Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis

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Summary

Background **Several randomised controlled studies and a previous meta-analysis have reported conflicting results regarding the effect of combined targeted therapy compared with monotherapy for pulmonary arterial hypertension (PAH). We did a systematic review and meta-analysis to assess the effects of a combination of PAH-specific therapies compared with monotherapy on predefined clinical worsening in PAH.**

Methods **We searched MEDLINE, Embase, and the Cochrane Library for reports published from Jan 1, 1990, to May 31, 2015, of prospective randomised controlled trials of at least 12 weeks that assessed a combination of PAH-specific therapies (upfront and sequential add-on) compared with background PAH-specific monotherapy in patients older than 12 years. We extracted data from the reports, and assessed the primary outcome of risk of clinical worsening, as defined a priori in each trial, using the Mantel-Haenszel method based on a fixed-effects model.**

Findings **Of 2017 studies that we identified from our search, we included 17 (4095 patients) in our analysis. 15 studies assessed clinical worsening and were included in the primary analysis. Combined therapy was associated with significant risk reduction for clinical worsening compared with monotherapy (combined therapy 17% [332 of 1940 patients] *vs* monotherapy 28% [517 of 1862 patients], risk ratio [RR] 0·65 [95% CI 0·58–0·72], p<0·00001). We noted no heterogeneity between the studies (I^2=18%, $p_{homogeneity}$=0·25). A publication bias was suggested by the results of an Egger test (t=–2·3982, p=0·031), but when we excluded the four studies with the highest SEs, the RR for clinical worsening was identical (0·65 [95% CI 0·58–0·73], p<0·00001).**

Interpretation **In our analysis, combined therapy for PAH was associated with a significant reduction in clinical worsening compared with monotherapy. However, our study was limited by the variable definition of clinical worsening among the trials and possible publication bias. Because many patients still had clinical worsening with combination therapy, identification of innovative therapeutic targets for PAH is thus urgently needed.**

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Introduction

Pulmonary arterial hypertension (PAH; group 1 of the clinical classification) is a life-threatening disease characterised by a progressive increase in pulmonary vascular resistance, ultimately leading to right-heart failure and death.[1,2] Throughout the past 20 years, several specific drugs targeting the endothelial dysfunction associated with PAH have emerged.[3] Licensed PAH-specific therapies include phosphodiesterase-5 inhibitors, endothelin receptor antagonists, prostaglandins, soluble guanylate cyclase stimulators, and a selective prostacyclin receptor agonist.[3,4]

Findings from short-term randomised controlled trials investigating PAH-specific monotherapy with these molecules have reported improvements in pulmonary haemodynamics and exercise capacity.[5] A meta-analysis also documented a reduction in short-term mortality of about 40% with such drugs.[6] However, long-term survival with PAH-specific monotherapy remains poor, with a mortality rate of 15% per year for incident idiopathic PAH.[7,8] In an attempt to improve patients' outcomes, combination therapy was proposed to modulate disease pathways at several sites while potentially limiting drug toxicity. Several randomised clinical trials assessing PAH-specific combination therapies have been done but they report conflicting results in terms of efficacy. In 2011, findings from a systematic review and meta-analysis[9] suggested that combining therapies did not offer any advantage over monotherapy except a modest increase in exercise capacity. However, the combination trials included in that review were mainly of short-term duration and used the 6-min walk distance (6MWD) as the primary efficacy endpoint.[10–15] Although 6MWD might have a good discriminative capacity to predict outcomes in patients at the time of diagnosis, changes in exercise capacity might not predict clinically relevant outcomes for patients with PAH, such as death, admission to hospital, and clinical worsening,[16–18] especially in the setting of combination therapy or in patients who are less severely impaired. Moreover, initial trials of combination therapies were underpowered to detect significant improvements in event-free survival, which was a secondary endpoint in many of those trials.[11–15] As a result, recommendations regarding combination therapy in PAH remain based on limited evidence.[2]

Research in context

Evidence before this study

Several randomised clinical trials assessing combination therapy specifically for pulmonary arterial hypertension (PAH) have been done but have reported conflicting results in terms of efficacy. In 2011, results from a meta-analysis suggested that combining therapies did not offer any advantage over monotherapy except a modest increase in exercise capacity. Combination trials included in this meta-analysis were mainly of short-term duration and assessed the 6-min walk distance as the primary efficacy endpoint. Since then, numerous studies of longer duration and using a time-to-clinical-worsening endpoint, a composition of outcomes consisting mostly of death, admission to hospital, treatment escalation, transplantation, atrial septostomy, and PAH worsening, have been published. We searched MEDLINE, Embase, the Cochrane Library, and the relevant grey literature with no language restrictions from Jan 1, 1990, through May 31, 2015, for prospective, randomised controlled trials of at least 12 weeks duration comparing combinations of approved PAH-targeted therapies with monotherapy and reporting on our primary outcome of interest (clinical worsening) or one of the secondary outcomes (all-cause mortality, PAH-related mortality, PAH-related admission to hospital, lung transplantation, treatment escalation, symptomatic progression, changes in WHO functional class, treatment discontinuation, and treatment duration).

Added value of this study

17 studies judged to be of high quality using the Cochrane's Risk of Bias Tool were included in this meta-analysis, which showed that combination therapy significantly reduced the risk of clinical worsening compared with monotherapy (risk ratio 0·65 [95% CI 0·58–0·72], p<0·00001). This effect was consistent across subgroups, including drug classes, study duration and design, and patients' characteristics. Combination therapy was also associated with an enhanced improvement in patients' functional status. This first meta-analysis including a substantial proportion of studies of longer duration using clinical worsening as a primary endpoint supports the effect of combination therapy on clinically relevant outcomes in PAH.

Implications of all the available evidence

Combination therapy, either upfront or sequential, is progressively becoming the standard of care in PAH. This meta-analysis provides strong evidence supporting this treatment strategy. Nevertheless, a substantial proportion of patients with PAH had clinical worsening despite combination therapy, underscoring the need for the identification of innovative new therapeutic targets in PAH. This meta-analysis also points out the importance for future studies to capture total events as a broader and more inclusive endpoint than time to first event, and to standardise the definition of clinical worsening.

In light of inconclusive evidence regarding the benefits of combination therapy, and with the publication of large-scale, long-term, randomised controlled trials with event-free survival as the primary efficacy outcome, we reviewed the scientific literature to assess the efficacy of combination of PAH-specific therapies compared with monotherapy.

Methods

Search strategy and selection criteria

We did a systematic review and meta-analysis in accordance with the "Methodologic guidelines for systematic review of randomised control trials in health care from the Potsdam consultation on meta-analysis".[19]

We searched MEDLINE, Embase, and the Cochrane Library for randomised controlled trials investigating combination therapy versus monotherapy with PAH-specific therapies for patients with PAH published from Jan 1, 1990, through May 31, 2015. Our search terms were designed to provide maximum sensitivity for detecting therapeutic trials in PAH (appendix p 3). We also searched for articles using the bibliographies of each of the included studies and any review articles that we retrieved. Additionally, we explored the grey literature by hand, searching the conference abstracts of the American Heart Association, American College of Cardiology, European Society of Cardiology, American Thoracic Society, American College of Chest Physicians, European Respiratory Society, and British Thoracic Society from Jan 1, 2000, to May 31, 2015. The search was not restricted to English language, and non-English papers were translated into English.

See Online for appendix

Inclusion criteria were defined a priori. We included studies in the systematic review if (1) they were prospective, randomised trials assessing the effect of additional PAH-specific combination therapies (both upfront and sequential add-on) compared with background PAH-specific therapy in adult patients with PAH, including idiopathic PAH, associated PAH, or hereditary PAH (studies in which background therapy included more than one treatment were eligible); (2) the comparator was clearly identified; (3) they reported one of the primary and secondary outcomes of interest; (4) they assessed licensed therapies, or those expected to be licensed shortly, that were specific for PAH, including prostaglandins (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (ambrisentan, bosentan, and macitentan), phosphodiesterase-5 inhibitors (sildenafil, tadalafil, and vardenafil), soluble guanylate cyclase stimulators (riociguat) and a selective prostacyclin receptor agonist (selexipag); and (5) had a duration of at least 12 weeks. For studies in which many doses were tested, analyses were restricted to approved doses. Studies allowing patients older than 12 years were eligible if most of their participants were adults. For studies that included both treatment-naive patients and patients on

background therapy, analyses were restricted to patients on background therapy, thus comparing combination therapy with monotherapy. When subgroup analyses were not available, the active group was regarded as being on combination therapy when over 80% of patients were on background therapy at study entry. Otherwise, the study was excluded from the analysis.

Two authors (ACL and GL) independently assessed all study titles and abstracts to determine eligibility. When there was any possibility that it might be relevant, the full paper was retrieved and independently assessed by the same authors for a final decision about its inclusion in the meta-analysis. Throughout this process, ACL and GL were blinded to authors' names, journal, and year of publication of the papers to reduce bias. If studies were reported in several papers, the analysis was limited to the largest cohort unless the necessary data had appeared only in another paper. Discrepancies or uncertainties were resolved by consensus or by consulting a third author (SP). A log of reasons for rejection of citations identified from the searches was kept. The agreement between the two primary reviewers was measured using the quadratic weighted κ statistic.[20]

The validity of the selected studies was also assessed independently by ACL and GL using the Cochrane's Risk of Bias Assessment Tool,[21] which assesses sequence generation, allocation concealment, masking, and incomplete outcome data. The reviewers classified studies as low risk, unclear risk, or high risk of bias, and only those classified as low risk were considered. No ethics approval was needed for our study.

The primary aim of our analysis was to assess whether a combination of PAH-specific therapies reduced the risk of clinical worsening in PAH, as defined in each individual trial, compared with monotherapy. In PAH trials, clinical worsening is a composite endpoint generally defined as a combination of death, admission to hospital, lung transplantation, treatment escalation including initiation of prostaglandins, and symptomatic progression.[22] Whenever possible, we also assessed if this outcome was homogeneous among subgroups of PAH-specific therapy classes (non-parenteral prostaglandins, phosphodiesterase-5 inhibitors, endothelin receptor antagonists, soluble guanylate cyclase stimulators, and selective prostacyclin receptor agonists), trial duration (>6 months *vs* ≤6 months), study design (sequential add-on therapy or initial upfront), PAH type (idiopathic, heritable, or anorexigen-induced PAH [idiopathic PAH] *vs* PAH associated with connective tissue disease, congenital heart disease, HIV, and portal hypertension [associated PAH]), WHO functional class (I–II and III–IV), and patients with a 6MWD either less than or more than the median. Our secondary objectives were to assess whether combination PAH-specific therapies improved (1) survival (assessed by all-cause mortality and PAH-related mortality), (2) the proportion of patients receiving a lung transplantation, (3) the proportion of patients with a PAH-related admission to hospital, (4) the proportion of patients with treatment escalation (including parenteral prostaglandin initiation), (5) changes in WHO functional class, (6) symptomatic progression, and (7) changes in exercise capacity (6MWD) after 3–6 months of treatment. We also assessed whether changes in 6MWD after 3–6 months of treatment correlated with subsequent clinical worsening. Finally, we compared discontinuations and duration of drug exposure (in the case of event-driven trials) for combination versus monotherapy as an indirect surrogate for both efficacy and safety.

Data extraction and analysis

ACL and GL independently extracted information from all reports retained in the meta-analysis, including on study design, patient characteristics, mean treatment effect on clinical worsening, PAH-related admissions to

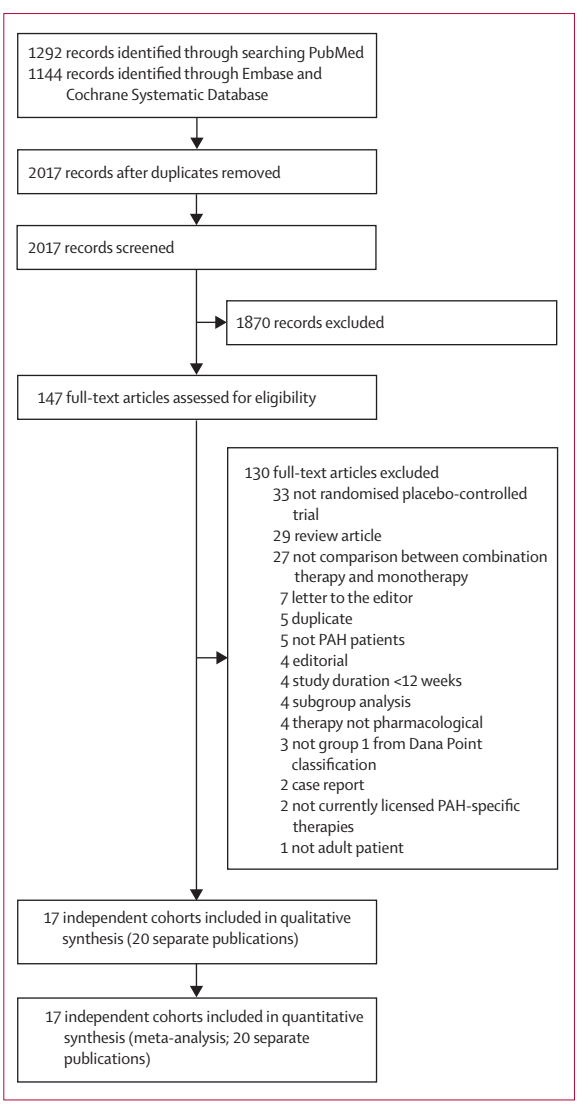

***Figure 1*: Study selection**

For **protocol** see http://www.hypertensionarteriellepulmonaire.ca/fileadmin/documents/hypertensionpulmonaire/Meta-analysis_Combination_protocol_synopsis_FINAL.pdf

	Number of patients	Length (weeks)	Baseline therapy (proportion %)	Therapeutic arm	Proportion of females (%)	PAH type (%)	WHO functional class (%)	Mean (SD) combined therapy baseline 6MWD (m)	Mean (SD) monotherapy baseline 6MWD (m)	Outcomes
Addition of non-parenteral prostaglandins										
COMBI, 2006[11]	40	12*	Bosentan (100%)	Iloprost 5 µg per inhalation six times per day	31/40 (78%)	IPAH (40/40; 100%)	III (40/40; 100%)	317 (74)	296 (79)	Primary: 6MWD Secondary: changes in WHO functional class, peak oxygen uptake, peak SBP during exercise, ventilatory efficacy during cardiopulmonary exercise, EQ-5D, and clinical worsening
STEP, 2006[12]	67	12	Bosentan (100%)	Iloprost 5 µg per inhalation six to nine times per day	53/67 (79%)	IPAH (37/67; 55%), APAH (30/67; 45%)	II (1/67; 2%), III (63/67; 94%), IV (3/67; 4%)	Overall: 335 (67)	..	Primary: 6MWD Secondary: NYHA functional class, BDS, TTCW, haemodynamic parameters
TRIUMPH, 2010[14]	235	12	Bosentan (70%) or sildenafil (30%)	Treprostinil 18–54 µg per inhalation four times per day	191/235 (81%)	IPAH (131/235; 56%), APAH (CTD 77/235; 33%), others (27/235; 11%)	III (230/235; 98%), IV (5/235; 2%)	346 (63)	351 (69)	Primary: peak 6MWD Secondary: TTCW, BDS, NYHA functional class, through 6MWD at week 12, peak 6MWD at week 6, QoL (MLWHF questionnaire), PAH signs and symptoms, NT-proBNP
FREEDOM-C, 2012[38]	350	16	Phosphodiesterase-5 inhibitors (25%), ERA (30%), both (45%)	Oral treprostinil (maximum 16 mg twice per day	288/350 (82%)	IPAH (232/350; 66%), APAH (117/350; 34%; CTD 92/350; 26%)	I (3/350; <1%), II (72/350; 21%) III (266/350; 76%), IV (9/350; 3%)	346 (71)	345 (76)	Primary: 6MWD Secondary: clinical deterioration (TTCW), combined ranking of 6MWD and BDS, dyspnoea fatigue index score
FREEDOM-C2, 2013[37]	310	16	Phosphodiesterase-5 inhibitors (43%), ERA (17%), both (40%)	Oral treprostinil 3·1 mg (1·9) twice per day	241/310 (78%)	IPAH (203/310; 66%), APAH (107/310; 34%; CTD 97/310; 31%)	I (0), II (80/310; 26%), III (225/310; 73%), IV (3/310; <1%)	329 (69)	337 (64)	Primary: 6MWD Secondary: clinical worsening, BDS, combined BDS and 6MWD, NT-proBNP, WHO functional class, signs and symptoms of PAH, Cambridge pulmonary hypertension outcome review, safety
Addition of phosphodiesterase type 5 inhibitor										
PACES, 2008[13]	267	16	Intravenous epoprostenol (100%)	Sildenafil 80 mg three times per day	213/267 (80%)	IPAH (212/267; 79%), APAH (55/267; 21%; CTD 45/267; 17%)	I (3/267; 1%), II (68/267; 25%), III (175/267; 66%), IV (16/267; 6%), missing (5/267; 2%)	349 (71)	342 (77)	Primary: 6MWD Secondary: haemodynamic measurements, TTCW, BDS after completion of the 6MWD
Iversen et al, 2010[33]†	21	24	Bosentan (100%)	Sildenafil 50 mg three times per day	14/21 (67%)	APAH (CHD; 21/21; 100%)	II (9/21; 43%), III (10/21; 48%), IV (2/21; 9%)	Overall: 377 (SD not specified)	..	Primary: 6MWD Secondary: haemodynamic measurements, NYHA functional class, NT-proBNP
PHIRST, 2011[31]	87‡	16	Bosentan (53%), treatment-naive (47%)	Tadalafil 40 mg once per day	68/87 (78%)	IPAH (89/124; 63%), APAH (32/87; 37%; of which CTD 19/87; 22%)	I (1/87; 1%), II (30/87; 35%), III (55/87; 63%), IV (1/87; 1%)	361 (75)	349 (85)	Primary: 6MWD Secondary: WHO functional class, TTCW, BDS, haemodynamic measurements

(Table 1 continues on next page)

	Number of patients	Length (weeks)	Baseline therapy (proportion %)	Therapeutic arm	Proportion of females (%)	PAH type (%)	WHO functional class (%)	Mean (SD) combined therapy baseline 6MWD (m)	Mean (SD) monotherapy baseline 6MWD (m)	Outcomes
(Continued from previous page)										
Zhuang et al, 2014[39]	124	16	Ambrisentan (100%)	Tadalafil 40 mg once per day	98/124 (79%)	IPAH (89/124; 72%), APAH (35/124; 28%; of which CTD 28/124; 23%)	I (0), II (71/124; 57%), III (48/124; 39%), IV (5/124; 4%)	356 (87)	343 (71)	Primary: 6MWD Secondary: WHO functional class, TTCW, haemodynamic measurements
Addition of endothelin receptor antagonist										
BREATHE-2, 2004[10]	33	16	Epoprostenol (100%)	Bosentan 125 mg twice per day§	22/33 (70%)	IPAH (27/33; 82%), APAH (CTD; 6/33; 18%)	III (25/33; 76%), IV (8/33; 24%)	..	..	Primary: TPR Secondary: Haemodynamic measurements, 6MWD, dyspnoea-fatigue rating, modified NYHA functional class
EARLY, 2008[40]	29¶	24	Sildenafil (16%), treatment-naive (84%)	Bosentan 125 mg twice per day	129/185 (70%)‖	IPAH (112/185; 61%)‖, APAH (73/185; 39%; of which CTD 33/185; 18%)	II (185/185; 100%)‖	..	..	Primary: PVR and 6MWD Secondary: TTCW, WHO functional class, BDS, haemodynamic measurements
COMPASS-2, 2015[34]	334	165**	Sildenafil (100%)	Bosentan 125 mg twice per day	253/334 (78%)	IPAH (226/334; 68%), APAH (108/334; 32%; of which CTD 88/334; 26%)	II (140/334; 42%), III (192/334; 58%), IV (2/334; <1%)	363 (79)	358 (73)	Primary: time to first morbidity or mortality event. Secondary: 6MWD; WHO functional class; NT-proBNP; time to first occurrence of death from any cause, admission to hospital for PAH or start of intravenous prostaglandin therapy, atrial septostomy or lung transplantation, death from any cause
SERAPHIN, 2013[35]	308††	104‡‡	Non-parenteral prostaglandins (5%), phosphodiesterase-5 inhibitors (61%), treatment-naive (34%)	Macitentan 10 mg per day	565/742 (77%)‖	IPAH (439/742; 59%)‖, APAH (296/742; 40%, of which CTD 224/742; 30%), missing (7/742; 1%)	I (1/742; <1%)‖, II (387/742; 52%), III (337/742; 45%), IV (14/742; 2%), missing (3/742; <1%)	..	..	Primary: TTCW Secondary: 6MWD; WHO functional class; death due to PAH or admission to hospital for PAH up to the end of the treatment, and death from any cause up to the end of the study
Addition of soluble guanylate cyclase stimulator										
PATENT-1, 2013[29]	191§§	12	ERA (87%), non-parenteral prostaglandins (13%)	Riociguat 2·5 mg three times per day	81%¶¶ (proportions not specified)	IPAH (60%)¶¶, APAH (40%; CTD 26%; proportions not specified)	I (2%)¶¶, II (45%), III (52%), IV (1%; proportions not specified)	363 (68)¶¶	..	Primary: 6MWD Secondary: PVR, NT-proBNP, WHO functional class; TTCW; BDS; EQ-5D and LPH questionnaires
Addition of selective prostacyclin receptor agonist										
Simonneau et al, 2012[30]	43	17	ERA (37%), sildenafil (28%), both (35%)	Selexipag 200–800 µg twice per day‖ ‖	35/43 (81%)	IPAH (35/43; 81%), APAH (8/43; 19%), CTD (6/43; 14%)	II (17/43; 40%), III (26/43; 60%)	396 (71)	350 (124)	Primary: PVR Secondary: haemodynamic measurements, 6MWD, aggravation of PAH (TTCW), BDS, WHO functional class, NT-proBNP.

(Table 1 continues on next page)

	Number of patients	Length (weeks)	Baseline therapy (proportion %)	Therapeutic arm	Proportion of females (%)	PAH type (%)	WHO functional class (%)	Mean (SD) combined therapy baseline 6MWD (m)	Mean (SD) monotherapy baseline 6MWD (m)	Outcomes
(Continued from previous page)										
GRIPHON, 2015[36]	1156	71***	ERA (15%), phosphodiesterase-5 inhibitors (32%), or both (33%), treatment naive (20%)†††	Selexipag 200–1600 µg twice daily‖ ‖	923/1156 (80%)	IPAH (702/1156; 61%), APAH (454/1156; 39%), CTD (334/1156; 29%)	I (9/1156; <1%), II (529/1156; 46%), III (607/1156; 53%), IV (11/1156; 1%)	..	..	Primary: First event of death or a complication related to PAH‡‡‡ Secondary: Change in 6MWD from baseline, absence of worsening WHO functional class from baseline, death due to PAH or admission to hospital for worsening PAH up to the end of treatment period (analysed in a time-to-event analysis), death from any cause up to the end of treatment, and change in NT-proBNP (exploratory)
Addition of either phosphodiesterase type 5 inhibitor or endothelin receptor antagonist										
AMBITION, 2015[32]	500§§§	79¶¶¶¶	Ambrisentan 10 mg per day or tadalafil 40 mg per day‖ ‖ ‖ ‖	Ambrisentan 10 mg plus tadalafil 40 mg per day	388/500 (78%)	IPAH (295/500; 59%), APAH (205/500; 41%; CTD 187/500; 37%)	II (155/500; 31%), III (345/500; 69%)	354 (88)	352 (92)	Primary: time-to-event analysis of first event of clinical failure Secondary: NT-proBNP, 6MWD, WHO functional class, BDS, satisfactory clinical response at week 24****

Data are estimated means (SD). PAH=pulmonary arterial hypertension. 6MWD=6-min walk distance. IPAH=idiopathic pulmonary arterial hypertension (includes familial or hereditary hypertension, or PAH due to drug or toxins and anorexigens). SBP=systolic blood pressure. QoL=quality of life. APAH=associated pulmonary arterial hypertension (includes PAH related to connective tissue disease [CTD], congenital heart disease [CHD], HIV, and portal hypertension). NYHA=New York Heart Association. BDS=Borg Dyspnea Scale. TTCW=time to clinical worsening. MLWHF=Minnesota Living with Heart Failure. NT-proBNP=N-terminal pro-brain natriuretic peptide. ERA=endothelin receptor antagonist. TPR=total pulmonary resistance. PVR=pulmonary vascular resistance. EQ-5D=EuroQoL Group 5-Dimension self-report questionnaire on QoL. LPH=living with pulmonary hypertension. ..=not applicable. *This study started in September, 2004, and ended prematurely in December, 2005, when only 40 patients had been enrolled. †Crossover study—the same 21 patients were treated with sildenafil for 12 weeks, then a crossover was done. ‡Only patients receiving background bosentan therapy (87/405, 21%) at randomisation AND receiving either placebo or tadalafil 40 mg per day (approved dose) were included in our analysis. §Bosentan therapy was started after only 2 days of epoprostenol therapy. ¶Our analysis included only the subgroup (29/185, 16%) of patients on background sildenafil before randomisation. ||Data available for all patients, independently of the presence or absence of background therapy. **The mean duration of study treatment was 39·7 months (SD 22·6) and 38·0 months (21·9) for the patients receiving placebo and bosentan, respectively. ††Only patients on background therapy and randomly assigned to placebo versus macitentan 10 mg (approved dose) per day (308/742, 42%) were included in our analyses for the primary outcome. ‡‡The mean duration of study treatment was 85·3 weeks and 103·9 weeks for the patients receiving placebo and macitentan 10 mg dose, respectively. §§Only patients on background therapy and randomly assigned to placebo versus the riociguat 2·5 mg dose groups (191/443, 43%) were included in our analyses. ¶¶Data from patients pretreated with background therapy only.[44] || ||Dose of selexipag was progressively uptitrated over a period of 21 to 35 days, depending on tolerance. Mean maximum dose achieved was 607 µg (SD 220) twice per day at the end of the uptitration phase for the phase 2 clinical trial (Simonneau and colleagues).[30] In the GRIPHON study,[36] titration occurred on a 12-week period, and most patients (43%) reached the high-dose stratum (selexipag 1200, 1400, or 1600 µg twice per day). ***The mean duration of study treatment was 63·7 and 70·7 weeks for the patients receiving placebo and selexipag, respectively. †††Since 80% of patients were on background therapy and subgroup analyses were not available, analyses were done for the whole study population, as defined a priori. ‡‡‡Disease progression, worsening PAH resulting in admission to hospital, initiation of parenteral prostanoid therapy or oxygen therapy, lung transplantation, or atrial septostomy. §§§Analyses were done from the primary-analysis set that comprised 500 participants who fulfilled the amended entry criteria. ¶¶¶Mean duration of study treatment was 79 weeks and 69 weeks in the combination-therapy and pooled-monotherapy groups, respectively. || || ||Patients were randomly assigned to either ambrisentan 10 mg per day, tadalafil 40 mg per day, or a combination of both uptitrated over a period of 8 weeks for ambrisentan, and 4 weeks for tadalafil. ****Increase of 10% from baseline in 6MWD, with a reduction in symptoms of, or maintenance of, WHO functional class I or II, and no events of worsening clinical condition before or at the week 24 visit.

Table 1: **Characteristics of included studies**

hospital, lung transplantation rate, death (all-cause and PAH-related), changes in WHO functional class, and changes in 6MWD at 3–6 months. 2×2 tables were constructed on the basis of treatment received (combination *vs* monotherapy) and available data for the primary and secondary outcomes. We contacted abstract sponsors or the steering committee of trials to obtain subgroup data if necessary.

We created forest plots for each outcome. We analysed data using the Mantel-Haenszel method based on a fixed-effects model. We computed the summary measures of effects across studies or subgroups as a weighted effect, whereby the weights were linked to the inverse variance of each studies' effect. We stated that all inferences are conditional on the studies actually done. For continuous variables such as 6MWD, the mean treatment effect of combination therapy was calculated from the difference between the mean change from baseline in patients receiving combination therapy and the mean change from baseline in patients receiving monotherapy. Some trials reported their results using medians with minimum and maximum values, or first and third quartiles, or both. To combine all results, we estimated the sample means and their associated SD using the approach proposed by Wan and colleagues.[23] For the outcome measuring occurrence of clinical worsening, the risk ratio (RR) was calculated. If one of the cells contained a value of zero, or the risk in either the combination therapy group or

monotherapy group was 100%, we added 0·5 to each cell to calculate the RR. We included a multiarmed trial in this review, and to overcome potential issues due to multiple correlated comparisons, we analysed this multiarmed trial using methods described in the Cochrane Handbook for Systematic Reviews of Interventions.[24] We divided the shared group of multiple-comparison groups into two groups with smaller sample size divided out evenly. We used Cochran's *Q* test and the I^2 test to assess between-study heterogeneity (deemed significant at p <0·10 and I^2>50%). p<0·05 was considered statistically significant for this study.

We did a sensitivity analysis using the random-effects model, which accounts for variability within studies and

	Death	Admission to hospital	Trans-plantation	Atrial septostomy	Parenteral prostaglandin initiation*	Treatment escalation	Symptomatic progression (or PAH worsening)	Centrally adjudicated?
Addition of non-parenteral prostaglandins								
COMBI, 2006[11]	All-cause	PAH-related	..	..	..	..	Deterioration in functional class or decrease in 6MWD by 20% from baseline or <150 m	Not described
STEP, 2006[12]	PAH-related	PAH-related	Yes	Yes	..	Initiation of new PAH therapy	..	Not described
TRIUMPH, 2010[14]	All-cause	PAH-related	Yes	..	..	Initiation of new PAH therapy	..	Not described
FREEDOM-C, 2012[38]	All-cause	..†	Yes	Yes	..	Initiation of new PAH therapy (included in the clinical deterioration definition)	Composite endpoint of: admission to hospital related to PAH, ≥20% decrease in 6MWD from baseline, decrease in WHO functional class, initiation of a new PAH therapy	Not described
FREEDOM-C2, 2013[37]	All-cause	Yes	Yes	Yes	Yes	Addition of inhaled prostaglandins, ERA or phosphodiesterase-5 inhibitors, or initiation of parenteral prostacyclin therapy	≥20% decrease in 6MWD from baseline (or being too ill to walk)	Not described
Addition of phosphodiesterase type 5 inhibitor								
PACES, 2008[13]	All-cause	PAH-related	Yes	..	..	Initation of bosentan therapy or change in epoprostenol dose of >10% because of clinical deterioration	..	Not described
PHIRST, 2011[31]	All-cause	PAH-related	Yes	Yes	Included in the initiation of new PAH therapy	Initiation of new PAH therapy (prostaglandins, ERA, phosphodiesterase-5 inhibitors)	Worsening WHO functional class	Not described
Zhuang et al, 2014[39]	All-cause	PAH-related	Yes	Yes	..	Initiation of new PAH therapy	Worsening WHO functional class	Not described
Addition of endothelin receptor antagonist								
EARLY, 2008[40]	All-cause	PAH-related	..	..	..	..	Symptomatic progression: appearance or worsening of right-heart failure, decrease of ≥10% from baseline in two 6MWD done ≥2 weeks apart, ≥5% decrease from baseline in two 6MWD done ≥2 weeks apart and associated with a ≥2-point increase in BDS	Not described
COMPASS-2, 2015[34]	All-cause	PAH-related	Yes	Yes	Yes	Start of intravenous prostaglandin therapy	Either (1) moderate or marked worsening of PAH symptoms on the PGSA together with initiation of subcutaneous or inhaled prostaglandins or use of open-label bosentan, or (2) no change or mild worsening of PAH symptoms accompanied by a decrease in 6MWD of >20% from the previous visit, or by >30% from the baseline visit, together with initiation of subcutaneous or inhaled prostaglandins or use of open-label bosentan	Yes
SERAPHIN, 2013[35]	All-cause	..	Yes	Yes	Yes	Initiation of treatment with intravenous or subcutaneous prostaglandins	Worsening of PAH was defined by the occurrence of all three of the following: a decrease in 6MWD of ≥15% from baseline, substantiated by a second 6MWD done on a different day within 2 weeks, worsening of symptoms of PAH,[10] need for additional treatment for PAH	Yes

(Table 2 continues on next page)

	Death	Admission to hospital	Trans plantation	Atrial septostomy	Parenteral prostaglandin initiation*	Treatment escalation	Symptomatic progression (or PAH worsening)	Centrally adjudicated?
(Continued from previous age)								
Addition of soluble guanylate cyclase stimulator								
PATENT-1, 2013[29]	All-cause	PAH-related	Yes	Yes	Yes	Start of new specific PAH treatment or modification of a pre-existing prostaglandin treatment because of worsening PAH	Persistent decrease of >15% from baseline or >30% compared with the last study-related measurement of 6MWD because of worsening PAH, substantiated by a second measurement 14 days later. Persistent worsening of WHO functional class because of deterioration of PAH, substantiated by a second measurement 14 days later	Not described
Addition of selective prostacyclin receptor agonist								
Simonneau et al, 2012[30]	All-cause	PAH-related	Yes	..	..	Need for additional PAH therapy	Aggravation of PAH symptoms—ie, ≥10% deterioration in 6MWD	Not described
GRIPHON, 2015[36]	All-cause	PAH-related	Yes	Yes	Yes	Initiation of parenteral prostaglandins therapy or long-term oxygen therapy	Disease progression‡ or worsening of PAH that resulted in admission to hospital, initiation of parenteral prostanoid therapy, oxygen therapy, or the need for lung transplantation or atrial septostomy	Yes
Addition of either phosphodiesterase type 5 inhibitor or endothelin receptor antagonist								
AMBITION, 2015[32]	All-cause	PAH-related	Yes§	..	..	..	A decrease >15% from baseline in 6MWD combined with WHO functional class III or IV symptoms at two consecutive visits separated by at least 14 days¶	Yes

Clinical worsening was not an endpoint in the BREATHE-2[10] and Iversen et al, 2010,[33] studies. PAH=pulmonary arterial hypertension. 6MWD=6-min walk distance. ERA=endothelin receptor antagonist. BDS=Borg Dyspnea Scale. PGSA=patient global self-assessment. *Initiation of parenteral prostaglandins was a specific component of the clinical worsening definition. Thus, the proportion of patients with parenteral prostaglandin initiation as the first clinical event was described in the manuscript. †Included in the definition of clinical deterioration, therefore no specific results for admission to hospital are in the report. ‡Defined as 15% decrease from baseline in 6MWD accompanied by a worsening of WHO functional class (for patients with class II–III at baseline), or need for additional PAH therapy (for patients with WHO functional class III–IV at baseline). §Included in the definition for admission to hospital for worsening PAH. ¶The trial also included unsatisfactory long-term clinical response as part of the definition of clinical failure. This was defined as any decrease from baseline in 6MWD at two consecutive clinic visits after baseline separated by ≥14 days, and WHO functional class III symptoms assessed at two clinic visits separated by ≥6 months; assessed only in participants who were in the study for ≥6 months.

Table 2: **Study definitions of clinical worsening**

between studies.[25] Sensitivity analyses were also planned a priori using more homogeneous definitions for clinical worsening, including only deaths, admission to hospital, and symptomatic progression. We also did subgroup analyses with a fixed-effects model to investigate sources of heterogeneity in the main analysis according to class of added PAH-specific therapy (prostaglandins, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, and a selective prostacyclin receptor agonist), PAH type (idiopathic PAH *vs* associated PAH), baseline WHO functional capacity (I–II *vs* III–IV), baseline 6MWD (higher *vs* lower than the median value), study design (upfront combination therapy *vs* sequential add-on therapy), and duration of trial (≤6 months or >6 months).

We assessed publication bias visually using funnel plots. We assumed that the effect of publication bias would be minor if the plot of the magnitude of treatment effect in each study versus its precision estimate showed a roughly symmetrical funnel shape.[26] We also formally tested the presence of publication bias using the Egger test for funnel plot asymmetry.[27] The CIs were calculated with 95% Gaussian intervals. We did all analyses with Review Manager and the statistical packages SAS version 9.4 and R version 3.0.2. We wrote the report according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[28]

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We retrieved and screened 2017 studies from our literature search (figure 1). 2000 were excluded, leaving 17 independent cohorts (4095 patients)[10–14,29–40] that contributed to 20 separate publications[10–14,29–43] for the analysis (κ 0·86 [95% CI 0·74–0·98]).

15 trials investigated the effect of sequential add-on PAH-specific combination therapies,[11–14,29–31,33–40] while two assessed the effect of upfront combination therapy,[10,32] compared with PAH-specific monotherapy in adult patients with PAH (table 1). The 15 sequential add-on trials assessed the additional effect of oral or inhaled prostaglandins (n=5),[11,12,14,37,38] phosphodiesterase-5 inhibitors (n=4),[11,31,33,39] endothelin receptor antagonists (n=3),[34,35,40] soluble guanylate cyclase stimulators (n=1),[29] and a selective prostacyclin receptor agonist (n=2).[30,36] The two upfront therapy trials assessed the combination of an endothelin receptor antagonist with either

	Number of studies	Proportion of events (%)			Fixed-effect model		Random-effects model		Homogeneity	
		With combined therapy	With monotherapy	Total	Pooled RR	95 % CI (p value)	Pooled RR	95% CI (p value)	P value	I^2 (%)
Primary outcome										
Clinical worsening (all events)	15[11–14,29–32,34–40]	332/1940 (17%)	517/1862 (28%)	849/3802 (22%)	0·65	0·58–0·72 (p<0·00001)	0·65	0·56–0·76 (p<0·00001)	0·25	18%
Secondary outcomes as first event of clinical worsening										
All-cause mortality	12[11–14, 30,32,34–40]	54/1711 (3%)	60/1712 (4%)	114/3423 (3%)	0·92	0·65–1·32 (p=0·65)	0·97	0·63–1·49 (p=0·88)	0·33	13%
Admission to hospital (PAH-related)†	8[11–13,32,34–37]	172/1658 (10%)	245/1680 (15%)	417/3338 (13%)	0·71	0·60–0·85 (p=0·0002)	0·71	0·53–0·96 (p=0·03)	0·12	37%
Lung transplantation	7[12–14,34,36,38,39]	2/1248 (<1%)	4/1281 (<1%)	6/2529 (<1%)	0·56	0·12–2·60 (p=0·46)	0·57	0·12–2·75 (p=0·48)	0·86	0
Treatment escalation including initiation of parenteral prostaglandin therapy	6[12–14,36,37,39]	13/1072 (1%)	36/1083 (3%)	49/2155 (2%)	0·38	0·21–0·70 (p=0·002)	0·35	0·14–0·91 (p=0·03)	0·22	31%
Symptomatic progression	10[11,12,30–32,34,36–39]	119/1504 (8%)	231/1506 (15%)	350/3010 (12%)	0·53	0·43–0·65 (p<0·00001)	0·55	0·44–0·69 (p<0·00001)	0·40	5%
Other secondary outcomes										
All-cause mortality‡	16[10–14,29–32,34–40]	192/2391 (8%)	227/2147 (11%)	419/4538 (9%)	0·86	0·72–1·03 (p=0·09)	0·88	0·74–1·05 (p=0·15)	0·74	0
PAH-related mortality§	8[10–13,30,35,36,39]	80/1116 (7%)	104/1102 (9%)	184/2218 (8%)	0·77	0·59–1·01 (p=0·06)	0·68	0·33–1·40 (p=0·30)	0·15	43%
Improvement in WHO functional class	10[10,12,29–32,34,36,38,39]	241/907 (27%)	182/817 (22%)	423/1724 (25%)	1·19	1·01–1·41 (p=0·04)	1·19	0·97–1·45 (p=0·09)	0·26	20%
Worsening in WHO functional class	9[12,29–32,34,36,38,39]	188/1454 (13%)	220/1380 (16%)	408/2834 (14%)	0·84	0·71–1·00 (p=0·05)	0·83	0·67–1·03 (p=0·09)	0·39	6%
Treatment discontinuation	15[10–14,29–34,36–39]	282/2087 (14%)	194/1951 (10%)	476/4038 (12%)	1·43	1·21–1·69 (p=0·0001)	1·32	0·98–1·76 (p=0·07)	0·05	39%

RR=rate ratio. PAH=pulmonary arterial hypertension. *Atrial septostomy were not reported in any study. †Data from the combination subgroup of the SERAPHIN trial are included in this analysis because they were available in a subsequent article.[45] However, these data were not included in the primary analysis because admission to hospital was not included in the definition of clinical worsening in SERAPHIN. ‡All deaths, including those as first event of clinical worsening and those after censoring for another event. Data from PHIRST,[31] EARLY,[40] PATENT-1,[29] and SERAPHIN[35] for the subgroup of patients already on background therapy were not available. Therefore, data from the entire study population were included for this secondary analysis. However, the exclusion of these studies did not modify the results for the all-cause mortality (RR 0·88 [95% CI 0·72–1·06], p=0·18). §Data from SERAPHIN[35] for the subgroup of patients already on background therapy were not available. The exclusion of this study yielded similar RRs for PAH-related mortality (RR 0·81 [95% CI 0·61–1·08]).

Table 3*: Primary and secondary outcomes

intravenous prostaglandins (n=1),[10] or a phosphodiesterase type 5 inhibitor (n=1).[32]

Clinical worsening was assessed in 15 studies, was the primary outcome in four[32,34–36] and the secondary outcome in 11.[11–14,29–31,37–40] In two studies, clinical worsening was not assessed;[10,33] nevertheless, these studies were included for analysis of secondary outcomes of interest. The duration of the different trials ranged from 12 weeks to 172 weeks (median 16 weeks). Included patients were mostly female (77%), white (79%), with idiopathic PAH (64%) or PAH associated with connective tissue disease (23%). Most patients included in this analysis were prevalent cases (ie, not newly diagnosed patients), and most trials recruited a substantial proportion of patients in WHO functional class I–II (36% [1455 of 4095 patients]). Few studies included exclusively WHO functional class II[40] or III[13] patients, or patients with idiopathic PAH[11] or PAH associated with congenital heart disease.[33] The definition of clinical worsening significantly differed from one study to the other (table 2). All included studies had a low risk of bias (appendix, p 6).

Clinical worsening occurred in 22% (849 of 3802) participants: 17% (332 of 1940) in the combination therapy group and 28% (517 of 1862) in the monotherapy group (table 3). Importantly, these cumulative data do not consider the different randomisation proportions and the different durations of the included trials and are thus descriptive only.

Combination therapy was associated with significant risk reduction for clinical worsening compared with monotherapy (cumulative pooled RR 0·65 [95% CI 0·58–0·72], p<0·00001; table 3, figure 2). We noted no significant heterogeneity between included studies (I^2=18%, $p_{homogeneity}$=0·25). Similar results were noted with the random-effects model, suggesting no absence of homogeneity and similar CI compared with the fixed-effect model.

Visual inspection of the funnel plot suggested publication bias in favour of positive studies (figure 3), which was substantiated with an Egger test (t=–2·3982,

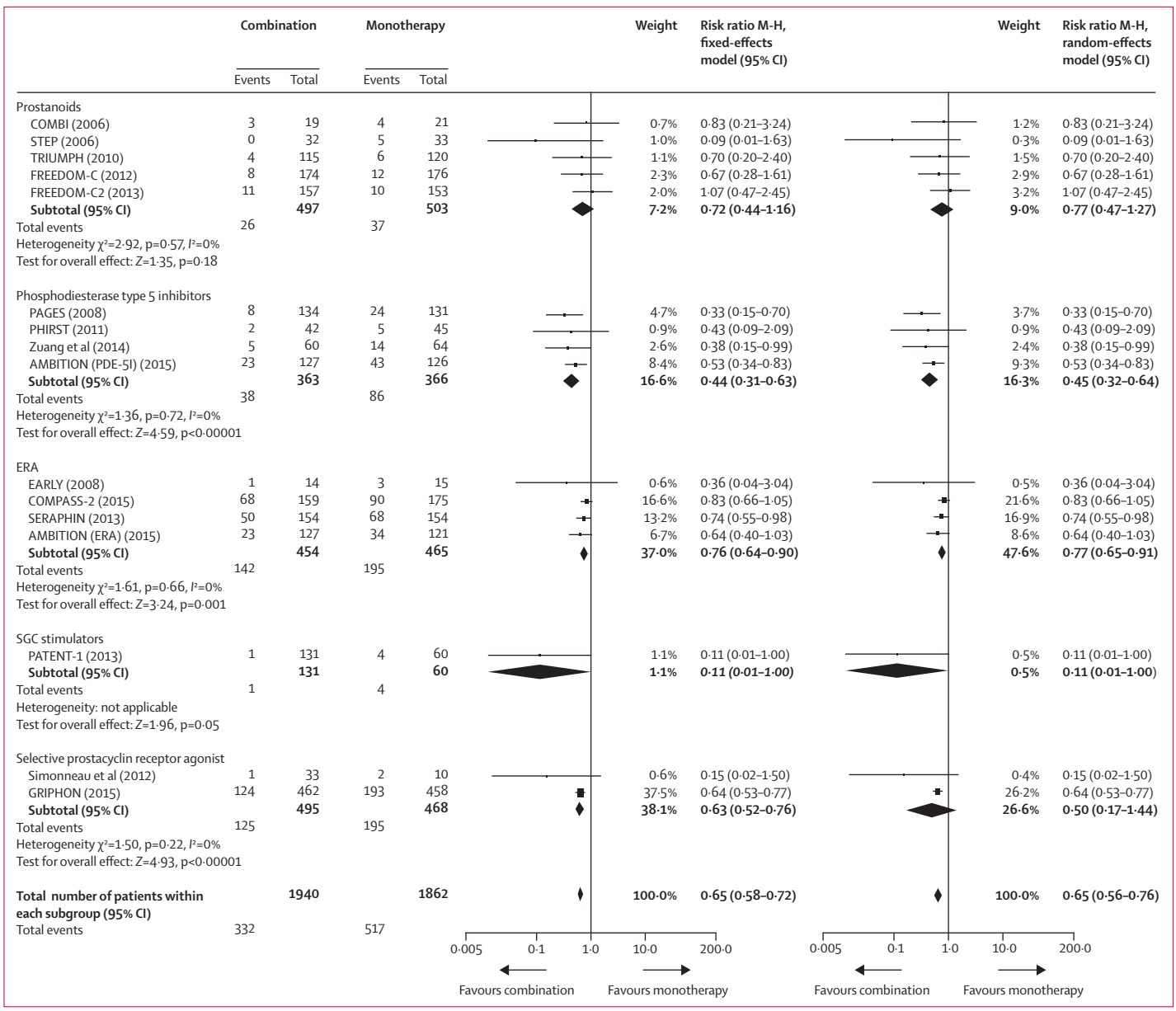

***Figure 2*: Cumulative risk ratio estimates of clinical worsening with combination therapy versus monotherapy**
Data are shown for the fixed-effects (left) and random-effects (right) models. p<0·00001 for the overall estimate of the primary analysis by inverse variance method. M-H=Mantel-Haenszel. ERA=endothelin receptor antagonist. SGC=soluble guanylate cyclase.

p=0·031). However, when we excluded the four studies with the highest SEs from the analysis,[14,29,30,40] this resulted in an identical RR for clinical worsening (0·65 [95% CI 0·58–0·73], p<0·00001).

Further analyses suggested that combination therapy was associated with reduced risk of clinical worsening across subgroups (table 4). Results of several sensitivity analyses, including the use of a random-effects model (table 3) and the inclusion of more homogeneous definitions of clinical worsening (appendix, p 9), were consistent with those of the primary analysis.

12 trials[11–14,30,32,34,36–40] reported all-cause mortality, eight[10–13,30,35,36,39] reported PAH-related mortality, eight[11–13,32,34–37] reported PAH-related admissions to hospital, seven[12–14,34,36,38,39] reported lung transplantations, six[12–14,36,37,39] reported treatment escalation (including initiation of parenteral prostaglandin therapy), and ten[7,13,14,31,32,34,36–39] reported symptomatic progression as the first event defining clinical worsening (table 3). Results were homogeneous across predefined subgroups (appendix, p 9–15). Combination therapy was associated with a significant risk reduction for PAH-related admissions to hospital, treatment escalation, and symptomatic progression.

Combination therapy was not associated with reduced all-cause mortality, PAH-related mortality, or lung transplantation (table 3). Combination therapy was associated with a significant increase in the proportion of patients with WHO functional class improvement and a significant decrease in the proportion of patients with WHO functional class worsening (RR 0·84 [95% CI 0·71–1·00], p=0·05; table 3). Combination therapy was also associated with a significant improvement in 6MWD after 3–6 months compared with monotherapy, with consistent results across drug classes (figure 4); no heterogeneity was noted ($p_{homogeneity}$=0·20, I^2=22%). Study-level changes in 6MWD after 3–6 months of combination therapy significantly correlated with the subsequent risk of clinical worsening (R^2=0·296, p=0·018; appendix p 16).

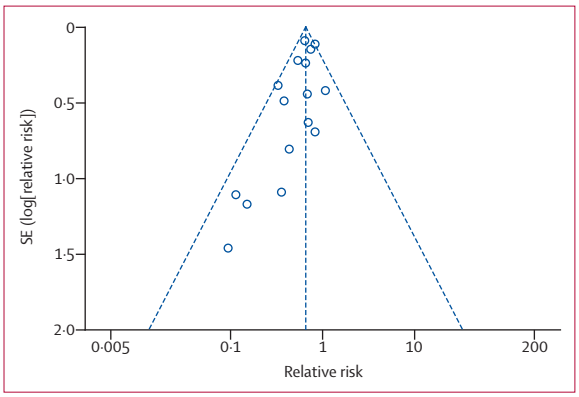

Figure 3: **Publication bias of the meta-analysis**
The figure shows a funnel plot for the primary outcome of the meta-analysis (clinical worsening).

Treatment discontinuation was more likely to occur in patients receiving combination therapy (table 3). This finding was related to a significant increase in treatment discontinuation in patients treated with non-parenteral prostaglandins and a selective prostacyclin receptor agonist (appendix, p 14), whereas discontinuation rates were similar between treatment arms for other classes of PAH therapies. Treatment duration was also similar when endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and a selective prostacyclin receptor agonist were added to background therapy compared with monotherapy in event-driven studies (mean 106 [SD 41] *vs* 99 [49] weeks, p=0·42).[32,34–36]

	Number of studies	Proportion of events (%)		Fixed-effects model pooled RR	95% CI	Homogeneity	
		With combined therapy	With monotherapy			p value	I^2 (%)
Class of added PAH-specific therapy							
Non-parenteral prostaglandins	5[11,12,14,37,38]	26/497 (5%)	37/503 (7%)	0·72	0·44–1·16	0·57	0
Phosphodiesterase-5 inhibitors	4[13,31,32,39]	38/363 (11%)	86/366 (24%)	0·44	0·31–0·63	0·72	0
Endothelin receptor antagonists	4[32,34,35,40]	142/454 (31%)	195/465 (42%)	0·76	0·64–0·90	0·66	0
Soluble guanylate cyclase stimulators	1[29]	1/131 (<1%)	4/60 (7%)	0·11	0·01–1·00	..	..
Selective prostacyclin receptor agonist	2[30,36]	125/495 (25%)	195/468 (42%)	0·63	0·52–0·76	0·22	33%
Trial duration							
>6 months	4[32,34–36]	288/1028 (28%)	428/1034 (41%)	0·68	0·60–0·77	0·21	34%
≤6 months	11[11–14,29–31,37–40]	44/911 (5%)	89/828 (11%)	0·48	0·34–0·68	0·41	4%
Study design							
Sequential add-on therapy	14[11–14,29–31,34–40]	286/1686 (17%)	440/1615 (27%)	0·65	0·58–0·72	0·21	22%
Initial upfront combination therapy	1[32]	46/253 (18%)	77/247 (31%)	0·58	0·42–0·80	..	..
PAH type							
IPAH*	3[32,34,36]	167/588 (28%)	262/629 (42%)	0·68	0·56–0·80	0·36	1%
APAH	3[32,34,36]	45/171 (26%)	61/158 (39%)	0·67	0·54–0·82	0·34	8%
WHO functional class							
I or II	3[32,34,36]	80/425 (19%)	119/408 (29%)	0·64	0·50–0·82	0·19	33%
III or IV	3[32,34,36]	189/561 (34%)	290/596 (49%)	0·69	0·61–0·77	0·19	33%
Baseline 6MWD							
Less than median	2[32,34]	78/205 (38%)	104/218 (48%)	0·83	0·67–1·03	0·03	79%
More than median	2[32,34]	36/207 (17%)	63/204 (31%)	0·55	0·39–0·78	0·31	2%

RR=risk ratio. PAH=pulmonary arterial hypertension. IPAH=idiopathic pulmonary arterial hypertension. APAH=associated pulmonary arterial hypertension. 6MWD=6-min walk distance. *Included idiopathic, heritable, drug or toxin-induced, and HIV-associated PAH in the GRIPHON study.[36]

Table 4: **Predefined subgroup analyses for the primary outcome**

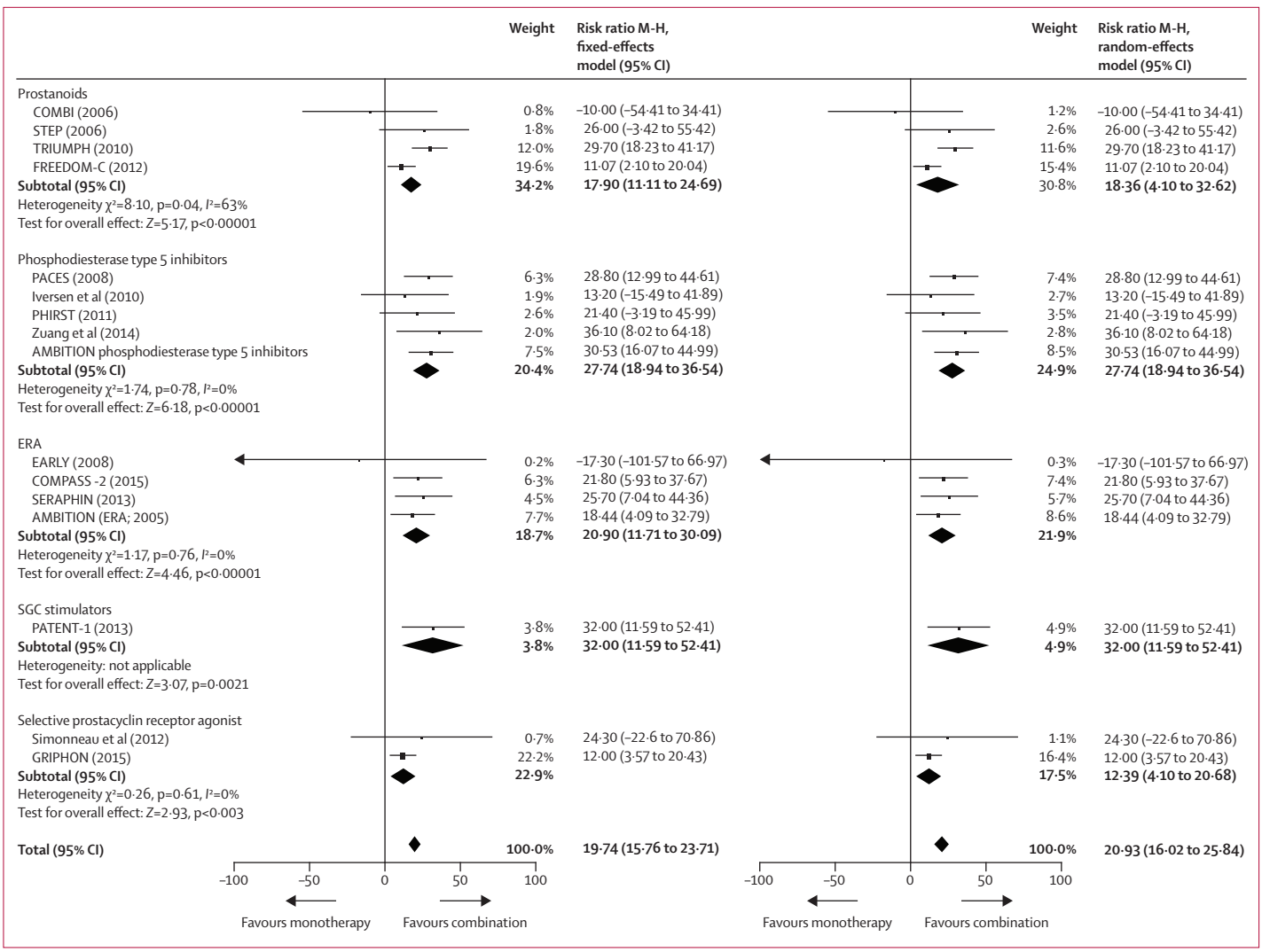

***Figure 4*: Weighted mean treatment effect of combination therapy versus monotherapy on 6-min walked distance**
Data are from the fixed-effects (left) and random-effects (right) models. p<0·00001 for the overall estimate of the primary analysis by the Mantel-Haenszel (M-H) method. ERA=endothelin receptor antagonist. SGC=soluble guanylate cyclase.

Discussion

Our meta-analysis lends support to the view that combination therapy for PAH significantly reduces the risk of predefined clinical worsening compared with monotherapy. We noted a reduction in the overall risk of clinical worsening of 35% for patients randomly assigned to combination therapies when compared with patients assigned to active monotherapy. The findings from our sensitivity and subgroup analyses substantiated the robustness of these results and suggested that the effect of combination therapy on clinical worsening was not driven by any one particular class of drugs, type of study design, or group of patients with specific disease characteristics. Combination therapy also improved patients' functional status and was associated with risk reductions of 29%, 62%, and 47% for PAH-related admissions to hospital, treatment escalation, and PAH symptomatic progression, respectively. Combination therapy was also associated with increased risk for treatment discontinuation, although this result was driven by trials adding non-parenteral prostaglandins and selective prostacyclin receptor agonists.

Findings from a previous meta-analysis[6] support the short-term survival benefit associated with PAH-targeted monotherapy. Results from observational studies, however, show that PAH remains a devastating disease with poor long-term outcomes with PAH-specific monotherapy.[7,8] Consistent with these observations, clinical worsening, symptomatic progression, PAH-related admissions to hospital, and deaths in our analysis occurred in 28%, 15%, 15%, and 4%, respectively, of the patients randomly assigned to monotherapy, which contributed to these analyses after a median observation period of 16 weeks (range 12–172). This result probably represents an

underestimation of the disease burden, since most patients included in this meta-analysis were prevalent cases and most trials recruited a substantial proportion of patients in WHO functional class I–II patients (36%; the mean of all patients recruited in these trials), substantiating the severity of the condition even in the stable and selected patient populations included in the trials. In an attempt to improve patients' outcomes, combination therapy targeting the endothelin, nitric oxide, and prostaglandin pathways at several sites was thus proposed. Our meta-analysis substantiates the beneficial effects of such approaches on clinical worsening.

Conversely, combination therapy was not associated with significant reductions in deaths and transplantation occurring as first events. However, the analysis of death, transplantation, and admission to hospital as first events is limited by informative censoring by other components of the definition of clinical worsening. Indeed, the time from the initiation of treatment to the first PAH-related event was used as the primary outcome in four studies[32,34–36] and the secondary outcome in 11 studies[11–14,29–31,37–40] included in this meta-analysis. The treatment effect for the composite outcome is not necessarily the same as the effects on its components, and the single components of a composite endpoint assessed as a time to first event are thus competing risks. Because admissions to hospital, transplantations, and deaths most commonly occur subsequent to symptomatic progression or admission to hospital, the use of a time-to-first-event outcome might have underestimated the treatment effect of combination therapy on these subsequent outcomes. Indeed, combination therapy was associated with a trend for reduced all-cause mortality and PAH-related mortality when all deaths were taken into account. However, the transition of patients to an open-label phase or to approved therapies after censoring might have minimised the risk of subsequent death or transplantation. Moreover, PAH-related mortality was reported for less than 50% of patients contributing to the mortality assessment, which might have led to underestimation of the effects of combination therapy on PAH-related mortality. Future PAH clinical trials should therefore capture total events as a broader, more inclusive, and therefore stronger endpoint than time to first event, or capture all clinically relevant outcomes (eg, all-cause and PAH-related deaths or admissions to hospital) occurring after censoring. Moreover, the sample size for future clinical trials using composite endpoints should ideally provide enough power not only to detect a clinically relevant effect for the composite, but also to assess its components in an adequate way.

Previous reports recommended that a uniform definition of clinical worsening should be used in pivotal randomised controlled trials of PAH.[22] However, clinical worsening has been inconsistently defined across studies, making comparisons difficult. Although common components of the definition have generally included mortality, admission to hospital for PAH, need for intervention, and clinical progression of PAH, the definitions of treatment escalation and symptomatic progression of PAH have been highly heterogeneous. The AMBITION trial[32] even included a newer component—unsatisfactory long-term clinical response—as part of the definition of clinical failure. Nevertheless, the effects of combination therapy on clinical worsening were strikingly homogeneous within each class of PAH therapies. Moreover, sensitivity analyses using more stringent definitions of clinical worsening produced similar results, suggesting that the various definitions appropriately captured clinically relevant events in patients with PAH, especially when adjudicated. This finding is in agreement with those from previous observational studies[46] that supported the concept that the occurrence of the composite worsening endpoint predicted subsequent major events (death, transplantation, or septostomy) in both previously diagnosed and newly diagnosed patients with PAH. Additionally, the rates of first unsatisfactory long-term clinical response were similar between all treatment arms of the AMBITION trial,[32] whereas only six (0·2%) randomly assigned patients underwent lung transplantation and none underwent atrial septostomy as a defining event of clinical worsening. The relevance of including these components of the composite endpoint should thus be reassessed for future clinical trials.

Improving exercise capacity and wellbeing is also a valuable goal for patients with PAH in whom functional capacity and health-related quality of life are severely compromised.[47] Our meta-analysis substantiated that combination therapy improved patients' functional status. Indeed, improvement by one WHO functional class was noted more often for patients assigned to active treatments, although only about 27% of the patients achieved this result on combination therapy compared with 22% on monotherapy in the ten trials that specifically reported this outcome. Similarly, the treatment effect of combination therapy compared with monotherapy on the 6MWD was an increase of about 20 m. These improvements are lower compared with increases in 6MWD noted with monotherapy compared with placebo in a previous trial.[6] However, the minimally important difference in 6MWD that translates into substantial changes in patients' perception of wellbeing remains to be substantiated for patients of WHO functional class II or those on combination therapy.

The use of changes in 6MWD for defining a clinical worsening event supposes that this endpoint translates into clinically relevant outcomes (eg, death, admission to hospital, or transplantation). Although baseline 6MWD has a good discriminative capacity to prognosticate patients at the time of diagnosis, findings from previous studies have suggested small associations between mean changes in 6MWD and the subsequent clinical worsening in trials comparing PAH monotherapy with placebo.[16,17,48] Consistent with these findings, mean changes in 6MWD moderately correlated with the risk of clinical worsening

in our meta-analysis. However, results from some large observational studies have substantiated that patients who had significant decreases in 6MWD (eg, >15%) were at increased risk of death.[45,49] Taken together, these results suggest that individual decreases in exercise capacity accurately predict outcomes (ie, patient-level data), and are therefore a clinically relevant event, whereas mean increases in 6MWD should be regarded as descriptive of the mean effects of therapies on functional status in the setting of a clinical trial (ie, study-level data).

Despite variable study populations and designs, the effect of combination therapy on clinical worsening was strikingly homogeneous among classes of PAH therapies, especially for non-parenteral prostaglandins, phosphodiesterase-5 inhibitors, and endothelin receptor antagonists (I^2=0%). Our findings from predefined subgroup analyses also suggested that the effect of combination therapy on clinical worsening was not driven by just one type of study design or by subgroups of patients with specific disease characteristics. Similarly, no significant heterogeneity was noted in the primary outcome analysis. However, the possibility that results might not apply to all categories of patients with PAH cannot be excluded because the power of the meta-analysis might not have been sufficient to show a difference between drug classes, disease severity groups, and study designs. Non-parenteral prostaglandins, endothelin receptor antagonists, and a selective prostacyclin receptor agonist were shown to be associated with a significantly higher risk of treatment discontinuation; however, merging non-parenteral prostaglandins into one drug class is limited by the heterogeneity of the compounds and route of administration. More importantly, these comparisons are only indirect and subject to artifacts caused by study designs and duration, patient populations, and other covariates. These results should therefore be interpreted with extreme caution in the absence of head-to-head clinical trials.

The limitations of our systematic review and meta-analysis include the variable definition of clinical worsening among the trials, the different duration of the trials (ranging from 12 to 172 weeks), the protracted period between the publication of the first and last trials (around 9 years), and potential heterogeneity in undertaking the trials and between the definitions of PAH-related admissions to hospital, treatment escalation, and symptomatic progression of the disease. However, clinical worsening events were adjudicated in many trials and all participants were analysed (ie, an intention-to-treat analysis). Our funnel plot analysis also showed graphic and statistical asymmetry for clinical worsening (the primary outcome of interest), and thus a publication bias, favouring the publication of positive studies, is possible. Moreover, the effects of combination therapy on specific components of the composite endpoint or on changes in WHO functional class were reported in only some of the trials. Similarly, subgroup analyses for trials that included both treatment-naive patients and patients on background therapy heterogeneously reported secondary outcomes of this meta-analysis, resulting in possible reporting bias. Finally, the timing of combination-therapy initiation and the type of background therapy used in prevalent cases might have influenced the treatment effects noted in the included studies. The absence of data at the patient level or even at the subgroup levels for some studies could thus reduce the external validity of some outcomes of interest.

In conclusion, combining PAH-targeted therapies significantly reduced the risk of clinical worsening as predefined in clinical studies, for patients with PAH. This effect was generally consistent across subgroups. Combination therapy also reduced the risk for admission to hospital, treatment escalation, and symptomatic progression, and resulted in improved patient functional status. Notably, however, none of these trials investigated the cost-effectiveness of these therapies. Moreover, 17% of patients with PAH receiving combination therapy had clinical worsening over a median exposure of 16 weeks. Identification of innovative therapeutic targets and validation of these complementary therapeutic interventions are thus urgently needed for PAH.

Contributors

ACL and GL completed the literature search, data collection, data analysis, data interpretation, and drafted the first version of the manuscript. J-CL, SB, and YL contributed to study design, data interpretation, and revision of the manuscript. SM completed the literature search and data collection. SS contributed to data interpretation. SP contributed to literature search, data analysis, data interpretation, and wrote and revised the manuscript.

Declaration of interests

J-CL has received lecture fees from Actelion Pharmaceuticals. SB holds a Canadian Research Chair in translational research in pulmonary vascular diseases at Université Laval. SP is clinician-scientist of the Fonds de Recherche en Santé du Québec (FRSQ) and has received research grants from Actelion Pharmaceuticals, Bayer, and GlaxoSmithKline, and speaker fees from Actelion Pharmaceuticals. The Pulmonary Hypertension Research Group is also supported by the Réseau en Santé Respiratoire of the FRSQ. All other authors declare no competing interests. This study received no funding.

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