

Quality control

Supplementary Table S1. The Agency for Healthcare Research and Quality (AHRQ) checklist for the observational studies included in the metanalysis.

	Castellví <i>et al.</i> 2020	Trombetta <i>et al.</i> 2016	Murdaca <i>et al.</i> 2016	Ahmadi Simab <i>et al.</i> 2006	Rotondo <i>et al.</i> 2017	Hamaguchi <i>et al.</i> 2009	Giordano <i>et al.</i> 2010	Romaniello <i>et al.</i> 2014	Giannelli <i>et al.</i> 2006	Funauchi <i>et al.</i> 2009
1. Define the source of information (surgery, record review)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. List inclusion and exclusion criteria	Y	Y	N	N	Y	Y	Y	Y	Y	Y
3. Indicate time period used for identifying patients	Y	Y	Y	Y	Y	N	Y	N	N	N
4. Indicate whether or not subjects were consecutive if not population-based	U	Y	Y	U	Y	N	Y	N	Y	N
5. Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	U	U	N	N	U	N	U	N	N	N
6. Describe any assessments undertaken for quality assurance purposes	N	N	N	Y	N	N	U	N	N	N
7. Explain any patient exclusions from analysis	Y	Y	N	N	Y	N	Y	N	N	N
8. Describe how confounding was assessed and/or controlled	U	Y	N	N	N	N	N	N	N	N
9. If applicable, explain how missing data were handled in the analysis	U	N	U	U	U	N	U	N	N	N
10. Summarize patient response rates and completeness of data collection	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
11. Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Total items	6	8	5	5	7	4	7	4	4	4

Y: Yes; N: No; U: Unclear.

Supplementary Table S2. The Revised Cochrane risk-of-bias tool for randomised trials (RoB 2).

	Phat <i>et al.</i> 2022
Domain 1	High risk
Domain 2: effect of assignment to intervention	Some concerns
Domain 2: effect of adhering to intervention	Low risk
Domain 4	Some concerns
Domain 5:	Low risk

Bosentan effect on resting sPAP at TTE

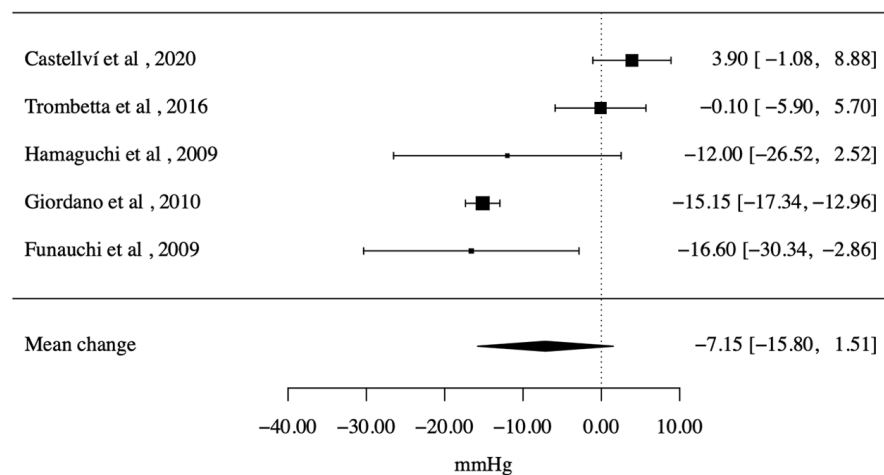
Supplementary Table S3. Influence analysis.

	estimate	SE	z value	p value	CI lower limit	CI upper limit	Q	Qp	tau ²	I ²	H ²
Castellví <i>et al.</i> 2020	-6.688	2.079	-3.218	0.001	-10.762	-2.614	106.5	<0.001	29.169	92.075	12.618
Phat <i>et al.</i> 2022	-5.936	2.409	-2.464	0.014	-10.659	-1.214	114.4	<0.001	41.335	91.943	12.411
Trombetta <i>et al.</i> 2016	-6.293	2.287	-2.752	0.006	-10.775	-1.811	118.9	<0.001	37.333	93.780	16.076
Murdaca <i>et al.</i> 2016	-5.463	2.393	-2.282	0.023	-10.154	-0.772	120.2	<0.001	40.591	90.746	10.806
Ahmadi Simab <i>et al.</i> 2006	-5.279	2.162	-2.441	0.015	-9.517	-1.040	122.8	<0.001	35.460	93.681	15.8254
Rotondo <i>et al.</i> 2017	-5.655	2.265	-2.497	0.012	-10.095	-1.216	123.7	<0.001	38.446	94.116	16.996
Hamaguchi Y <i>et al.</i> 2009	-5.313	2.198	-2.416	0.016	-9.620	-1.002	123.1	<0.001	36.290	93.804	16.138
Giordano <i>et al.</i> 2010	-3.782	1.727	-2.190	0.028	-7.167	-0.397	52.6	<0.001	17.339	84.694	6.533
Romaniello <i>et al.</i> 2014	-6.530	2.230	-2.929	0.003	-10.900	-2.160	90.8	<0.001	34.129	92.277	12.946
Giannelli <i>et al.</i> 2006	-5.799	2.354	-2.463	0.014	-10.413	-1.185	123.4	<0.001	40.349	94.261	17.423
Funauchi <i>et al.</i> 2009	-5.005	2.134	-2.346	0.019	-9.188	-0.823	121.6	<0.001	33.620	93.340	15.014

Subgroup analysis: Combination therapy and monotherapy

Combination therapy

Reduction of sPAP – Combination therapy



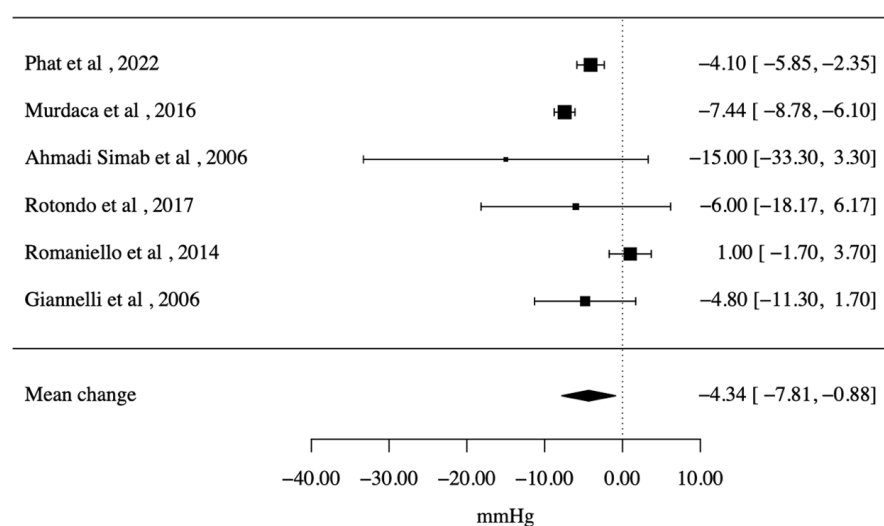
Supplementary Fig. S1. Forest plot.

Supplementary Table S4. Influence analysis.

	estimate	SE	z value	p value	CI lower limit	CI upper limit	Q	Q p value	tau ²	I ²	H ²
Castellví <i>et al.</i> 2020	-10.333	4.327	-2.388	0.017	-18.815	-1.851	22.872	<0.001	53.361	82.573	5.738
Trombetta <i>et al.</i> 2016	-9.248	5.291	-1.748	0.080	-19.619	1.122	47.422	<0.001	89.071	90.580	10.616
Hamaguchi <i>et al.</i> 2009	-6.382	5.196	-1.228	0.219	-16.566	3.802	62.264	<0.001	94.377	93.627	15.692
Giordano <i>et al.</i> 2010	-4.261	4.672	-0.912	0.362	-13.418	4.895	10.576	0.014	62.837	79.462	4.869
Funauchi <i>et al.</i> 2009	-5.441	4.872	-1.117	0.264	-14.990	4.109	61.615	<0.001	80.924	92.598	13.509

Bosentan monotherapy

Reduction of sPAP – Monotherapy



Supplementary Fig. S2. Forest plot.

Subgroup analysis: indication for bosentan therapy
Indication PAH

Supplementary Table S5. Influence analysis.

	estimate	SE	z value	p value limit	CI lower limit	CI upper limit	Q	Q p value	tau ²	I ²	H ²
Phat <i>et al.</i> 2022	-14.845	1.070	-13.879	<0.0001	-16.941	-12.748	2.313	0.678	<0.0001	<0.0001	1.00
Ahmadi Simab <i>et al.</i> 2006	-10.199	3.062	-3.331	0.001	-16.200	-4.197	61.216	<0.001	28.810	88.523	8.713
Rotondo <i>et al.</i> 2017	-11.286	3.246	-3.476	0.0005	-17.649	-4.923	61.534	<0.001	31.066	89.072	9.151
Hamaguchi <i>et al.</i> 2009	-10.417	3.184	-3.271	0.001	-16.659	-4.176	61.478	<0.001	30.647	89.045	9.128
Giordano <i>et al.</i> 2010	-7.857	2.902	-2.708	0.007	-13.544	-2.169	5.524	0.238	15.605	36.351	1.571
Funauchi <i>et al.</i> 2009	-9.798	3.102	-3.158	0.002	-15.878	-3.7176	60.360	0.001	28.276	88.203	8.477

Mixed indication (DU with/without PH)

Supplementary Table S6. Influence analysis.

	estimate	SE	z value	p value	CI lower limit	CI upper limit	Q	Q p value	tau ²	I ²	H ²
Castellví <i>et al.</i> 2020	-2.9801	2.2540	-1.3221	0.1861	-7.3979	1.4377	33.8037	0.0001	15.7212	86.0445	7.1656
Trombetta <i>et al.</i> 2016	-1.9466	2.6857	-0.7248	0.4686	-7.2104	3.3173	43.9281	0.0001	24.4528	90.9767	11.0824
Hamaguchi <i>et al.</i> 2009	0.7701	1.0608	0.7259	0.4679	-1.3092	2.8493	4.4495	0.2168	0.001	0.0001	1.0000
Giordano <i>et al.</i> 2010	-2.3946	2.6943	-0.8888	0.3741	-7.6753	2.8861	23.4729	0.001	22.9365	83.2434	5.9678
Funauchi <i>et al.</i> 2009	-0.9974	2.5937	-0.3846	0.7006	-6.0810	4.0862	46.8147	0.001	22.9228	90.6703	10.7185