

# Combination therapy in pulmonary arterial hypertension: recent accomplishments and future challenges

Annie-Christine Lajoie<sup>1,2</sup>, Sebastien Bonnet<sup>1,2,3</sup> and Steeve Provencher<sup>1,2,3</sup>

<sup>1</sup>Pulmonary Hypertension Research Group, Canada; <sup>2</sup>Institut universitaire de cardiologie et de pneumologie de Québec Research Center, Laval University, Quebec City, Canada; <sup>3</sup>Department of Medicine, Université Laval, Québec, Canada

## Abstract

Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by a progressive increase in pulmonary vascular resistance, ultimately leading to right heart failure and death. Throughout the past 20 years, numerous specific pharmacologic agents, including phosphodiesterase-5 inhibitors, endothelin receptor antagonists, prostaglandins, and more recently, soluble guanylate cyclase stimulators and selective IP prostacyclin receptor agonist, have emerged for the treatment of PAH. Early clinical trials were typically of short-term duration, comparing the effects of PAH-targeted therapies versus placebo and using exercise tolerance as the primary endpoint in most trials. A meta-analysis of these trials documented a reduction in short-term mortality of ~40% with monotherapy. More recently, we have witnessed a progressive shift in PAH study designs using longer event-driven trials comparing the effects of upfront and sequential combination therapy on clinical worsening that is perceived as a more clinically relevant outcome measure. Recent meta-analyses also documented that combination therapy significantly reduced the risk of clinical worsening by ~35% compared with monotherapy alone.

In this review article, we will discuss the evolution of treatments and clinical trial design in the field of PAH over the past decades with a special focus on combination therapy and its current role in the management of PAH. We will also detail unresolved questions regarding the future of PAH patients' care and the challenges of future clinical trials.

## Keywords

pulmonary hypertension, pulmonary arterial hypertension combination therapy, clinical trials, endothelin, prostaglandins, phosphodiesterase type 5

Date received: 20 January 2017; accepted: 27 April 2017

Pulmonary Circulation 2017; 7(2) 312–325

DOI: 10.1177/2045893217710639

## Introduction

Pulmonary arterial hypertension (PAH, group 1 of the clinical classification) is characterized by intense pulmonary vascular remodeling, resulting in increased pulmonary vascular resistance (PVR) and ultimately leading to right heart failure and death.<sup>1,2</sup> PAH encompasses a variety of different pathologies, such as idiopathic, heritable, anorexigen-induced PAH, as well as PAH associated with concomitant diseases such as connective tissue disease, congenital heart disease, and portal hypertension. Initially shrouded with mystery, the definition of this orphan disease has greatly evolved in past decades. Even though the pathophysiology of the disease is still incompletely understood, extensive research in the field has led to the identification of three key

pathways of abnormal vasoconstriction and cell growth, and the elaboration of numerous specific pharmacologic agents targeting the endothelin, the nitric oxide, and prostaglandin pathways that have been progressively used in combination. This article reviews the evolution of treatments and clinical trial conception in the field of PAH over the past decades with a special focus on combination therapy and its current role in the management of PAH. Unresolved questions regarding

Corresponding author:

Steeve Provencher, Pulmonary Hypertension Research Group, Institut universitaire de cardiologie et de pneumologie de Québec Research Center, Laval University, Quebec City, Canada.

Email: [steeve.provencher@criucpq.ulaval.ca](mailto:steeve.provencher@criucpq.ulaval.ca)



Creative Commons Non Commercial CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<http://www.creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

© The Author(s) 2017.

Reprints and permissions:  
[sagepub.co.uk/journalsPermissions.nav](http://sagepub.co.uk/journalsPermissions.nav)  
[journals.sagepub.com/home/pul](http://journals.sagepub.com/home/pul)



the future of PAH patients' care and the challenges of future clinical trials are also discussed.

### *Initial days of PAH therapies*

The past decades have been thriving in terms of treatments for PAH. However, the field experienced a slow start as it took more than 20 years to develop and approve a specific treatment for PAH after the first World Symposium on Pulmonary Hypertension held in 1973. Before the late 1990s, treatments for PAH patients consisted of supportive therapy with diuretics, digoxin, anticoagulants, and oxygen supplementation with or without calcium channel blockers, the latter being now reserved for selected patients who are responsive to acute vasodilators during right heart catheterization.<sup>3</sup> This treatment approach mainly addressed symptoms related to right heart failure and merely altered the devastating course of the disease, with a median survival of 2.8 years.<sup>4</sup>

Subsequent developments in the understanding of PAH led to development of numerous specific therapies targeting the well-described pathways characterizing endothelial dysfunction in PAH: the endothelin-1, nitric oxide, and prostacyclin pathways. In 1995, the U.S. Food and Drug Administration (FDA) approved epoprostenol, a parenteral prostaglandin, making it the very first available specific therapy for PAH. The landmark randomized controlled trial (RCT) confirmed that i.v. prostacyclin was associated with improvement of pulmonary hemodynamics and exercise tolerance. Although survival was not the primary endpoint, epoprostenol was associated with a significantly lower mortality at 12 weeks (0% versus 20%,  $P < 0.002$ ).<sup>5</sup> The following long-term observational studies suggested that these effects persisted over time.<sup>6,7</sup> Subsequently, a multitude of other PAH-targeted molecules were formerly assessed in RCTs, approved, and emerged on the market. The current therapeutic arsenal includes phosphodiesterase-5 inhibitors (PDE5i, sildenafil, and tadalafil), endothelin receptor antagonists (ERA, ambrisentan, bosentan, and macitentan), prostaglandins (epoprostenol, iloprost, treprostinil), and, more recently, the soluble guanylate cyclase stimulator (riociguat) and selective IP prostacyclin receptor agonist (selexipag). Although the primary outcome in initial trials was most commonly the change in six-minute walk distance (6MWD), a meta-analysis of the 23 short-term (mean duration of 14 weeks) RCTs comparing monotherapy with supportive care documented a 43% and 61% reduction in mortality and hospitalization, respectively.<sup>8</sup> Patients in the active arm group also experienced improvements in pulmonary hemodynamics, exercise capacity, and functional status, and health-related quality of life.<sup>9</sup>

### *The journey to combination therapy*

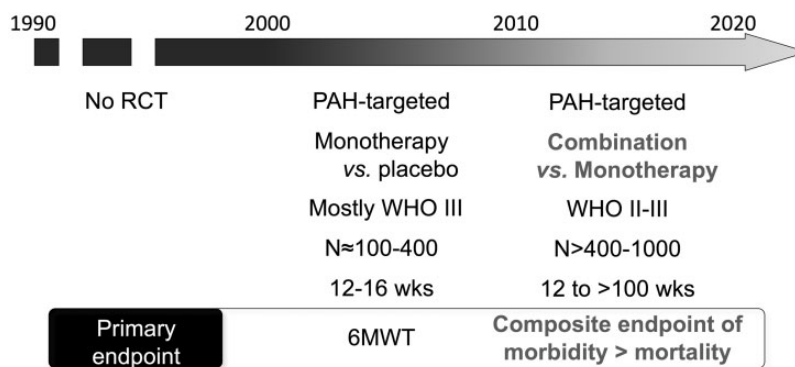
Despite these promising findings, a significant proportion of PAH patients had unsatisfactory clinical response on monotherapy and long-term prognosis remained poor, with a

mortality rate of ~15% per year in incident PAH patients.<sup>10,11</sup> Combination therapy emerged as a logical alternative to monotherapy. The strategy of combining multiple drugs is not restricted to the field of PAH and has been used extensively in other chronic debilitating diseases such as systemic hypertension,<sup>12</sup> chronic heart failure,<sup>13</sup> and diabetes,<sup>14-17</sup> where patients on combination therapy have better outcomes than those on single drug therapy. The rationale is that targeting simultaneously multiple pathways involved in the disease's pathogenesis rather than increasing doses is expected to lead to additive or even synergistic beneficial effects, further improving patients' outcomes while minimizing potential drug interactions or adverse events. Moreover, because of the early benefit observed in short-term trials,<sup>8</sup> the principle of equipoise for placebo-controlled trials was considered to be no longer respected, making combination therapy trials a mandatory step to assess novel therapies. As a result, most RCTs performed in the last decade in PAH patients included at least one subgroup of patients on background therapy.

### **A progressive shift in the clinical trial paradigm**

Many of the early clinical trials documented improvement in functional capacity, exercise capacity, and pulmonary hemodynamics with combination therapy compared to monotherapy,<sup>18-27</sup> while others failed to demonstrate a significant improvement in their primary endpoint.<sup>28-30</sup> In 2011, adding to the already conflicting literature, findings from a systematic review and meta-analysis suggested that combining PAH-targeted therapies did not offer any advantage over monotherapy except a modest increase in exercise capacity.<sup>31</sup> Importantly, clinical trials conducted at that time were mainly of short-term duration and used the 6MWD as the primary endpoint.<sup>18-21,26,28</sup> Although baseline 6MWD has a good discriminative capacity to predict outcomes in patients at the time of diagnosis,<sup>32</sup> changes in 6MWD appeared to be an inappropriate surrogate marker of disease progression, and meta-analyses suggested that changes in exercise capacity may not predict clinically relevant events such as all-cause death, hospitalization, or lung transplantation.<sup>33-35</sup> There was also the concern of a certain "ceiling" effect in patients who have already been stabilized on background monotherapy, leaving little room for improvement when another therapy was added.<sup>36</sup> As expected, combination therapy trials were shown to result in lower changes in 6MWD<sup>37</sup> compared with monotherapy trials.<sup>8</sup>

Directly assessing mortality would have been the most relevant endpoint in PAH trials, but it was felt hardly realizable for a disease like PAH. Indeed, PAH is a rare disease and mortality incidence is low in clinical trials, thus jeopardizing study power and feasibility. Moreover, none of the biomarkers currently used in PAH has been validated as a surrogate clinical endpoint.<sup>38</sup> Consequently, there was dire a need to develop endpoints that would capture



**Fig. 1** Recent paradigm shift in the design of clinical trials in pulmonary arterial hypertension. 6MWD, six-minute walking distance; WHO FC, World Health Organization functional class; PAH, pulmonary arterial hypertension; RCT, randomized control trial.

clinically relevant events.<sup>4,10,11,39,40</sup> Following the example of other chronic diseases, especially chronic left heart failure, the concept of clinical worsening emerged in an attempt to represent events that are undesirable and clinically relevant for patients, including hospitalization, symptomatic progression of disease, treatment escalation, transplantation, atrial septostomy, and death.<sup>41</sup> Although this definition slightly diverged from one study to the other, clinical worsening was proven to effectively predict subsequent mortality events in an observational study from the REVEAL registry,<sup>42</sup> and was shown to be consistently reproducible when adjudicated by an independent committee.<sup>41</sup> We have thus witnessed a progressive change in the design of clinical trials (Fig. 1), from smaller scale short-term trials using clinical worsening as a secondary endpoint to large-scale event-driven trials evaluating combination therapy versus monotherapy of PAH-targeted drugs in which clinical worsening was the primary efficacy endpoint.

### Sequential dual combination therapy

The majority of trials that have examined sequential combination therapy in PAH have investigated whether targeting two pathogenic pathways at once is superior to monotherapy. Two recent meta-analyses confirmed that combination therapy was associated with a 35–40% relative risk reduction of clinical worsening.<sup>37,43</sup> These findings reinforced the allocated grade of recommendation I and level of evidence A in PAH patients with inadequate clinical response to initial monotherapy in the recent updated treatment algorithm of PAH.<sup>2</sup> However, diverse combination therapies may not be equivalent and few combinations have been adequately assessed in RCTs (Table 1).

### Prostanoids in addition to ERAs and/or PDE-5 inhibitors

Seven trials specifically assessed the efficacy of adding non-parenteral prostaglandins to background ERAs and/or PDE-5 inhibitors. In the STEP trial, inhaled iloprost added to background bosentan was not associated with a significant increase in 6MWD (+26 m ( $P=0.051$ ),<sup>19</sup> but was

associated with improvements in functional status, pulmonary hemodynamics and time to clinical worsening ( $P=0.022$ ). The COMBI trial that had a very similar study design and population failed to show any benefit with this combination.<sup>18</sup> Disappointing results were also seen with the addition of oral treprostinil to ERAs, PDE-5i, or both.<sup>29,30</sup> Conversely, inhaled treprostinil in addition to background therapy with ERAs or PDE-5i improved exercise capacity.<sup>20</sup> More recently, the GRIPHON study, a multicenter, double-blind, event-driven, phase III RCT confirmed that the addition of selexipag was associated with a 40% decrease in the risk of clinical worsening when compared with placebo in 1156 PAH patients on background therapy. Subgroups of patients receiving either an ERA, a PDE-5 inhibitor, or a combination of the two, corresponding to 15%, 32%, and 33% of the study population, respectively, experienced similar treatment benefit.<sup>44</sup>

### ERAs in addition to PDE-5 inhibitors or prostanoids

SERAPHIN, a multicenter, double-blind, randomized, event-driven, phase III study randomized 742 patients to receive macitentan 10 mg, macitentan 3 mg, or placebo. In the overall study population, macitentan 10 mg significantly reduced the risk of morbidity/mortality events by 45% ( $P<0.001$ ) versus placebo. Predefined subgroup analyses showed that macitentan similarly delayed time to first PAH-related events in both treatment-naïve and pre-treated patients (PDE-5i or non-parenteral prostaglandins), confirming that sequential combination therapy improves long-term outcomes in PAH.<sup>45</sup> Macitentan also improved functional status and pulmonary hemodynamics.<sup>46</sup> More recently, however, the COMPASS-2 study, a double-blind, placebo-controlled, phase IV clinical trial, where 334 patients on baseline sildenafil were randomized to bosentan or placebo, failed to demonstrate a reduction in the risk of morbidity/mortality. An exploratory analysis suggested that bosentan on top of sildenafil improved 6MWD at week 16 (+22 m,  $P=0.01$ ).<sup>47</sup> Whether the discrepancy between these two trials is related to differences in the study population and design, power of the study, drug efficacy, or drug–drug

**Table 1.** Randomized controlled trials evaluating combination therapy in PAH.

Study	n	Length (week)	Baseline therapy (proportion %)	Therapeutic arm	PAH type (%)	WHO FC (%)	Treatment effect
<i>Addition of parenteral prostaglandins</i>							
COMBI, 2006 <sup>18</sup>	40	12	Bosentan (100%)	Inhaled Iloprost	IPA: 100	III: 100	Mean treatment effect of -10 m ( $P=0.49$ ) No significant changes were observed for WHO FC, peak oxygen uptake, ventilator efficacy, peak SAP, HRQoL, or clinical worsening*
STEP, 2006 <sup>19</sup>	67	12	Bosentan (100%)	Inhaled Iloprost	IPA: 55 APAH: 45	II: 2 III: 94 IV: 5	Mean treatment effect (post-inhalation) of +26 m ( $P=0.051$ ) Significant improvements in WHO FC, time to clinical worsening,* and pulmonary hemodynamics (post-inhalation) were also observed No changes in Borg dyspnea score were seen
TRIUMPH, 2010 <sup>20</sup>	235	12	Bosentan (70%) or Sildenafil (30%)	Inhaled Treprostinil	IPA: 56 APAH (CTD): 33 Others: 11	III: 98 IV: 2	Median treatment effect of 20 m ( $P<0.001$ ) (+25 m for patients on background bosentan [ $P<0.001$ ] and +9 m for patients on background sildenafil [ $P=NS$ ]) Improvements in HRQoL and NT-proBNP were also observed No changes in time to clinical worsening,* Borg dyspnea score, WHO FC, and PAH signs and symptoms were seen
FREEDOM-C1, 2012 <sup>29</sup>	350	16	PDE5i (25%) ERA (30%) both (45%)	Oral Treprostinil	IPA: 66 APAH: 34 (CTD:26)	I: 1 II: 21 III: 76 IV: 3	Mean treatment effect of 11 m ( $P=0.07$ ) Significant improvements in median dyspnea fatigue index score ( $P=0.01$ ) and combined 6MWD and Borg dyspnea score ( $P=0.01$ ) were observed No change in time to clinical worsening,* WHO FC, and Borg dyspnea score were seen
FREEDOM-C2, 2013 <sup>30</sup>	310	16	PDE5i (43%) ERA (17%) Both (40%)	Oral treprostinil	IPA: 66 APAH:44 (CTD): 31	I:0 II: 26 III: 73 IV: 1	Mean treatment effect of 10 m ( $P=0.09$ ) No significant differences were observed for any secondary efficacy endpoints (clinical worsening,* Borg dyspnea score, combined 6MWD/Borg score, NT-proBNP, WHO FC, HRQoL, signs and symptoms of PAH)

(continued)

Table 1. Continued

Study	n	Length (week)	Baseline therapy (proportion %)	Therapeutic arm	PAH type (%)	WHO FC (%)	Treatment effect
Simonneau et al., 2012 <sup>24</sup>	43	17	ERA (37%) Sildenafil (28%) Both (35%)	Selexipag	IPAH: 81 APAH: 19	II: 40 III: 60	Reduction of 30.3% of mean PVR and improvement in cardiac index and systemic vascular resistance Mean treatment effect of +24.2 m No difference in Borg dyspnea scale and NT-proBNP
GRIPHON, 2015 <sup>44</sup>	1156	76 <sup>§</sup>	ERA (15%), PDE5i (32%) or both (33%) <sup>¶</sup>	Selexipag	IPAH: 61 APAH: 39 (CTD: 29)	I: 1 II: 46 III: 53 IV: 1	40% reduction in first event of death or a complication related to PAH* (HR = 0.60, 95% CI = 0.46–0.78, P < 0.001) Significant improvement in 6MWD (treatment effect = 12.0 m, 99% CI = 1–24, P = 0.003) No significant difference in the proportion of patients with no worsening in WHO FC
Addition of ERAs BREATHE-2, 2004 <sup>28</sup>	33	16	Epoprostenol (100%)	Oral Bosentan	IPAH: 82 APAH: 18 (CTD)	III: 76 IV: 24	No significant change between groups in TPR and other hemodynamic parameters (CI, PVR, mPAP, mRAP) No significant change in 6MWD, dyspnea fatigue rating, or FC
EARLY, 2008 <sup>25</sup>	185	24	Sildenafil (16%)	Oral Bosentan	IPAH: 61 APAH: 39 (CTD: 18)	II: 100	Mean treatment effect –22.6% (P < 0.0001, similar results for treatment-naïve and sildenafil-treated patients) and +19 m (P = 0.0758) for PVR and 6MWD, respectively Significant improvements in TTCW* and NT-proBNP were also observed No changes for Borg dyspnea score and HRQoL were seen
COMPASS-2, 2015 <sup>47</sup>	334	165 <sup>±</sup>	Sildenafil (100%)	Oral Bosentan	IPAH: 68 APAH: 32 (CTD: 26)	II: 42 III: 58 IV: <1	No difference in time to first event of morbidity/mortality No change in FC or time to first occurrence of death from any cause, hospitalization for PAH, or start of intravenous prostaglandin therapy, atrial septostomy, or lung transplant; death from any cause. Mean treatment effect +22 m (P = 0.01) (exploratory)

(continued)

Table 1. Continued

Study	n	Length (week)	Baseline therapy (proportion %)	Therapeutic arm	PAH type (%)	WHO FC (%)	Treatment effect
SERAPHIN, 2013 <sup>45</sup>	308 <sup>#</sup>	104 <sup>≈</sup>	Non-parenteral prostaglandins (5%) PDE5i (61%)	Oral Macitentan	IPAH: 60 APAH: 40	I: <1 II: 52 III: 46 IV: 2	HR = 0.55 (97.5% CI = 0.39–0.76, P < 0.001) for first PAH-related event (10 mg dose) (similar effects in treatment-naïve and pre-treated patients) Significant improvements in 6MWD (+22 m), WHO FC, pulmonary hemodynamics at six months, as well as death or hospitalization due to PAH were also observed No changes in death from any cause were seen. However, macitentan was associated with a trend for decreased adjudicated death due to PAH (P = 0.07)
<i>Addition of PDE-5i or soluble guanylate cyclase stimulators</i>							
PACES, 2008 <sup>21</sup>	267	16	IV Epoprostenol (100%)	Sildenafil 80 mg three times daily	IPAH: 79 APAH: 21	I: 1 II: 26 III: 66 IV: 6	Median treatment effect of +29 m (P < 0.001) Significant improvements in pulmonary hemodynamics, clinical worsening,* and HRQoL were also observed No changes in Borg dyspnea score were seen
PHIRST, 2011 <sup>26</sup>	87	16	Bosentan (53%)	Tadalafil 40 mg once daily	IPAH: 63 APAH: 37 (CTD: 22)	I: 1 II: 35 III: 63 IV: 1	+33 m for patients receiving 40 mg (+44 m for treatment-naïve (P < 0.01); +23 m on background bosentan (P = 0.09); +24 m for WHO FC I–II (P = 0.04); +36 m for WHO FC III–IV (P = 0.02) Tadalafil 40 mg delayed TTCW and improved HRQoL Both 20 mg and 40 mg improved pulmonary hemodynamics No changes in WHO FC and Borg dyspnea score were seen
PATENT-1, 2013 <sup>27</sup>	191 <sup>∞</sup>	12	ERA (87%) non-parenteral prostaglandins (13%)	Riociguat 2.5 mg three times daily	IPAH: 60 <sup>°</sup> APAH: 40 (CTD 32)	I: 2 <sup>°</sup> II: 34 III: 63 IV: 1	+36 m (2.5 mg t.i.d maximum group, P < 0.001) Similar effects in treatment-naïve and pre-treated patients and non-significant in WHO FC I–II patients Significant improvements in pulmonary hemodynamics, NT-proBNP, WHO FC, TTCW,* and Borg dyspnea score were also observed

(continued)

**Table 1.** Continued

Study	n	Length (week)	Baseline therapy (proportion %)	Therapeutic arm	PAH type (%)	WHO FC (%)	Treatment effect
Zhuang and al., 2014 <sup>23</sup>	124	16	Ambrisentan (100%)	Tadalafil 40 mg daily	IPAH: 72 APAH: 28 (CTD: 23)	II: 57 III: 39 IV: 4	No statistical difference in 6MWD, hemodynamics, FC, and clinical worsening
<i>Upfront combination of PDE5i and ERA</i> AMBITION <sup>48</sup>	500 <sup>§</sup>	79	None (100%)	Ambrisentan + tadalafil OR ambrisentan/ tadalafil monotherapy	IPAH: 59 APAH: 41 (CTD 37)	II: 31 III: 69	Improvement of time-to-event analysis of first event of clinical failure: - CT vs. pooled MT: HR = 0.50 (95% CI = 0.35–0.72, P < 0.001) - CT vs. ambrisentan MT: HR = 0.48 (95% CI = 0.31–0.72, P < 0.001) - CT vs. tadalafil MT: HR = 0.53 (95% CI = 0.34–0.83, P = 0.005) Significant differences in NT-proBNP, % patients with satisfactory clinical response (except CT vs. ambrisentan MT), change in baseline 6MWD were observed with CT over pooled MT or MT with ambrisentan or tadalafil No significant difference in WHO FC between groups

Definitions of clinical worsening varied between studies (see Table 4).

\*The definition of clinical worsening differed from one study to the other.

§The mean duration of study treatment was 63.7 and 70.7 weeks for the patients receiving placebo and selexipag, respectively.

¶80% of patients were on 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%).

≈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%).

°Patients pretreated with background therapy only.

§§Modified intention-to-treat.

6MWD, six-minute walking distance; APAH, associated pulmonary arterial hypertension; CI, cardiac index; CT, confidence interval; CTD, connective tissue disease; CW, clinical worsening; ERA, endothelin receptor antagonist; HR, hazard ratio; HRQoL, health-related quality of life; IPAH, idiopathic pulmonary arterial hypertension; i.v., intravenous; MT, monotherapy; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitors; PVR, pulmonary vascular resistance; SAP, systolic arterial pressure; TTCW, time to clinical worsening; WHO FC, World Health Organization functional class.

interactions (bosentan reducing plasma levels of sildenafil and tadalafil) remains unknown. Importantly, the COMPASS-2 trial had an important amount of missing data due to premature discontinuation of study before any event of clinical worsening. Also, the trial was designed to detect a treatment effect of 40% with combination therapy and the events encountered in the trial were too few. Thus, the study may have lacked statistical power to detect a smaller difference between treatments.

### *PDE-5i or soluble guanylate cyclase stimulation in addition to prostanoids or ERAs*

In the PACES-1 study,<sup>21</sup> the addition of sildenafil in patients with poor exercise capacity despite background i.v. epoprostenol was associated with significant delay in clinical worsening compared to placebo. Improvements in exercise capacity (adjusted treatment difference of 29 m,  $P=0.001$ ) and hemodynamics were also observed. Although not a predefined endpoint, more deaths were recorded in the placebo group compared with the sildenafil group. Riociguat also improved exercise capacity after 12 weeks in both treatment-naïve patients and those on background PAH therapy (mostly ERAs).<sup>27</sup> Conversely, the addition of tadalafil on top of bosentan did not result in significant improvement in exercise capacity (+23 m,  $P=0.09$ ).<sup>26</sup> The last two trials were not designed to assess the effect of combination therapy with riociguat or tadalafil on clinical worsening.<sup>22,23</sup>

### **Initial upfront combination therapy**

Only two RCTs compared initial upfront combination therapy versus monotherapy in treatment-naïve patients. In the BREATHE-2 trial, upfront combination of epoprostenol and bosentan was associated with a  $-36 \pm 4\%$  decrease of total pulmonary resistance from baseline to week 16, compared with a  $23 \pm 3\%$  decrease in the epoprostenol/placebo group ( $P=0.08$  for the difference between groups).<sup>28</sup> Unfortunately, with a small number of patients ( $n=33$ ), it lacked power to detect significant difference between treatments.<sup>28</sup> More recently, the AMBITION trial<sup>48</sup> has brought new evidence in favor of upfront combination therapy in treatment-naïve patients. In this event-driven, double-blind, placebo-controlled RCT, 500 patients with WHO functional class II–III were randomized into three treatment arms: ambrisentan and tadalafil in upfront combination or monotherapy of ambrisentan or tadalafil combined with placebo. Upfront combination therapy led to a 50% reduction in clinical failure compared with the combined monotherapy arms ( $HR=0.50$ , 95%  $CI=0.35-0.72$ ,  $P<0.001$ ).<sup>48</sup> Importantly, this benefit was not influenced by baseline patients' characteristics, precluding the identification of the small subgroup of patients that has an excellent long-term prognosis on monotherapy. Patients on combination therapy also had better performance on the 6MWD (median increase of 49 m versus 24 m,  $P<0.001$ ) and larger decrease

of NTproBNP ( $-67\%$  versus  $-50\%$ ,  $P<0.001$ ). Although adverse events were more common in the combination therapy group, there was no difference among groups for serious adverse events and treatment discontinuation. More recently, a post-hoc analysis of the AMBITION study evaluating survival at seven days after the termination of each individual patient's randomized treatment suggested a lower mortality in patients initially treated with combination therapy (1% versus 4%,  $HR=0.21$ , 95%  $CI=0.06-0.73$ ,  $P=0.0065$ ).<sup>49</sup> Because of the exploratory nature of this analysis, this hypothesis needs to be confirmed in future studies. Finally, a recent retrospective analysis of real-world data suggested that these effects were similar regardless of the combination regimen used (ambrisentan/bosentan and tadalafil/sildenafil),<sup>50</sup> which also remains to be confirmed.

### **Overall assessment of combination therapy efficacy and safety**

A recent systematic review and meta-analysis evaluated the effects of combination of PAH-specific therapies compared with monotherapy on clinical worsening.<sup>37</sup> A total of 4095 patients from 15 studies, including recent long-term event-driven trials, were assessed. Globally, combination therapy resulted in a 35% reduction of clinical worsening compared with monotherapy. This was mainly driven by reduction in non-fatal endpoints such as PAH-related hospitalization, treatment escalation, and symptomatic progression (Table 2). Combination therapy was also associated with improved functional status in patients. Non-parenteral prostanoids represented the only class of PAH-specific therapies not associated with a reduced risk of clinical worsening (Table 3). Otherwise, the risk of clinical worsening was homogeneously decreased in other predefined subgroups, suggesting that the treatment effect was not driven by study design or patients' characteristics, including PAH type and baseline functional status. Conversely, combination therapy was associated with increased risk of treatment discontinuation, mainly attributed to trials adding non-parenteral prostaglandins and selective prostacyclin receptor agonists. Combination therapy was also associated with a trend for reduced all cause ( $RR=0.86$ , 95%  $CI=0.72-1.03$ ,  $P=0.09$ ) and PAH-related ( $RR=0.77$ , 95%  $CI=0.59-1.01$ ,  $P=0.06$ ) mortality. Importantly, the transition of patients to an open-label phase or to currently approved therapies after censoring may have minimized the risk of subsequent death. Similarly, PAH-related mortality was reported for fewer than 50% of patients contributing to mortality assessment, which may lead to underestimation of the effects of combination therapy on PAH-related mortality. A subsequent meta-analysis also had similar conclusions and confirmed the improvements of pulmonary hemodynamics with combination therapy.<sup>43</sup> Altogether, these results support the rationale of combination therapy in PAH, much like in other debilitating diseases. Although some data might also suggest that combination



**Table 2.** Secondary outcomes of combination therapy vs. monotherapy in PAH.

	Proportion of events (%)			95% CI	P value
	With CT	With MT	Pooled RR		
Secondary outcomes as first event of clinical worsening					
All-cause mortality	3	4	0.92	0.65–1.32	0.65
Admission to hospital (PAH-related)	10	15	0.71	0.60–0.85	0.0002
Lung transplantation	<1	1	0.56	0.12–2.60	0.46
Treatment escalation	1	3	0.38	0.21–0.70	0.002
Symptomatic progression	8	15	0.53	0.43–0.65	<0.00001
All-cause and PAH-related mortality (including those occurring after censoring)					
All-cause mortality (total events)	8	11	0.86	0.72–1.03	0.09
PAH-related mortality	7	9	0.77	0.59–1.01	0.06

Adapted from Lajoie et al.<sup>37</sup>

CI, confidence interval; CT, combination therapy; MT, monotherapy; PAH, pulmonary arterial hypertension; RR, risk ratio.

therapy could be associated with decreased mortality, these findings must be interpreted cautiously in the absence of RCTs designed to specifically address this outcome.

## Unsolved questions

Although a growing body of evidence confirms that combination therapy of PAH-targeted drugs delays progression of disease, there are still many clinically relevant but unsolved questions.

### Upfront versus sequential combination therapy

Sequential combination therapy is the most widely used strategy, both in clinical practice and clinical trials.<sup>18–24,26,27,29,30,44,45,47</sup> It consists of adding a second, or perhaps third, drug to background therapy in order to achieve satisfactory clinical response according to a goal-directed approach. This treatment strategy was found to be effective in improving patients' prognosis in observational studies.<sup>51</sup> Current guidelines<sup>2,52</sup> also recommend that therapy should be increased until patients reach a WHO-FC I or II or a near normalization of resting cardiac index or NT-proBNP plasma levels.<sup>53</sup>

Until recently, the body of evidence supporting upfront combination therapy was scarce. As stated earlier, the recent AMBITION trial convincingly demonstrated that upfront combination therapy with ambrisentan and tadalafil reduced the risk of clinical worsening compared with initial monotherapy.<sup>48</sup> It is noteworthy, however, that the two drugs were initiated at half of their maximum approved doses and then up-titrated to their maximum approved

**Table 3.** Predefined subgroup analyses for the risk of clinical worsening with combination therapy compared with monotherapy.

	Pooled RR (fixed-effects)	95% CI
Class of added PAH-specific therapy		
Non-parenteral prostaglandins	0.72	0.44–1.16
Phosphodiesterase-5 inhibitors	0.44	0.31–0.63
Endothelin receptor antagonists	0.76	0.64–0.90
Soluble guanylate cyclase stimulators	0.11	0.01–1.00
Selective prostacyclin receptor agonist	0.63	0.52–0.76
Trial duration (months)		
>6	0.68	0.60–0.77
≤6	0.48	0.34–0.68
Study design		
Sequential add-on therapy	0.65	0.58–0.72
Initial upfront combination therapy	0.58	0.42–0.80
PAH type		
IPAH	0.68	0.56–0.80
APAH	0.67	0.54–0.82
WHO FC		
I or II	0.64	0.50–0.82
III or IV	0.69	0.61–0.77
Baseline 6MWD		
Less than median	0.83	0.67–1.03
More than median	0.55	0.39–0.78

Adapted from Lajoie et al.<sup>37</sup>

6MWD, six-minute walking distance; APAH, associated pulmonary arterial hypertension; CI, confidence interval; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; RR, risk ratio; WHO, World Health Organization functional class.

doses (tadalafil 40 mg and ambrisentan 10 mg) over a period of eight weeks. Thus, it remains unknown whether upfront combination therapy improves long-term outcomes compared with rapid (e.g. after three to four months) sequential add-on therapy in case of unsatisfactory response to initial monotherapy such as persistence of WHO FC ≥ 3, low exercise capacity, elevated brain natriuretic peptide, and poor hemodynamics (right atrial pressure ≥ 8 mmHg or cardiac index < 2.5 L/min/m<sup>2</sup>), as recommended.<sup>2</sup> As stated above, it is also unclear at this time if these results represent a class effect or are specific to these two agents.

### Choice of combination therapies

In the past, because they were fewer oral formulations, combination therapy most commonly consisted of a combination of an ERA and a PDE5i until parenteral prostaglandins were required. The recent arrival of new orally delivered drugs, such as soluble guanylate cyclase stimulators or selective IP prostacyclin receptor agonists, has increased the choice of combination therapy. Importantly, no information exists on the optimal drug combination. Recently, the concept of network meta-analysis emerged as an alternative way to

indirectly compare PAH-targeted therapies. An extensive network meta-analysis including 31 studies and over 6000 patients treated with current PAH-specific therapies alone or in combination suggested that ERA, PDE5i, riociguat, and a combination of ERA/PDE5i significantly reduced clinical worsening and improved functional capacity.<sup>54</sup> Surprisingly, they concluded that only the ERA/PDE5i combination was associated with reduced hospitalization. Even though they were associated with the most important increase in functional capacity, parenteral prostaglandins were associated with higher adverse events and treatment discontinuation, which is also consistent with findings of standard meta-analyses.<sup>37,43</sup>

It is noteworthy that while these meta-analyses strengthen the benefits of combination therapy on clinical worsening in PAH, they are not meant to assess the best treatment strategy. Indeed, comparisons among treatments would be only indirect and subject to artefacts caused by study designs and duration, patient populations, and other co-variables, and should therefore be interpreted with extreme caution in the absence of head-to-head clinical trials. Moreover, these results are not necessarily generalizable to all molecules within the same class of drugs. Indeed, individual therapies differ in terms of pharmacokinetics, pharmacodynamics, selectivity, and drug–drug interactions, and only approximately half of the theoretically possible dual combinations have been systematically evaluated in RCTs. Therefore, the choice of the initial PAH therapy is dependent on a variety of factors including PAH type, approval status, route of administration, patients' preference, side effect profile, drug–drug interactions, physicians' experience, and disease severity.

### *Dual versus triple combination therapy*

Despite the reduction in clinical worsening with dual combination therapy, many patients still witness events of clinical deterioration or fail to reach established treatment goals. Triple combination therapy therefore seems the logical next therapeutic option, although current evidences supporting sequential or upfront triple combination therapy are scarce. Nowadays, no RCTs were specifically designed to assess the benefits of sequentially adding a third molecule to dual combination therapy in PAH. Nonetheless, the study population of some clinical trials, such as the FREEDOM-C, FREEDOM-C2, and GRIPHON studies, have included 32–45% of patients on background combination therapy.<sup>29,30,44</sup> Interestingly, a prespecified analysis of the GRIPHON study confirmed that triple combination therapy with selexipag still reduced morbidity/mortality events by 37% compared with dual combination therapy of ERA/PDE5i.<sup>44</sup>

Upfront combination triple therapy was evaluated in one retrospective pilot study where 19 patients with newly diagnosed, severe PAH were initiated on upfront triple combination therapy sildenafil, bosentan, and i.v. epoprostenol.<sup>55</sup> After four months, they observed significant improvements in 6MWD and a 67% decrease in PVR. Overall survival

estimates were better than expected survival calculated from the French equation (100% versus 49% at three years, respectively).<sup>55</sup> This offers preliminary evidence that upfront triple combination therapy could be beneficial in patients with severe PAH at presentation. The ongoing TRITON study, a phase 3b trial, will attempt confirming the role of upfront combination therapy by comparing upfront triple therapy of macitentan, tadalafil, and selexipag versus a combination of macitentan and tadalafil plus placebo on PVR (primary endpoint).<sup>56</sup>

### *Cost-effectiveness of combination therapy*

It is well established that the treatment of chronic diseases is a burden on the financial health of a society and great efforts have been made to try reducing the costs related to the treatment of these diseases. Previous studies confirmed that the economic burden of PAH is substantial, with direct healthcare costs per patient per month in the range of \$2576–\$11,875 (excluding indirect cost).<sup>57–59</sup> However, few studies have evaluated the cost-effectiveness of PAH drugs.<sup>60</sup> Cost-effectiveness is frequently assessed by estimating the incremental cost per quality-adjusted life-years (QALYs), with values generally less than US\$50,000 but up to US\$200,000 being considered cost-effective.<sup>61</sup> A recent cost-effectiveness analysis suggested that first-line monotherapy was associated with cost higher than CAN\$140,000 and CAN\$350,000 for PDE5i and ERA, respectively. It is noteworthy, however, that although many clinical trials reported measured quality of life,<sup>9</sup> none have reported the impact of treatment in a format that would allow precise estimation of QALYs. These calculations generally rely on utility estimates based on WHO FC that are derived from a single cohort<sup>62</sup> and few studies evaluated the cost-effectiveness of combination therapy.<sup>63</sup> More importantly, the available economic evaluation studies are likely country-specific and have merely concentrated on certain PAH treatments, and the lack of head-to-head comparison studies covering all comparable medications limit the validity of cost-effectiveness comparisons. Nonetheless, the emergence of novel drug therapies will necessitate the assessment of their cost-effectiveness, especially when it comes to combination therapy. Further studies addressing this issue and weighting against the efficacy, tolerability, availability, and patient preference will thus be needed.

### **Challenges of future clinical trials in PAH**

The tremendous advances in the treatment of PAH over the last few years are indisputable. However, recent meta-analyses confirmed that patients on combination therapy still witness a significant number of clinical worsening events, which is probably an underestimation of the real disease burden since most patients included in PAH trials were prevalent cases with a substantial proportion of WHO FC I–II. In addition to answering unresolved questions, future clinical trials will face numerous challenges.

**Table 4.** Study definitions of clinical worsening in combination therapy trials.

	Death	Admission to hospital	Transplant	AS	Need for new therapy	Symptomatic progression	Centrally adjudicated
COMBI <sup>18</sup>	✓	✓				↗ WHO or ↘ 6MWD (≥20%)	N/A
STEP <sup>19</sup>	✓	✓	✓	✓	✓		N/A
TRIUMPH <sup>20</sup>	✓	✓	✓		✓		N/A
FREEDOM-C <sup>29</sup>	✓	✓	✓	✓	✓	↗ WHO or ↘ 6MWD (≥20%)	N/A
FREEDOM-C2 <sup>30</sup>	✓	✓	✓	✓	✓	↘ 6MWD (≥20%)	N/A
PACES <sup>21</sup>	✓	✓	✓		✓*		N/A
PHIRST <sup>26</sup>	✓	✓	✓	✓	✓	↗ WHO	N/A
Zhuang <sup>23</sup>	✓	✓	✓	✓	✓	↗ WHO	N/A
EARLY <sup>25</sup>	✓	✓				RVF, ↘ 6MWD (≥10% or ≥5% with increases in BDS)	N/A
COMPASS-2 <sup>47</sup>	✓	✓	✓	✓	✓†	Worsening of PGSA or ↘ 6MWD (>20%) + new Tx.	Yes
SERAPHIN <sup>45</sup>	✓		✓	✓	✓†	↘ 6MWD (≥15%) + symptoms worsening + need for Tx	Yes
PATENT-1 <sup>27</sup>	✓	✓	✓	✓	✓	↗ WHO or ↘ 6MWD (≥15%)	N/A
Simonneau <sup>24</sup>	✓	✓	✓			↘ 6MWD (≥15%)	N/A
GRIPHON <sup>44</sup>	✓	✓	✓	✓	✓‡	↘ 6MWD (≥20%), disease progression	Yes
AMBITION <sup>48</sup>	✓	✓	✓			↘ 6MWD (≥15%) or unsatisfactory clinical response	Yes

\*Initiation of bosentan or ↗ in epoprostenol dose (>10%).

†Initiation of parenteral prostaglandin.

‡Initiation of parenteral prostaglandin or LTOT.

6MWD, six-minute walking distance; AS, atrial septation; BDS, Borg dyspnea scale; N/A, not applicable; PGSA, patient global self-assessment scale; RVF, right ventricular failure; WHO, World Health Organization.

Recent meta-analyses have outlined that definition of time to clinical worsening varies widely across studies (Table 4)<sup>37,43</sup> despite recommendations by expert consensus.<sup>41</sup> While mortality, transplantation, and hospitalization are straightforward, the definitions of the most subjective components of clinical worsening, like symptomatic progression and treatment escalation, were largely inconsistent between studies. The AMBITION study also introduced a new concept of unsatisfactory long-term clinical response.<sup>48</sup> This is important since these components accounted for most clinical worsening events in recent trials. Of note, the integrity of a composite endpoint is related to the reliability of each of its components. It is thus mandatory that its more subjective components are robustly defined and adjudicated by a blinded committee to ensure the robustness of the data. Furthermore, future clinical trials will need to take into account patient-reported outcomes such as quality of life and perception of symptoms.

Future clinical trials will also need to address the problem of informative censoring inherent to the time to clinical worsening endpoint. Often in such trials, only the first event of clinical worsening is reported, subsequent events being ignored. As an example, a recent meta-analysis noted that PAH-related mortality was reported for fewer than 50% of patients contributing to the mortality assessment. When all deaths (first event or not) were taken into account, they observed a trend toward mortality reduction.<sup>37</sup> Thus the time to first event might have

underestimated the true impact of therapy on mortality. It is important to keep in mind that the treatment effect for the composite outcome is not necessarily the same as the effects on its individual components. Therefore, future studies should be designed to provide enough power not only to detect a clinically relevant effect for the composite, but also detect an impact on its individual components.

In the attempt to better capture events of clinical worsening, clinical trials also evolved from short-term trials with a fixed length to long-term trials continued until a prespecified number of clinical events occurred. These recent event-driven studies lasted four to six years, patients being exposed to the study drugs on average for approximately two years.<sup>44,45,47,48</sup> However, the treatment effect was evident by 12 months. There are thus certain ethical considerations in maintaining a patient in a study for such lengthy periods. In the context of an orphan disease with limited and competing recruitment for trials and the rapidly changing treatment paradigm in PAH, the optimal duration of future trials should be revisited, balancing study power with the possibility for patients to contribute to subsequent trials and benefit from newer PAH-target therapies and treatment algorithms.

It has also become increasingly difficult for clinical studies to obtain the statistical power required to detect a reduction in clinically relevant endpoints, especially mortality, since there are few events in the populations studied.

Populations currently being studied are most commonly prevalent rather than incident PAH patients, and a significant proportion of them have a relatively preserved FC. In order to improve statistical power in clinical trials, enriching the population of patients enrolled in these studies has been proposed as a possible solution. Previous observational studies and registries<sup>4,11</sup> as well as a recent sub-study of the SERAPHIN trial confirmed that incident PAH patients have an increased rate of clinical worsening despite comparable baseline characteristics.<sup>64</sup> Therefore, enrolling more patient with recent PAH diagnosis would be one way to enrich patient population in PAH clinical trials. Another alternative trial would be to include a greater proportion of patients who are clinically deteriorating since it is known that patients who recently had an event of clinical worsening are at higher risk of mortality.<sup>42</sup> This is a concept largely used in clinical trials in heart failure and idiopathic pulmonary fibrosis.<sup>65,66</sup> These suggestions do not address, however, the real need to move forward to endpoints that reflect disease improvement rather than progression as a relevant and important goal for PAH patients.

Novel clinical trial designs are also increasingly being used in other chronic diseases.<sup>67</sup> The N of one study design systematically evaluates different treatments in the same patient. The patient is thus exposed to a predetermined treatment for a predetermined period of time after which he is exposed either to placebo or another active therapy. This allows a more personalized approach, but makes the results difficult to generalize to an entire population. The factorial design allows testing multiple hypotheses at once and can be conducted as a 2 × 2 confrontation where treatment A and treatment B are matched with placebos and combined in different fashion. However, interaction between drugs must be taken into account when conducting such a trial.

Finally, albeit great effort and promising results have been made to delay disease progression in PAH with combination therapy, it remains an ultimately incurable disease.<sup>37,43</sup> We are entering an exciting era for new therapeutics in the treatment of PAH when novel agents are expected to synergize with currently approved vasodilators to reverse vascular remodeling.<sup>68</sup> Novel potential targets of PAH drug currently under development target vascular inflammation, autoimmunity, metabolic derangements, and aberrant BMPRII signaling.<sup>69,70</sup> These newer trials also face specific challenges. First, these new approaches will need to demonstrate benefit on top of currently available therapies<sup>68,71</sup> a barrier not faced in the original PAH trials. This makes the detection of any putative benefit potentially challenging. Moreover, some new therapies carry novel risks of adverse events not encountered with approved agents, including immunosuppression, epigenetics,<sup>72,73</sup> and metabolism.<sup>74</sup> Finally, the pathway to development for these novel drugs may not be supported by standard industry, requiring convincing-enough rationale to site investigators who are accustomed to getting more attractive compensation for examining already-trusted vasodilation pathways.

## Conclusion

There is a growing body of evidence confirming that dual combination of PAH-targeted therapy significantly delays disease progression in PAH patients. Combination therapy has progressively become the standard of care treatment for a large proportion of patients with advanced PAH. However, patients' quality of life and long-term prognosis remain suboptimal for many of them. Future research is thus mandatory to identifying the best treatment strategy, such as initial upfront versus rapid sequential combination and dual versus triple combination therapy, as well as to investigating treatments beyond the traditional signaling pathways targeted by the currently available PAH therapies.

## Conflict of interest

ACL has no conflict of interest; 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 and has received research grants from Actelion Pharmaceuticals, Bayer and GlaxoSmithKline, and has received speaker fees from Actelion Pharmaceuticals. The Pulmonary Hypertension Research Group is also supported by the "Réseau en Santé Respiratoire" of the FRSQ.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## References

1. Simonneau G, Gatzoulis M, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62(25): D34–D41.
2. Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2015; 46(4): 903–975.
3. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005; 111(23): 3105–3111.
4. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; 115(5): 343–349.
5. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996; 334(5): 296–301.
6. McLaughlin V, Shillington A and Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; 106(12): 1477–1482.
7. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; 40(4): 780–788.
8. Galiè N, Manes A, Negro L, et al. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J* 2009; 30(4): 394–403.
9. Rival G, Lacasse Y, Martin S, et al. Effect of pulmonary arterial hypertension-specific therapies on health-related quality of life: a systematic review. *Chest* 2014; 146(3): 686–708.

10. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; 122(2): 156–163.
11. Humbert M, Sitbon O, Yaïci A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010; 36(3): 549–555.
12. Tedesco MA, Natale F and Calabrò R. Effects of monotherapy and combination therapy on blood pressure control and target organ damage: a randomized prospective intervention study in a large population of hypertensive patients. *J Clin Hypertens* 2006; 8(9): 634–641.
13. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364(1): 11–21.
14. Kaku K, Kiyosue A, Ono Y, et al. Liraglutide is effective and well tolerated in combination with an oral antidiabetic drug in Japanese patients with type 2 diabetes: A randomized, 52-week, open-label, parallel-group trial. *J Diabetes Investig* 2016; 7(1): 76–84.
15. Rosenstock J, Chuck L, González-Ortiz M, et al. Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy for drug-naïve type 2 diabetes. *Diabetes Care* 2016; 39(3): 353–362.
16. Tinahones FJ, Gallwitz B, Nordaby M, et al. Linagliptin as add-on to empagliflozin and metformin in patients with type 2 diabetes: Two 24-week randomized, double-blind, double-dummy, parallel-group trials. *Diabetes Obes Metab* 2017; 19(2): 266–274.
17. Søfteland E, Meier JJ, Vangen B, et al. Empagliflozin as add-on therapy in patients with type 2 diabetes inadequately controlled with linagliptin and metformin: a 24-week randomized, double-blind, parallel-group trial. *Diabetes Care* 2016; 40(2): 201–209.
18. Hoeper M, Leuchte H, Halank M, et al. Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2006; 28(4): 691–694.
19. McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006; 174(11): 1257–1263.
20. McLaughlin V, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol* 2010; 55(18): 1915–1922.
21. Simonneau G, Rubin LJ, Galiè N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008; 149(8): 521–530.
22. Iversen K, Jensen AS, Jensen TV, et al. Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. *Eur Heart J* 2014; 31(2010): 1124–1131.
23. Zhuang Y, Jiang B, Gao H, et al. Randomized study of adding tadalafil to existing ambrisentan in pulmonary arterial hypertension. *Hypertens Res* 2014; 37(6): 507–512.
24. Simonneau G, Torbicki A, Hoeper MM, et al. Selexipag: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2012; 40(4): 874–880.
25. Galiè N, Rubin L, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008; 371(9630): 2093–2100.
26. Barst RJ, Oudiz RJ, Beardsworth A, et al. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension. *J Heart Lung Transplant* 2011; 30(6): 632–643.
27. Ghofrani H-A, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013; 369(4): 330–340.
28. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004; 24(3): 353–359.
29. Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): A randomized controlled trial. *Chest* 2012; 142(6): 1383–1390.
30. Tapson VF, Jing Z-C, Xu K-F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the freedom-c2 study): a randomized controlled trial. *Chest* 2013; 144(3): 952–958.
31. Fox BD, Shimony A and Langleben D. Meta-analysis of monotherapy versus combination therapy for pulmonary arterial hypertension. *Am J Cardiol* 2011; 108(8): 1177–1182.
32. Farber HW, Miller DP, McGoan MD, et al. Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. *J Heart Lung Transplant* 2015; 34(3): 362–368.
33. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000; 161(2 Pt 1): 487–492.
34. Gabler NB, French B, Strom BL, et al. Validation of 6-minute walk distance as a surrogate end point in pulmonary arterial hypertension trials. *Circulation* 2012; 126(3): 349–356.
35. Savarese G, Paolillo S, Costanzo P, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. *J Am Coll Cardiol* 2012; 60(13): 1192–1201.
36. Frost AE, Langleben D, Oudiz R, et al. The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: demonstration of a ceiling effect. *Vascul Pharmacol* 2005; 43(1): 36–39.
37. Lajoie AC, Lauzière G, Lega J-C, et al. Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis. *Lancet Respir Med* 2016; 2600(16): 1–15.
38. Fleming TR and Powers JH. Biomarkers and surrogate endpoints in clinical trials. *Stat Med* 2012; 31(25): 2973–2984.
39. Benza RL, Miller DP, Foreman AJ, et al. Prognostic implications of serial risk score assessments in patients with pulmonary arterial hypertension: A Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) analysis. *J Heart Lung Transplant* 2015; 34(3): 356–361.

40. Lee W-TN, Ling Y, Sheares KK, et al. Predicting survival in pulmonary arterial hypertension in the UK. *Eur Respir J* 2012; 40(3): 604–611.
41. McLaughlin VV, Badesch DB, Delcroix M, et al. End points and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54(1 Suppl. 1): S97–S107.
42. Frost AE, Badesch DB, Miller DP, et al. Evaluation of the predictive value of a clinical worsening definition using 2-year outcomes in patients with pulmonary arterial hypertension: a REVEAL Registry analysis. *Chest* 2013; 144(5): 1521–1529.
43. Fox BD, Shtraichman O, Langleben D, et al. Combination therapy for pulmonary arterial hypertension. a systematic review and meta-analysis. *Can J Cardiol* 2016; 32(12): 1520–1530.
44. Sitbon O, Channick RN, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2015; 373(26): 2522–2533.
45. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; 369(9): 809–818.
46. Sitbon O, Channick R, Delcroix M, et al. Effect of macitentan on haemodynamics in SERAPHIN, a randomised controlled trial in pulmonary arterial hypertension (PAH). *Eur Respir J* 2014; 42(Suppl. 57): P4060.
47. McLaughlin V, Channick RN, Ghofrani H-A, et al. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. *Eur Respir J* 2015; 46(2): 1–9.
48. Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 373(9): 834–844.
49. Hoeper MM, McLaughlin VV, Barberà JA, et al. Initial combination therapy with ambrisentan and tadalafil and mortality in patients with pulmonary arterial hypertension: a secondary analysis of the results from the randomised, controlled AMBITION study. *Lancet Respir Med* 2016; 4(11): 894–901.
50. Sitbon O, Sattler C, Bertoletti L, et al. Initial dual oral combination therapy in pulmonary arterial hypertension. *Eur Respir J* 2016; 47(6): 1727–1736.
51. Hoeper M, Markevych I, Spiekerkoetter E, et al. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J* 2005; 26(5): 858–863.
52. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2009; 30(20): 2493–2537.
53. Nickel N, Golpon H, Greer M, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2012; 39(3): 589–596.
54. Jain S, Khera R, Girotra S, et al. Comparative effectiveness of pharmacological interventions for pulmonary arterial hypertension: a systematic review and network meta-analysis. *Chest* 2016; 151(1): 90–105.
55. Sitbon O, Jaïs X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J* 2014; 43(6): 1691–1697.
56. Actelion. The Efficacy and Safety of Initial Triple Versus Initial Dual Oral Combination Therapy in Patients With Newly Diagnosed Pulmonary Arterial Hypertension (TRITON). *ClinicalTrials.gov*. 2017:NCT02558231.
57. Gu S, Hu H and Dong H. Systematic review of the economic burden of pulmonary arterial hypertension. *Pharmacoeconomics* 2016; 34(6): 533–550.
58. Sikirica M, Iorga SR, Bancroft T, et al. The economic burden of pulmonary arterial hypertension (PAH) in the US on payers and patients. *BMC Health Serv Res* 2014; 14: 676.
59. Said Q, Martin BC, Joish VN, et al. The cost to managed care of managing pulmonary hypertension. *J Med Econ* 2012; 15(3): 500–508.
60. Tran K, Coyle K, Jabr MF, et al. Drugs for pulmonary arterial hypertension: comparative efficacy, safety, and cost-effectiveness. *CADTH Therapeutic Reviews* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27077175> (accessed 15 January 2017).
61. Hirth RA, Chernew ME, Miller E, et al. Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making* 2000; 20(3): 332–342.
62. Keogh AM, McNeil KD, Wlodarczyk J, et al. Quality of life in pulmonary arterial hypertension: improvement and maintenance with bosentan. *J Heart Lung Transplant* 2007; 26(2): 181–187.
63. Garin MC, Clark L, Chumney ECG, et al. Cost-utility of treatments for pulmonary arterial hypertension: a Markov state-transition decision analysis model. *Clin Drug Investig* 2009; 29(10): 635–646.
64. Simonneau G, Channick RN, Delcroix M, et al. Incident and prevalent cohorts with pulmonary arterial hypertension: Insight from SERAPHIN. *Eur Respir J* 2015; 46(6): 1711–1720.
65. King TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370(22): 2083–2092.
66. Richeldi L, Du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370(22): 2071–2082.
67. Ryan JJ, Rich JD and Maron BA. Building the case for novel clinical trials in pulmonary arterial hypertension. *Circ Cardiovasc Qual Outcomes* 2015; 8(1): 114–123.
68. Bonnet S, Provencher S, Guignabert C, et al. Translating research into improved patient care in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2016; 195(5): 583–595.
69. Paulin R, Courboulin A, Barrier M, et al. From oncoproteins/tumor suppressors to microRNAs, the newest therapeutic targets for pulmonary arterial hypertension. *J Mol Med* 2011; 89(11): 1089–1101.
70. Malenfant S, Margailan G, Loehr JE, et al. The emergence of new therapeutic targets in pulmonary arterial hypertension: from now to the near future. *Expert Rev Respir Med* 2013; 7(1): 43–55.
71. Meloche J, Pflieger A, Vaillancourt M, et al. Role for DNA damage signaling in pulmonary arterial hypertension. *Circulation* 2014; 129(7): 786–797.
72. Meloche J, Pflieger A, Vaillancourt M, et al. miRNAs in PAH: biomarker, therapeutic target or both? *Drug Discov Today* 2014; 19(8): 1264–1269.
73. Chun HJ, Bonnet S and Chan SY. Translational advances in the field of pulmonary hypertension. Translating MicroRNA biology in pulmonary hypertension. It will take more than miR words. *Am J Respir Crit Care Med* 2017; 195(2): 167–178.
74. Paulin R and Michelakis ED. The metabolic theory of pulmonary arterial hypertension. *Circ Res* 2014; 115(1): 148–164.