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Haemodynamic effects of initial combination therapy in pulmonary arterial hypertension: A systematic review and meta-analysis

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Take-home message: Initial combination therapy in PAH results in >50% reduction in pulmonary vascular resistance compared to baseline. Parenteral prostanoids accentuate this response and should be considered early to enable timely right ventricular reverse remodeling.

Abstract

Background: Although the initial use of combination treatment has been proved beneficial for patients' clinical outcome, there is scarce data on its hemodynamic effects.

Objective: To evaluate the effect of an initial combination of PAH-targeted therapies on hemodynamic parameters in treatment-naïve PAH patients.

Methods: A systematic search of PubMed, CENTRAL and Web of Science was performed. We considered eligible studies with an intervention of initial PAH-targeted combination therapy in treatment-naïve PAH patients with or without monotherapy control. A random effects meta-analysis was performed for the difference between baseline and follow-up in pulmonary vascular resistance (PVR) and other hemodynamic parameters.

Results: Of 880 patients receiving initial combination therapy PVR was reduced by -6.5 WU (95%CI -7.4;-5.7) or by -52% (95%CI -56%;-48%, I^2=0%) compared to baseline. Initial triple therapy including a parenteral prostanoid resulted in significantly greater PVR reduction (-67% vs. -50% with all other combination therapies, p=0.01). The effect was more pronounced in younger patients (p=0.02). Compared to baseline, there was -12.2 mmHg (95%CI -14.0; -10.4) decrease in mean pulmonary artery pressure, 0.9 l/min/m^2 (95%CI 0.8; 1.1) increase in cardiac index, -3.2 mmHg (95%CI, -4.1; -2.3) decrease in right atrial pressure and 8.6% (95%CI 6.9; 10.3) increase in mixed venous oxygen saturation. In the controlled studies, initial combination therapy reduced PVR by -4.2 WU (95%CI -6.1;-2.4) compared to monotherapy.

Conclusion: Initial combination therapy leads to remarkable hemodynamic amelioration. Parenteral prostanoids should be considered early, especially in more severely affected patients, to enable RV reverse remodeling.

Introduction

Pulmonary arterial hypertension (PAH) is a chronic condition with great pathobiologic complexity, which involves multiple pathogenetic pathways, including the endothelin, nitric oxide and prostacyclin pathway. Current management strategies depend on a multivariable-based risk stratification in order to guide pathway-targeted therapy titration and both initial and sequential combination therapies are now the proposed treatment strategy [1]. The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION trial) showed that among participants with PAH who are treatment-naïve, an initial combination therapy of ambrisentan and tadalafil resulted in a significantly reduced risk for clinical failure events than monotherapy with each one of the combination's components [2]. Hence, although the initial use of combination treatment has been proved beneficial for patients' clinical outcome, there is scarce data on its hemodynamic effects.

Aim of this study was to systematically evaluate the effect of an initial combination of PAH-targeted therapies on hemodynamic parameters in treatment-naïve PAH patients.

Methods

This systematic review and meta-analysis was performed according to the PRISMA Guidelines and was registered in PROSPERO (CRD42021283091) [3]. The PubMed, CENTRAL and Web of Science databases were searched from inception up until August 2021. The search terms included the currently approved targeted medication classes and substances for the treatment of PAH, a term for PAH, and the keywords "initial" and "upfront". The search strategy is available in the *Supplemental Material 1*.

We considered eligible both prospective and retrospective studies with an intervention of initial PAH-targeted combination therapy [endothelin receptor antagonists (ERA), phosphodiesterase 5 inhibitors (PDE-5Is), soluble guanylyl cyclase stimulators (sGC), prostanoids (PGI), prostacyclin receptor agonists] in treatment-naïve PAH patients with or without a comparison with PAH-targeted monotherapy. The primary efficacy outcome was the mean difference between baseline and follow-up in pulmonary vascular resistance (PVR). Other hemodynamic parameters regarded as efficacy outcomes included the mean difference between baseline and follow-up in mean pulmonary arterial pressure (mPAP), cardiac index (CI), right atrial pressure (RAP) and mixed venous oxygen saturation (SvO_2) as assessed by right heart catheterization. We also assessed the mean difference between baseline and follow-up in the 6-minute walking distance (6MWD) and brain natriuretic peptide (BNP). Safety outcomes included serious adverse events.

Study selection and data extraction were performed according to standard procedures as described in the Cochrane Handbook, namely both processes were performed independently by two investigators (IF, EV) and in case of disagreement a third investigator (SZ) was consulted. We used the Cochrane collaboration tool for assessing the risk of bias for non-randomized studies of interventions (ROBINS-I) [4].

We performed a single-arm random effects model meta-analysis of the eligible studies to evaluate the effect of initial PAH-targeted combination therapy on the hemodynamic efficacy outcomes and we additionally performed a second analysis with the studies providing a control monotherapy arm. The effect measure for all outcomes was the mean difference (MD) or the standardized mean difference (SMD) as appropriate with corresponding 95% confidence intervals (CI). We used

the standard Der-Simonian-Laird equations to produce estimates of variance in the summary measures. Heterogeneity was assessed with the Cochran's Q and the I^2 statistic. Publication bias was assessed with the use of funnel plots and the Egger's test. A sensitivity analysis was performed to exclude studies not providing the variance of difference between baseline and follow-up in the outcomes. Subgroup analyses included the use of double or triple therapy and the use of parenteral prostanoids in the combination therapy. Meta-regression analysis was performed adjusting for the age and sex of participants (each baseline variable evaluated in separate univariate analyses). All analyses were performed by IF with the *meta* package in R (the R Project for Statistical Computing, version 4.0.2).

Results

The search strategy resulted in 681 identified studies after duplicates were removed. Subsequently, 59 full-text articles were assessed for eligibility and, eventually, we considered 13 studies eligible [5–17]. The study selection process and the corresponding flow chart is presented in *Supplemental Material 2*. In total, 880 patients received initial combination therapy (comprising 17 treatment arms), while four studies reported a control monotherapy group comprising a total of 194 patients. Eight studies reported the initial use of an ERA + PDE5-I combination, three studies the use of mono-oral + parenteral prostanoid combination, one study studied the ERA + sGC combination, while three studies reported the use of an initial triple combination therapy (ERA + PDE5i + prostanoids). The mean age of participants was 52 ± 16 years and 74% were women, while 80.7% of patients belonged to WHO functional class III or IV. The mean baseline mPAP was 53 ± 13 mmHg and mean

baseline 6MWD was 334 ± 123 meters. Baseline characteristics of eligible studies are demonstrated in Table 1.

In the quality assessment, the majority of studies were in moderate risk of bias, while the most frequent category of serious bias was bias due to confounding. The summary risk of bias plot, as well as the traffic light plot of individual study assessment are presented in *Supplemental Material 3*.

In the single arm meta-analysis, initial combination therapy reduced PVR by -6.5 (95% CI -7.4; -5.7) Woods Units (WU) or by -52% (95% CI -56%; -48%) compared to the baseline value, with no heterogeneity in the model (I^2 = 0%, p = 0.49) (*Figure 1*). Compared to baseline, there was -12.2 mmHg (95% CI -14.0; -10.4) decrease in mPAP, 0.9 l/min/m^2 (95% CI 0.8; 1.1) increase in CI, -3.2 mmHg (95% CI, -4.1; -2.3) decrease in RAP and 8.6% (95% CI 6.9; 10.3) increase in SvO_2 (*Figure 2*). The was a decrease in BNP levels (SMD -1046.7, 95% CI -1511; -581.4) and an increase in 6MWD (MD 86 m, 95% CI 67.2; 104.8). No significant differences were observed in the sensitivity analysis.

Initial triple therapy including a parenteral prostanoid resulted in significantly greater PVR reduction (-67% vs. -50% with all other combination therapies, p = 0.01). The inclusion of a parenteral prostanoid in any combination treatment resulted in greater numerical PVR reduction (-58% with vs. -50% without) although not statistically significant (p = 0.15). The meta-regression analysis showed that the effect was more pronounced in younger patients in all outcomes (p = 0.02) (*Figure 3* presents the effect of age on the PVR outcome). There was no evidence of publication bias for the primary efficacy outcome PVR (*Supplemental Material 4*), but there was publication bias for the CI and SvO_2 outcomes.

In the controlled arm meta-analysis, initial combination therapy reduced PVR by -4.2 WU (95%CI -6.1; -2.4) compared to monotherapy, with substantial heterogeneity in the model (I^2 = 87%, p < 0.01). Compared to monotherapy, there was -6.7 mmHg (95% CI -8.6; -4.8) decrease in mPAP, 0.4 l/min/m^2 (95% CI 0.2; 0.6) increase in CI, -1.7 mmHg (95% CI, -2.6; -0.8) decrease in RAP and 4% (95% CI 0.5; 7.4) increase in SvO_2 (*Supplemental Material 5*).

In general, most adverse events were similar across the included studies and were consistent with the most frequently presented adverse events of different PAH regimens.

Discussion

In this meta-analysis, initial combination therapy was associated with remarkable hemodynamic changes in treatment-naïve PAH patients. In particular, we observed a -52% reduction in the PVR after the initiation of initial combination therapy; this reduction was even more prominent, reaching -67%, when a parenteral prostanoid treatment component was included in a triple initial PAH-targeted combination therapy.

In severe PAH, pressure overload, represented by PVR, results in an “adaptive” remodeling of the right ventricle (RV), however, its constant increase inevitably leads to ventriculoarterial uncoupling, RV distension and decompensation [18]. Our analysis of pooled results estimates a -48% to -56% reduction of PVR with the use of initial combination therapy and may also suggest an opportunity for reverse remodeling of the RV [5, 16]. The inclusion of a parenteral prostanoid treatment compound results in a more pronounced hemodynamic effect. Survival rates have been shown to be higher with initial triple therapy (two oral medications

and a parenteral prostacyclin) compared with dual therapy or monotherapy [19], which is in line with the greater PVR reduction with the use of an initial triple therapy suggested by the current analysis, favoring timely initiation [20]. On the contrary, initial double oral combination produces similar PVR drop compared to initial triple oral combination [7].

A more prominent effect of PVR reduction was observed in younger patients with more typical PAH and lesser comorbidities, probably underlying the treatment effect on their vascular pathology. There seems to be a significant variation in the hemodynamic response even in patients receiving similar PAH drug treatment [6]. Patients with significant PVR lowering (>45-50%) are those who obtain the reverse right heart remodeling and improve their RV systolic function [16, 21].

A limitation of this analysis is that it did not have access to individual patient data and, therefore, effects of therapy could not be stratified by risk profiles and selection bias of severely affected patients could exist. There was also great variability in the components of the initial combination therapy and not all comparisons between them were possible. For instance, a known pharmacokinetic interaction between sildenafil and bosentan leads to reduction of plasma levels of sildenafil and increase of the plasma levels of bosentan and may lead to a blunted hemodynamic response [13]. The contribution of the specific components in PVR reduction (mPAP lowering versus CI increase) was not studied in the current analysis. RV function assessed by RVEF change is a better predictor of survival than PVR, however, the association between PVR reduction and RVEF improvement could not be assessed in this analysis [21]. Lastly, since no hard endpoints were assessed, absolute value of PVR at follow-up after initial combination treatment may be more important predictor of outcome than PVR drop rate.

Conclusion

Initial combination therapy leads to remarkable hemodynamic amelioration. Parenteral prostanoids should be considered early, especially in more severely affected patients, to enable RV reverse remodeling. Treatment delays have deleterious effects in patients' functional capacity and outcomes, therefore a "watch-and-wait" approach does not help achieving low-risk status and should be avoided.

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Conflicts of interest

George Giannakoulas has received fees for lectures and/or consultations from Actelion, Bayer, ELPEN Pharmaceuticals, GlaxoSmithKline, Janssen, MSD, Pfizer, Lilly, and United Therapeutics. The rest of the authors have nothing to declare.

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Figure legend

Figure 1. Forest plot of the effects of initial combination therapy on the pulmonary vascular resistance expressed as percentage difference compared to baseline.

Figure 2. Effects of upfront combination therapy on hemodynamic outcomes in the single-arm meta-analysis.

Figure 3. Bubble plot for the effect of participants' mean age on the PVR outcome.

Table 1. Baseline characteristics of included studies.

Study	Number of participants	PAH subgroup	Mean age	Follow-up duration	WHO FC	Interventional group treatment (Upfront therapy)	Control group treatment	Outcome measures	Adverse events
Badagliacca* et al. 2018 [5]	165	IPAH	54	155±65 days	3.2±0.4	Group 1: Prostanoids + ERAs or PDE5i Group 2: ERAs + PDE5i	Group 3: ERAs or PDE5i Group 4: Prostanoids	PVR, mPAP, CI, RAP, 6MWD	NR
Badagliacca et al. 2021 [6]	181	IPAH, CTD-PAH, CHD-PAH with	53	180 (144-363) days	I-II: 37 (20.4%) III: 127 (70.2%) IV: 17	a) Ambrisentan-Tadalafil or b) Ambrisentan-Sildenafil or c)	NA	PVR, mPAP, CI, RAP, 6MWD	NR

		closed shunt			(9.4%)	Bosentan-Tadalafil or d) Bosentan-Sildenafil or e) Macitentan-Tadalafil or f) Macitentan-Sildenafil			
Chin et al. 2021 [7]	247	PAH	51.9	26 weeks	I-II: 50 (20.2%) III-IV: 197 (79.8%)	Macitentan-Tadalafil-Selexipag	Macitentan-Tadalafil-Placebo	PVR, mPAP, CI, RAP, SVO2, NT-proBNP, 6MWD	Headache, diarrhea, nausea, pain in extremity, jaw pain, vomiting
D'Alto et al. 2020 [8]	21	IPAH	44	24±14 months	III: 12 (57%)	Ambrisentan-Tadalafil-	a) Bosentan or b)	PVR, mPAP, CI,	Peripheral oedema, nasal

					IV: 9 (43%)	Treprostinil	Ambrisentan or c) Sildenafil or d) Tadalafil;	RAP, SVO2, NT-proBNP, 6MWD	congestion, flushing
Hassoun et al. 2015 [9]	24	SSc-PAH	59.9	36 weeks	II: 8 (35%) III: 15 (65%)	Ambrisentan-Tadalafil	NA	PVR, mPAP, CI, RAP, NT-proBNP, 6MWD	Peripheral oedema, nasal congestion, dyspnoea, cough, headache, dizziness, fatigue, abdominal pain, nausea-vomiting, hypotension, diarrhea
Kemp et al. 2012 [10]	23	IPAH, HPAH, DPAH	43	4±1 months	III: 16 (70%) IV: 7 (30%)	Epoprostenol-Bosentan	Epoprostenol monotherapy	PVR, mPAP, CI, RAP, SVO2,	Jaw pain, facial flushing, headache, gastrointestinal disturbance, leg

								6MWD	pain, catheter infections, increase in liver enzymes
Rinaldi et al. 2018 [11]	19	PAH	NR	NR	II-III: 100%	Ambrisentan-Tadalafil	a) Bosentan or Sildenafil monotherapy or b) other ERAs or PDE5is monotherapy or c) Bosentan-Seldenafil or d) Macitentan-Sildenafil	PVR, mPAP, CI, RAP, SVO2, 6MWD	
Sitbon et al.	19	IPAH,	39.4	4	III: 8	Bosentan-	NA	PVR,	Jaw pain, headache,

2014 [12]		HPAH, DPAH		months	(42%) IV: 11 (58%)	Sildenafil-Epoprostenol		mPAP, CI, RAP, SVO2, 6MWD	diarrhea, flushing, increase in liver enzymes
Sitbon et al. 2016 [13]	97	PAH	54.1	4.1 (3.5–4.9) months	II: 15 (15%) III: 70 (72%) IV: 12 (12%)	a) Bosentan-Sildenafil or b) Bosentan-Tadalafil or c) Ambrisentan-Sildenafil or d) Ambrisentan-Tadalafil	NA	PVR, mPAP, CI, RAP, SVO2, BNP, 6MWD	Peripheral oedema, increase in liver enzymes, blurred vision
Sitbon et al. 2020 [14]	46	PAH	57.4	16 weeks	II: 10 (21.7%) III: 36 (78.3%)	Macitentan-Tadalafil	NA	PVR, mPAP, CI, RAP, SVO2, NT-	Peripheral oedema, headache, diarrhea, dyspnoea, anemia, asthenia, fatigue, increase in lever

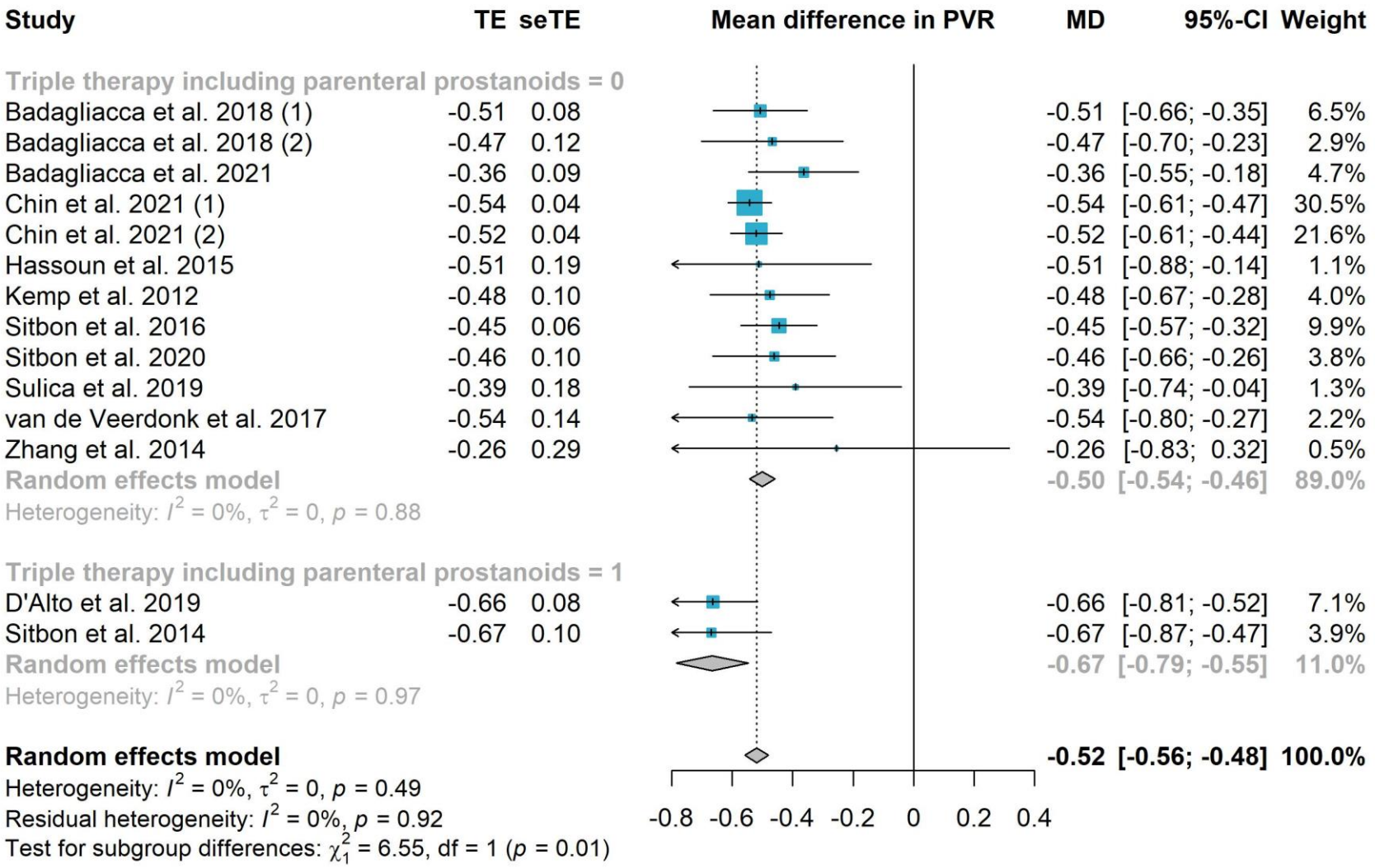
								proBNP, 6MWD	enzymes
Sulica et al. 2019 [15]	15	PAH	55.8	13.7±3.6 months	III: 93% IV: 7%	Macitentan-Riociguat	NA	PVR, mPAP, CI, RAP, SVO2, BNP, 6MWD	Peripheral oedema, nasal congestion, headache, hypotension
van de Veerdonk et al. 2017 [16]	80	IPAH, HPAH, DPAH	49	12 months	II: 24 (30%) III: 56 (70%)	a) Bosentan-Sildenafil or b) Bosentan-Tadalafil or c) Ambrisentan-Sildenafil or d) Ambrisentan-Tadalafil	a) Bosentan or b) Ambrisentan or c) Macitentan or d) Sitaxentanor or e) Sildenafil or	PVR, mPAP, CI, RAP, SVO2, NT-proBNP, 6MWD	Increase in lever enzymes

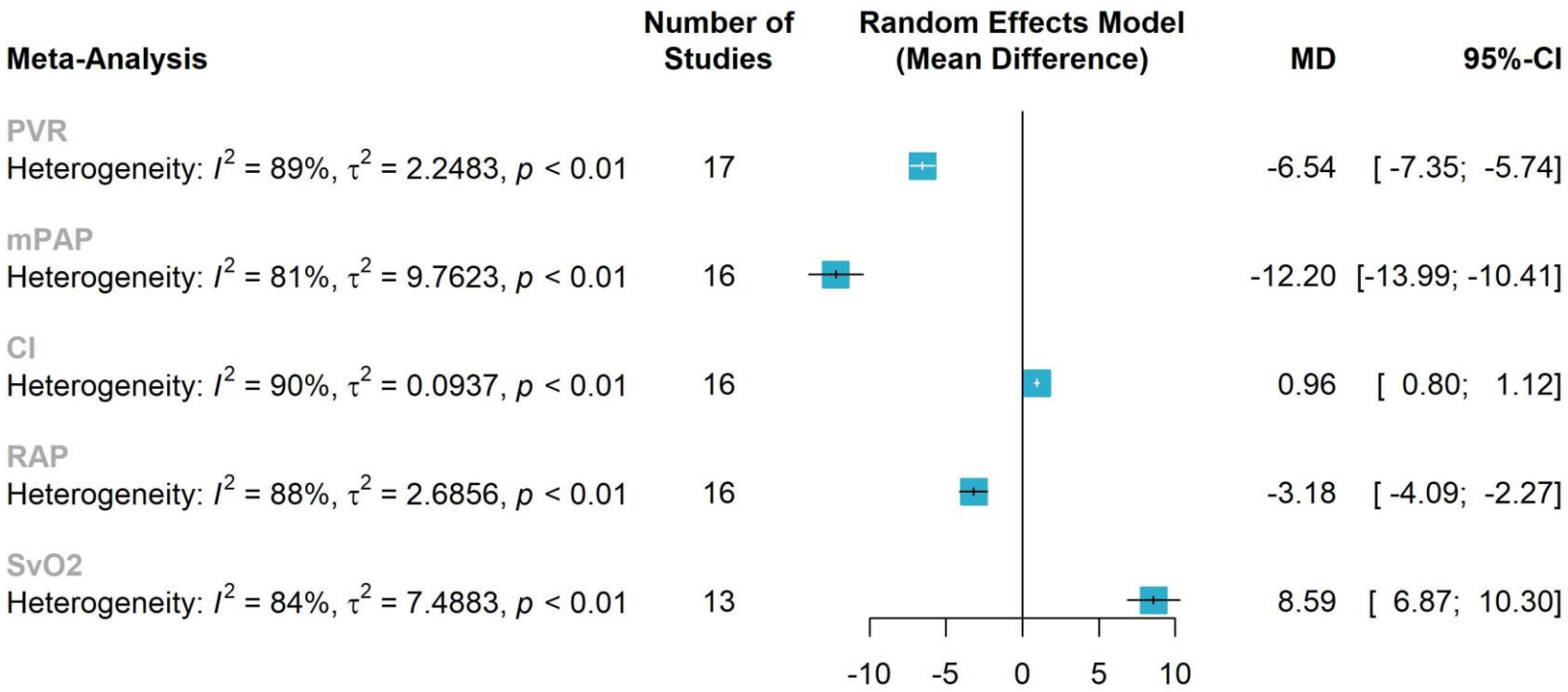
							f) Tadalafil		
Zhang et al. 2014 [17]	68	CHD-PAH	NR	6 months	NR	Upfront Iloprost-Tadalafil	Sequential Iloprost-Tadalafil	PVR, SVO2, 6MWD	

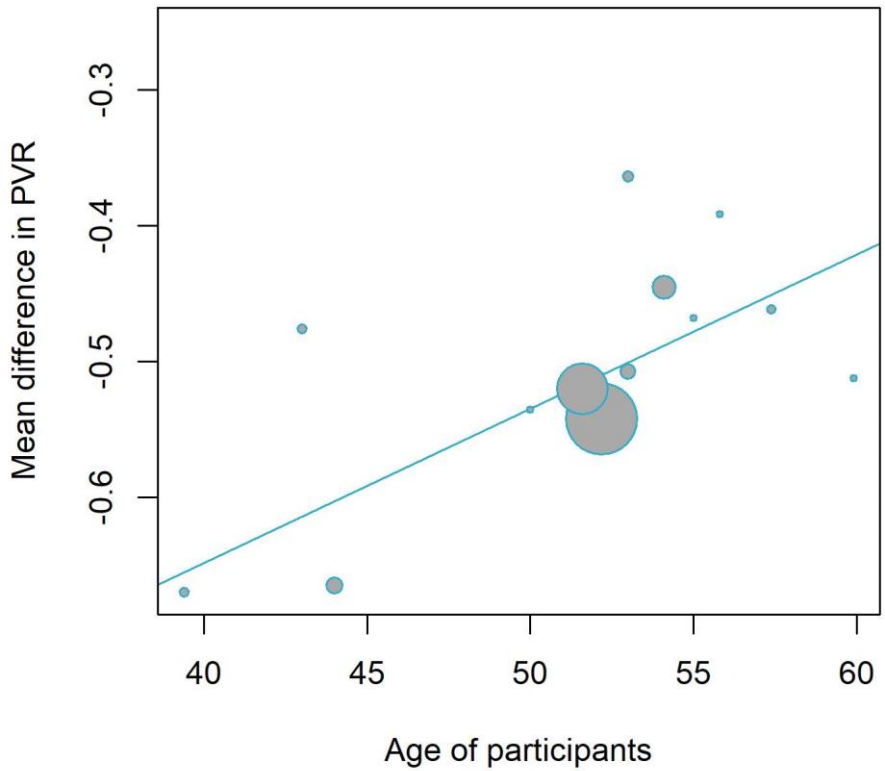
Values are expressed as mean ± SD, or median with IQR

6MWD, 6-minute walking distance; CHD, congenital heart disease; CI, cardiac index; CTD, connective tissue disorders; DPAH, drug-induced pulmonary arterial hypertension; ERA, endothelin receptor antagonist; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; IQR, interquartile range; mPAP, mean pulmonary arterial pressure; NA, not applicable; NR, not reported; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitor; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SD, standard deviation; SSc, systemic sclerosis; SVO2, mixed venous oxygen saturation; WHO FC, World Health Organization functional class

*** In this study Group 1 was treated with a) Treprostinil-Tadalafil or b) Treprostinil-Ambrisentan or c) Treprostinil-Bosentan or d) Epoprostenol-Tadalafil or e) Epoprostenol-Bosentan or f). Iloprost-Ambrisentan; Group 2 with a) Ambrisentan-Tadalafil or b) Ambrisentan-Sildenafil or c) Bosentan-Tadalafil or d) Bosentan-Sildenafil or e) Macitentan-Tadalafil or f) Macitentan-Sildenafil; Group 3 with a) Bosentan or b) Ambrisentan or c) Sildenafil or d) Tadalafil; Group 4 with a) Treprostinil or b) Epoprostenol**


Study
TE
seTE
Mean difference in PVR
MD
95%-CI
Weight
Triple therapy including parenteral prostanoids = 0
Badagliacca et al. 2018 (1) -0.51 0.08 -0.51 [-0.66; -0.35] 6.5%
Badagliacca et al. 2018 (2) -0.47 0.12 -0.47 [-0.70; -0.23] 2.9%
Badagliacca et al. 2021 -0.36 0.09 -0.36 [-0.55; -0.18] 4.7%
Chin et al. 2021 (1) -0.54 0.04 -0.54 [-0.61; -0.47] 30.5%
Chin et al. 2021 (2) -0.52 0.04 -0.52 [-0.61; -0.44] 21.6%
Hassoun et al. 2015 -0.51 0.19 -0.51 [-0.88; -0.14] 1.1%
Kemp et al. 2012 -0.48 0.10 -0.48 [-0.67; -0.28] 4.0%
Sitbon et al. 2016 -0.45 0.06 -0.45 [-0.57; -0.32] 9.9%
Sitbon et al. 2020 -0.46 0.10 -0.46 [-0.66; -0.26] 3.8%
Sulica et al. 2019 -0.39 0.18 -0.39 [-0.74; -0.04] 1.3%
van de Veerdonk et al. 2017 -0.54 0.14 -0.54 [-0.80; -0.27] 2.2%
Zhang et al. 2014 -0.26 0.29 -0.26 [-0.83; 0.32] 0.5%
Random effects model -0.50 [-0.54; -0.46] 89.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.88
Triple therapy including parenteral prostanoids = 1
D'Alto et al. 2019 -0.66 0.08 -0.66 [-0.81; -0.52] 7.1%
Sitbon et al. 2014 -0.67 0.10 -0.67 [-0.87; -0.47] 3.9%
Random effects model -0.67 [-0.79; -0.55] 11.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.97
Random effects model -0.52 [-0.56; -0.48] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.49
Residual heterogeneity: I^2 = 0%, p = 0.92
Test for subgroup differences: χ^2_1 = 6.55, df = 1 (p = 0.01)
-0.8 -0.6 -0.4 -0.2 0 0.2 0.4


Meta-Analysis
Number of Studies
Random Effects Model (Mean Difference)
MD
95%-CI
PVR
Heterogeneity: I^2 = 89%, τ^2 = 2.2483, p < 0.01
17
-6.54
[-7.35; -5.74]
mPAP
Heterogeneity: I^2 = 81%, τ^2 = 9.7623, p < 0.01
16
-12.20
[-13.99; -10.41]
CI
Heterogeneity: I^2 = 90%, τ^2 = 0.0937, p < 0.01
16
0.96
[0.80; 1.12]
RAP
Heterogeneity: I^2 = 88%, τ^2 = 2.6856, p < 0.01
16
-3.18
[-4.09; -2.27]
SvO2
Heterogeneity: I^2 = 84%, τ^2 = 7.4883, p < 0.01
13
8.59
[6.87; 10.30]
-10
-5
0
5
10


Mean difference in PVR
-0.3
-0.4
-0.5
-0.6
40
45
50
55
60
Age of participants

Haemodynamic effects of upfront combination therapy PAH: A systematic review and meta-analysis – Supplemental Material

Contents

Supplemental Material 1 – Search strategy

MEDLINE search strategy

via PubMed

Search syntax:

1 endothelin receptor antagonists

2 bosentan

3 ambrisentan

4 macitentan

5 phosphodiesterase type 5 inhibitor

6 sildenafil

7 tadalafil

8 soluble guanylate cyclase stimulators

9 riociguat

10 prostanoids

11 epoprostenol

12 treprostinil

13 iloprost

14 selexipag

15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16 pulmonary arterial hypertension

17 initial

18 upfront

19 17 or 18

31 15 AND 16 AND 19

Search string

(((upfront) OR (initial)) AND ((((((((((((endothelin receptor antagonists) OR (bosentan)) OR (ambrisentan)) OR (macitentan)) OR (phosphodiesterase type 5 inhibitor)) OR (sildenafil)) OR (tadalafil)) OR (soluble guanylate cyclase stimulators)) OR (riociguat)) OR (prostanoids)) OR (epoprostenol)) OR (treprostinil)) OR (iloprost)) OR (selexipag))) AND (pulmonary arterial hypertension)

("upfront"[All Fields] OR ("initial"[All Fields] OR "initially"[All Fields] OR "initials"[All Fields] OR "initiate"[All Fields] OR "initiated"[All Fields] OR "initiates"[All Fields] OR "initiating"[All Fields] OR "initiation"[All Fields] OR "initiations"[All Fields] OR "initiator"[All Fields] OR "initiators"[All Fields])) AND ("endothelin receptor antagonists"[Pharmacological Action] OR "endothelin receptor antagonists"[MeSH Terms] OR ("endothelin"[All Fields] AND "receptor"[All Fields] AND "antagonists"[All Fields]) OR "endothelin receptor antagonists"[All Fields] OR ("bosentan"[MeSH Terms] OR "bosentan"[All Fields]) OR ("ambrisentan"[Supplementary Concept] OR "ambrisentan"[All Fields]) OR ("macitentan"[Supplementary Concept] OR "macitentan"[All Fields]) OR ("phosphodiesterase 5 inhibitors"[Pharmacological Action] OR "phosphodiesterase 5 inhibitors"[MeSH Terms] OR "phosphodiesterase 5 inhibitors"[All Fields] OR "phosphodiesterase type 5 inhibitor"[All Fields]) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR "sildenafil"[All Fields] OR "sildenafil s"[All Fields]) OR ("tadalafil"[MeSH Terms] OR "tadalafil"[All Fields]) OR (("soluble guanylyl cyclase"[MeSH Terms] OR ("soluble"[All Fields] AND "guanylyl"[All Fields] AND "cyclase"[All Fields]) OR "soluble guanylyl cyclase"[All Fields] OR ("soluble"[All Fields] AND "guanylate"[All Fields] AND "cyclase"[All Fields]) OR "soluble guanylate cyclase"[All Fields]) AND ("stimulate"[All Fields] OR "stimulated"[All Fields] OR "stimulates"[All Fields] OR "stimulating"[All Fields] OR "stimulation"[All Fields] OR "stimulations"[All Fields] OR "stimulative"[All Fields] OR "stimulator"[All Fields] OR "stimulators"[All Fields])) OR ("riociguat"[Supplementary Concept] OR "riociguat"[All Fields]) OR ("prostaglandins"[MeSH Terms] OR "prostaglandins"[All Fields] OR "prostanoid"[All Fields] OR "prostanoids"[All Fields] OR "prostanoides"[All Fields]) OR ("epoprostenol"[MeSH Terms] OR "epoprostenol"[All Fields]) OR ("treprostinil"[Supplementary Concept] OR "treprostinil"[All Fields]) OR ("iloprost"[MeSH Terms] OR "iloprost"[All Fields]) OR ("selexipag"[Supplementary Concept] OR "selexipag"[All Fields])) AND ("pulmonary arterial hypertension"[MeSH Terms] OR ("pulmonary"[All Fields] AND "arterial"[All Fields] AND "hypertension"[All Fields]) OR "pulmonary arterial hypertension"[All Fields])

Translations

initial: "initial"[All Fields] OR "initially"[All Fields] OR "initials"[All Fields] OR "initiate"[All Fields] OR "initiated"[All Fields] OR "initiates"[All Fields] OR "initiating"[All Fields] OR "initiation"[All Fields] OR "initiations"[All Fields] OR "initiator"[All Fields] OR "initiators"[All Fields]

endothelin receptor antagonists: "endothelin receptor antagonists"[Pharmacological Action] OR "endothelin receptor antagonists"[MeSH Terms] OR ("endothelin"[All Fields] AND "receptor"[All Fields] AND "antagonists"[All Fields]) OR "endothelin receptor antagonists"[All Fields]

bosentan: "bosentan"[MeSH Terms] OR "bosentan"[All Fields]

ambrisentan: "ambrisentan"[Supplementary Concept] OR "ambrisentan"[All Fields]

macitentan: "macitentan"[Supplementary Concept] OR "macitentan"[All Fields]

phosphodiesterase type 5 inhibitor: "phosphodiesterase 5 inhibitors"[Pharmacological Action] OR "phosphodiesterase 5 inhibitors"[MeSH Terms] OR "phosphodiesterase 5 inhibitors"[All Fields] OR "phosphodiesterase type 5 inhibitor"[All Fields]

sildenafil: "sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR "sildenafil"[All Fields] OR "sildenafil's"[All Fields]

tadalafil: "tadalafil"[MeSH Terms] OR "tadalafil"[All Fields]

soluble guanylate cyclase: "soluble guanylyl cyclase"[MeSH Terms] OR ("soluble"[All Fields] AND "guanylyl"[All Fields] AND "cyclase"[All Fields]) OR "soluble guanylyl cyclase"[All Fields] OR ("soluble"[All Fields] AND "guanylate"[All Fields] AND "cyclase"[All Fields]) OR "soluble guanylate cyclase"[All Fields]

stimulators: "stimulate"[All Fields] OR "stimulated"[All Fields] OR "stimulates"[All Fields] OR "stimulating"[All Fields] OR "stimulation"[All Fields] OR "stimulations"[All Fields] OR "stimulative"[All Fields] OR "stimulator"[All Fields] OR "stimulator's"[All Fields] OR "stimulators"[All Fields]

riociguat: "riociguat"[Supplementary Concept] OR "riociguat"[All Fields]

prostanoids: "prostaglandins"[MeSH Terms] OR "prostaglandins"[All Fields] OR "prostanoid"[All Fields] OR "prostanoids"[All Fields] OR "prostanoides"[All Fields]

epoprostenol: "epoprostenol"[MeSH Terms] OR "epoprostenol"[All Fields]

treprostinil: "treprostinil"[Supplementary Concept] OR "treprostinil"[All Fields]

iloprost: "iloprost"[MeSH Terms] OR "iloprost"[All Fields]

selexipag: "selexipag"[Supplementary Concept] OR "selexipag"[All Fields]

pulmonary arterial hypertension: "pulmonary arterial hypertension"[MeSH Terms] OR ("pulmonary"[All Fields] AND "arterial"[All Fields] AND "hypertension"[All Fields]) OR "pulmonary arterial hypertension"[All Fields]

Supplemental Material 2 – PRISMA Flowchart

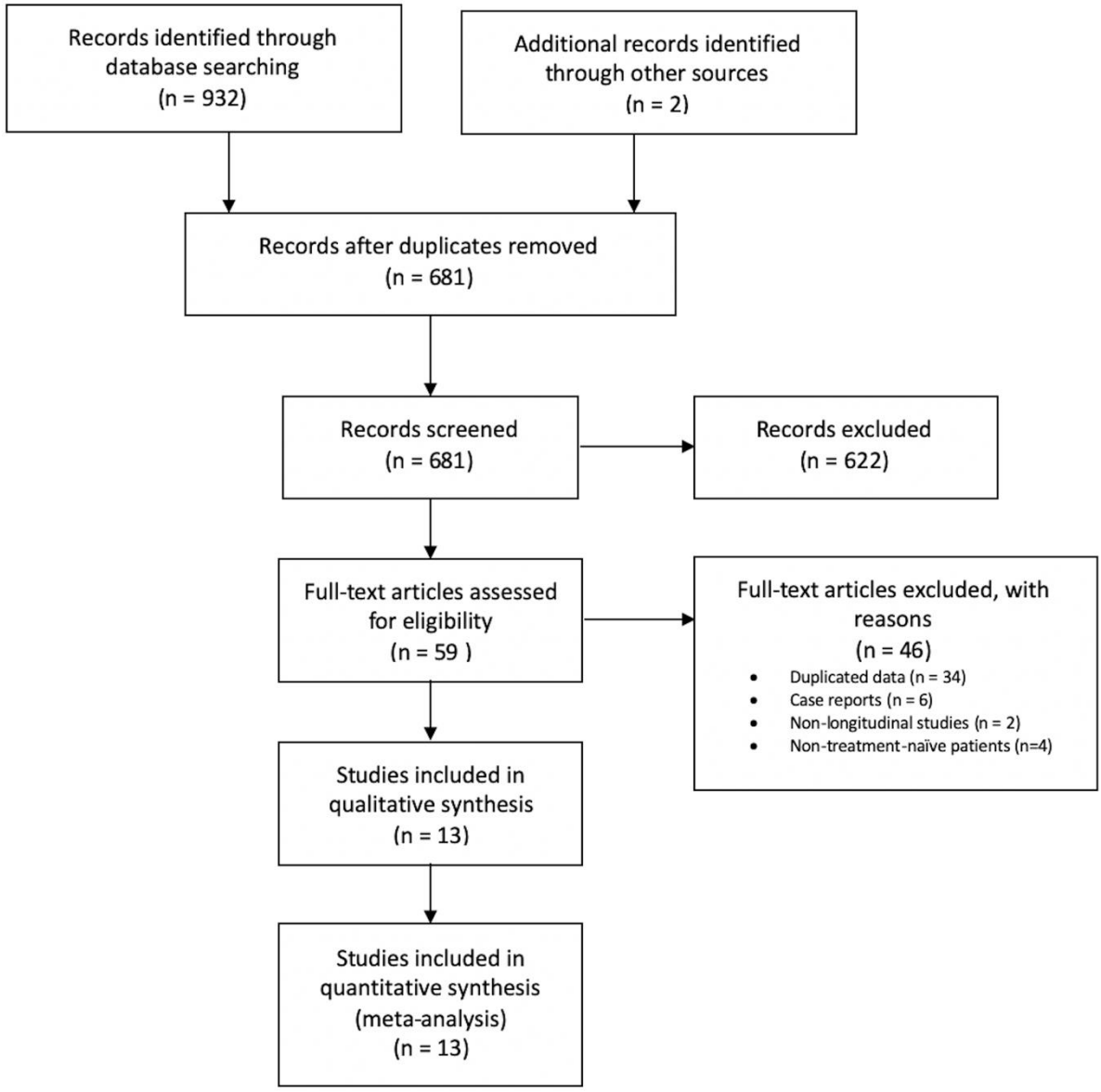


Figure S1. PRISMA Flowchart.

Supplemental Material 3 – Quality assessment

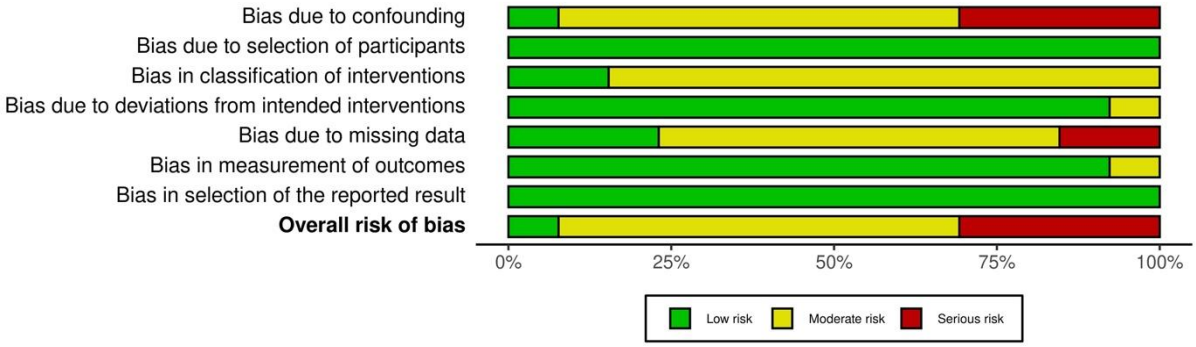


Figure S2. Summary plot.

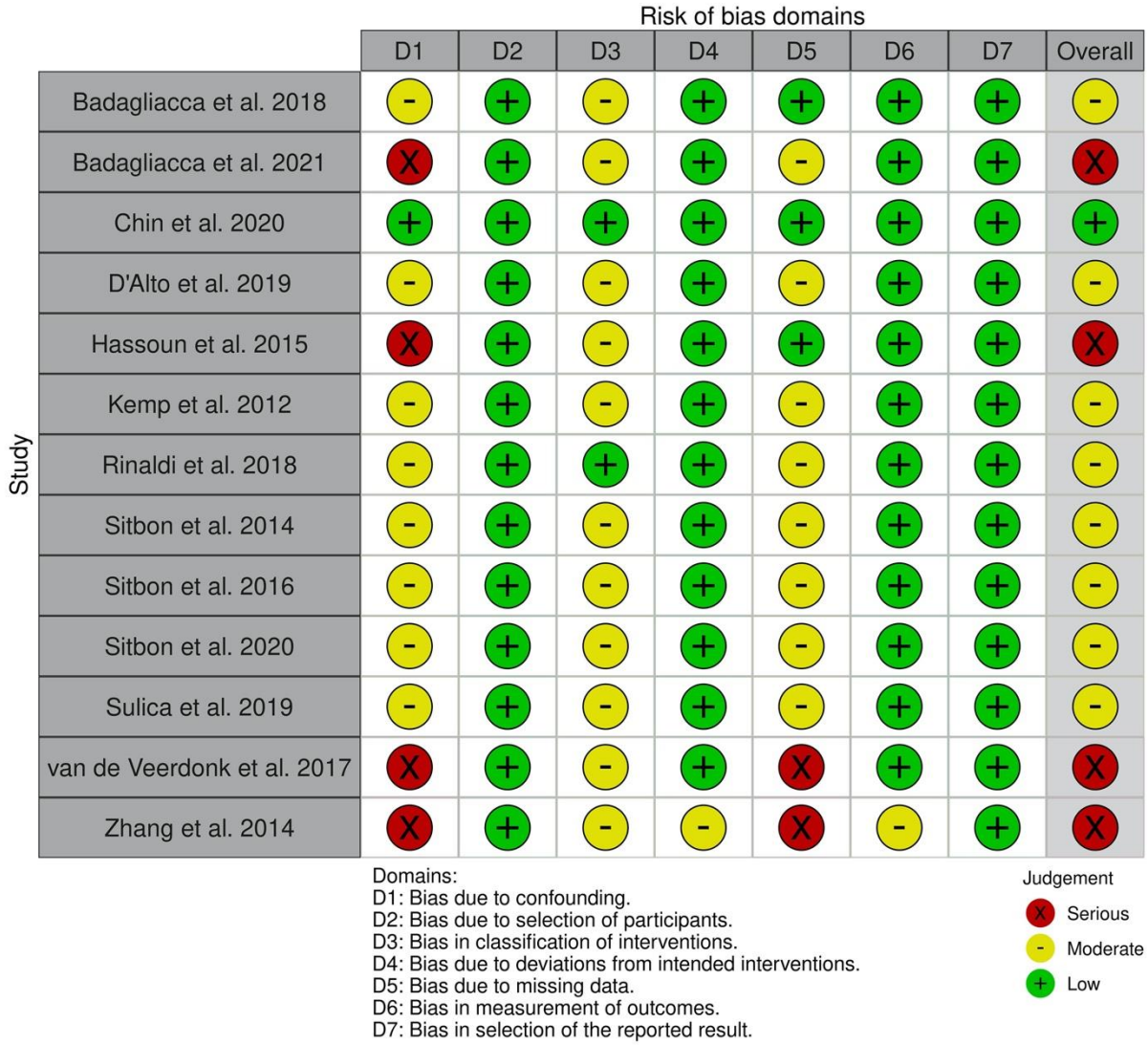


Figure S3. Traffic light plot.

Supplemental Material 4 – Funnel plot

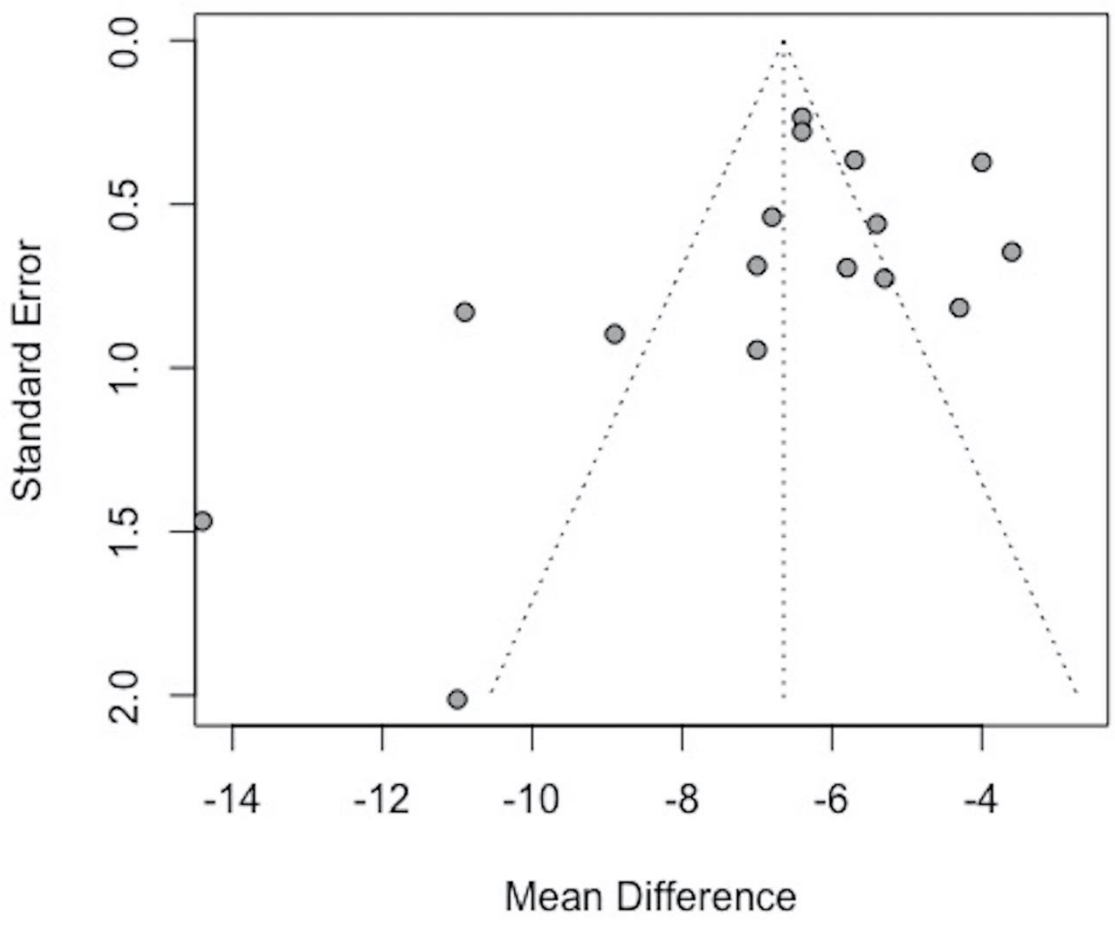


Figure S2. Funnel plot for the PVR outcome in the single-arm meta-analysis.

Supplemental Material 5 – Forest plots

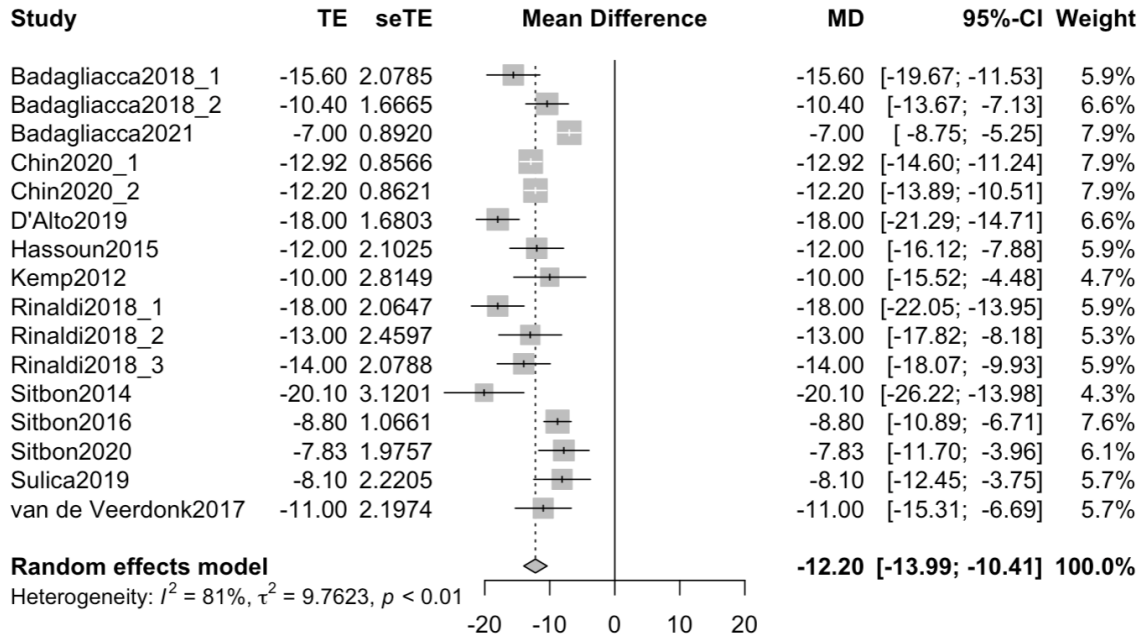


Figure S4. Effects of upfront combination therapy on mPAP in the single-arm meta-analysis.

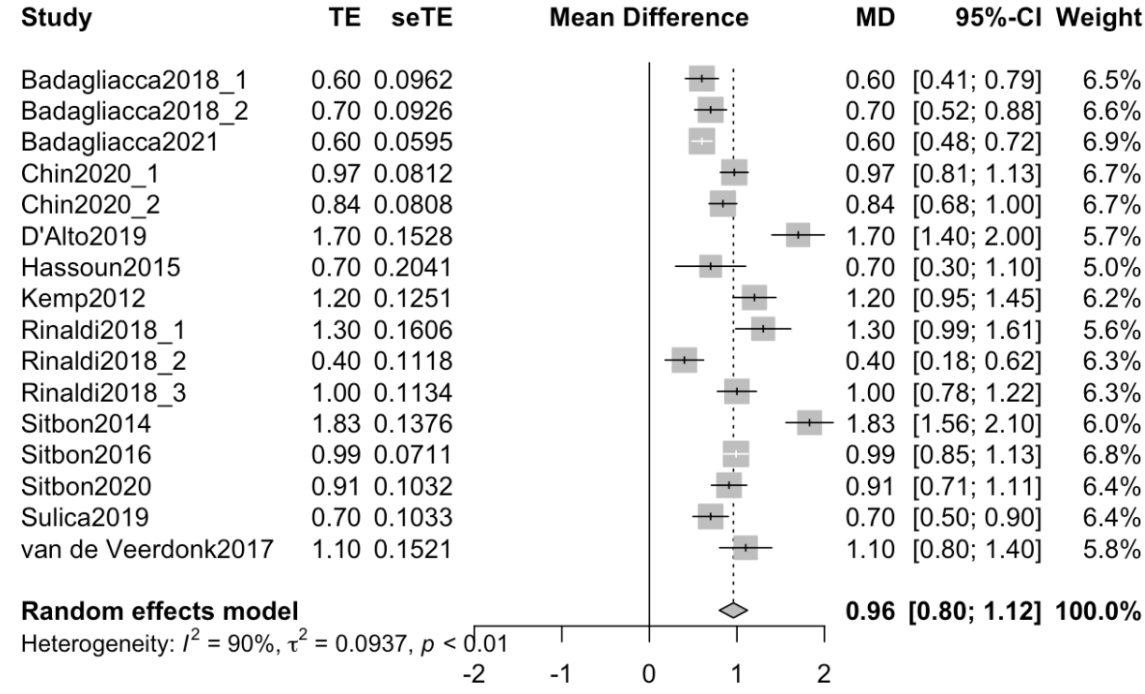


Figure S5. Effects of upfront combination therapy on cardiac index in the single-arm meta-analysis.

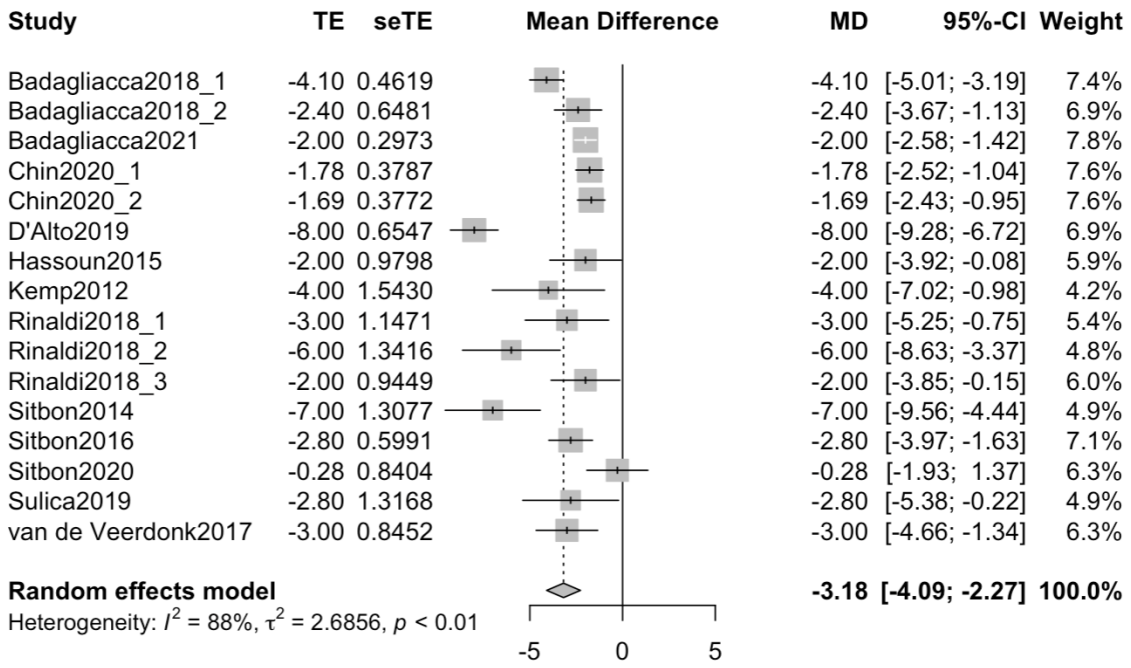


Figure S6. Effects of upfront combination therapy on right atrial pressure in the single-arm meta-analysis.

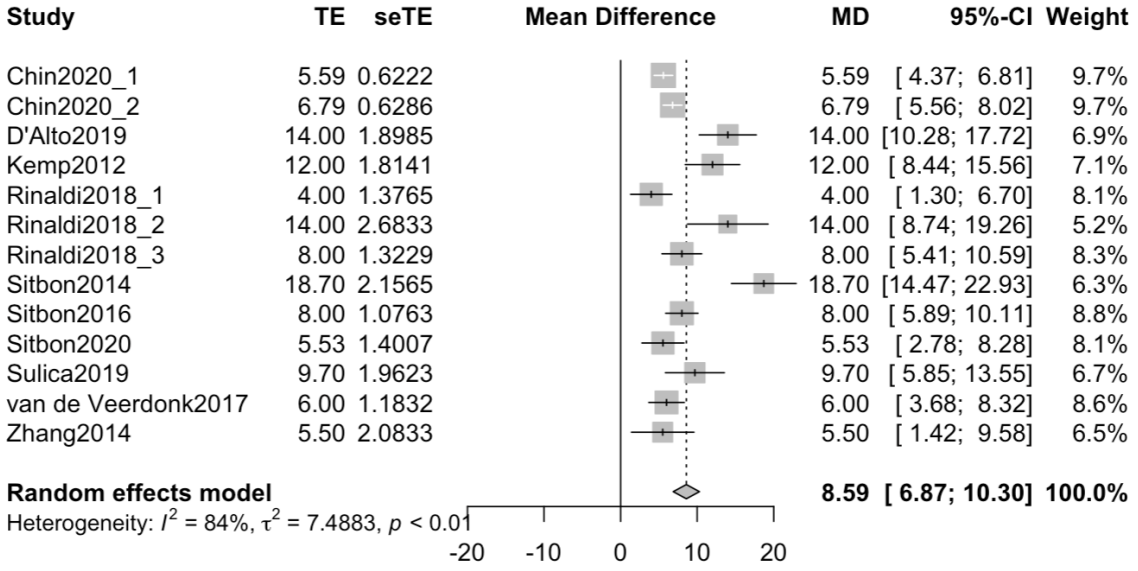


Figure S7. Effects of upfront combination therapy on mixed venous oxygen saturation in the single-arm meta-analysis.

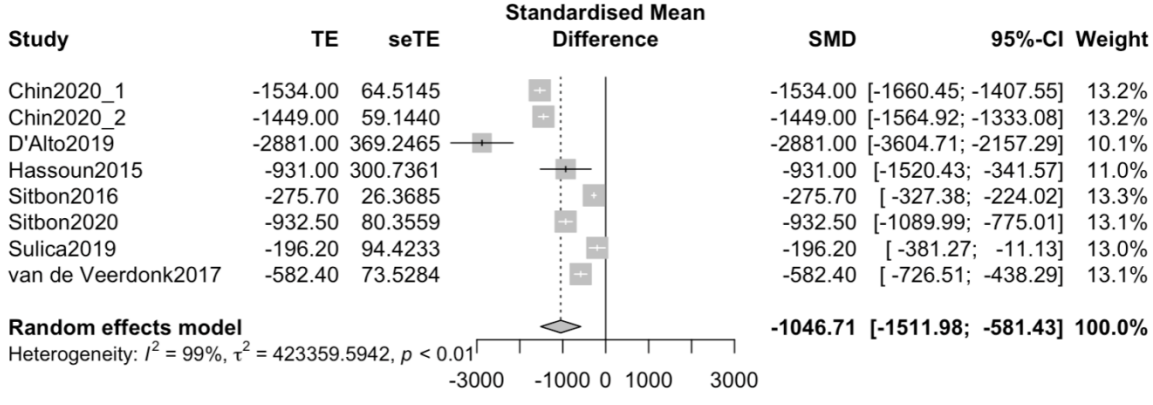


Figure S8. Effects of upfront combination therapy on BNP levels in the single-arm meta-analysis.

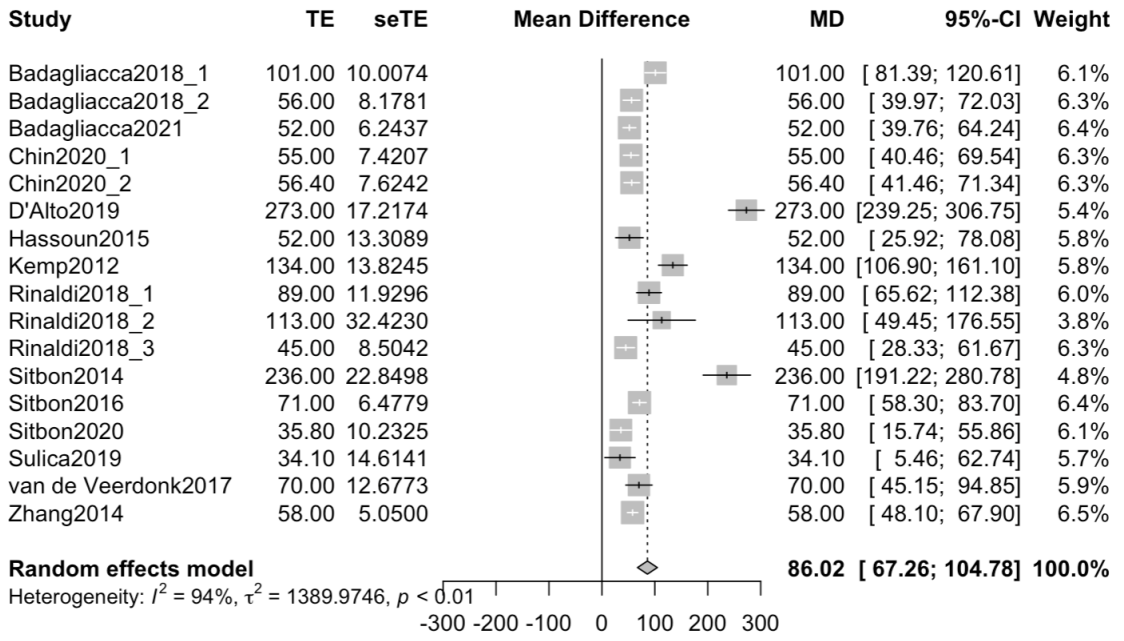


Figure S9. Effects of upfront combination therapy on the 6-minute walking distance in the single-arm meta-analysis.

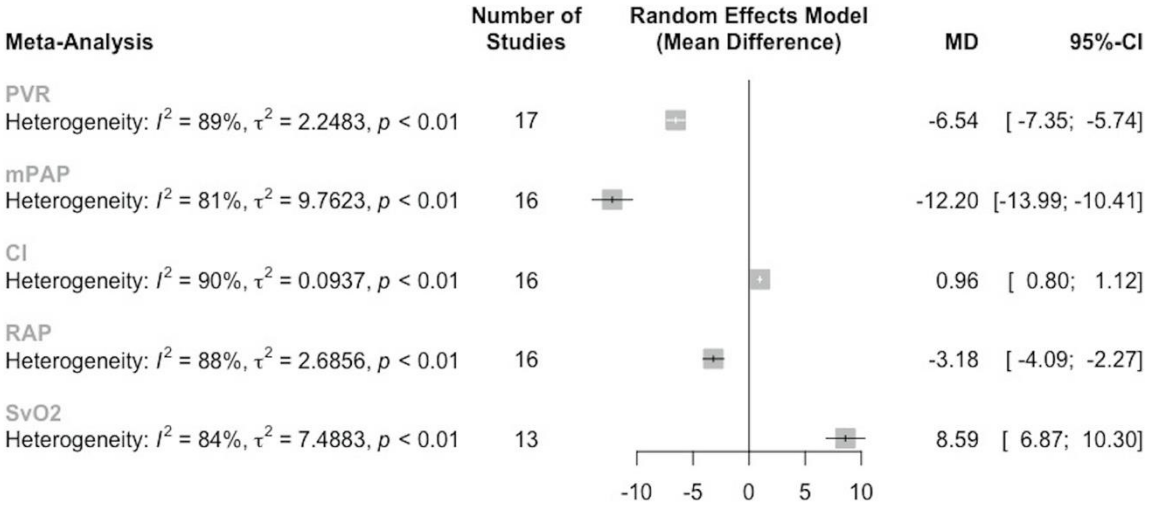


Figure S10. Effects of upfront combination therapy on hemodynamic outcomes in the single-arm meta-analysis.

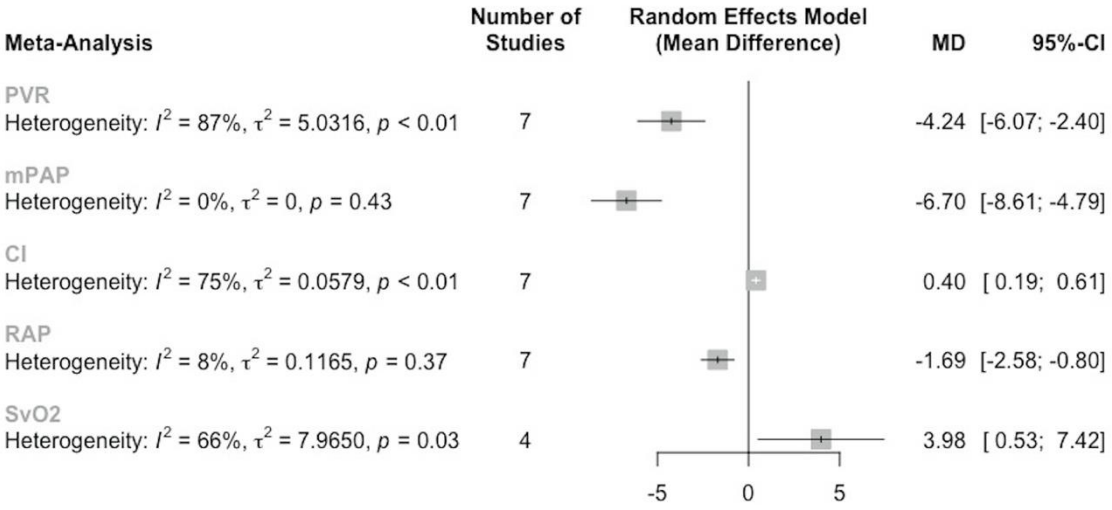


Figure S11. Effects of upfront combination therapy on hemodynamic outcomes in the controlled-arm meta-analysis.