Meta-Analysis of Monotherapy Versus Combination Therapy for Pulmonary Arterial Hypertension

Benjamin D. Fox, BM, BS[a,b], Avi Shimony, MD[a,c], and David Langleben, MD[a,*]

Previous studies comparing combination therapy (CT) of pulmonary vasodilators to monotherapy (MT) in patients with pulmonary arterial hypertension (PAH) report conflicting results as to whether CT is more efficacious than MT. We systematically searched the Cochrane Library, EMBASE, and MEDLINE databases for randomized controlled trials comparing CT to MT for patients with PAH. Data were pooled using the DerSimonian–Laird random-effects model. Six randomized controlled trials including 729 patients met our inclusion criteria. Follow-up ranged from 12 to 16 weeks. Compared to MT, CT resulted in a modest increase in 6-minute walk distance at the end of follow-up (weighted mean difference 25.2 m, 95% confidence interval [CI] 13.3 to 37.2). CT did not decrease mortality (risk ratio [RR] 0.42, 95% CI 0.08 to 2.25), admissions for worsening PAH (RR 0.72, 95% CI 0.36 to 1.44), or escalation of therapy (RR 0.36, 95% CI 0.09 to 1.39) and did not improve New York Heart Association functional class (RR 1.32, 95% CI 0.38 to 4.5) compared to MT. Incidence of study-drug discontinuation was similar between groups (RR 0.89, 95% CI 0.53 to 1.48). CT did not decrease the combined end point of mortality, admission for worsening PAH, lung transplantation, or escalation of PAH therapy (RR 0.42, 95% CI 0.17 to 1.04). In conclusion, this meta-analysis suggests that in PAH CT does not offer an advantage over MT apart from modestly increasing exercise capacity. However, given the paucity of good-quality data, more studies are required to define the efficacy of CT in this population before establishing final guidelines. **(Am J Cardiol 2011;108:1177–1182)**

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature causing inexorable right heart failure and death.[1] Although the condition remains incurable, the previous 15 years have seen the development of novel pharmacologic agents for treating PAH. The 3 main classes of drug currently licensed for PAH are prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors.[2–4] A recent meta-analysis of monotherapy (MT) trials has suggested weak mortality benefit of vasodilator therapy over placebo.[5] Combination therapy (CT) modulates disease pathways at multiple sites and may improve patient outcomes without necessarily increasing drug toxicity.[6] Several randomized clinical trials of CT have been published with conflicting results in terms of efficacy (exercise capacity or clinical worsening events) but with good safety outcomes.[7,8] Abraham et al[9] published a systematic review of CT in 2010 but the study did not include searches in EMBASE and the Cochrane Library and incorporated several observational studies. Pooling of results was not performed in that study. The current "Dana Point" PAH guidelines have given a grade IIA to IIB recommendation for CT, indicating weak support for its use.[1] In view of the inconclusive data from the published literature we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) of CT for PAH and its effect on clinical worsening events and 6-minute walk distance (6MWD).

Methods

We searched MEDLINE, EMBASE, and the Cochrane Library from 1980 through January 2011. Search terms were designed to provide maximum sensitivity in detecting therapeutic trials in PAH. The search terms were "([prostanoid or epoprostenol or prostacyclin or Flolan or iloprost or Ventavis or Remodulin or treprostinil] or ['endothelin receptor antagonist' or bosentan or Tracleer or sitaxsentan or Thelin or ambrisentan or Volibris] or ['phosphodiesterase 5 inhibitor' or sildenafil or Viagra or Revatio or vardenafil or Levitra or tadalafil or Adcirca] and [pulmonary hypertension] and Humans)." There was no language restriction. We subsequently hand-searched the references of narrative reviews, guidelines, and other retrieved documents to identify any publications not identified in the database search. We excluded conference abstracts because the data therein are often preliminary and have not been thoroughly peer reviewed.

We included a study in the systematic review if (1) it was a trial in which subjects were randomly assigned to placebo

[a]Center for Pulmonary Vascular Disease and Lady Davis Institute for Medical Research, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; [b]Pulmonary Institute, Rabin Medical Center, Tel Aviv University, Petach Tikva, Israel; [c]Cardiology Department, Soroka Medical Center, Ben Gurion University, Be'er-Sheva, Israel. Manuscript received April 14, 2011; revised manuscript received and accepted June 2, 2011.

This work was funded by the Bank of Montreal Center for the Study of Heart Disease in Women at the Jewish General Hospital, Montreal, Quebec, Canada. Dr. Fox is supported by the William and Ida Pencer Family Foundation at the Jewish General Hospital, Montreal, Quebec, Canada and the American Fellowship Program for Medicine in Israel, Boston, Massachusetts. Dr. Shimony is supported by the Azrieli Fellowship Fund Montreal, Quebec, Canada and the American Fellowship Program for Medicine in Israel.

*Corresponding author: Tel: 1-514-340-7531; fax: 1-514-340-7534.

E-mail address: david.langleben@mcgill.ca (D. Langleben).

0002-9149/11/$ – see front matter
doi:10.1016/j.amjcard.2011.06.021

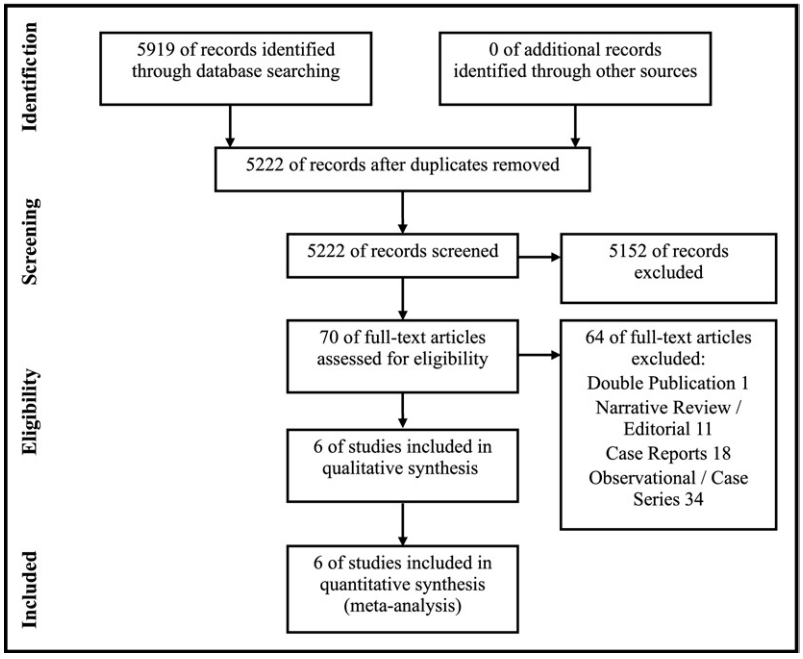

Figure 1. Progress of systematic review of literature.

Table 1
Study-level characteristics of randomized controlled trials comparing dual combination therapy to monotherapy/placebo

Study	Year	Follow-up (weeks)	Baseline Therapy	Active Therapy Arm	Jadad Score
PHIRST-1b[16]	2011	16	Bosentan PO	Tadalafil 40 mg/day PO	5 (excellent)
TRIUMPH-1[8]	2010	12	Bosentan (70%) or sildenafil (30%) PO	INH treprostinil 18–54 μg 4×/day	3 (good)
PACES[7]	2008	16	Epoprostenol IV	Sildenafil 20–80 mg 3×/day PO	5 (excellent)
STEP[17]	2006	12	Bosentan PO	INH iloprost 5 μg 6–9×/day	4 (very good)
COMBI[18]	2006	12	Bosentan PO	INH iloprost 5 μg 6×/day	3 (good)
BREATHE-2[19]	2004	16	Epoprostenol IV	Bosentan 125 mg 2×/day PO	3 (good)

INH = inhaled; IV = intravenously; PO = orally.

Table 2
Patient characteristics of randomized controlled trials comparing dual combination therapy to monotherapy/placebo

	Placebo Arm			Active Therapy Arm		
	Age, Mean ± SD	Women	IPAH/CTD/Other	Age, Mean ± SD	Women	IPAH/CTD/Other
PHIRST-1b	52±16	78%	69%/18%/13%	50 ± 13	79%	52%/26%/48%
TRIUMPH-1	52 (18–75)*	82%	56%/31%/13%	55 (20–75)*	81%	56%/35%/9%
PACES	48 ± 13	77%	79%/17%/4%	48 ± 13	82%	80%/16%/4%
STEP	49 ± 15	79%	61%/39%†	51 ± 14	79%	61%/39%†
COMBI	56 ± 13	76%	100%/0%/0%	48 ± 14	79%	100%/0%/0%
BREATHE-2	47 ± 19	55%	91%/9%/0%	45 ± 17	77%	77%/23%/0%

* Only range given.
† Combined CTD and others.
CTD = connective tissue disease; IPAH = idiopathic pulmonary arterial hypertension. Other abbreviations as in Table 1.

or active therapy on the background of treatment with an approved PAH therapy in a parallel-group design; (2) it reported the clinical outcomes of interest; and (3) follow-up was ≥12 weeks. Two investigators (B.D.F. and A.S.) independently extracted data from each trial. Results were compared and any disagreements were resolved by consensus. Data extracted for each trial included the author, trial title, year of publication, study design, length of follow-up, number of participants and their characteristics, drug in the active treatment arm, and background PAH therapy. Pooled efficacy outcomes were 6MWD and clinical worsening end points: death, admission to a hospital for PAH deterioration, lung transplantation, and escalation of treatment (defined as addition of another approved PAH therapy or increase in epoprostenol dose >10%, where appropriate). A combined clinical worsening end point was calculated for each study

Table 3
Prespecified clinical end points in the different studies

Study	Death	Admission	Transplantation	Treatment Escalation	NYHA Change	Septostomy
PHIRST-1b	+	+	+	+	+	+
TRIUMPH-1	+	+	+	+	+	−
PACES	+	+	+	+	−	−
STEP	+	+	+	+	+	+
COMBI	+	+	−	−	+	−
BREATHE-2	−	−	−	−	+	−

NYHA = New York Heart Association. Other abbreviations as in Table 1.

Table 4
Study outcomes in randomized controlled trials comparing dual combination therapy to monotherapy/placebo

Study	MT							CT						
	Number	Death	Adm	Tx	Esc	DATE	Disc	Number	Death	Adm	Tx	Esc	DATE	Disc
PHIRST-1b	45	1	0	0	0	1	—	42	0	1	0	1	2	—
TRIUMPH-1	120	1	5	0	0	6	9	115	0	4	0	0	4	13
PACES	133	7	11	1	17	36	14	134	0	8	0	2	10	8
STEP	33	0	4	—	1	5	5	34	0	0	—	0	0	4
COMBI	21	0	0	—	—	—	0	19	0	0	—	—	—	0
BREATHE-2	11	0	—	—	—	—	1	22	3	—	—	—	—	1

— = not available; Adm = admission to hospital for deterioration of pulmonary arterial hypertension; DATE = combined outcomes of clinical worsening (death, admission, transplantation, escalation of treatment); Disc = discontinued study; Esc = escalation of pulmonary arterial hypertension therapy; Tx = need for lung transplantation. Other abbreviations as in Table 1.

as the sum of end points just described. For a surrogate safety analysis we extracted data on study discontinuations for any reason. Where available, data on pulmonary hemodynamics were qualitatively compared. When data were incompletely presented in the published article, we contacted the study sponsor directly to request the information required. For every study we scored the quality of the trial according to the scale of Jadad et al.[10]

We used the DerSimonian–Laird random-effects model, which accounts for within-study and between-study variability to estimate pooled risk ratios (RRs) with their 95% confidence intervals (CIs) for event data.[11] Pooled effects on 6MWD are presented as weighted mean differences with corresponding 95% CIs. Forest plots were created for each outcome. Where there were no events in 1 treatment group, we used a 0.5 continuity correction. If there were no events in either group, then any measurement of effect summarized as a ratio cannot be defined, and the trial was excluded from pooled analysis. Statistical heterogeneity was assessed using the Cochrane Q statistic ($p < 0.1$ considered significant). We also calculated the I^2 statistics to estimate the proportion of variation attributable to between-study heterogeneity. We used R 2.11.1 with the meta package for statistical analysis.[12,13] The report was drafted with reference to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[14]

Results

Our database search identified 5,222 studies after removal of duplicate studies (Figure 1). No further articles were retrieved by manual searching. After reviewing title and abstracts to exclude irrelevant articles, 70 studies were reviewed in detail. Of these, 64 were rejected (11 narrative reviews or editorials, 34 uncontrolled case series/observational studies, 18 single-case reports). One RCT (Pulmonary Arterial Hypertension and Response to Tadalafil [PHIRST-1] study comparing tadalafil to placebo) was reported 2 times—1 time with all patients and then by a prespecified analysis of patients recruited to the study on baseline therapy with bosentan.[15,16] We used the bosentan subgroup study for the meta-analysis (referred to as PHIRST-1b) and extracted data for placebo and tadalafil 40 mg/day. Overall 6 RCTs met the prespecified inclusion criteria.[7,8,16–19]

Characteristics of the 6 included RCTs are presented in Table 1. All studies were randomized and placebo controlled. Studies were double-blinded, except for the COMbination of Bosentan and aerosolized Iloprost in idiopathic pulmonary arterial hypertension (COMBI) study.[18] All scored ≥3 on the Jadad scale, indicating good study design. In total 729 patients were enrolled; 363 received MT with placebo and 366 received CT; demographic data are listed in Table 2. All studies presented data on clinical outcomes and 6MWD, although Bosentan: Randomized trial of Endothelin receptor Antagonists THErapy for PAH (BREATHE)-2 did not define the end points of death, admission, transplantation, and treatment escalation a priori (Table 3). Raw event data are presented in Table 4.

At study enrollment there were no significant differences between treatment and placebo groups in 6MWD (5 RCTs, n = 685, weighted mean differences 3.82 m, 95% CI 6.8 to 14.4) or number of patients in New York Heart Association class III (6 RCTs, n = 714, RR 0.99, 95% CI 0.96 to 1.03). There was evidence of mild heterogeneity between studies in 6MWD ($I^2 = 0\%$, $p = 0.84$) and New York Heart Association class ($I^2 = 27\%$, $p = 0.25$).

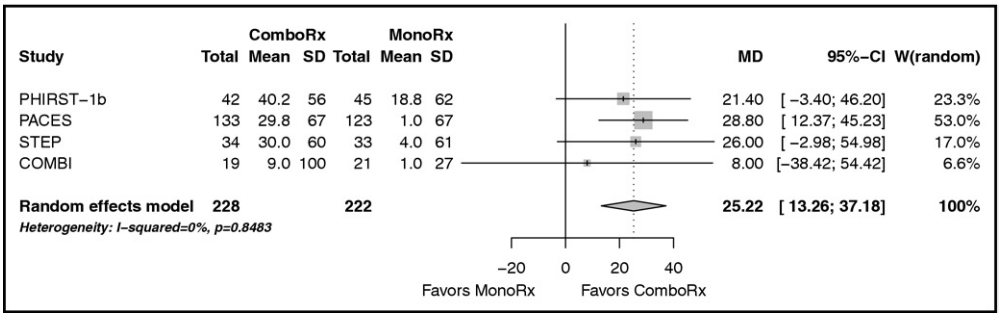

Figure 2. Forest plot of effect of combination therapy (ComboRx) on change in 6-minute walk distance. MD = mean difference; MonoRx = monotherapy; W = weight.

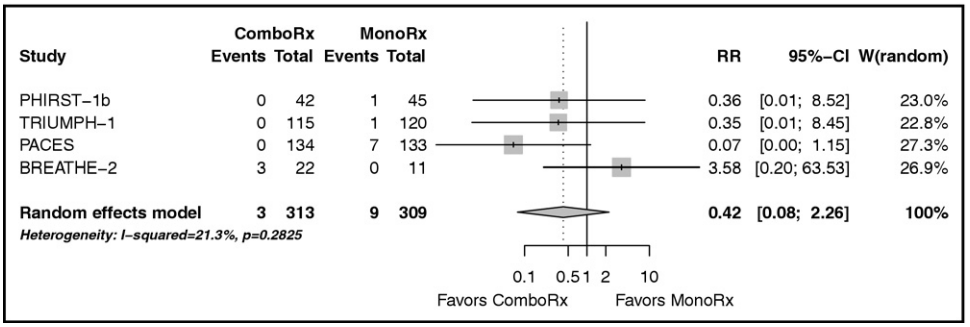

Figure 3. Forest plot of effect of combination therapy on death. Other abbreviations as in Figure 2.

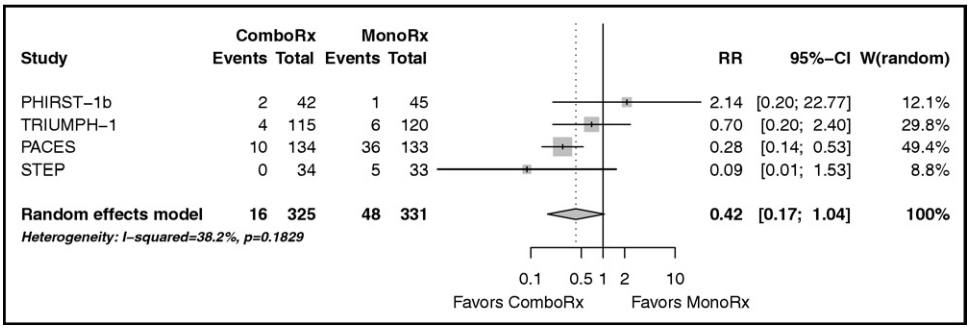

Figure 4. Forest plot of effect of combination therapy on combined clinical worsening (death, admissions, transplantation, and escalation of treatment). Abbreviations as in Figures 2 and 3.

In pooled analysis of change in 6MWD there was a significant increase favoring the CT group (4 RCTs, n = 450, weighted mean differences +25.2 m, 95% CI 13.3 to 37.2; Figure 2). There was no significant heterogeneity between studies (I^2 = 0%, p = 0.85). With regard to improvement in New York Heart Association functional class, we found no difference between MT and CT (3 RCTs, n = 183, RR 1.32, 95% CI 0.38 to 4.5), with significant heterogeneity between studies (I^2 = 77%, p = 0.01). Heterogeneity was driven by a larger number of New York Heart Association class improvements in the placebo arm of the PHIRST-1b study.[16] For worsening New York Heart Association class, there was also no beneficial effect of CT (3 RCTs, n = 194, RR 0.78, 95% CI 0.32 to 1.89). There was no heterogeneity between studies for worsening New York Heart Association class (I^2 = 0%, p = 0.85).

In mortality analysis there was no advantage to CT compared to MT (4 RCTs, n = 624, RR 0.42, 95% CI 0.08 to 2.25; Figure 3). There was evidence of mild heterogeneity in mortality analysis (I^2 = 48%, p = 0.15). Number of admissions to a hospital was unchanged by CT (4 RCTs, n = 594, RR 0.72, 95% CI 0.36 to 1.44). There was mild heterogeneity between studies in hospital admission (I^2 = 21%, p = 0.28). Transplantation end points were not subjected to pooled analysis because only 1 transplantation event was reported in all 6 studies Pulmonary Arterial hypertension Combination study of Epoprostenol and Sildenafil (PACES) study, placebo arm).[7] Examining the need for escalation of therapy, there was no significant difference between CT and MT (3 RCTs, n = 421, RR 0.36, 95% CI 0.09 to 1.39). There was no evidence of heterogeneity between studies in treatment escalation data (I^2 = 0%, p = 0.46). Premature study discontinuations were similar for CT and MT (5 RCTs, n = 642, RR 0.89, 95% CI 0.53 to 1.48). There was no between-study heterogeneity for study discontinuation (I^2 = 0%, p = 0.40). For the combined clinical

Table 5
Changes in pulmonary hemodynamics in combination therapy clinical trials

Study	RAP	MPAP	CO	PVR	SvO_2
PHIRST-1b	?	?	?	+	?
TRIUMPH-1	?	?	?	?	?
PACES	+	+	+	+	+
STEP*	?	+	?	+	?
COMBI	?	?	?	?	?
BREATHE-2	0	0	0	0	0

* Postinhalation hemodynamics only.
− = favors monotherapy; ? = not available; + = favors combination therapy; 0 = no difference; CO = cardiac output; MPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SvO_2 = mixed venous oxygen saturation. Other abbreviations as in Table 1.

worsening end point (death, admission, transplantation, treatment escalation), pooled analysis revealed that CT was not different from MT (4 RCTs, n = 656, RR 0.42, 95% CI 0.17 to 1.04; Figure 4). There was evidence of mild heterogeneity between studies for the end point of death, admission, transplantation, and treatment escalation (I^2 = 38%, p = 0.18). Forest plots for admission, escalations, and discontinuations are in the supplementary data file.

Pulmonary hemodynamics were not reported with sufficient consistency to allow for pooled analysis. In general patients receiving CT had modest improvements in right atrial pressure, mean pulmonary artery pressure, and cardiac output compared to the MT group (Table 5).

Discussion

We performed a meta-analysis of 6 RCTs of CT versus MT for treating patients with PAH. The clinical worsening end points examined were death, admission to hospital, transplantation and escalation of PAH therapy, a combined end point of these events (death, admission, transplantation, and treatment escalation), and change in 6MWD. In the entire meta-analysis of clinical worsening events (alone and combined) CT did not have a statistically significant beneficial effect. 6MWD did increase significantly in the CT arm, although New York Heart Association functional class did not improve. Discontinuations from the study were similar in the 2 groups, providing an indirect signal that safety was acceptable with CT.

This is the first comprehensive meta-analysis of RCTs to specifically address the efficacy of CT in PAH. Previous investigators reviewing the literature have concluded that the evidence is insufficient or have given support to the concept of CT.[9,20] Current American Heart Association/European Society of Cardiology guidelines for treatment of PAH have given a grade IIA to IIB recommendation for CT in PAH (interpretation—weight of evidence/opinion is in favor of usefulness/efficacy).[1] Our study supports this conclusion only for improving exercise capacity but not for preventing clinical worsening.

The main limitation in interpreting this meta-analysis is that we pooled data from studies comparing different combinations of pulmonary vasodilators. Five of the 6 studies included parenteral prostanoids (3 inhaled, 2 intravenous) with an endothelin receptor antagonist (bosentan, 5 RCTs) or phosphodiesterase-5 inhibitor (sildenafil, 2 RCTs; Table 1). Only 1 study evaluated 2 oral medications (PHIRST-1b). However, the prevailing concept of CT in PAH is that a combination of any 2 classes of therapy is superior to MT. Current guidelines imply that any form of CT is acceptable.[1] Our meta-analysis therefore addresses current thinking directly and our results are highly relevant to the debate. With such a limited number of studies and many potential combinations, it is not possible to say which 2 medications might be the most effective in combination. It is also unlikely that this question will ever be answered definitively because this would require a large multiarm trial and open cooperation among different pharmaceutical companies. When commencing CT, the physician must rely on clinical judgment alone.

In addition to between-study heterogeneity for which medications are combined, there were some important differences in study design. Five of 6 studies analyzed included patients who were "clinically stable" on their baseline treatment and the experimental treatment was added "stepwise," as suggested by Hoeper et al.[21] An alternative model of CT is immediate commencement in newly diagnosed patients. This model of CT was examined in only 1 trial (BREATHE-2) where all patients were commenced on treatment with intravenous epoprostenol and after 2 days were randomized to additional bosentan or placebo.[19] This was the only study in which mortality was higher in the treatment group (Figure 3). This evidence does not, in our opinion, disqualify the approach of de novo CT but simply highlights the need for large RCTs to evaluate it. When mortality analysis is performed without the BREATHE-2 study, the RR and 95% CI remain nonsignificant (3 RCTs, n = 594, RR 0.18, 95% CI 0.03 to 1.05).

For our meta-analysis there was a relatively limited body of quality evidence in the small number of patients and short duration of follow-up. This is a recurring theme in the literature of PAH therapy and our meta-analysis is clearly unable to overcome this limitation. It does underline the need for longer-term RCTs of CT to properly understand the risks and benefits over time. For the same reason we cannot say whether the minor beneficial effects of CT over MT are maintained over time. Reporting of events and physiologic outcomes is inconsistent between studies and the precise definition of overall clinical worsening is variable. This meant that pooled analyses were performed typically on 3 to 4 studies, which increases the likelihood for type I statistical error.

The utility of "escalations of PAH therapy" as a clinical worsening end point must also be questioned in this context. In all studies "escalation" meant treating the subject with an additional pulmonary vasodilator. In the PACES study an increase of >10% in epoprostenol dose was also considered escalation.[7] In the pooled placebo data only 37 of 211 subjects "required" escalation of treatment, indicating that 83% of placebo-treated patients did not. All patients in the CT arm had treatment escalations by definition and 12 of 210 of them seem to have required a second escalation to triple therapy. It seems illogical to promote escalating to CT as a means to prevent treatment escalations. We suggest that

treatment escalations should not form part of the combined clinical end points in CT trials. Preventing escalations to intravenous/subcutaneous prostanoids would be more suitable in a study combining nonprostanoid vasodilators. Requirement for any additional PAH drug would certainly be a useful end point in clinical trials of nonvasodilator drugs being investigated for PAH such as tyrosine kinase inhibitors and statins.[22,23] The transplantation event occurred only 1 time in all the studies and septostomy did not occur so these end points may also lack sensitivity in the context of such short studies.

It is also possible that there is publication bias in the CT literature. We are aware of 2 clinical trials that have been completed but their results have not been fully published (FREEDOM-DR and AmbRIsentan in pulmonary arterial hypertension, randomized double blind Efficacy Study (ARIES)-3, *http://www.clinicaltrials.org*, identifiers NCT00760916 and NCT00380068, respectively). There are several clinical trials of CT in progress. We note with particular interest the AMBrIsentan and Tadalafil combinatION therapy in subjects with pulmonary arterial hypertension (AMBITION) study (*http://www.clinicaltrials.org*, NCT01178073), which has a novel 3-arm design: 2 MTs (ambrisentan and tadalafil) and their combination are compared over 24 weeks in treatment-naive patients. In the meantime our meta-analysis shows only modest advantages of CT over MT. More studies are required to define the efficacy of CT in this population. Investigators and industry should publish all data on CT in PAH irrespective of study results to enable a future meta-analysis to reach firmer conclusions and help finalize guidelines.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2011.06.021.

1. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J, Harrington RA, Anderson JL, Bates ER, Bridges CR, Eisenberg MJ, Ferrari VA, Grines CL, Hlatky MA, Jacobs AK, Kaul S, Lichtenberg RC, Lindner JR, Moliterno DJ, Mukherjee D, Pohost GM, Rosenson RS, Schofield RS, Shubrooks SJ, Stein JH, Tracy CM, Weitz HH, Wesley DJ. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation* 2009;119:2250–2294.
2. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Clayton LM, Jobsis MM, Blackburn SD, Shortino D, Crow JW. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;334:296–302.
3. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M, Simonneau G. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896–903.
4. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;353:2148–2157.
5. Macchia A, Marchioli R, Tognoni G, Scarano M, Marfisi R, Tavazzi L, Rich S. Systematic review of trials using vasodilators in pulmonary arterial hypertension: why a new approach is needed. *Am Heart J* 2010;159:245–257.
6. Toews ML, Bylund DB. Pharmacologic principles for combination therapy. *Proc Am Thorac Soc* 2005;2:282–289.
7. Simonneau G, Rubin LJ, Galiè N, Barst RJ, Fleming TR, Frost AE, Engel PJ, Kramer MR, Burgess G, Collings L, Cossons N, Sitbon O, Badesch DB; PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008;149:521–530.
8. McLaughlin VV, Benza RL, Rubin LJ, Channick RN, Voswinckel R, Tapson VF, Robbins IM, Olschewski H, Rubenfire M, Seeger W. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol* 2010;55:1915–1922.
9. Abraham T, Wu G, Vastey F, Rapp J, Saad N, Balmir E. Role of combination therapy in the treatment of pulmonary arterial hypertension. *Pharmacotherapy* 2010;30:390–404.
10. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–188.
12. R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2010.
13. Schwarzer G. Meta-Analysis with R. R Package Version 1.6-1. 2010.
14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA Statement. *PLoS Med*: 2009;6:e1000097.
15. Galiè N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, Shapiro S, White RJ, Chan M, Beardsworth A, Frumkin L, Barst RJ; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009;119:2894–2903.
16. Barst RJ, Oudiz RJ, Beardsworth A, Brundage BH, Simonneau G, Ghofrani HA, Sundin DP, Galiè N; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension. *J Heart Lung Transplant* 2011;30:632–643.
17. McLaughlin VV, Oudiz RJ, Frost A, Tapson VF, Murali S, Channick RN, Badesch DB, Barst RJ, Hsu HH, Rubin LJ. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006;174:1257–1263.
18. Hoeper MM, Leuchte H, Halank M, Wilkens H, Meyer FJ, Seyfarth HJ, Wensel R, Ripken F, Bremer H, Kluge S, Hoeffken G, Behr J. Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2006;28:691–694.
19. Humbert M, Barst RJ, Robbins IM, Channick RN, Galiè N, Boonstra A, Rubin LJ, Horn EM, Manes A, Simonneau G. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004;24:353–359.
20. Galiè N, Negro L, Simonneau G. The use of combination therapy in pulmonary arterial hypertension: new developments. *Eur Respir Rev* 2009;18:148–153.
21. Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J* 2005;26:858–863.
22. Ghofrani HA, Morrell NW, Hoeper MM, Olschewski H, Peacock AJ, Barst RJ, Shapiro S, Golpon H, Toshner M, Grimminger F, Pascoe S. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. *Am J Respir Crit Care Med* 2010;182:1171–1177.
23. Wilkins MR, Ali O, Bradlow W, Wharton J, Taegtmeyer A, Rhodes CJ, Ghofrani HA, Howard L, Nihoyannopoulos P, Mohiaddin RH, Gibbs JS; Simvastatin Pulmonary Hypertension Trial (SiPHT) Study Group. Simvastatin as a treatment for pulmonary hypertension trial. *Am J Respir Crit Care Med* 2010;181:1106–1113.