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Original Article

Pulmonary Vasodilator and Inodilator Drugs in Cardiac Surgery: A Systematic Review With Bayesian Network Meta-Analysis

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Objective: The authors performed a systematic review to evaluate the effect of pharmacologic therapy on pulmonary hypertension in the perioperative setting of elective cardiac surgery (PROSPERO CRD42023321041).
Design: Systematic review of randomized controlled trials with a Bayesian network meta-analysis.
Setting: The authors searched biomedical databases for randomized controlled trials on the perioperative use of inodilators and pulmonary vasodilators in adult cardiac surgery, with in-hospital mortality as the primary outcome and duration of ventilation, length of stay in the intensive care unit, stage 3 acute kidney injury, cardiogenic shock requiring mechanical support, and change in mean pulmonary artery pressure as secondary outcomes.
Participants: Twenty-eight studies randomizing 1,879 patients were included.
Interventions: Catecholamines and noncatecholamine inodilators, arterial pulmonary vasodilators, vasodilators, or their combination were considered eligible interventions compared with placebo or standard care.
Measurements and Main Results: Ten studies reported in-hospital mortality and assigned 855 patients to 12 interventions. Only inhaled prostacyclin use was supported by a statistically discernible improvement in mortality, with a number-needed-to-treat estimate of at least 3.3, but a wide credible interval (relative risk $1.26 \times 10^{-17} - 0.7$). Inhaled prostacyclin and nitric oxide were associated with a reduction in intensive care unit stay, and none of the included interventions reached a statistically evident difference compared to usual care or placebo in the other secondary clinical outcomes.
Conclusions: Inhaled prostacyclin was the only pharmacologic intervention whose use is supported by a statistically discernible improvement in mortality in the perioperative cardiac surgery setting as treatment of pulmonary hypertension. However, available evidence has significant limitations, mainly the low number of events and imprecision.

Key Words: cardiac; pulmonary hypertension; meta-analysis; vasodilator; cardiopulmonary bypass; network meta-analysis

PULMONARY HYPERTENSION (PH) is currently defined as an increase in mean pulmonary pressure (mPAP) >20 mmHg, measured by catheterization of the right heart chambers at rest and in the supine position.[1] The proposed value uses the statistical criterion of an increase more than 2 standard deviations from the mean, and replaces the previous threshold value of ≥25 mmHg, which, given the novelty of this revision, has been employed by most of the published literature.[1,2]

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The clinical syndrome of pulmonary hypertension is divided into several groups based on pathophysiologic mechanisms and treatment as follows: pulmonary arterial hypertension (PAH, group 1), PH caused by left chamber heart disease (group 2), PH caused by pulmonary disease and/or hypoxia (group 3), PH from pulmonary artery obstruction (eg, chronic pulmonary thromboembolism, group 4), and PH with uncertain and/or multifactorial etiology (group 5).[1]

Pulmonary hypertension in cardiac surgery is caused mainly by diseases of the left ventricle (group 2), such as left ventricular failure or mitral valvopathy, most often stenosis, which causes pulmonary venous hypertension by the retrograde transmission of increased left atrial pressure and left ventricular diastolic pressure (ie, postcapillary PH).[3,4]

Inodilators and vasodilators are often combined with vasoconstrictors such as phenylephrine, norepinephrine, and vasopressin to maintain systemic vascular resistance and avoid myocardial hypoperfusion, which aggravates the vicious cycle of right ventricular dysfunction.[5]

In the early stages, the right ventricle increases contractility by up to 4-to-5 times with compensatory hypertrophy to maintain a favorable coupling with increased afterload.[6] However, this mechanism is limited, as it reduces ventricular compliance, and a reduction in systolic output is inevitable.[6] This is followed by ventricular dilatation and an increase in heart rate, with a significant increase in wall stress, oxygen consumption, relative ischemia, reduced mechanical efficiency, and negative impact on the left ventricle through a shift of the left septum.[6]

The incidence of acute and refractory decompensation of the right ventricle after cardiotomy is estimated at 0.04% to 0.1%, is higher in patients undergoing cardiac transplantation, 2% to 3%, or left ventricular assist device implantation, 20% to 30%.[7]

In summary, PH and acute right ventricular decompensation can complicate several cardiac surgical procedures, including coronary artery bypass grafting, valvuloplasty, especially mitral or combined valve surgery, left ventricular assist device implantation, cardiac transplantation, and pulmonary endarterectomy.

Nitric oxide (NO) is an endogenous vasodilator that is produced by the enzyme NO synthase.[8–12] Nitric oxide is administered in varying concentrations up to 80 ppm, and produces selective vasodilation in ventilated lung areas, resulting in reductions in pulmonary artery pressure, pulmonary vascular resistance, and right ventricular afterload without a reduction in systemic vascular resistance while potentially decreasing shunt fraction.[13,14] The onset (5-10 s) and offset (10-20 s) are extremely rapid.[15] Administration of exogenous NO induces downregulation of endothelial nitric oxide synthase and a relative increase of ET1, so sudden or rapid interruption of NO inhalation may cause rebound pulmonary vasospasm and right ventricular decompensation.[13] The interaction of NO with oxyhemoglobin produces nitrate and methemoglobin. However, the incidence of clinically significant methemoglobinemia may vary depending on factors such as NO accumulation in the mechanical ventilator circuit, incorrect administration, monitoring error, and congenital metabolic defects.[16,17] The need for devices specifically designed for NO delivery and the associated expense of $220/h limit the use of this drug.[15]

Prostanoid agonists include several drugs used in PAH therapy and the perioperative or intensive care setting: prostacyclin or epoprostenol, iloprost, treprostinil, PGE1, and selexipag.[18] Nebulized epoprostenol, similarly to NO, produces selective pulmonary vasodilation and has a rapid onset and half-life of 30-to-60 seconds and 1-to-2 minutes, respectively.[15] The dosage is generally 0.01-to-0.05 μg/kg/min. It also has an antiplatelet effect, but it has not been described in the literature as having an increased incidence of bleeding complications associated with its use. Nebulization of epoprostenol has been associated with filter obstruction of the ventilation circuit due to diluent (glycine) condensation, tracheitis, and a case of severe interstitial pneumonia.[19-21] The expense associated with using epoprostenol is estimated to be about $1.30-to-$10/hour.[15]

PDE-5 inhibitors, such as sildenafil and tadalafil, have an indication for group 1 PH (PAH).[22] A recent systematic review of the Cochrane literature confirmed their role in PAH but not in PH resulting from pulmonary disease and chronic thromboembolism (groups 3 and 4), whereas the role in group 2 PH remains uncertain.[23] Milrinone is a PDE-3 inhibitor, a nonspecific inodilator when administered intravenously, and commonly used in intensive care and anesthesiology, but used also as a selective pulmonary vasodilator by inhalation and tracheal routes.[24,25]

Levosimendan improves biventricular systolic and diastolic function via sensitization of myocardial troponin C to calcium, and causes vasodilation through modulation of vascular smooth muscle cells' voltage-gated K+ channels and large conductance Ca2+-activated K+ channels.[26]

ET receptor antagonist drugs include bosentan (dual antagonist of ETA and ETB, oral), ambrisentan (selective ETA, oral), and tezosentan (dual antagonist of ETA and ETB, intravenous), and are currently indicated in the treatment of PAH.[22]

Using pulmonary vasodilators in patients with non-PAH in cardiac surgery is controversial, and there are no evidence-based recommendations. The most recent consensus statement of the International Society for Heart and Lung Transplantation on the perioperative management of pulmonary hypertension and right heart failure provides clinically and physiologically sounding suggestions to improve the overall management of these patients, including a preoperative assessment and optimization by a multidisciplinary team, and a comprehensive discussion of both pharmacologic and extracorporeal treatments.[27] However, the authors acknowledge the expert-level evidence supporting their recommendations and the significant knowledge gap in this particular setting.[27]

Due to the heterogeneous pharmacologic options used in clinical management, and the difficulty in conducting pairwise comparisons as in conventional meta-analysis in similar cases, the authors analyzed the available evidence in a network meta-analysis framework.

Methods

Protocol Registration

The protocol of this systematic review was registered on the International Prospective Register of Systematic Reviews (CRD42023321041).

Eligibility Criteria

The authors identified and included studies on randomized controlled trials comparing inodilators and pulmonary vasodilator drugs (eg, NO, endothelin antagonists, phosphodiesterase inhibitors, and inhaled vasodilators) with any other pharmacologic intervention, standard care, or placebo in adult patients with established pulmonary hypertension undergoing elective cardiac surgery. The authors regarded a combination of various inodilators or vasodilators as a single intervention if this association was the intervention reported by the study methods.

Studies involving nonpharmacologic interventions or comparing extracorporeal devices (eg, hemadsorption) were excluded. The authors also excluded studies including patients undergoing heart transplant procedures or conducted outside the perioperative setting (ie, operating room and postoperative intensive care unit).

The primary outcome sought was in-hospital mortality, and the secondary outcomes of interest were the duration of mechanical ventilation or intubation (hours), the length of stay in the intensive care unit (days), the incidence of acute kidney injury Kidney Disease: Improving Global Outcomes stage 3 requiring renal replacement therapy, the incidence of cardiogenic shock requiring mechanical circulatory support, and the change in mean pulmonary artery pressure (mmHg).

Search Strategy

The authors searched PubMed, The Cochrane Library for clinical trials in CENTRAL, and Embase via Elsevier. Databases were searched from inception until May 14, 2023 (Supplementary Material, "Search Strategies" section, pages 57-61). The authors searched the references lists of included articles as snowballing methods. The authors included studies in the English language. The authors based their search strategy on the following MeSH terms: [Hypertension, Pulmonary], [Phosphodiesterase 5 Inhibitors], [Prostaglandins], [Endothelin Receptor Antagonists], [Cardiac Surgical Procedures], [Cardiopulmonary Bypass], and [Coronary Artery Bypass]. The full search strategies for each database are detailed in the Supplementary Material "Search Strategies" section, pages 57-61.

Study Screening and Election

Screening

The references were screened independently against the eligibility criteria by F.G. and V.T. using ASReview LAB.[28] Once the initial title/abstract screening was completed, the full texts of the included studies from that stage were reviewed by 2 authors (F.G. and V.T.) to determine if they should be included. Discrepancies were resolved by referring to a third author (S.S.). The inclusion/exclusion process was summarized in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram (Supplementary Figure S1), and a list of excluded full-text studies with reasons for exclusions was created (Supplementary Material "Excluded studies after full text screening" section, pages 54-56).[29]

Data Extraction

A standardized form (initially piloted on 5 included studies) was used for data extraction of characteristics of studies, outcomes, and risk of bias. The study authors (F.G., V.F.T.) extracted the following data from the included studies: study first author, year, setting; type of intervention, dose, timing of administration; comparators used; characteristics and number of participants; and any reported outcomes of interest. Data reported only on graphs were extracted using WebPlotDigitizer, and the median and interquartile ranges were converted into mean and standard deviations according to Hozo et al., as implemented in the Deep Meta Tool software.[30-32]

Risk of Bias Assessment

The risk of bias was assessed using the first version of the Cochrane Risk of Bias tool.[33] Two authors (F.G., V.F.T.) independently assessed the risk of bias for each study. The evidence for the primary outcome was summarized in the Confidence in Network Meta-Analysis framework.[34]

Data Analysis

The author S.S. performed the quantitative synthesis using the MetaInsight web app based on the R packages "netmeta," "gemtc," "BUGSnet," "rjags," and "coda."[35-40] The different interventions covered by the Network Meta-analysis were mapped onto a graph; the size of the nodes was proportional to the number of studies, and the edges were proportional to the number of comparisons. The same interventions at different doses were merged into a single group, whose mean and SDs for continuous outcomes were calculated according to Higgins et al. through a personalized function written in Python language.[41] Generalized linear models (GLMs), namely a fixed-effects model and a random-effects model for continuous outcomes, were constructed on an *a priori* noninformative distribution, normal likelihood distribution, and a link function identity. In contrast, GLMs for dichotomous outcomes were constructed on an *a priori* noninformative distribution, binomial likelihood distribution, and a link function log. Meta-analyses were performed using Markov Chain Monte Carlo simulation with 4 chains, a burn-in of 5,000 iterations followed by 20,000 iterations, with a thinning factor equal to one. Statistical models were selected according to a trial-error process based on Markov chain Monte Carlo convergence diagnostics (Gelman-Rubin trace plots and potential scale reduction factors) and the analysis of leverage plots.[42] The leverage plots were analyzed considering the distribution of observations, the

number of effective parameters, the model fitness, and the Deviance Information Criterion (DIC). The DIC is a function of model deviance and a measure of the effective number of parameters, so it penalizes the complexity of the model.[43] A difference of >5 points in total residual deviance, or DIC, was used to detect a substantial difference across different generalized linear models.[44] A compromise between accuracy and the number of effective parameters (complexity), as expressed by a smaller DIC, was one of the criteria for choosing the GLM models for this meta-analysis. The precision of the estimates was expressed by the 95% credibility intervals (95% CrIs).

All comparisons were summarized with a forest plot using placebo or usual care as a comparator and a radial "Surface Under the Cumulative Ranking Curve" (SUCRA) plot.[45] The formal evaluation of the coherence of the meta-analysis GLM model was performed by comparing the current model, which is based on mixed comparisons, with a model in which the principle of coherence was not considered valid, which is based solely on direct comparisons and is referred to as the "inconsistency" model. As previously indicated, leverage plots, deviance plots, and fitness statistics were used to compare the 2 models.

The effect of the intervention on dichotomous results was expressed as risk ratios (median and 95% CrI). For continuous outcomes, the effect of the intervention was calculated using the mean difference and the 95% CrI. The unit of analysis was individual patients. The authors did not contact investigators or study sponsors to retrieve missing data. The authors did not evaluate publication bias because few studies directly compared interventions of interest to perform a pairwise meta-analysis.

Reporting of the Meta-analysis

A detailed “Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions” checklist was added in the Supplementary Material, pages 1-4.[22]

Results

Included Studies

From the 934 records identified, 28 studies were included in the systematic review (Fig 1, Supplementary Table S1).[46-73] The timing of intervention administration was the following: before induction of general anesthesia (7, 26%), before cardiopulmonary bypass (7, 26%), during CPB (3, 11%), during separation from CPB (5, 18.5%), and in the postoperative intensive care unit (ICU) (5, 18.5%). Placebo and usual care were reported as comparators in 13 and 3 studies, respectively.

Some of the included studies that compared their intervention to standard care or placebo described details of the anesthesiologic management that could be relevant to the perioperative pulmonary hypertension management are as follows: invasive hemodynamic monitoring with a pulmonary artery catheter[48,52-54,57,59,61,73]; transesophageal echocardiographic monitoring[54,60,73]; maintenance of a normal or supranormal oxygen tension[52-54,56]; prevention of hypercarbia with a carbon dioxide tension in the lower range of normality[53,54,56]; liberal use of vasoactive medication according to the attending physician or according to local policies[52,53,57,63]; epinephrine with vasopressin as rescue vasoconstrictor or sodium nitroprusside during CPB[59]; routine use of dobutamine at CPB separation[57]; a single bolus of milrinone before cross-clamp[46]; standardized use of vasoactive medication (norepinephrine or milrinone) during CPB separation, with a dosage threshold over which the patients were defined as recipients of excessive inotropic support as adverse event[66,73]; and use of different vasoactive medication for pulmonary hypertension crisis episodes (iloprost and NO).[56]

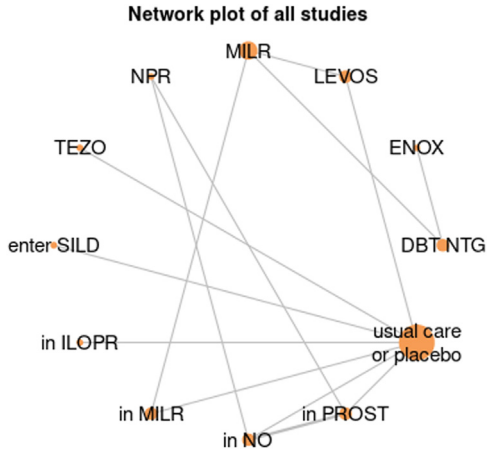

Fig 1. A network plot of the studies included in the mortality analysis. The number of studies that examined a treatment and compared 2 given treatments is represented by the size of the nodes and the thickness of the edges. DBT NTG, iv dobutamine + nitroglycerine; ENOX, iv enoximone; enter SILD, enteral sildenafil; in ILOPR, inhaled iloprost; in MILR, inhaled milrinone; in NO, inhaled nitric oxide; in PROST, inhaled prostacyclin or epoprostenol; LEVOS, iv levosimendan; MILR, iv milrinone; NPR, iv nitroprusside; TEZO, iv tezosentan.

The most reported outcome of interest was the change in mean pulmonary artery pressure mmHg (25, 89%), whereas other clinical outcomes were less consistently described: in-hospital mortality (11, 39%), duration of mechanical ventilation (11, 39%), stay in the ICU (14, 50%), incidence of renal replacement therapy or acute kidney injury III (3, 11%), and incidence of mechanical circulatory support (2, 7%). Adverse events were reported by a minority of studies, and were described heterogeneously (9, 32%), preventing a quantitative synthesis of this outcome (Supplementary Table S3).

The full details, including the number of patients, number of comparisons, number of studies, and summary statistics of each outcome for each comparison, were reported in Supplementary Tables S4 to S9.

The results of each pairwise comparison also were summarized in forest plots and SUCRA plots (Figs 2-4; Supplementary Figures S6, S7, S10, S11, S14, S15, S18, and S19).

In-hospital Mortality

Eleven studies reported in-hospital mortality, and assigned 855 patients to 12 different interventions.[46,48-51,53,55,58,62,70,73]

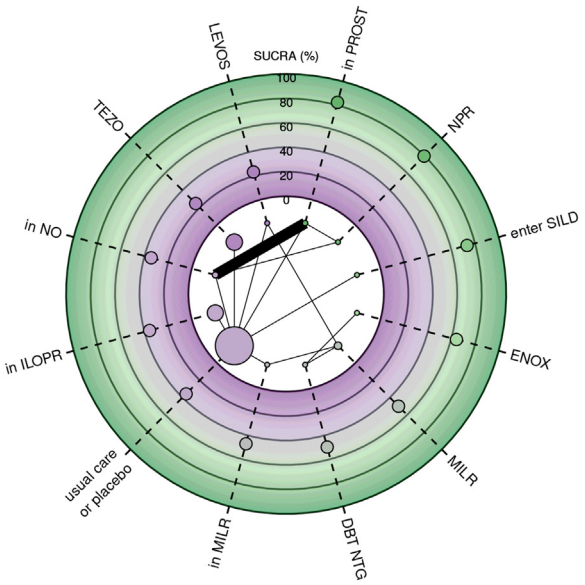

Fig 2. Radial Surface Under the Cumulative Ranking Curve (SUCRA) plot. The treatments are ordered clockwise starting at "12 o'clock," with the SUCRA value of each treatment plotted radially. The radial SUCRA contains a network of interventions with node sizes proportional to the evidence supporting them. DBT NTG, iv dobutamine + nitroglycerine; ENOX, iv enoximone; enter SILD, enteral sildenafil; ILOPR, iv iloprost; in ILOPR, inhaled iloprost; in MILR, inhaled milrinone; in NO, inhaled nitric oxide; in PROST, inhaled prostacyclin or epoprostenol; LEVOS, iv levosimendan; MILR, iv milrinone; NPR, iv nitroprusside; SUCRA, Surface Under the Cumulative Ranking Curve; TEZO, iv tezosentan.

Of the 66 possible pairwise comparisons, only 14 were direct. Only 4 of the included studies had no zero-event cells. The network graph was connected (Fig 1). The analysis was conducted under a fixed-effect model.

Enoximone (p = 0.27), inhaled prostacyclin (p = 0.29), and nitroprusside (p = 0.26) were found to have the highest likelihood of being classified as the best intervention to reduce in-hospital mortality in the quantitative synthesis under the fixed-effects model, using placebo or usual care as a comparator.

Inhaled prostacyclin, nitroprusside, eneteral sildenafil, enoximone, milrinone, dobutamine and nitroglycerine, and intravenous milrinone were categorized by the integration of the complete ranking distribution as being superior to placebo or standard care (Fig 2). Levosimendan and tezosentan received the worst SUCRA ratings. The size of the graph nodes indicates how little information is available to support these comparisons.

The number of zero-event arms significantly reduced the precision of the relative risk estimation for all comparisons. This issue is readily apparent in visualizing the forest plot, where many CrIs span several orders of magnitude (Fig 3).

Only inhaled prostacyclin use was supported by a statistically discernible improvement in mortality, with the 95th percentile of the CrI estimated at relative risk (RR) = 0.7. Two hundred fifty-two patients, or about 30% of the population included in this quantitative synthesis, served as the basis for this analysis.

Therefore, even considering the most conservative estimate of the relative risk, inhaled prostacyclin could be associated with a number needed-to-treat of $\leq$3.3 that can be regarded as clinically relevant. When compared with usual care or placebo, NO effect on mortality was not statistically evident (RR 1.01, CrI 95% 0.03-41).

The authors could not perform a subanalysis excluding high risk of bias trials because of network disconnection, but they performed a subanalysis excluding all zero-event arms.

The authors determined that the available evidence was insufficient to provide clinical recommendations because of the low precision of the effect size estimations, and the impossibility of subanalyses according to the risk of bias.

The evidence was accordingly downgraded to a low or very low level (Fig 5).

Mechanical Ventilation

Eleven studies reported the duration of mechanical ventilation or intubation. This analysis was based on 796 patients assigned to 11 different interventions.[46,49,51,53,55,56,58,60,64,70] Standard care and placebo were grouped as a unique intervention.

The number of direct comparisons was 11 on a total of 55 possible pairwise comparisons.

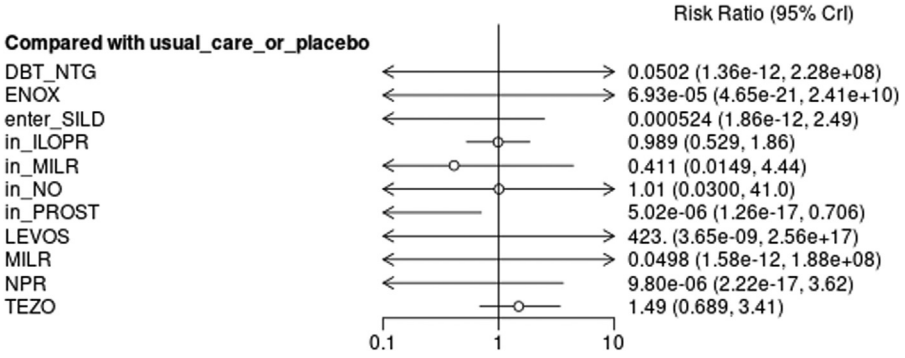

Fig 3. Forest plot for pairwise comparisons of included interventions versus placebo or usual care for the in-hospital mortality. The effect size is expressed as risk ratio. DBT NTG, iv dobutamine + nitroglycerine; ENOX, iv enoximone; enter SILD, enteral sildenafil; in ILOPR, inhaled iloprost; in MILR, inhaled milrinone; in NO, inhaled nitric oxide; in PROST, inhaled prostacyclin or epoprostenol; LEVOS, iv levosimendan; MILR, iv milrinone; NPR, iv nitroprusside; TEZO, iv tezosentan.

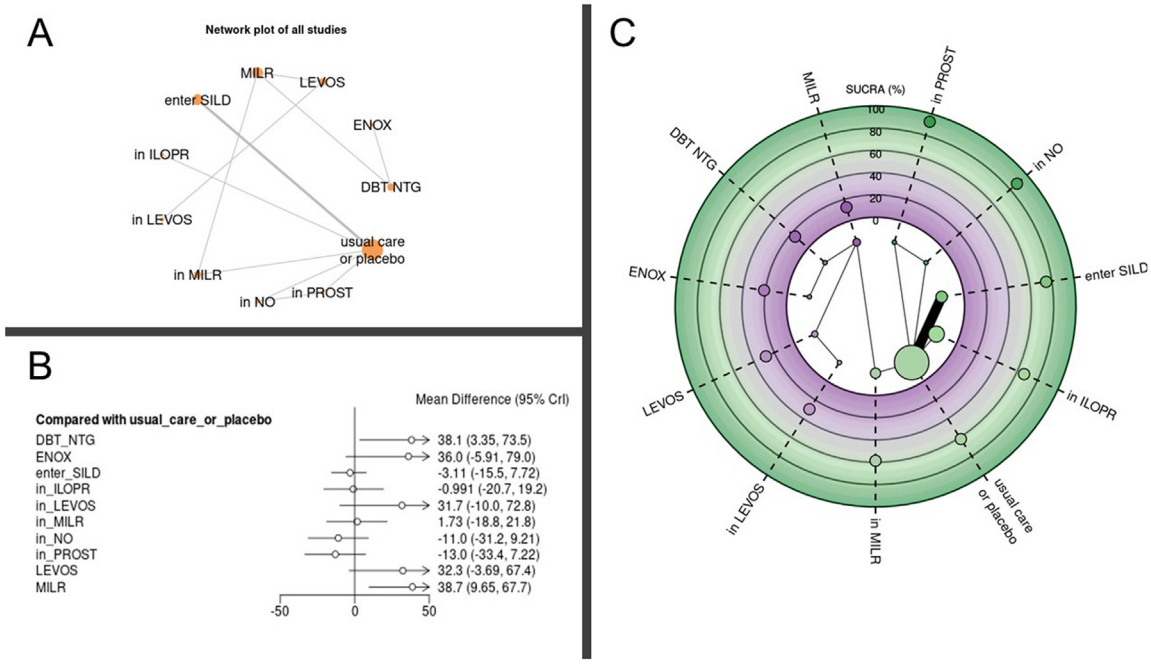

Fig 4. Summary of the findings of the meta-analysis of the duration of ventilation in hours. (A) network plot of the studies included in the analysis. (B) Forest plot for pairwise comparisons of included interventions versus placebo or usual care The effect size is expressed as the mean difference with the 95% CrI. (C) Radial Surface Under the Cumulative Ranking Curve plot depicting both the Surface Under the Cumulative Ranking Curve ranking of treatments and their relationship in the network. DBT+NGT, iv dobutamine + nitroglycerine; ENOX, iv enoximone; enter SILD, enteral sildenafil; in_ILOPR, inhaled iloprost; in_LEVOS, inhaled levosimendan; in_MILR, inhaled milrinone; in_NO, inhaled nitric oxide; in_PROST, inhaled prostacyclin or epoprostenol; LEVOS, iv levosimendan; MILR, iv milrinone.

The network graph was connected (Fig 4, A).

In the quantitative synthesis using a random effects model and comparing them to placebo or usual care, inhaled prostacyclin (p = 0.62) and NO (p = 0.26) demonstrated the highest likelihood of being considered the most effective interventions for reducing the duration of mechanical ventilation.

Based on the integration of the complete ranking distribution, inhaled prostacyclin, NO, sildenafil, and inhaled iloprost were deemed superior to placebo or standard care (Fig 4, B). On the contrary, inhaled milrinone and levosimendan for inhalation received the lowest SUCRA ratings.

However, the reduction in the duration of mechanical ventilation due to inhaled prostacyclin, NO, sildenafil, and inhaled iloprost did not receive statistical support from the relative risk estimations because the CrIs for each comparison included the possibility of no difference (Fig 4, C).

However, if further evidence confirmed the mean difference in mechanical ventilation duration of NO (mean difference −11 hours, CrI 95% −31.2 to 9.2) and inhaled prostacyclin (mean difference −13 hours, CrI 95% −33.4 to 7.2) compared with usual care or placebo, it could hold clinical significance in the postoperative care of elective cardiac surgery.

Other Secondary Outcomes

Fourteen studies reported ICU length of stay and assigned 863 patients to 10 interventions.[47-49,51-53,55,56,58,62-64,70,73] Inhaled prostacyclin had the highest probability of being the best intervention to reduce ICU length of stay (p = 0.89). When compared with standard care or placebo, inhaled prostacyclin (mean difference −1.43 days, CrI 95% −2.17 to −0.66) and NO (mean difference, CrI 95% −1.96 to −0.48) were associated with a statistically discernible reduction in ICU stay, whereas inhaled milrinone was associated with a slight increase (mean difference, CrI 95% 0.51-0.87).

Tezosentan and usual care or placebo were rated as the best treatments to prevent acute kidney injury out of 4 interventions that were assigned randomly to 344 patients across 3 studies.[46,48,59] Pairwise comparisons revealed that tezosentan was not significantly associated with lower relative risks.

Two studies assigned 294 patients to 3 interventions, and reported the prevalence of mechanical circulatory support.[25,26,46,48] Levosimendan or tezosentan had no statistically discernible association with a better outcome.

Twenty-six studies reported multiple measurements of mPAP, and 1,612 patients were allocated to 17 interventions.[47-59,61-73] The random-effects model showed that milrinone, inhaled prostacyclin, NO, and nitroprusside reduced mPAP compared to usual care or placebo.

The full report of these analyses is available in the Supplementary Material, Supplementary Figures S4 to S19 and Supplementary Tables S6 to S9.

Risk of Bias

The authors evaluated the overall risk of bias of 17 studies as low, 6 as moderate, and 5 as high, based on the single-

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Mixed evidence									
LEVOS vs usual care or placebo	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low	| Within-study bias | Imprecision |
TEZO vs usual care or placebo	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	| Within-study bias | Imprecision |
enter_SILD vs usual care or placebo	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	| Imprecision |
in_ILOPR vs usual care or placebo	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	| Imprecision |
in_MILR vs usual care or placebo	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	| Imprecision |
in_NO vs usual care or placebo	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	| Within-study bias | Imprecision |
in_PROST vs usual care or placebo	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	| Within-study bias | Imprecision |
Indirect evidence									
DBT+NTG vs usual care or placebo	--	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	| Imprecision |
ENOX vs usual care or placebo	--	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	| Imprecision |
MILR vs usual care or placebo	--	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	| Imprecision |
NPR vs usual care or placebo	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	| Within-study bias | Imprecision |

Fig 5. The evidence from the mortality analysis was graded and framed according to the Confidence in Network Meta-Analysis approach. The Confidence in Network Meta-Analysis takes into account the following domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. Both direct and indirect evidence are represented separately. DBT+NGT, iv dobutamine + nitroglycerine; enter SILD, enteral sildenafil; ENOX, iv enoximone; in_ILOPR, inhaled iloprost; in_MILR, inhaled milrinone; in_NO, inhaled nitric oxide; in_PROST, inhaled prostacyclin or epoprostenol; LEVOS, iv levosimendan; NPR, iv nitroprusside; TEZO, iv tezosentan.

domain risk of bias and its potential effect on the outcomes studied by this systematic review (Fig 5 and Supplementary Figure S20).

The most affected domains with a high risk of bias were the blinding of personnel and outcome assessment. At least 11 studies did not report details on randomization or allocation concealment procedures.

As shown by the Confidence in Network Meta-Analysis table (Fig 5), the evidence generated by the quantitative synthesis was downgraded because of imprecision. Due to the significant risk of bias in the included study, the evidence supporting one comparison—levosimendan versus standard treatment or placebo—was lowered further to a very low degree of confidence.

Sensitivity Analysis

The authors performed a sensitivity analysis of the primary outcome to address the imprecision bias related to the frequent zero-event cells. Every study containing zero events and an arm from a single three-armed study was removed from the quantitative synthesis. After this restriction, only 4 studies allocating 586 patients to 4 different interventions contributed to these results.

No intervention produced a statistically discernible effect on mortality compared with usual care or placebo. The SUCRA radial plot showed that the best ranking could be attributed to inhaled milrinone (Fig 6).

Discussion

Considering usual care or placebo as the comparator, the systematic review results showed a protective effect of inhaled prostacyclin on in-hospital mortality and a statistically evident effect of milrinone, inhaled prostacyclin, NO, and nitroprusside on mPAP.

Most of the authors of the included studies chose an mPAP threshold of 25 mmHg to define pulmonary hypertension, or they included patients with more severe PH or right ventricular involvement. Despite the last revision of PH classification criteria setting at 20 mmHg as the diagnostic cut-off, the authors believed this methodologic choice was appropriate to evaluate the interventions of interest in their meta-analysis because this sicker population might have a superior risk of developing right ventricular dysfunction and organ failure.[1]

However, some caveats are necessary. Most studies did not have a size compatible with sufficient power to study the clinical outcomes of interest for the systematic review.

The frequent zero-events arms severely affected the estimation of relative risks for the mortality outcome, leading to high imprecision. The authors addressed this issue with a sensitivity analysis, but this led to a significant reduction of the included studies.

The main limitation to the generalization of these results was the evidence on which they were constructed. The authors could find some heterogeneity in the enrolled population, comparators, aims and outcomes, and sample size in the included clinical studies (Supplementary Tables S1-S3). A frequent comparator is standard care or placebo, which shows great intratrial and intertrial variability, and may include treatments that may influence the outcomes under investigation in both directions (eg, vasodilator drugs with effect on the pulmonary circulation and vasopressors).

The studies in this review spanned from 1997 to 2022. The standard of care and intraoperative management of cardiac surgery patients has evolved in this period, which makes comparison of these studies difficult and may have contributed to a source of bias.

Cardiothoracic and vascular anesthesia is one of the fastest growing fields of clinical anesthesiology, with a significant

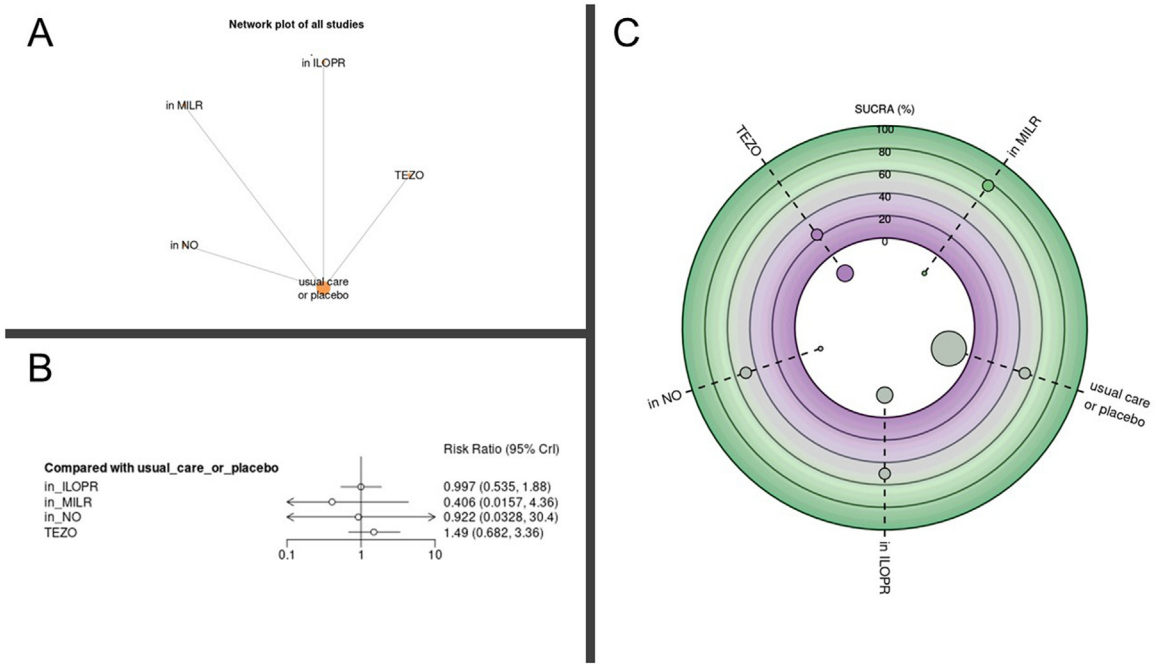

Fig 6. The summary of the findings of the sensitivity analysis of the in-hospital mortality. (A) Network plot of the studies included in the analysis. (B) Forest plot for pairwise comparisons of included interventions versus placebo or usual care The effect size is expressed as the mean difference with the 95% CrI. (C) Radial Surface Under the Cumulative Ranking Curve plot depicting both the Surface Under the Cumulative Ranking Curve ranking of treatments and their relationship in the network. in_ILOPR, inhaled iloprost; in_MILR, inhaled milrinone; in_NO, inhaled nitric oxide; TEZO, iv tezosentan.

improvement in outcomes despite steady increases in average age, frailty, and comorbidity burden among patients.

In the United Kingdom, the in-hospital mortality for all cardiac surgery procedures dropped from 4.0% to 2.8% in the 2002-to-2016 period, despite an increase of the mean EuroSCORE from 5.6 ± 8.7 to 8.5 ± 11.4.[74]

A similar trend was observed in the United States, where 30-day mortality after coronary artery bypass grafting fell from 3.05% in 1997 to 1999 to 2.5%in 2021.[75,76]

The size of the nodes of the network meta-analysis (NMA) networks demonstrated the numerical imbalance among the different treatments and, consequently, the evidence available to support them. The overall risk of bias analysis demonstrated that the evidence was of low-to-moderate quality.

A quite unexpected finding in the authors' mortality analysis was the low ranking of intravenous levosimendan.

Levosimendan is regarded as a highly effective medication within the authors' target population. This is attributed to its ability to produce a favorable impact on ventricular-arterial coupling by synergistically enhancing right ventricle contractility and promoting pulmonary vasodilation.[77]

The authors' interpretation of this observation was centered around the significant imprecision of the effect estimation that penalized the ranking of this agent, as depicted in the forest plot (Fig 3).

The choice of outcomes in the systematic review was certainly relevant, and reflected common considerations in perioperative and intensive care medicine; they were also easily measurable and correlated with costs.

Mechanical ventilation duration, especially given the forced interchangeability with the concept of the duration of intubation, is particularly difficult to interpret without data on the modality and protocol of spontaneous breathing trial and extubation. This is extremely relevant in a population vulnerable to increased right ventricular afterload, which is affected by positive airway pressure and hypoxemia or hypercapnia.[78]

The perioperative use of pulmonary vasodilators in cardiac surgery is controversial, especially for adult patients with non-PAH PH, such as group 2, the most common in clinical practice.

The reasons could be related to the complex pathophysiology and natural history of this subset of PH, in which the "reactive" component, which is sensitive to vasodilators, is progressively reduced in favor of the "fixed" component, resulting from structural remodeling, as well as the function of the right ventricle and its ability to adapt to the determining factors of increased afterload and left ventricular function.[79] These variables could have been heterogeneously distributed in the population included in clinical trials. The reasons for heterogeneity in the clinical trial populations of group 2 PH could be attributed, at least partially, to the complex pathophysiology and natural history of this PH subset. Despite the classic view of a simple build-up of backward pressure from an increased left atrial intracavitary pressure, inflammation, endothelial dysfunction, vasoconstriction, and remodeling play a significant role.[79]

In addition, intraoperative factors such as cardiac protection quality, duration of CPB, the extent of microembolism, and surgical results are variables that interact with individual susceptibility determined by preoperative fitness.

It also should be noted that acute refractory right ventricular decompensation is a high-risk condition for survival, associated with 70%-to-75% mortality, and, therefore, does not

justify the potential harm to the patient resulting from the application of rigid experimental protocols.[80,81] Given the possible combinations of factors, it is not surprising that it is difficult to weigh the isolated relative effect of a treatment in this context. If the authors add to this the low frequency of refractory right heart failure compared with the volume of elective cardiac surgery, 0.1% of postcardiotomy patients, and the difficulty of designing and conducting a randomized controlled trial (RCT) in this population, good observational evidence could be useful in guiding the use of these drugs.[80-82] In particular, large observational data and big data approaches might be suitable tools to investigate this topic.[83]

Most published studies analyzed hemodynamic effects assuming that reduction in pulmonary arterial pressure is the mediator of clinical benefit, but it is possible that modulation of endothelial dysfunction and organ damage may be equally or more significant. Nitric oxide–based homeostasis is impaired severely by cardioplegic arrest and extracorporeal circulation.[84] Several meta-analyses on using certain pulmonary vasodilators in cardiac surgery have been published.

A recent NMA compared inhaled milrinone with intravenous milrinone and placebo in hemodynamic, echocardiographic, and clinical outcome variables, and included 30 studies, of which 6 used nebulized milrinone (RCTs and observational studies) without finding any significant benefit of intravenous or inhaled milrinone over placebo.[85] A pairwise meta-analysis on the use of NO in cardiac surgery without age restriction based on 18 RCTs, with parallel groups, demonstrated a minimal decrease in the duration of mechanical ventilation and ICU stay, quantified at a mean difference of approximately 9 hours and 5 hours, respectively, compared with a group consisting of all comparators.[86] A pairwise meta-analysis on inhaled vasodilator agents in cardiac surgical patients with PH based on 10 RCTs demonstrated an effect on hemodynamic and echocardiographic variables, and a negligible increase in the length of stay of about 16 hours compared with placebo (5 studies).[87] The results of this systematic review can best be compared with the pairwise meta-analysis on NO because it was more inclusive of the different treatments, and its results were based on data from adult patients. Compared with the pairwise work, this NMA better summarized the state-of-the-art of anesthetic management of pulmonary hypertension in cardiac surgery patients, as it included all treatments and especially allowed comparison of the main competitors, NO and nebulized prostacyclin, with each other and with a standard care or placebo group. However, the final message is the same—clinical studies on pulmonary vasodilators in cardiac surgery are weak and often inadequate to investigate the effects on relevant clinical outcomes.

Conclusions

A quantitative synthesis of available evidence on the effectiveness of pulmonary vasodilators and inodilators in elective cardiac surgery under a Bayesian framework showed that inhaled prostacyclin, nitroprusside, and enoximone could be the best interventions to reduce in-hospital mortality. Inhaled prostacyclin, in particular, was associated with a statistically discernible effect that could be translated into a number needed-to-treat of ≤3.3. The most effective interventions for reducing mechanical ventilation duration were inhaled prostacyclin, NO, sildenafil, and inhaled iloprost. Although NO and inhaled prostacyclin are the most effective interventions for decreasing ICU length of stay, neither is associated with statistically evident lower relative risks. Furthermore, none of the interventions was statistically superior to usual care or placebo for the incidence of acute kidney injury grade 3 or mechanical circulatory support. Among the studied interventions, milrinone, inhaled prostacyclin, NO, and nitroprusside were associated with a statistically discernible reduction of mPAP. However, the overall quality of the evidence was low.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2023.07.041.

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