**Lessons from the trials**

# AMBITION: An important piece in the therapeutic puzzle of pulmonary arterial hypertension

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## ABSTRACT

It is believed that simultaneous targeting of two or more of the three pathogenic pathways of pulmonary arterial hypertension (the endothelin, nitric oxide, and prostacyclin pathways) is associated with additive or synergistic effects with subsequent increasing efficacy and improving outcomes. However, there is lack of evidence to guide the use of combination strategy among pulmonary arterial hypertension patients and many questions remain to be answered. One of these vital questions is whether the strategy of upfront initiation of combination therapy could improve patients outcomes compared to the strategy of initial monotherapy. The recently published AMBITION trial represents an important forward step towards answering this question by comparing a strategy of first-line combination therapy (ambrisentan and tadalafil) versus first-line monotherapy (ambrisentan or tadalafil) in patients with pulmonary arterial hypertension.

## BACKGROUND

Combining drugs with different mechanisms of action has been used successfully in several cardiovascular (e.g. congestive heart failure and hypertension) and non-cardiovascular (cancer and HIV) diseases. However, the strategy of combination therapy was introduced relatively late in the field of pulmonary arterial hypertension (PAH) despite the fact that PAH is a highly progressive life-threatening disease in which no single drug has been consistently demonstrated to be effective. Nevertheless, the use of combination strategy among patients with PAH is surrounded by many crucial questions, including when to start the combination therapy? (early de novo versus late); which combination to use and at what dose?; and what target to aim for? In line with this, it is unknown if PAH patients may have significant improvement if they have initial combination therapy (upfront combination therapy), rather than initial monotherapy with the addition of the second therapy only in cases of inadequate clinical response or in cases of deterioration while receiving monotherapy (sequential combination therapy). In this regard, it is important to mention that most previous clinical studies that have investigated combination therapy for PAH have evaluated sequential add-on therapies with only one small randomized controlled trial (BREATHE-2 study) which failed to demonstrate any significant advantage of initial combination of epoprostenol and bosentan compared with epoprostenol alone.[1]

The results of the recently published The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial demonstrated, for the first time, that a strategy of up-front combination therapy (with ambrisentan and tadalafil) resulted in a significantly lower risk of clinical-failure events than with a monotherapy strategy (with either ambrisentan or tadalafil).[2] According to these results, the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension recommended the use of the combination of ambrisentan and tadalafil when initial combination therapy is considered (Class of recommendation I, Level of evidence: B).[3]

## THE AMBITION TRIAL

The AMBITION trial[2] was a multicentre, randomised, double-blind phase 3/4 study designed to compare the efficacy and safety of ambrisentan in combination with tadalafil, versus monotherapy in treatment-naïve patients with WHO functional class II and III PAH. The study randomized 500 PAH patients in 2:1:1 fashion to receive combination therapy (ambrisentan and tadalafil, n = 253); or monotherapy with ambrisentan (n = 126); or monotherapy with tadalafil (n = 121).

The primary efficacy end point was the time to first clinical failure event, defined as time from randomisation to the first occurrence of a composite of (1) all cause mortality; (2) hospitalization for worsening PAH; (3) disease progression; or (4) unsatisfactory long-term clinical response. The trial had five secondary efficacy endpoints, all assessed at six months: changes in N-terminal pro−brain natriuretic peptide level, 6-minute walk distance, WHO functional class, and Borg dyspnea index, as well as percentage of patients with a satisfactory clinical response.

The mean duration of use of randomly-assigned medications from the start of therapy to the final-assessment visit was 517 days (550 days in the combination-therapy group and 484 days in the pooled-monotherapy group, P = 0.03). Results of the study can be summarized as below.

### (1) Profile of patients

The mean age of the patients was 54.4 years, and 78% were women. Most patients had either idiopathic PAH (53%) or PAH due to connective tissue disease (37%): 69% of patients had WHO functional class III symptoms. A total of 95% of patients did not have prior PAH-specific therapy with a short time from diagnosis to first administration of study drug (median time ranged between 20 and 29 days among study groups).

### (2) Primary efficacy endpoints

A primary end-point event occurred in 18% of patients in combination therapy and in 31% of patients in the pooled-monotherapy group (hazard ratio  = 0.50; 95% confidence interval [CI], 0.35 − 0.72; p < 0.001). The combination was also statistically significant versus the individual ambrisentan and tadalafil monotherapy groups for the primary endpoint. Importantly, the difference in the composite primary endpoints was driven mainly by a marked reduction in hospitalization due to PAH - from 12% with monotherapy to 4% with combination therapy (hazard ratio = 0.37; 95 % CI: 0.22 − 0.64;

p < 0.001). In a predefined subgroup analysis, the favorable outcome associated with the combination therapy was consistently observed when patients were subgrouped according to etiology, WHO functional class, age, gender, and geographical area.

### (3) Secondary efficacy endpoints

The combination-therapy group demonstrated significant favorable outcomes in three secondary endpoints in term of: (1) greater reductions in N-terminal pro-brain natriuretic peptide level (− 67.2% vs. − 50.4%; p < 0.001); (2) greater improvements in the 6-minute walk distance (48.98 m vs. 23.80 m; p < 0.001); and (3) higher percentage of patients with a satisfactory clinical response (39% vs. 29%; odds ratio, 1.56; 95% CI: 1.05 − 2.32; p = 0.03). There was no difference between study groups in the change for WHO functional class or Borg-dyspnea index.

### (4) Safety data

There were no statistically significant differences in adverse events between study groups. Specifically, rates of hypotension and discontinuation of a study drug were similar. However, patients in combination therapy group had higher rates of peripheral edema (45 % versus 30%), headache (42% vs. 34%), nasal congestion (21% versus 14%), and anemia (15% versus 9%) than patients in the pooled-monotherapy group.

### WHAT HAVE WE LEARNED?

The AMBITION trial filled a true gap in our knowledge about the use of combination therapy in patients with PAH. The main message of the trial is that in treatment-naïve patients with WHO functional class II and III PAH, the combination of ambrisentan and tadalafil should be the first line therapeutic strategy. Based upon the study data, this combination reduced the risk of clinical failure by 50% when compared to the use of these drugs as monotherapies. According to the study results, this combination has become the only one to receive class I recommendation by the 2015 ESC/ERS Guidelines when initial combination therapy is considered in PAH patients.[3] There are many lessons to be learned from the AMBITION trial and still several questions to be answered.

### THE AMBRISENTAN-TADALAFIL COMBINATION: A DRUG OR CLASS EFFECT?

A vital question is whether the favorable results of ambrisentan- tadalafil combination stem from a class or drug effect (i.e. can the favorable results seen with ambrisentan- tadalafil combination extend to different endothelin-1 (ET-1) receptor antagonists and phosphodiesterase type 5 (PDE5-I) inhibitors combinations? In the absence of "head-to-head" comparisons between different combinations, ambrisentan and tadalafil combination, in our opinion, should be the standard recommended combination for the following reasons:

First, It is hypothesized that selective $ET_A$ receptor antagonist (ambrisentan) but not nonselective $ET_A$ and $ET_B$ receptor antagonists (bosentan and macitentan) would act synergistically with a PDE5-I. Normally, $ET_A$ receptors mediate vasoconstriction and remodeling, whereas the $ET_B$ receptors mediate clearance of ET-1 and the release of nitric oxide (NO).[4−5] Accordingly, blockage of $ET_A$ receptors with ambrisentan would not interfere with the $ET_B$ receptors mediated NO release with subsequent cGMP-mediated vasodilatation.[6] Consequently, the combination of ambrisentan and tadalafil (which acts to prevent or slow the degradation of cGMP) would enable a synergistic vasorelaxant effect. On the other hand, blockage of $ET_A$ and $ET_B$ receptors with nonselective antagonists would prevent the formation of NO mediated via $ET_B$ receptors with subsequent lack of this synergistic effect (Figure 1). In a study of ET-1-stimulated constriction of rat intrapulmonary arterial rings, ambrisentan and tadalafil synergistically inhibited ET-1-induced constriction whereas this synergism was not seen when tadalafil was combined with bosentan or macitentan.[7] In this study it appeared that $ET_B$ receptors are necessary to enable a synergistic vasorelaxant effect of the drug combination.[7]

Second, the ambrisentan-tadalafil combination does not appear to have significant drug-drug interaction.[8] Tadalafil is metabolized by CYP3A4 isoenzyme and since ambrisentan has no influence on CYP3A4 (ambrisentan itself is a substrate of CYP3A4 and CYP2C9), both drugs appear to be appropriate for the use as combination therapy. For the same reason, the combination of tadalafil and bosentan
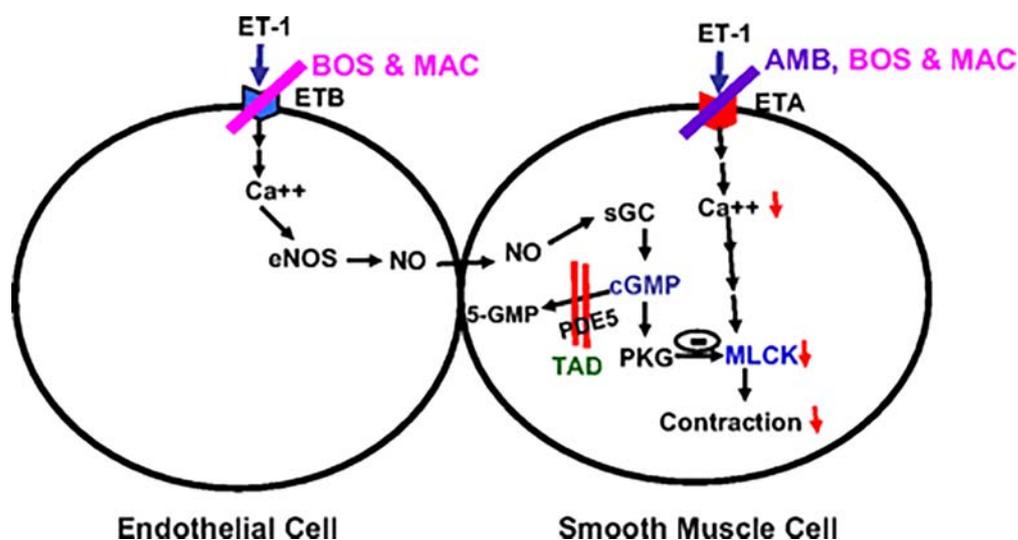
**Figure 1. Mechanism of the synergistic action of ambrisentan and tadalafil.** Ambrisentan does not interfere with $ET_A$-mediated NO release with subsequent formation of second messenger cGMP, which produces (through a number of downstream mechanisms) vasorelaxation. Since tadalafil interferes with the degradation of cGMP, combining ambrisentan with tadalafil is associated with a synergistic vasorelaxant effect. This vasodilatory synergism is not seen when tadalafil is combined with nonselective $ET_B$ and $ET_A$ blockers (bosentan or macitentan). Double bars indicate block by drug of a target receptor or enzyme. Red down arrows indicate effects of ET-1 receptor antagonists. Circle with horizontal line indicates inhibition. AMB: ambrisentan; BOS: bosentan; ET-1: endothelin-1; NO: nitric oxide; TAD: tadalail. *Source:* Liang F, Yang S, Yao L, et al. Ambrisentan and tadalafil synergistically relax endothelin-induced contraction of rat pulmonary arteries. Hypertension 2012; 59: 705–711.

(an inducer of cytochrome CYP3A4 isoenzymes) may not be favorable. Similarly, bosentan can reduce circulating levels of sildenafil (a CYP3A4 substrate).[9] Conversely, as a CYP3A4 inhibitor, sildenafil can increase the systemic level of bosentan. This drug-drug interaction may be one of the reasons for the negative results of the COMPASS-2 trial that examined the value of bosentan as an add-on combination therapy in patients already treated with sildenafil.[10]

Third, ambrisentan and tadalafil are both orally administered once a day, enhancing compliance and patient convenience - bearing in mind the polypharmacy of medications that PAH patients often take. On the contrary, the three-daily doses of sildenafil and the two-daily doses of bosentan may interfere with compliance.

### CHALLENGES IN DIFFERENTIATING PAH AND PH DUE TO LEFT HEART DISEASE

Distinction between patients with PAH and patients with PH due to left heart disease (LHD) is critical, because the safety and efficacy of PAH-specific drugs are unclear in patients with PH due to LHD. Although pulmonary capillary wedge pressure (PCWP) has been used to distinguish PAH patients (PCWP ≤ 15 mm) and patients with PH due to LHD (PCWP > 15 mm),[3,11] this is not a black and white differentiating tool: PCWP measurements can show significant variability related to altered volume status, diuresis, or measurement technique. In addition, data suggest that PCWP does not always correlate closely with LV end-diastolic pressure.[12] To complicate matter even further, a subset of patients with PH due to LHD have combined precapillary and postcapillary PH; this group of patients are characterized by having pulmonary vascular resistance (PVR) > 3 Wood units and/or diastolic pulmonary gradient ≥ 5 mmHg.[3]

The AMBITION trial encountered this challenge during the trial process where review of demographic data for patients enrolled during the first 6 months of the study showed a high prevalence of risk factors for LHD (e.g. old age, coronary artery disease, diabetes, hypertension) compared to previous PAH trials. To limit the potential inclusion of patients with PH due to LHD, the AMBITION trial implemented an amendment with the following stringent haemodynamic and clinical criteria:

1. In addition to mean pulmonary arterial pressure ≥ 25 mmHg, patients should have PVR ≥ 3.75 Wood units, and PCWP of 12 mmHg (if PVR ≥ 3.75 to < 6.25 Wood units), or PCWP ≤ 15 mmHg (if PVR ≥ 6.25 Wood units).

2. Patients must not have 3 or more of the following risk factors: body mass index $\geq$ 30; hypertension; diabetes mellitus; significant coronary disease

The main lesson here is that it is critical to consider the patient's phenotype (rather than depending solely on hemodynamic numbers) in the diagnosis of PH due to LHD; these patients are often older, female, with a higher prevalence of hypertension, diabetes mellitus, obesity, coronary artery disease, and metabolic syndrome.

### NEW ENDPOINTS TO ASSESS SATISFACTORY CLINICAL RESPONSE

The 2009 ESC/ERS guidelines recommended a target based treatment approach whereby patient status is divided into three categories: stable and satisfactory; stable and not satisfactory; unstable and deteriorating. The aim of treatment being to move all patients to the stable and satisfactory category.[13] In accordance with this, the AMBITION trial introduced two new endpoints to assess satisfactory clinical response:

1. Unsatisfactory long-term clinical response (a component of the composite primary endpoint). This endpoint requires all the following criteria to be fulfilled: (a) a decrease from baseline in 6-minute walk distance at 2 consecutive post-baseline clinic visits separated by $\geq$ 2 weeks and (b) sustained WHO class III or IV symptoms for $\geq$ 6 months and (c) receiving study treatment for at least 6 months.
2. Percentage of subjects with satisfactory clinical response measured at 6 months. This secondary endpoint was defined as: 10% improvement in 6-minute walk distance compared to baseline with improvement or maintenance of WHO class I or II symptoms without worsening clinical event.

These new endpoints are expected to implement a strategy in which physicians should not wait for a patient to experience a significant deterioration before the consideration of different treatment; rather physicians should intervene prior to this deterioration.

### UNCERTAINTIES REGARDING LONG-TERM EFFECTS

It is unknown whether the favorable effect of ambrisentan-tadalafil combination therapy could be maintained over a longer period. In the AMBITION trial, analysis of Kaplan–Meier curves for the probability of a first primary end-point event showed a tendency to converge after 144 weeks (Figure 2).
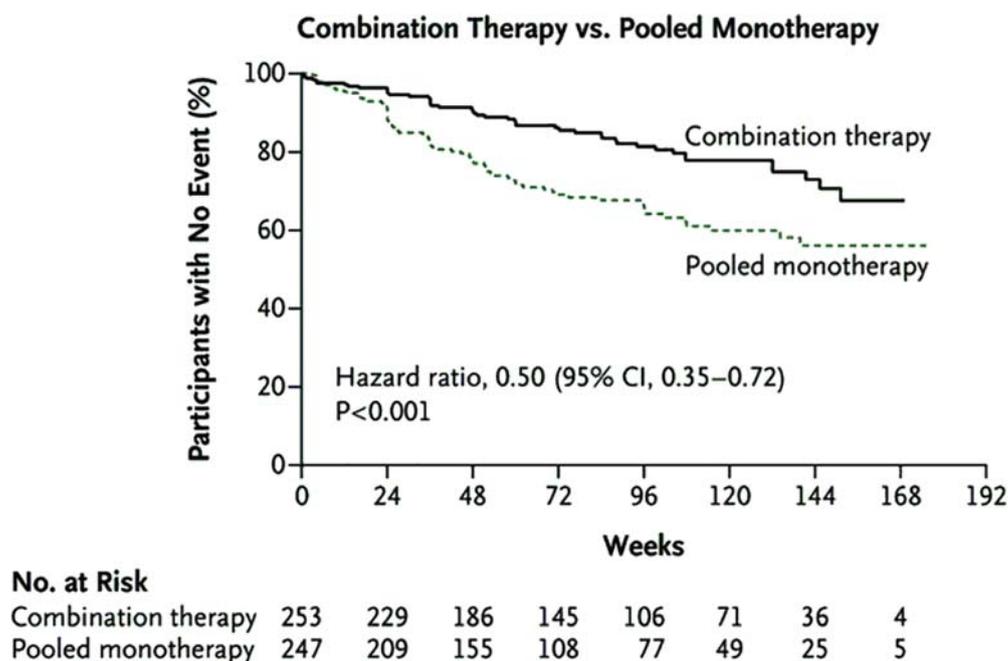


**Figure 2. Kaplan–Meier curve for the probability of a first primary end-point event in AMBITION trial.** There is a tendency of 2 curves to converge after 144 weeks. *Source:* Galiè N, Barbera JA, Frost A, et al. Initial use of Ambrisentan plus Tadalafil in pulmonary arterial hypertension. New Engl J Med 2015; 379(9):834–844.

This convergence may be of concern since it may denote a waning beneficial effect of initial combination therapy. This is important since the difference in the composite primary endpoints was driven mainly by a marked reduction in hospitalization *due to PAH*. With the progressive nature of PAH, rates of hospitalization due to PAH over a longer follow-up period is expected to increase significantly with attrition of the initial favorable effect of the combination therapy. Actually, rates of hospitalization due to *any cause* during the study period itself were high (37% in combination group; 43% in pooled monotherapy group) with no significant difference between the groups.

## UNANSWERED QUESTIONS

The AMBITION trial has answered vital questions, but a number of additional questions remain unanswered.

1. What is the cost effectiveness of initial combination therapy? Does the reduced rate of hospitalization due to PAH (which is costly and is associated with poor prognosis)[14–16] offset the cost of long-term use of combination therapy?
2. What is the effect of initial combination therapy on right ventricular remodeling and adaptation? This is important since changes in right ventricular structure and function are closely related to disease progression and long-term prognosis.[17]
3. How to compare the strategy of upfront fixed-combination therapy to the strategy of rapid sequential add-on therapy that utilizes a goal-oriented algorithm?
4. How to manage patients on upfront combination therapy who do not show satisfactory clinical response to the initial fixed combination? There are several options (dose up-titration; switch to other drug combination; or add a third drug) without evident superiority of one strategy over its competitors.

Addressing these and many other questions is expected to pave the way for better use of combination therapy among patients with PAH.

## REFERENCES

[1] Humbert M, Barst RJ, Robbins IM, Channick EM, 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.
[2] Galiè N, Barbera JA, Frost A, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grünig E, Oudiz RJ, Vonk-Noordegraaf A, White RJ, Blair C, Gillies H, Miller KL, Harris JH, Langley J, Rubin LJ, AMBITION Investigators. Initial use of Ambrisentan plus Tadalafil in pulmonary arterial hypertension. *New Engl J Med*. 2015;379(9):834–844.
[3] Galiè N, Humbert M, Vachieryc JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Angel M, Sanchez G, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT) European Heart Journal Aug 2015, DOI: 10.1093/eurheartj/ehv317.
[4] Fukuroda T, Fujikawa T, Ozaki S, Ishikawa K, Yano M, Nishikibe M. Clearance of circulating endothelin-1 by ETB receptors in rats. *Biochem Biophys Res Commun*. 1994;199:1461–1465.
[5] Hirata Y, Emori T, Eguchi S, Kanno K, Imai T, Ohta K, Marumo F. Endothelin receptor subtype B mediates synthesis of nitric oxide by cultured bovine endothelial cells. *J Clin Invest*. 1993;91:1367–1373.
[6] Girgis RE, Champion HC, Diette GB, Johns RA, Permutt S, Sylvester JT. Decreased exhaled nitric oxide in pulmonary arterial hypertension: response to bosentan therapy. *Am J Respir Crit Care Med*. 2005;172:352–357.
[7] Liang F, Yang S, Yao L, Belardinelli L, Shryock J. Ambrisentan and tadalafil synergistically relax endothelin-induced contraction of rat pulmonary arteries. *Hypertension*. 2012;59:705–711.
[8] Spence R1, Mandagere A, Harrison B, Dufton C, Boinpally R. No clinically relevant pharmacokinetic and safety interactions of ambrisentan in combination with tadalafil in healthy volunteers. *J Pharm Sci*. 2009;98(12):4962–4974.
[9] Paul GA, Gibbs JS, Boobis AR, Abbas A, Wilkins MR. Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension. *Br J Clin Pharmacol*. 2005;60:107–112.
[10] McLaughlin V, Channick RN, Ghofrani HA, Lemarié JC, Naeije R, Packer M, Souza R, Tapson VF, Tolson J, Al Hiti H, Meyer G, Hoeper MM. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. *Eur Respir J*. 2015;46:405–413.
[11] Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F, Wilkins MR, Badesch DB. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(Suppl):D42–D50.
[12] Halpern SD, Taichman DB. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. *Chest*. 2009;136:37–43.
[13] Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G. Guidelines for the

diagnosis and treatment of pulmonary hypertension. The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2009;30(20):2493–2537.

[14] Campo A, Mathai SC, Le Pavec J, Zaiman AL, Hummers LK, Boyce D, Housten T, Lechtzin N, Chami H, Girgis RE, Hassoun PM. Outcomes of hospitalisation for right heart failure in pulmonary arterial hypertension. *Eur Respir J.* 2011;38:359–367.

[15] Haddad F, Peterson T, Fuh E, Kudelko KT, de Jesus Perez V, Skhiri M, Vagelos R, Schnittger I, Denault AY, Rosenthal DN, Doyle RL, Zamanian RT. Characteristics and outcome after hospitalization for acute right heart failure in patients with pulmonary arterial hypertension. *Circ Heart Fail.* 2011;4:692–699.

[16] Sztrymf B, Souza R, Bertoletti L, Jaïs X, Sitbon O, Price LC, Simonneau G, Humbert M. Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. *Eur Respir J.* 2010;35:1286–1293.

[17] Sachdev A, Villarraga HR, Frantz RP, McGoon MD, Hsiao JF, Maalouf JF, Ammash NM, McCully RB, Miller FA, Pellikka PA, Oh JK, Kane GC. Right ventricular strain for prediction of survival in pulmonary arterial hypertension. *Chest.* 2011;139:1299–1309.