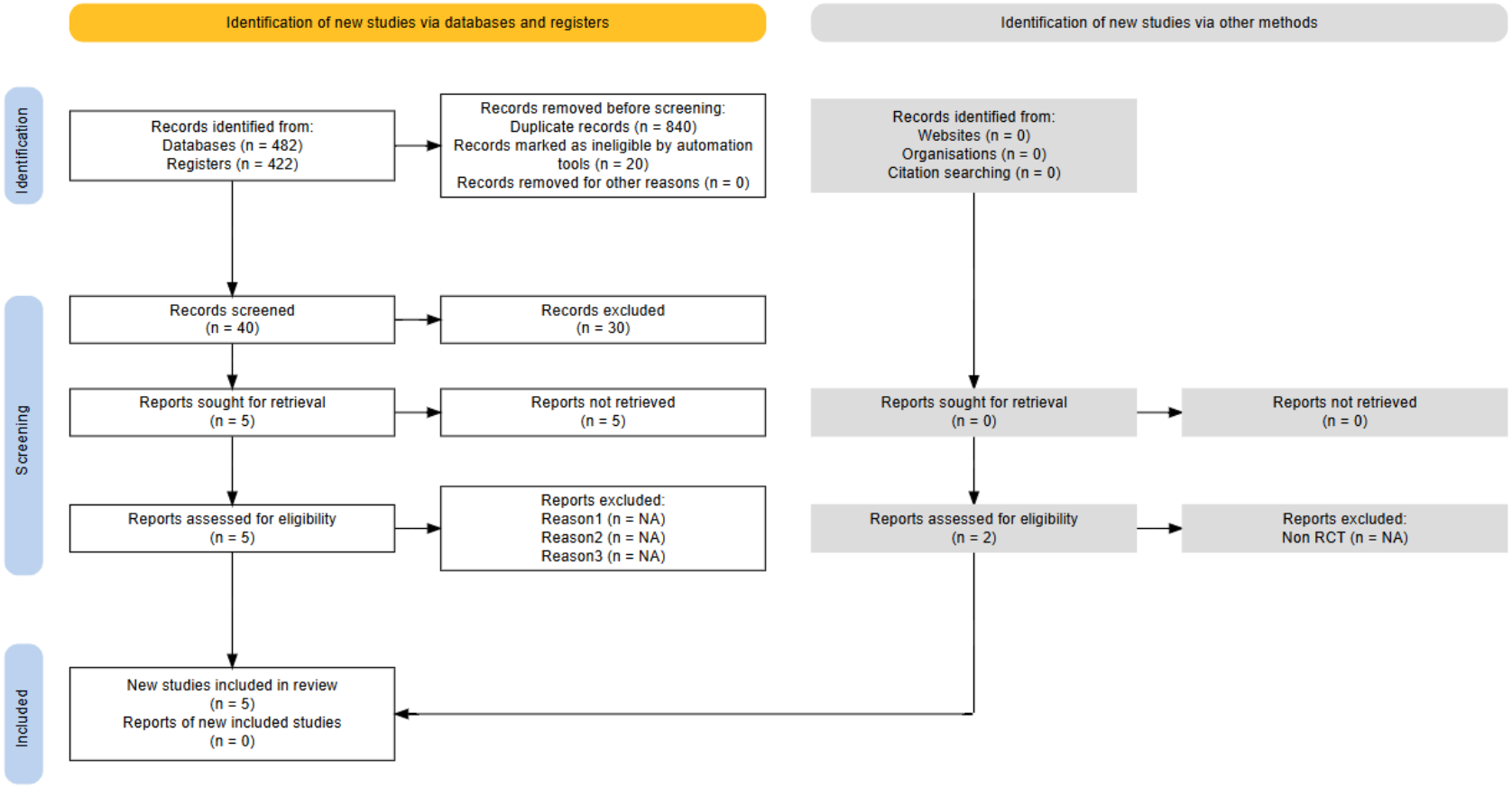
Legend: NO=nitric oxide; PH=pulmonary hypertension; PEA=pulmonary endarterectomy; mPAP=mean pulmonary artery pressure; PVR=pulmonary vascular resistance; PAP=pulmonary artery pressure; CVP=central venous pressure; CI=cardiac index; SvO2=mixed venous oxygen saturation; PHTC=pulmonary hypertensive crises; CO=cardiac output; SVR=systemic vascular resistance.

Table 2. Comparison of study outcomes on PH management post-cardiac surgery: inhaled iloprost vs NO

Study	Primary outcome: reduction in mPAP and PVR	Secondary outcome: CI, SvO2, PHTC	Side effects	Conclusion	Population	Interventions
Abe et al. (2017)	Significant reduction	Improvement in parameters	Minimal adverse events	Inhaled iloprost can be an alternative to NO for managing residual PH after PEA	13 patients post PEA	Inhaled iloprost (10 ng/kg/min) vs inhaled NO (20 ppm)
Khan et al. (2009)	Significant reduction	Improvement in SvO2, CI	Minimal adverse events	Both treatments are effective, but prostacyclin may offer advantages regarding side effects	25 heart and lung transplant recipients	Inhaled NO (20 ppm) vs inhaled prostacyclin (iloprost)
Kirbas et al. (2012)	Not applicable	No significant difference	Minimal adverse events	Both treatments are effective with no significant difference between them in managing PH	16 children with secondary PH post-cardiac surgery	Inhaled NO (20 ppm) vs aerosolized iloprost (0.5 μg/kg every 90 min)
Loukanov et al. (2011)	Significant reduction	No significant difference	Minimal adverse events	Aerosolized iloprost offers a comparable safety profile to NO in preventing PHTC	15 infants with congenital heart defects and PH	Inhaled NO (10 ppm) vs aerosolized iloprost (0.5 μg/kg every 2 hours)
Winterhalter et al. (2008)	Significant reduction	Improvement in CO and oxygenation parameters	Minimal adverse events	Iloprost provides superior hemodynamic improvements compared to NO in the post-cardiac surgery period	46 patients with PH post-cardiac surgery	Inhaled NO (20 ppm) vs iloprost (single dose of 20 μg)

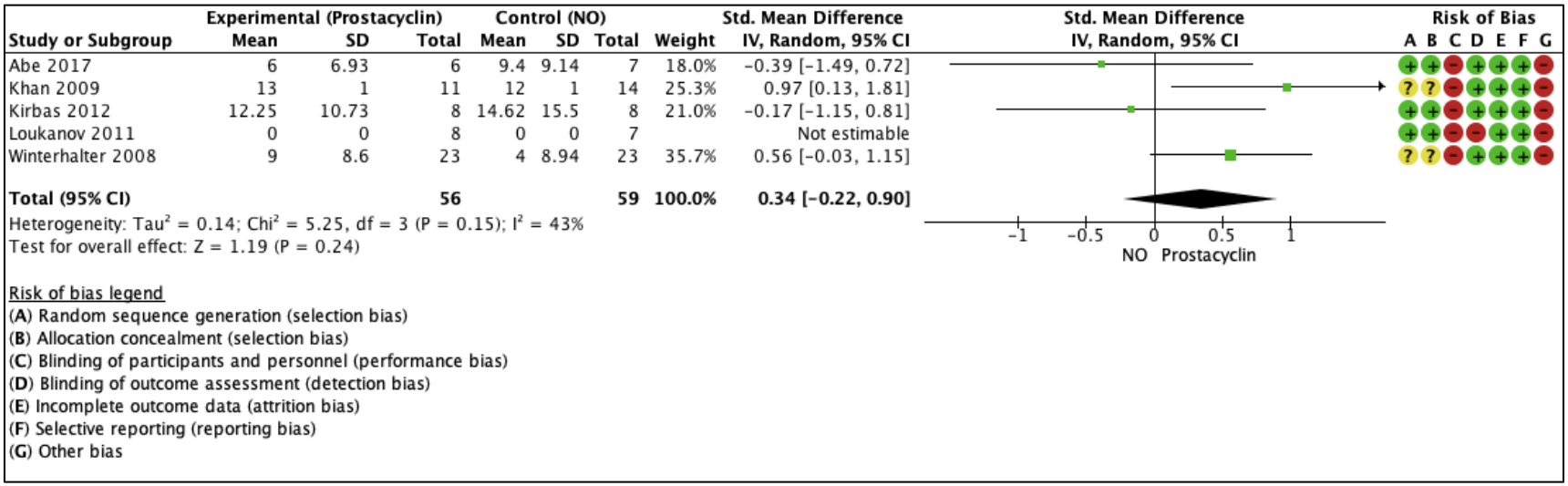
Legend: PH=pulmonary hypertension; NO=nitric oxide; mPAP=mean pulmonary artery pressure; PVR=pulmonary vascular resistance; CI=cardiac index; SvO2=mixed venous oxygen saturation; PHTC=pulmonary hypertensive crises; PEA=pulmonary endarterectomy; CO=cardiac output.

Figure 1. PRISMA diagram



Legend: PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NA=not available; RCT=randomized control trial.

Figure 2. Forest plot: Comparison of inhaled NO vs prostacyclin analogs on mPAP in postoperative PH



Legend: NO=nitric oxide; mPAP=mean pulmonary artery pressure; PH=pulmonary hypertension; SD=standard deviation; IV=inverse variance; CI=confidence interval.

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