DOI: 10.1002/pul2.70001

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRi | WILEY

Prostacyclin pathway vasodilators in patients with chronic thromboembolic pulmonary hypertension (CTEPH): A systemic review and meta-analysis of randomized controlled trials

Weijun Li[1] | **Xingxue Pang**[1] | **Jun Chen**[2] | **Xiaoxia Ren**[1] | **Huaibing Zhao**[1] | **Xu Wang**[1] | **Ning Zhao**[3] | **Dayi Hu**[4] | **Zhongyi Jin**[1]

[1]Department of Cardiovascular Medicine, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, People's Republic of China

[2]Capital Medical University, Beijing, People's Republic of China

[3]Department of Geriatrics, Chui Yang Liu Hospital Affiliated to Tsinghua University, Beijing, People's Republic of China

[4]Department of Cardiology, Peking University People's Hospital, Beijing, People's Republic of China

Correspondence
Zhongyi Jin, MD, Department of Cardiovascular Medicine, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, 100700, People's Republic of China.
Email: zhygold@163.com

Funding information
This work was supported by Science and Technology Foundation of Tongzhou District, Grant/Award Number: KJ2023CX060

Abstract

Although surgical and interventional therapy has emerged as the primary treatment for patients with chronic thromboembolic pulmonary hypertension (CTEPH), there remains a subset of patients who need medication therapy. This study aimed to evaluate the efficacy and safety outcomes of prostacyclin pathway vasodilators, providing further insight for clinical decision-making. A literature search was conducted in PubMed, Embase, and CENTRAL databases from inception to December 2023. Literature screening and quality assessment were carried out with the Cochrane Risk of Bias Tool. Data analysis was conducted using RevMan 5.4 software. We included 6 randomized controlled trials with 387 patients. Prostacyclin pathway vasodilators demonstrated a significant improvement in PVR (−125.26 dynes·sec·cm^{-5}, 95%CI: −219.29 to −31.23, $Z = 2.61$, and $p < 0.009$), RAP (−0.78 mmHg, 95% CI: −1.52 to −0.04, $Z = 2.06$, and $p = 0.04$), cardiac index (0.62, 95%CI: 0.54 to 0.69, $Z = 16.13$, and $p < 0.00001$), and the number of patients showing improvement in WHO functional class (3.86, 95%CI: 1,92 to 7.77, $Z = 3.79$, and $p = 0.0002$) compared to controls, moreover, a trend towards improvement was observed in mPAP, 6MWD, and NT-proBNP. Regarding the safety endpoints, no significant difference was found in both groups in terms of serious adverse events and all-cause deaths. The prostacyclin pathway vasodilators present therapeutic potential for CTEPH patients with inoperable or

Abbreviations: 6MWD, 6-min walk distance; BNP, Brain natriuretic peptide; BPA, Balloon pulmonary angioplasty; CTEPH, Chronic thromboembolic pulmonary hypertension; NTproBNP, N-terminal pro-B-type natriuretic peptide; PAP, Mean pulmonary artery pressure; PEA, Pulmonary endarterectomy; PH, Pulmonary hypertension; PH, Pulmonary hypertension; PVR, Pulmonary vascular resistance; RCTs, Randomized controlled trials.

The paper is not under consideration elsewhere. None of the paper's contents have been previously published. All authors have read and approved the manuscript. All authors have no conflict of interest to declare.

persistent/recurrent PH after PEA/BPA primarily characterized by distal small-vessel and microvasculopathy. However, the current clinical evidence remains insufficient and controversial, necessitating further validation.

KEYWORDS
chronic thromboembolic pulmonary hypertension, prostacyclin, pulmonary hypertension

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially lethal disease caused by non-resolving organized thrombi obstructing the single or multiple pulmonary arteries, resulting in a progressive increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), ultimately developing right ventricular failure.[1] It is currently classified under group IV of the clinical classification of pulmonary hypertension(PH).[2] The incidence of CTEPH ranges from 0.1% to 9.1% within the first 2 years following a symptomatic PE event and up to 10% among patients with a history of recurrent PE.[3]

The treatment in the CTEPH algorithm includes a multimodal approach of combinations of pulmonary endarterectomy (PEA), balloon pulmonary angioplasty (BPA), and medical therapies, targeting the mixed anatomical lesions: proximal, distal, and microvascular vasculopathy, respectively. In contrast to medication-based therapy for PAH, surgical PEA is the current first-choice treatment for patients with chronic thromboembolic pulmonary hypertension (CTEPH). Additionally, BPA is suitable for patients with inoperable CTEPH or persistent/recurrent PH after PEA, improving hemodynamics, right heart function, and exercise capacity. Overall, PEA and/or BPA are the main therapeutic efforts in CTEPH targeting mechanical vascular obstructions in vessels with a cross-sectional diameter of ~0.5–10 mm.[4]

However, a subset of patients with CTEPH remains unsuitable for PEA or BPA due to concerns about inaccessible vascular obstruction, significant prohibitive comorbidities, and microvascular vasculopathy. Furthermore, some patients present symptomatic persistent or recurrent PH following BPA/PEA.[5,6] Thus, an unmet need exists for these specific CTEPH patients, and medication therapy also plays a crucial role in their treatment. Histopathological studies have revealed that CTEPH is characterized by small-vessel vasculopathy similar to that observed in pulmonary arterial hypertension (PAH).[7] The pathogenesis of PH is associated with excessive vasoconstriction, an imbalance between vascular cell proliferation and apoptosis, an influx of cellular inflammation, and secondary thrombosis, which contribute to the narrowing of the pulmonary arteriolar lumen and increased pulmonary vascular afterload in CTEPH.[8] Vasoconstrictor endothelin-1 and deficiencies of vasodilators, including nitric oxide and prostacyclin (prostaglandin I^2), appear to play a role in the pathogenetic progress. Riociguat, a vasodilator used for the treatment of PAH, is currently approved as a medication treatment for inoperable CTEPH or persistent/recurrent PH after PEA based on the CHEST trials.[9] It specifically targets the nitric oxide (NO) pathway, which plays a crucial role in the management of distal vessels and microvascular vasculopathy.

Prostacyclin exhibits a unique pharmacological mechanism including potent vasodilatory, antithrombotic, anti-inflammatory, and antiproliferative effects. Various types of prostacyclin analogs, such as epoprostenol, iloprost, and beraprost, have been observed through these uncontrolled studies in CTEPH patients, revealing specific therapeutic benefits.[10–12] Recently, subcutaneous treprostinil has been approved by the European Medical Agency for treatment in CTEPH patients. Given the inconsistent findings from recently published RCTs assessing the efficacy of prostacyclin pathway vasodilators for CTEPH, there remains uncertainty with the overall benefits in the treatment of this class of drug in CTEPH, thereby we have conducted a comprehensive meta-analysis of RCTs to date, focusing on CTEPH patients treated with prostacyclin pathway vasodilators, aiming to assess both efficacy and safety outcomes crucial for clinical decision-making.

METHOD

Search strategy

We carried out a literature search on EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed from inception to December 1, 2023, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The main search terms were “chronic thromboembolic pulmonary

hypertension", "prostacyclin", "epoprostenol", "treprostinil", "beraprost", "iloprost", and "selexipag".

The specific literature strategy is presented in Table 1. Our literature search encompassed not only full-text articles but also included meeting abstracts, moreover, we did not preset language limitations during the literature screening process. To avoid duplication with our study, we searched PROSPERO for similar systematic reviews in progress and ClinicalTrials. gov for any ongoing studies. Additionally, we reached out to investigators or study sponsors for which only the abstract was available and tried to obtain the full text.

Literature inclusion and exclusion criteria

The eligible randomized controlled trials (RCTs) met the following inclusive criteria: (1) adult patients diagnosed with chronic thromboembolic pulmonary hypertension, (2) comparison of efficacy and safety between the group with prostacyclin pathway vasodilators and controls, (3) reporting of numerical data at baseline and the end of the study was carried out in both intervention and control groups, and (4) inclusion of a non-placebo control group.

The following exclusion criteria were: (1) studies with single-arm design, case reports, letters, retrospective studies, and cross-sectional studies, (2) RCTs without assessment of therapeutic efficacy for prostacyclin pathway drugs, and (3) a study with crossover design to assess clinical effects.

Data extraction and outcome measure

Two reviewers independently screened articles according to the inclusion criteria. All included studies were imported into a reference manager software program (EndNote x8.1, Thomson Reuters, Stanford, Connecticut, USA) and duplicate studies were excluded using the software. We designed and utilized a data collection form to extract data on study characteristics and outcomes. After duplicate removal, two investigators reviewed the

TABLE 1 Research strategy.

PUBMED	**chronic thromboembolic pulmonary hypertension**	**#1 chronic thromboembolic pulmonary hypertension [Title/Abstract]**	**3206**
		#2 Filters applied: Clinical Trial	106
		#3 (((((beraprost[Title/Abstract]) OR (iloprost[Title/Abstract])) OR (treprostinil[Title/Abstract])) OR (epoprostenol[Title/Abstract])) OR (selexipag[Title/Abstract])) OR (prostacyclin[Title/Abstract])	17523
		#4 Filters applied: Clinical Trial	1109
		(chronic thromboembolic pulmonary hypertension[Title/Abstract] AND (clinicaltrial[Filter])) AND ((((((beraprost[Title/Abstract]) OR (iloprost [Title/Abstract])) OR (treprostinil[Title/Abstract])) OR (epoprostenol [Title/Abstract])) OR (selexipag[Title/Abstract])) OR (prostacyclin[Title/Abstract]) AND (clinicaltrial[Filter]))	13
EMBASE	chronic thromboembolic pulmonary hypertension	#1 'chronic thromboembolic pulmonary hypertension'/exp OR 'chronic thromboembolic pulmonary hypertension'	6756
		#2 'prostacyclin'/exp OR prostacyclin OR beraprost:ti, ab, kw OR epoprostenol:ti, ab, kw OR iloprost:ti, ab, kw OR treprostinil:ti, ab, kw OR selexipag:ti, ab, kw	38417
		#3 #1AND#2	612
CENTRAL	chronic thromboembolic pulmonary hypertension	#1 ("chronic thromboembolic pulmonary hypertension"):ti, ab, kw; in Trials (Word variations have been searched)	292
		#2 ("prostacyclin"):ti, ab, kw OR ("epoprostenol"):ti, ab, kw OR ("beraprost"):ti, ab, kw OR ("iloprost"):ti, ab, kw OR ("treprostinil"):ti, ab, kw; in Trials (Word variations have been searched)	1977
		#3 (selexipag):ti, ab, kw; in Trials (Word variations have been searched)	139
		#4 #2 OR #3	2039
		#5 #1AND #4	33

full text and extracted the following data: (1) General information: study name (author, year), study design, duration of prostacyclin pathway therapy, and allocation concealment; (2) Participants information: mean age and age range, gender, inclusion criteria, number of participants; (3) Interventional information: drug names, administration route, dosage of administration; (4) Hemodynamic parameters include the change in mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), cardiac index (CI) or cardiac output (CO), and right atrial pressure (RAP) measured by right heart catheterization (RHC) both at baseline and the end of this study[5]; exercise capacity included 6-min walk distance (6MWD), WHO functional class.[6] N-terminal prohormone of brain natriuretic peptide (NT-proBNP),

Quality assessment

We conducted the quality assessment with the Cochrane Handbook for Systematic Review of Intervention-version 5.1.0 recommended risk assessment tool for bias in RCTs.[13] The assessment content included the following 7 items: (I) which random method to use (II) whether to perform allocation concealment; (III) the implementation of blinding between patients and investigators; (IV) the effect of blinding; (V) whether the results were complete; (VI) whether the survey results were credible; and (VII) other biases.

Sensitivity analysis

Sensitivity analysis aimed to identify the stability of the overall results of the pooled data set, which would have implications in various scenarios: when a study was deleted, the result would be significantly different, it indicated the high sensitivity of this study and the pooled results showed low stability. Conversely, if there was little difference in the overall results when a study was deleted, it indicated the low sensitivity of the combined results, and the results obtained were stable.

Statistical analysis

The meta-analysis was performed using the RevMan 5.4 software. continuous variables were presented by the mean difference (MD) when the outcomes of the included studies were measured using the same methodology; otherwise, the standardized mean difference (SMD) was applied when studies assessed the same outcome with different methodologies. The odds ratio (OR) was used as the effect size for dichotomous variables, both of which were reported along with 95% CI.[13,14] The included studies were first tested for heterogeneity, with $\alpha = 0.1$ as the test level. If there was no significant heterogeneity between the studies ($p > 0.1$, $I^2 < 50\%$), the fixed-effects model (FEM) was used; if there was significant heterogeneity between studies ($I^2 > 50\%$), the random-effects model (REM) was selected. $p < 0.05$ indicated that the difference was statistically significant.

RESULTS

Search results

Our search identified a total of 671 records, out of which the full texts and abstracts of 537 records were reviewed. Subsequently, 6 RCTs including 387 patients, comprising 5 full-text articles and 1 meeting abstract, met the eligibility criteria for inclusion in this review.[6,15–19] Further details and reasons for exclusion were present in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Figure 1 and Table 2). Among these included studies, prostacyclin pathway drugs including iloprost (2 articles), treprostinil (1 article), and selexipag (3 articles) were used in the treatment of CTEPH.

Quality assessment

We conducted a risk of bias analysis of all included studies to evaluate the overall quality of the studies. For all included RCTs, there was a lower risk of bias. There was an increased risk of bias in the SELECT study[17] due to the early termination of the trial (Figure 2).

HEMODYNAMIC METRICS

Pulmonary vascular resistance

The PVR was reported in five studies,[6,16–19] which showed a significant improvement in the prostacyclin pathway vasodilator treatment compared to controls. However, the results showed a significant heterogeneity, $Chi^2 = 15.69$, $I^2 = 74\%$, and $p = 0.003$. The REM was then used for analysis which showed that the mean difference (MD) was -125.26 dynes·s·cm^{-5}, 95%CI: -219.29 to -31.23, $Z = 2.61$, and $p < 0.009$ (Figure 3).

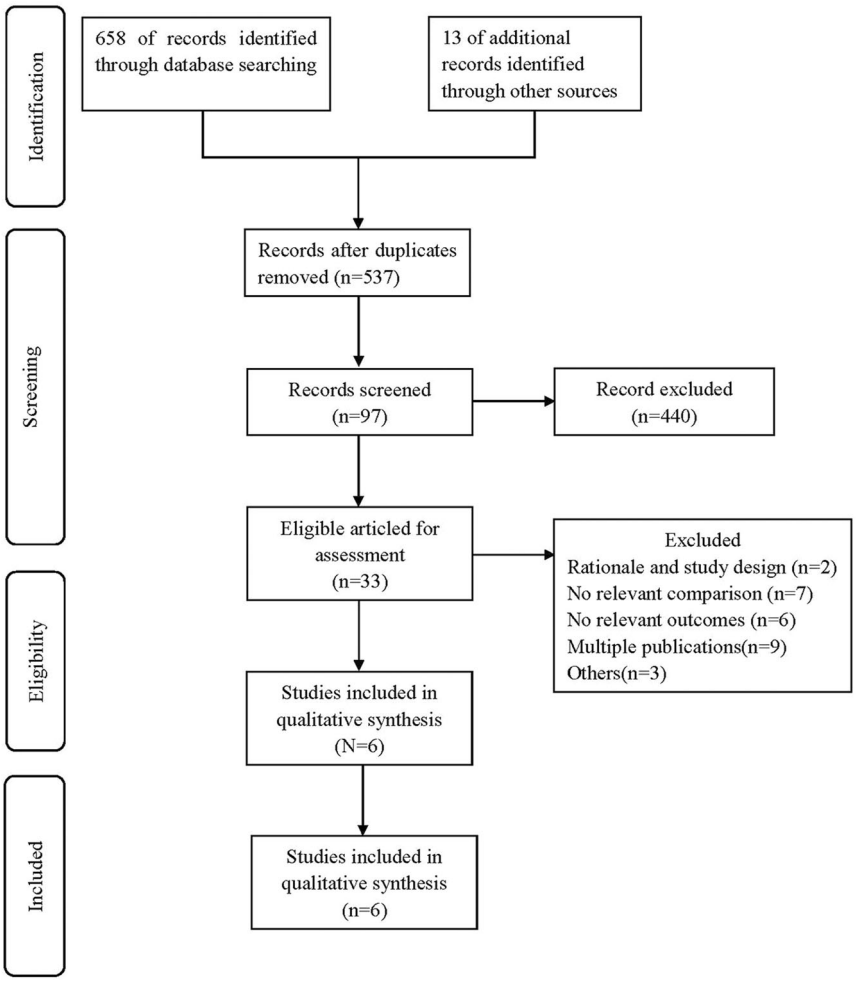

FIGURE 1 Selection flow chart of literature screening.

Mean pulmonary arterial pressure

The mPAP was reported in four studies,[6,16,18,19] which showed a trend improvement in the prostacyclin pathway vasodilator treatment compared to controls. There was no significant heterogeneity with $Chi^2 = 2.57$, $I^2 = 0\%$, and $p = 0.46$. The REM was then used for analysis which showed that the mean difference (MD) was −0.99 mmHg, 95%CI: −2.45 to 0.47, $Z = 1.33$, and $p = 0.18$ (Figure 3).

Right atrial pressure

The mRAP was reported in four studies,[6,16,18,19] which showed a significant improvement in the prostacyclin pathway vasodilator treatment compared to controls. There was no significant heterogeneity with $Chi^2 = 2.46$, $I^2 = 0\%$, and $p = 0.48$. The FEM was then used for analysis which showed that the mean difference (MD) was −0.78 mmHg, 95%CI: −1.52 to −0.04, $Z = 2.06$, and $p = 0.04$ (Figure 3).

Cardiac index

The cardiac index was reported in four studies,[6,16,18,19] which showed a significant improvement in the prostacyclin pathway vasodilator treatment compared to controls. There was no significant heterogeneity with $Chi^2 = 1.91$, $I^2 = 0\%$, and $p = 0.59$. The FEM was then used for analysis which showed that the mean difference (MD) was 0.62, 95%CI: 0.54 to 0.69, $Z = 16.13$, and $p < 0.00001$ (Figure 3).

6 min walking distance

The 6MWD was reported in four studies,[6,15,18,19] which showed a trend improvement in the prostacyclin pathway vasodilator treatment compared to controls. There was no

TABLE 2 Baseline characteristics of included clinical trials.

RCTs									
Study	Study type	Blinding	CTEPH	*N* patients (intervention/ control)	Ratio	Intervention	Dosage	Duration (weeks)	Endpoints
Thorsten Kramm et al. (2005)	Single-center RCT	Double-blind	Residual pulmonary hypertension following PEA	22 (11/11)	1:1	Inhaled iloprost	25 ug/single dose	Until hospital discharge	mPAP, PVR, Blood oxygenation
Roela Sadushi-Kolici et al. (2019)	Multicenter RCT	Double-blind	Non-operable; persistent or recurrent PH after PEA	105 (53/52)	1:1	Subcutaneous treprostinil	30 ng/kg per min :3 ng/kg per min	24 weeks	6MWD, Clinical worsening, NT-proBNP, mPAP, PVR, CI, RAP
Nobuhiro Tanabe et al. (2020)	Multicenter RCT	Double-blind	Non-operable; persistent or recurrent PH after PEA	34 (25/9)	3:1	Selexipag	800 ug bid	17 weeks	6MWD, PVR, mPAP
Takeshi Ogo, et al. (2022)	Multicenter RCT	Double-blind	Non-operable; persistent or recurrent PH after PEA/BPA	78 (39/39)	1:1	Selexipag	800 ug bid	20 weeks	PVR, 6MWD, WHO FC
Gaisin et al. (2022)	Single-center RCT	Non-blinding	Inoperable CTEPH	22 (11/11)	1:1	Intermittent inhaled iloprost	5.0ug/4 times daily for 2 weeks every 3 months	2 years	6MWD, WHO-FC,
Kim et al. (2023)	Multicenter RCT	Double-blind	Inoperable or persistent/ recurrent CTEPH, after PEA/BPA.	126 (62/64)	1:1	Selexipag	Titrated from 200 μg to 1600 μg bid	26 weeks	PVR, 6MWD, TTCW, NT-proBNP, WHO FC

Abbreviations: BNP, brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RCT, randomized controlled trial; TTCW, time to clinical worsening; WHO FC, WHO cardiac function; 6MWD, 6-min walking distance.

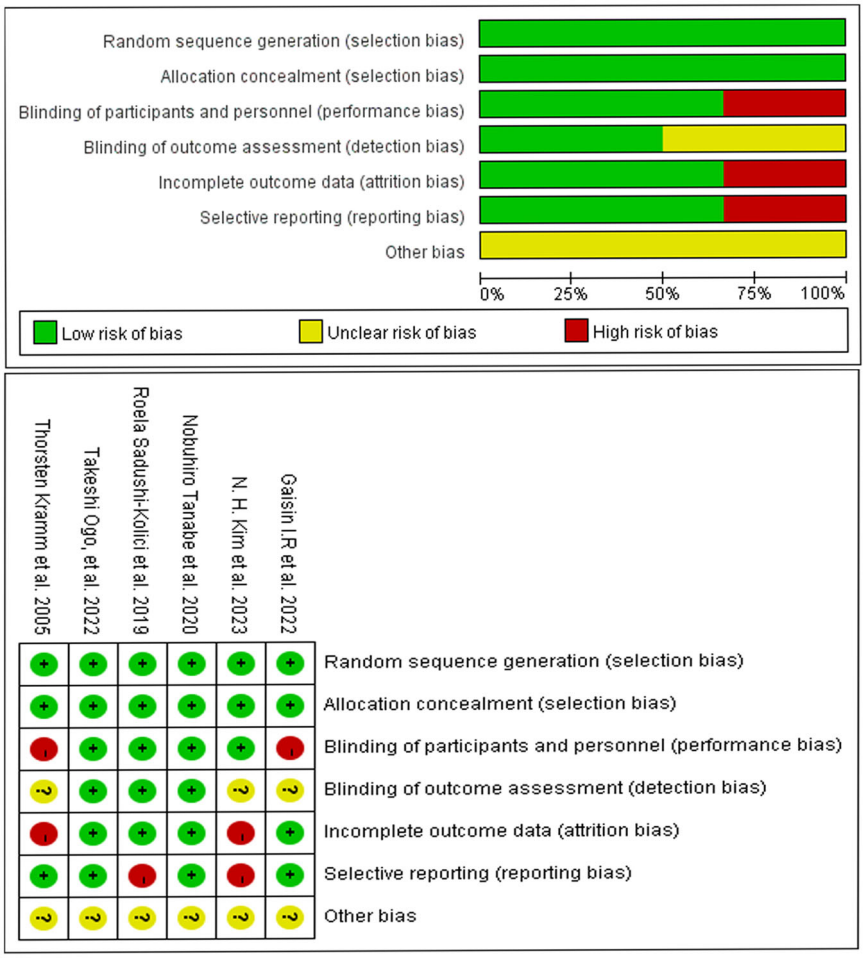

FIGURE 2 Risk of bias assessment of included studies.

significant heterogeneity with $Chi^2 = 6.33$, $I^2 = 53\%$, and $p = 0.10$. The REM was then used for analysis, showing that the mean difference (MD) was 18.95 m, 95%CI: −7.37 to 45.27, $Z = 1.41$, and $p = 0.16$ (Figure 4).

The improvement of WHO functional class

The improvement of WHO functional class was reported in four studies,[6,15,18,19] which showed a significant increase in patient numbers in the prostacyclin pathway vasodilator treatment group compared to controls. There was no significant heterogeneity with $Chi^2 = 5.2$, $I^2 = 42\%$, and $p = 0.16$. The FEM was then used for analysis which showed that the odds ratio (OR) was 3.86, 95%CI: 1,92 to 7.77, $Z = 3.79$, and $p = 0.0002$ (Figure 4).

NT-proBNP

The change of NT-proBNP from baseline was reported in four studies,[6,15,18,19] which showed a significant improvement of NT-proBNP in the prostacyclin pathway vasodilator treatment compared to controls. There was no significant heterogeneity with Chi2 = 3.0, $I^2 = 0\%$, and $p = 0.39$. The FEM was then used for analysis which showed that the mean difference (MD) was −209.55 pg/ml, 95%CI: −439.67 to 20.57, $Z = 1.78$, and $p = 0.07$ (Figure 4).

SAFETY

Serious adverse events

Six articles reported the number of serious adverse events,[6,15–19] which was a small number overall, and two studies reported zero occurrence in both groups. The number of serious adverse events was not significantly different in the prostacyclin pathway vasodilator group compared to controls (OR: 0.94, 95% CI: 0.39 to 2.29; $Z = 0.13$, and $p = 0.90$) (Figure 5).

All-cause deaths

Six articles reported the number of patients with all-cause deaths,[6,15–19] which occurred in a small number

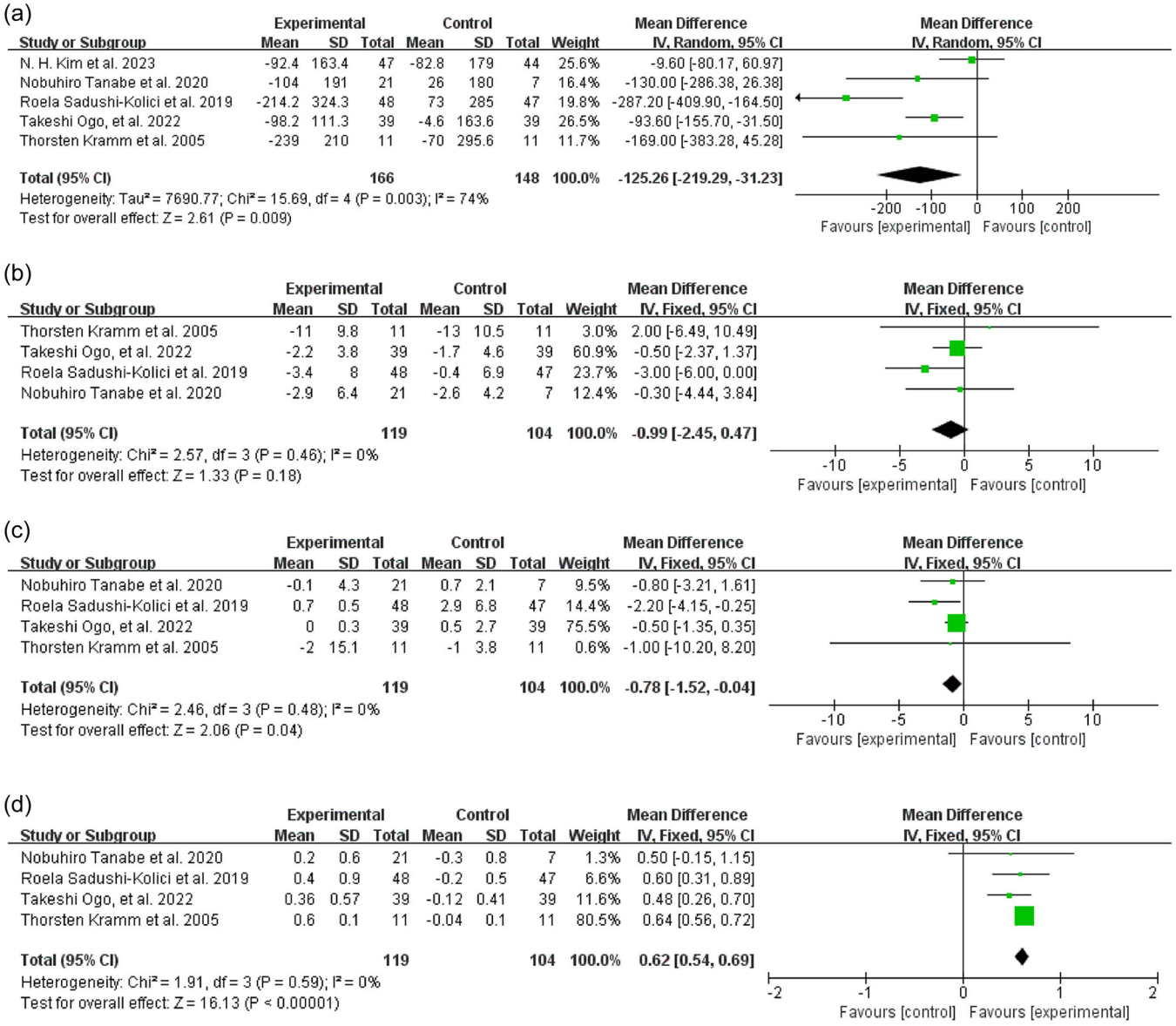

FIGURE 3 Forest plot illustrating a comparison of effects in prostacyclin pathway vasodilators on hemodynamic metrics with controls (a) Change of PVR from baseline. (b) Change of mPAP from baseline. (c) Change of cardiac index from baseline. (d) Change of RAP from baseline.

overall, and two studies reported zero deaths in both groups. The number of deaths was not significantly different in the prostacyclin pathway vasodilator group compared to controls (OR: 1.01, 95% CI: 0.21 to 4.88; $Z = 0.02$, and $p = 0.99$) (Figure 5).

DISCUSSION

We first presented the findings of a meta-analysis on all RCTs evaluating the benefits of prostacyclin pathway vasodilators in the treatment of CTEPH. The six eligible studies included three drugs of prostacyclin pathway vasodilators: subcutaneous treprostinil, oral selexipag, and inhaled iloprost, respectively. The majority of participants included were inoperable or persistent/recurrent PH after EPA/BPA, with a few patients in the perioperative stage of PEA. PVR, mRAP, cardiac index, and WHO functional class were significantly improved in CTEPH patients treated with the prostacyclin pathway vasodilators compared to the controls, additionally, there was an observed trend towards improvement in mPAP, 6MWD, and NT-proBNP.

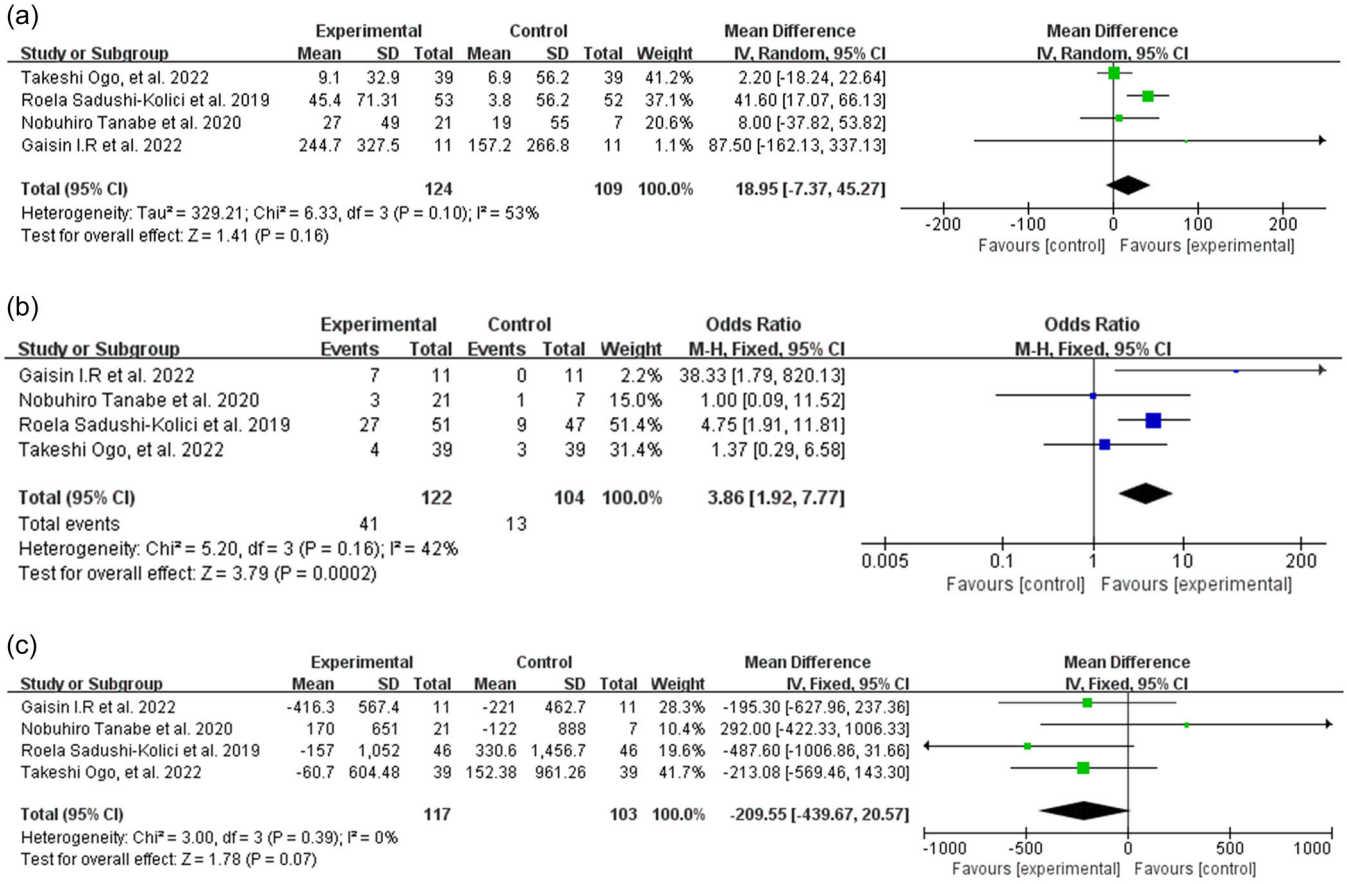

FIGURE 4 Forest plot illustrating a comparison of effects in prostacyclin pathway vasodilators on exercise capacity with controls in CTEPH. (a) Change of 6MWD from baseline (b) patients' number in improvement of WHO functional class (c) Change of NT-proBNP from baseline.

Our finding demonstrated that the hemodynamic metrics were significantly improved among patients with CTEPH treated with the prostacyclin pathway vasodilators. The PVR, which reflects the fundamental hemodynamic condition of pulmonary hypertension(PH), is closely associated with long-term prognosis in patients with PAH.[20] A decrease in PVR has been linked to improved prognosis after PEA in CTEPH patients.[21] Therefore, PVR holds clinical relevance and serves as a valuable measure for assessing treatment efficacy in PH. Additionally, PVR improvement was accompanied by an improvement in other hemodynamic characteristics such as cardiac index, and RAP, although mPAP only exhibited a trend towards improvement.

Riociguat exhibits a dual mode of action, directly stimulating soluble guanylate cyclase independently of nitric oxide, and increasing the sensitivity of soluble guanylate cyclase to nitric oxide. Its pharmacological action addresses one of the pathogenesis of PH which involves the impairment of nitric oxide synthesis and signaling through the nitric oxide–soluble guanylate cyclase–cyclic guanosine monophosphate pathway.[22,23] Riociguat, increases cyclic guanosine monophosphate (cGMP) levels, leading to vasorelaxation and exhibiting antiproliferative and antifibrotic effects, effectively manages the distal vessel and microvascular component of CTEPH.[9] The impairment of the prostacyclin-cyclic adenosine monophosphate(cAMP) pathway is another pathogenesis of PH. Prostacyclin pathway vasodilators act as vasodilative, antiproliferative, and antithrombotic effects through binding to prostacyclin receptors and elevating intracellular cyclic adenosine monophosphate (cAMP) levels leading to relaxation of vascular smooth muscle.[2,8] Previous uncontrolled studies assessing the efficacy of epoprostenol, iloprost, and beraprost in patients with CTEPH have demonstrated promising benefits,[11,20,24] however these results require further confirmation through RCTs.

Iloprost, a stable analog of prostacyclin, can be administered via inhalation due to its unique characteristics that differ from other administration routes, such as oral administration or subcutaneous injection. Notably, it

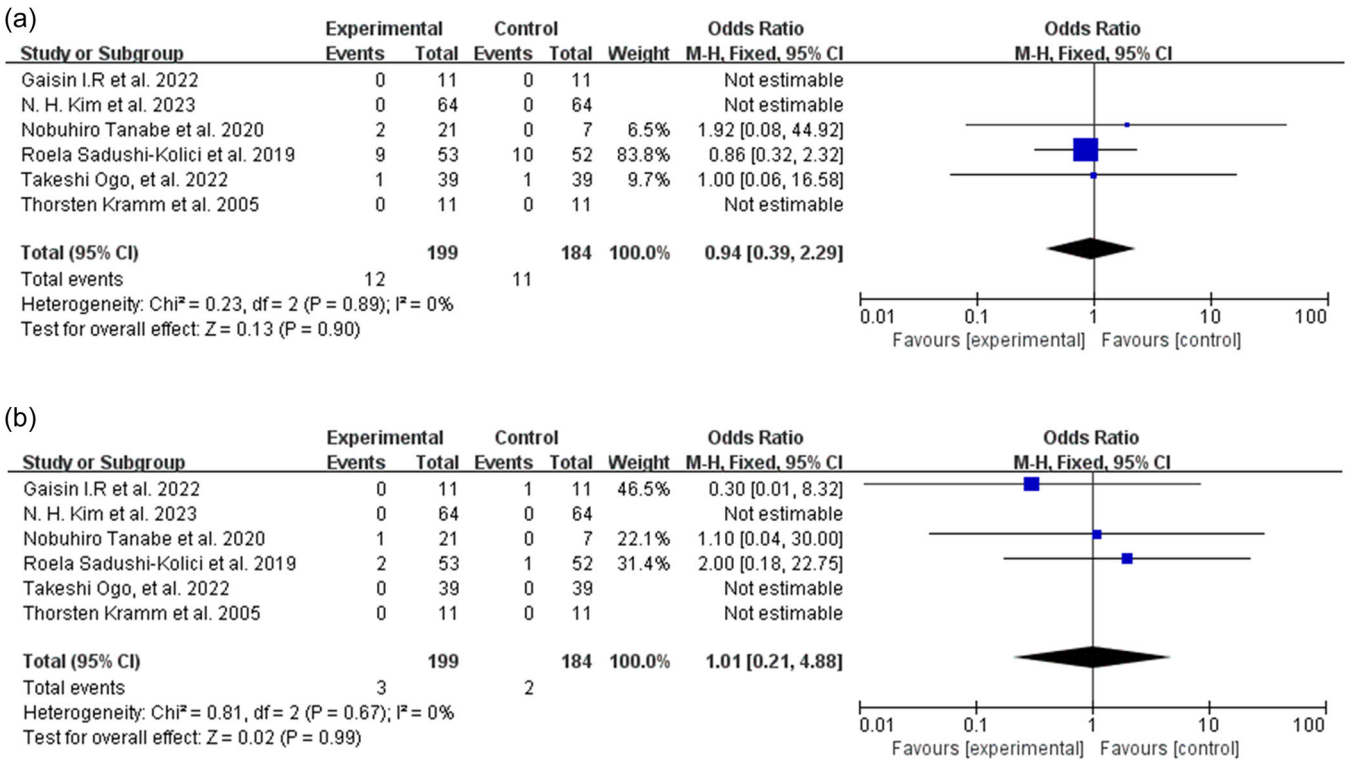

FIGURE 5 Forest plot illustrating a comparison of safety endpoints in prostacyclin pathway vasodilators with controls in CTEPH. (a) Patients' number of serious adverse events (b) Patients' number of all-cause deaths.

does not affect systemic hemodynamics and largely selective vasodilation of well-ventilated regions of the lung (intrapulmonary selectivity) was achieved, ensuring optimal gas exchange.[25] Inhalation of iloprost aerosol in short-term perioperative treatment with CTEPH patients improved pulmonary hemodynamics and decreased right ventricular afterload[16]; Additionally, a recent RCT demonstrated that long-term intermittent inhalation of iloprost aerosol for inoperable CTEPH still resulted in improvement of pulmonary hemodynamics and gas exchange, further significant pulmonary vasodilatation, which was accompanied by an increase in exercise capacity.[15]

Treprostinil, a prostacyclin analog, exhibits acute hemodynamic effects similar to epoprostenol. It has a longer half-life (3-4 h), permitting continuous subcutaneous infusion rather than continuous intravenous infusion, thereby mitigating the risks associated with severe infection and thrombosis.[26] A previous uncontrolled study has demonstrated the efficacy, safety, and tolerability of percutaneous treprostinil in the treatment of CTEPH.[27] The CTREPH study compared subcutaneous treprostinil at a high-dose group (30 ng/kg per min) to a low-dose group (3 ng/kg per min), with a change in 6-min walking distance as the primary endpoint. The results demonstrated subcutaneous treprostinil was safe and improved exercise capacity in patients with severe CTEPH,[18] leading to its approval for adult individuals in WHO FC III–IV, who were inoperable or persistent/recurrent PH after PEA/BPA in 2020.[28] A post-hoc study showed that standard-dose SC treprostinil therapy exhibited a favorable impact on the risk profile, measured by REVEAL risk score (RRS), in these patients. Thus, a high dose of subcutaneous treprostinil was recommended.[4]

Selexipag is an oral selective prostacyclin receptor (IP receptor) agonist with a non-prostanoid structure. Following oral administration, its active metabolite, MRE-269, exhibits a high selectivity for the prostacyclin receptor.[29,30] Selexipag demonstrated significant improvement in PVR and other hemodynamic variables in Japanese patients with CTEPH; however, exercise capacity did not show significant improvement.[6] Nevertheless, not all included studies reported positive results regarding the beneficial effects of prostacyclin pathway vasodilators for CTEPH patients. The SELECT study aimed to assess the efficacy of selexipag as an add-on to standard-of-care(SoC) therapy in patients with inoperable or persistent/recurrent CTEPH after surgery and/or interventional treatment, but it was terminated

early due to a lack of statistically significant treatment effect on PVR at an interim analysis.[17] Ogo et al. reported approximately 60% of the included CTEPH patients defined as "PEA not indicated because of distal organized thrombus",[6] and it was consistent with the recommendation from the 2022 ESC guideline which emphasized targeting medication therapy towards distal small-vessel and microvascular vasculopathy. However, a similar detailed description of vessel condition and etiological classification was not reported in the SELECT study,[17] which may account for the divergent findings observed in these two studies involving selexipag.[6,17]

Despite controversy over 6MWD as a study's primary endpoint, the measure has been used as a primary outcome measure in many pulmonary arterial hypertension studies. Our findings revealed a trend towards improvement in 6MWD following treatment with prostacyclin pathway vasodilators compared to controls. Furthermore, a significant improvement in NT-ProBNP and WHO functional class was observed, which also was consistent with hemodynamic characteristics.

Regarding safety, our study revealed that serious adverse events and all-cause deaths were few in the prostacyclin pathway vasodilator group and it was similar to those in controls. However, the different administration routes still resulted in a certain proportion of adverse events, but most of them were mild. The reported side effects were mild and generally typical for prostacyclin pathway vasodilator therapy (flushing and jaw pain).[25] In the CTREPH study, although 90 (86%) of patients experienced local adverse reactions including infusion site pain and infusion site reaction, they were manageable, with only four (4%) dropouts.[18] Subcutaneous treprostinil for CTEPH obviates the necessity for intravenous lines that could be sources of thromboembolism, additionally, intravenous catheter-related infections are rare but potentially fatal complications of intravenous prostacyclin administration.[31] While subcutaneous administration usually results in manageable painful infusion site reactions in the vast majority of patients,[32,33] which are generally well-tolerated.

Concerning real-world clinical practice, these CTEPH patients with inoperable or persistent/recurrent PH after PEA/BPA primarily characterized by distal small-vessel and microvascular vasculopathy may represent a potential target population for prostacyclin pathway vasodilators. The low mortality rates reported in the included studies may be related to the limited treatment duration, and it is imperative to obtain results from future real-world studies to confirm the impact of long-term treatment. Future research should aim to accurately identify patients with small-vessel and microvascular vasculopathy and investigate whether these individuals also derive long-term benefits from prostacyclin pathway vasodilators.

Multimodal treatment is a crucial issue for CTEPH, particularly for severe patients who may have complicated mixed anatomical lesions.[2] One scenario involves using PAH-targeted drugs in patients with higher preoperative PVR to improve pulmonary hemodynamics before PEA, due to hemodynamic severity leading to a higher rate of BPA-related lung injury. Despite being a common practice, there is still controversy over it. Piliero N et al.[34] recently reported three patients with upfront triple therapy involved parenteral prostacyclin as a bridge to BPA in severe chronic thromboembolic pulmonary hypertension. Another scenario is for these patients with inoperable CTEPH or persistent/recurrent PH after PEA. whether sequential combination or upfront combination therapy is needed when monotherapy fails to significantly improve pulmonary hemodynamics and exercise capacity. In fact, a certain proportion of patients in the included studies were taking prostacyclin pathway vasodilators in combination with other PAH-targeted drugs. Considering oral formulation for better patient compliance, the combination of selexipag and riociguat in efficacy and safety compared to monotherapy should be prioritized for exploration in future randomized controlled trials. Both subcutaneous treprostinil and riociguat have been approved for the treatment of CTEPH, so the combination of these two drugs should also be prioritized for exploration. In addition, when to start treatment, such as the perioperative stage, to benefit patients the most also needs to be further clarified.

The advances of PEA, BPA, and medical therapy have constituted the era of the multimodal CTEPH treatment, surgical and interventional treatment are preferred treatments, but medical therapy still plays a crucial irreplaceable role. However, some relatively unanswered questions require further identification through additional RCTs, such as optimal sequencing of medication and perioperative management, including the combination of prostacyclin pathway vasodilators.

LIMITATION

Our study has several potential limitations that should be considered. First, the inclusion of a small number of RCTs and a limited sample size for this class of drug may introduce the risk of bias and limit the reliability of the results. Second, the CTREPH study[18] used low-dose subcutaneous treprostinil (approximately 3 ng/kg per min) as a control to allow complete double-blinding for the drug that causes local infusion site reactions

acting as a control. Therefore, it may lead to an underestimation of the efficacy of treprostinil. Third, some differences were present in study design, administration of study drugs, and treatment duration, which may introduce the risk of bias. In one of the included studies,[16] it was observed that the effect of inhalation of iloprost aerosol controlled residual pulmonary hypertension following PEA in hospitalization, however, the effects of midterm or long-term treatment were absent in this study. After excluding hemodynamic data from this study, significant improvement in hemodynamic metrics including PVR, mPAP, RAP, and CI was still observed across the remaining 5 RCTs, which is consistent with the overall included population. Fourth, due to a limited number of studies and multiple background-targeted therapeutic options of the six studies, subgroup analysis could not be conducted to assess the impact of prostacyclin pathway vasodilator background-targeted therapies. The inclusion of a conference abstract[17] without undergoing peer-review introduces a potential source of bias in this study. Furthermore, we used the exclusion method for sensitivity analysis to identify the source of the significant heterogeneity observed in PVR. After excluding the data from the study with subcutaneous treprostinil, there was mild heterogeneity in the other four studies.[18] The potential factors contributing to the high heterogeneity may derive from low-dose subcutaneous treprostinil as a control leading to an underestimation of the efficacy of treprostinil. Because of the limited number of included studies, we could not perform subgroup analysis and meta-regression analysis. In brief, it should be acknowledged that differences in RCT design, the description of outcome measures, and study size may influence our findings. To mitigate these concerns, we adopted strict inclusion criteria.

CONCLUSION

In summary, our meta-analysis demonstrated that prostacyclin pathway vasodilator treatment significantly improved pulmonary hemodynamic metrics and exercise capacity in patients with severe CTEPH, especially those who present inoperable or persistent/recurrent PH after PEA/BPA primarily characterized by distal small-vessel and microvascular vasculopathy, furthermore, it was relatively well-tolerated. In the era of multimodal CTEPH treatment, prostacyclin pathway vasodilators present therapeutic potential for the specific subgroup of CTEPH patients, However, the current clinical evidence remains insufficient and controversial, necessitating further validation through larger-scale studies.

AUTHOR CONTRIBUTIONS

Study concept and design: **ZYJ**, **DYH**, and **JC**. Critical revision of the manuscript for important intellectual content, and study supervision: **XXP**, **WJL**; implementation, data collection; analysis, or interpretation of data: **XXR**, **XW**, **NZ**, **HBZ**, and **WJL**. JC drafted the manuscript. Final approval of the manuscript submitted: **ZYJ** and **WJ**L. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

Not applicable.

ACKNOWLEDGMENTS

This work was supported by Science and Technology Foundation of Tongzhou District (KJ2023CX060).

ORCID

Jun Chen http://orcid.org/0000-0002-7140-6935
Zhongyi Jin https://orcid.org/0009-0000-0943-9122

REFERENCES

1. Tyagi S, Batra V, Gautam A. Review of advances on management of chronic thromboembolic pulmonary hypertension. Int J Angiol. 2023;32(04):207–14.
2. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2023;61(1):2200879.
3. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Hamid AM, Jaïs X, Simonneau G. Chronic Thromboembolic Pulmonary Hypertension (CTEPH): results from an international prospective registry. Circulation. 2011;124(18):1973–81.
4. Jansa P, Kopeć G, Torbicki A, Sadushi-Kolici R, Campean IA, Halank M, Simkova I, Steringer-Mascherbauer R, Salobir B, Klepetko W, Lindner J, Lang IM. The risk profile change in patients with severe chronic thromboembolic pulmonary hypertension treated with subcutaneous treprostinil. Pulm Circ. 2023;13(3):1–10.
5. Brenot P, Jaïs X, Taniguchi Y, Garcia Alonso C, Gerardin B, Mussot S, Mercier O, Fabre D, Parent F, Jevnikar M, Montani D, Savale L, Sitbon O, Fadel E, Humbert M, Simonneau G. French experience of balloon pulmonary

angioplasty for chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53(5):1802095.
6. Ogo T, Shimokawahara H, Kinoshita H, Sakao S, Abe K, Matoba S, Motoki H, Takama N, Ako J, Ikeda Y, Joho S, Maki H, Saeki T, Sugano T, Tsujino I, Yoshioka K, Shiota N, Tanaka S, Yamamoto C, Tanabe N, Tatsumi K. Selexipag for the treatment of chronic thromboembolic pulmonary hypertension. Eur Respir J. 2022;60(1):2101694.
7. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, Ogo T, Tapson VF, Ghofrani HA, Jenkins DP. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53(1):1801915.
8. Lang IM, Dorfmüller P, Noordegraaf AV. The Pathobiology of Chronic Thromboembolic Pulmonary Hypertension. Ann Am Thorac Soc. 2016;13(Suppl_3):S215–21.
9. Ghofrani H-A, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C. Riociguat for the treatment of Chronic Thromboembolic Pulmonary Hypertension. N Engl J Med. 2013;369(4):319–29.
10. Reichenberger F, Mainwood A, Doughty N, Fineberg A, Morrell NW, Pepke-Zaba J. Effects of nebulised iloprost on pulmonary function and gas exchange in severe pulmonary hypertension. Respir Med. 2007;101(2):217–22.
11. Nagaya N. Oral beraprost sodium improves exercise capacity and ventilatory efficiency in patients with primary or thromboembolic pulmonary hypertension. Heart. 2002;87:340–5.
12. Cabrol S, Souza R, Jais X, Fadel E, Ali RHS, Humbert M, Dartevelle P, Simonneau G, Sitbon O. Intravenous epoprostenol in inoperable chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant. 2007;26(4):357–62.
13. Higgins JPGS. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration. 2011.
14. Higgins JPT. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
15. Gaisin IR, Rychkova LV, Gazimzyanova AS, Maksimov NI, Pomosov SA, Zaisanova GM, Nikolaeva NB, Shirobokova EG. Efficacy of intermittent inhaled iloprost in inoperable chronic thromboembolic pulmonary hypertension. Pulmonologiya. 2022;32(1):53–61.
16. Kramm T, Eberle B, Guth S, Mayer E. Inhaled iloprost to control residual pulmonary hypertension following pulmonary endarterectomy. Eur J Cardiothorac Surg. 2005;28(6):882–8.
17. Kim NH, Channick R, Delcroix M.The efficacy and safety of selexipag as an add-on to standard-of-care therapy in patients with inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension after surgical and/or interventional treatment (SELECT). Am J Respir Crit Care Med. 2023;207:A4235.
18. Sadushi-Kolici R, Jansa P, Kopec G, Torbicki A, Skoro-Sajer N, Campean IA, Halank M, Simkova I, Karlocai K, Steringer-Mascherbauer R, Samarzija M, Salobir B, Klepetko W, Lindner J, Lang IM. Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial. Lancet Respir Med. 2019;7(3):239–48.
19. Tanabe N, Fukuda K, Matsubara H, Nakanishi N, Tahara N, Ikeda S, Kishi T, Satoh T, Hirata K, Inoue T, Kimura H, Okano Y, Okazaki O, Sata M, Tsujino I, Ueno S, Yamada N, Yao A, Kuriyama T. Selexipag for chronic thromboembolic pulmonary hypertension in Japanese patients—a double-blind, randomized, placebo-controlled, multicenter phase II study. Circ J. 2020;84(10):1866–74.
20. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Hervé P, Rainisio M, Simonneau Gé. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension. J Am Coll Cardiol. 2002;40(4):780–8.
21. Bonderman D, Skoro-Sajer N, Jakowitsch J, Adlbrecht C, Dunkler D, Taghavi S, Klepetko W, Kneussl M, Lang IM. Predictors of outcome in chronic thromboembolic pulmonary hypertension. Circulation. 2007;115(16):2153–8.
22. Stasch J-P, Pacher P, Evgenov OV. Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. Circulation. 2011;123(20):2263–73.
23. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. N Engl J Med. 1995;333(4):214–21.
24. Naeije R, Rubin LJ, Nikkho S. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med. 2002;347(5):322–9.
25. Olschewski H. Inhaled iloprost for the treatment of pulmonary hypertension. Eur Respir Rev. 2009;18(111):29–34.
26. Simonneau G, Barst RJ, Galie N, NAEIJE R, RICH S, BOURGE RC, KEOGH A, OUDIZ R, FROST A, BLACKBURN SD, CROW JW, RUBIN LJ. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension. Am J Respir Crit Care Med. 2002;165:800–4.
27. Skoro-Sajer N, Bonderman D, Wiesbauer F, HARJA E, JAKOWITSCH J, KLEPETKO W, KNEUSSL MP, LANG IM. Treprostinil for severe inoperable chronic thromboembolic pulmonary hypertension. J Thromb Haemostasis. 2007;5(3):483–9.
28. Kim NH, Papamatheakis DG, Fernandes TM. Evolution of randomized, controlled studies of medical therapy in chronic thromboembolic pulmonary hypertension. Pulm Circ. 2021;11(2):1–8.
29. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, Ghofrani HA, Hoeper MM, Lang IM, Preiss R, Rubin LJ, Di Scala L, Tapson V, Adzerikho I, Liu J, Moiseeva O, Zeng X, Simonneau G, McLaughlin VV. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med. 2015;373(26):2522–33.
30. Asaki T, Kuwano K, Morrison K, Gatfield J, Hamamoto T, Clozel M. Selexipag: an oral and selective IP prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. J Med Chem. 2015;58(18):7128–37.
31. Kallen AJ, Lederman E, Balaji A. Bloodstream infections in patients given treatment with intravenous prostanoids. Infect Control Hosp Epidemiol. 2015;29(4):342–9.
32. Barst RJ, Galie N, Naeije R, Simonneau G, Jeffs R, Arneson C, Rubin LJ. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J. 2006;28(6):1195–203.
33. Sadushi-Koliçi R, Skoro-Sajer N, Zimmer D, Bonderman D, Schemper M, Klepetko W, Glatz J, Jakowitsch J, Lang IM. Long-term treatment, tolerability, and survival with subcutaneous treprostinil for severe pulmonary hypertension. J Heart Lung Transplant. 2012;31(7):735–43.

34. Piliero N, Salvat M, Finas M, Curioz F, Traclet J, Ahmad K, Bertoletti L, Vautrin E, Bouvaist H, Degano B. Upfront triple therapy with parenteral prostanoid as a bridge to balloon pulmonary angioplasty in severe chronic thromboembolic pulmonary hypertension. ERJ Open Res. 2024;10(2):00085.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Li W, Pang X, Chen J, Ren X, Zhao H, Wang X, Zhao N, Hu D, Jin Z. Prostacyclin pathway vasodilators in patients with chronic thromboembolic pulmonary hypertension (CTEPH): a systemic review and meta-analysis of randomized controlled trials. Pulm Circ. 2024;14:e70001. https://doi.org/10.1002/pul2.70001