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Updated Treatment Algorithm of Pulmonary Arterial Hypertension

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The demands on a pulmonary arterial hypertension (PAH) treatment algorithm are multiple and in some ways conflicting. The treatment algorithm usually includes different types of recommendations with varying degrees of scientific evidence. In addition, the algorithm is required to be comprehensive but not too complex, informative yet simple and straightforward. The type of information in the treatment algorithm are heterogeneous including clinical, hemodynamic, medical, interventional, pharmacological and regulatory recommendations. Stakeholders (or users) including physicians from various specialties and with variable expertise in PAH, nurses, patients and patients' associations, healthcare providers, regulatory agencies and industry are often interested in the PAH treatment algorithm for different reasons. These are the considerable challenges faced when proposing appropriate updates to the current evidence-based treatment algorithm.The current treatment algorithm may be divided into 3 main areas: 1) general measures, supportive therapy, referral strategy, acute vasoreactivity testing and chronic treatment with calcium channel blockers; 2) initial therapy with approved PAH drugs; and 3) clinical response to the initial therapy, combination therapy, balloon atrial septostomy, and lung transplantation. All three sections will be revisited highlighting information newly available in the past 5 years and proposing updates where appropriate. The European Society of Cardiology grades of recommendation and levels of evidence will be adopted to rank the proposed treatments. (J Am Coll Cardiol 2013;62:D60–72) © 2013 by the American College of Cardiology Foundation

The complexity of the treatment algorithm for pulmonary arterial hypertension (PAH) has progressively increased since the 2nd World Symposium on Pulmonary Hypertension (WSPH) in Evian, France in 1998 when, apart from calcium channel blockers (CCBs) for vasoreactive patients, the only approved therapy was epoprostenol administered by continuous intravenous infusion (1). Five years later at the 3rd WSPH held in Venice, Italy, in 2003, the treatment algorithm had expanded

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to 5 compounds belonging to 3 pharmacological classes, prostanoids, endothelin receptor antagonists (ERA), and phosphodiesterase type 5 inhibitors (PDE-5i), and included 4 different routes of administration (oral, inhaled, subcutaneous, and intravenous) (2). In 2008 the 4th WSPH was held in Dana Point, California, and the treatment algorithm included 4 additional compounds (1 of them, the ERA sitaxentan, was eventually withdrawn) (3,4). Although this progress in pharmacotherapy has been associated in different meta-analyses with a reduction of morbidity and mortality (5,6), limiting symptoms and poor outcome still characterize patients with PAH. Further advances observed in different areas of PAH treatment in the past 5 years and the evolution of the treatment algorithm discussed and updated at the 5th WSPH held in Nice, France, from February 27 to March 1, 2013, will be presented here.

The current treatment algorithm may be divided into 3 main areas: 1) general measures (rehabilitation/exercise and exercise training, psychosocial support, pregnancy, vaccinations), supportive therapy (anticoagulants, diuretics, digitalis, oxygen), the roles of referral centers, acute vasoreactivity testing, and chronic CCB therapy; 2) information about the initial therapy and includes all drugs approved in any country according to the World Health Organization functional class (WHO-FC) of the patients and the grade of recommendation and level of evidence of each individual compound; and 3) the clinical response to the initial therapy and in case of inadequate results, the recommendations/role of combinations of approved drugs and additional interventional procedures such as balloon atrial septostomy and lung transplantation.

All 3 sections will be revisited, highlighting the new information collected in the past 5 years and proposing updates where appropriate.

The European Society of Cardiology grades of recommendation and levels of evidence will be adopted to score the proposed treatments (Tables 1 and 2) (4).

The new proposed treatment algorithm is shown in Figure 1.

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General Measures, Supportive Therapy, Referral Centers, and Vasoreactivity Test

General measures. In this section new information is provided for pregnancy, rehabilitation, and exercise training.

Abbreviations and Acronyms

APAH = associated pulmonary arterial hypertension

BAS = balloon atrial septostomy

CCB = calcium channel blocker

ERA = endothelin receptor antagonist

PAH = pulmonary arterial hypertension

PVR = pulmonary vascular resistance

RCT = randomized controlled trials

6MWD = 6-min walk distance

WHO-FC = World Health Organization Functional Class

PREGNANCY. Pregnancy remains associated with a substantial mortality rate in PAH. However, a recent report indicates that the outcome of pregnancies in PAH has improved, at least when PAH is well controlled and particularly in long-term responders to CCBs (7). During a 3-year period, the 13 participating centers reported 26 pregnancies. Three women (12%) died and 1 (4%) developed right heart failure requiring urgent heart-lung transplantation. There were 8 abortions: 2 spontaneous and 6 induced. Sixteen pregnancies (62%) were successful (i.e., the women delivered healthy babies without complications). These data must be confirmed by larger series before the general recommendation to avoid pregnancy in all patients with PAH is reconsidered (grade of recommendation I, Level of Evidence: C).

REHABILITATION AND EXERCISE TRAINING. The 2009 pulmonary hypertension (PH) guidelines suggested that PAH patients should be encouraged to be active within symptom limits (4). It was recommended that patients should avoid excessive physical activity that leads to distressing symptoms, but when physically deconditioned may undertake supervised exercise rehabilitation. This was based on a randomized controlled trial (RCT) that demonstrated an improvement in exercise and functional capacity and in quality of life in patients with PH who took part in a training program as compared with a control untrained group (8). Since then, additional uncontrolled experiences have supported these data utilizing different models of exercise training (9–13). Two additional RCTs have also been published reports that trained PAH patients reached higher levels of physical activity, had decreased fatigue severity, showed improved 6-min walk distance (6MWD), cardiorespiratory function, and patient-reported quality of life as compared with untrained controls (14,15). The sample size of all these studies is quite small (ranging from 19 to 183 patients), and all or initial training was highly supervised and in some instances conducted in an in-patient setting. Despite these limitations, however, the concordance of the results and the overall publication of 3 RCTs suggest the upgrading of the recommendation for rehabilitation and exercise training to Class I with a Level of Evidence: A.

The limitations of this recommendation are based on the gaps in knowledge of the optimal method, intensity, and

JACC Vol. 62, No. 25, Suppl D, 2013
December 24, 2013:D60–72

Table 1 Classes of Recommendations

Class of Recommendations	Definition	Suggested Wording to Use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended, Is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/ effective, and in some cases may be harmful.	Is not recommended

duration of the training. In addition, neither the characteristics of the supervision and the mechanisms for the improvement of symptoms, exercise, and functional capacity nor the possible effects on prognosis are clear. Exercise training programs should be implemented by centers experienced in both PAH patient care and rehabilitation of compromised patients.

Supportive therapy. No major new information is available on anticoagulants, diuretics, digitalis, and oxygen, and no changes in the recommendations are proposed (4). Long-term oxygen therapy is suggested to maintain arterial blood O_2 pressure $\geq$8 kPa (60 mm Hg).

Referral centers and vasoreactivity testing. PAH is a rare chronic progressive condition that is lethal, disabling, costly, and treatable. High-volume specialized centers have been recurrently shown to obtain the best outcomes for patients in different areas of medicine while maintaining greatest patient satisfaction, lowest complication rates, shortest length of hospital stay and best value for healthcare payers (16). Suggestions on possible models of emergency treatments (17) and a survey on PAH care organization in developed countries have been published (18). The recommendation to refer patients after PAH diagnosis to expert centers is maintained.

Acute vasoreactivity testing remains mandatory in patients with idiopathic PAH to identify subjects that will respond favorably to long-term treatment with high doses of calcium-channel blockers. Inhaled nitric oxide (iNO) is the compound of choice for the acute test and, on the basis of previous experience, intravenous epoprostenol or adenosine may also be used as an alternative (but with a risk of systemic vasodilator effects) (4). More recently, inhaled iloprost has been able to identify patients who may benefit from long-term therapy with CCBs (19).

Initial Therapy With PAH-Approved Drugs

Therapy with PAH-approved drugs needs to be initiated in PAH patients who are not vasoreactive or are vasoreactive but not responding appropriately to CCBs (Fig. 1). For the initial therapy, drugs are classified according to the grade of recommendation (Table 1) and the level of evidence (Table 2) on the basis of published RCTs. In addition, initial drug therapies are also stratified according to WHO-FC.

Individual compounds. A summary of the RCTs performed in PAH for each compound is shown in Tables 3–6 on the basis of the related pathobiological pathway. The table also includes nonapproved drugs for PAH or drugs still under regulatory consideration at the time of this publication. Pharmacological classes and drugs are listed in alphabetical order. Only compounds approved for PAH or under regulatory approval process are included in the treatment algorithm and are listed in alphabetical order (Fig. 1).

A brief description of the compounds, according to their pharmacological class, is provided subsequently.

Endothelin pathway. Activation of the endothelin system has been demonstrated in the plasma and lung tissue of PAH patients (20). Although it is not clear if the increases in endothelin plasma levels are a cause or a consequence of PH (21), these data support a prominent role for the endothelin system in the pathogenesis of PAH (22).

Endothelin receptor antagonists. Endothelin exerts vasoconstrictor and mitogenic effects by binding to 2 distinct receptor isoforms in the pulmonary vascular smooth muscle cells, endothelin-A and -B receptors. Endothelin-B receptors are also present in endothelial cells, and their activation leads to release of vasodilators and antiproliferative substances such as NO and prostacyclin that may counterbalance the deleterious effects of endothelin-1. Despite potential differences in receptor isoform activity, the efficacy in PAH of the dual endothelin-A and -B receptor antagonist drugs and of the selective endothelin-A receptor antagonist compounds appear to be comparable.

AMBRISENTAN. Ambrisentan is a nonsulfonamide, propanoic acid class, ERA that is selective for the endothelin-A receptor. Ambrisentan has been evaluated in a pilot study (23) and

Table 2 Levels of Evidence

Level	Definition
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized clinical trial or large nonrandomized studies
C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Results on the basis of post-hoc and subgroup analyses of clinical trials most often do not meet the criteria of a level of evidence A.

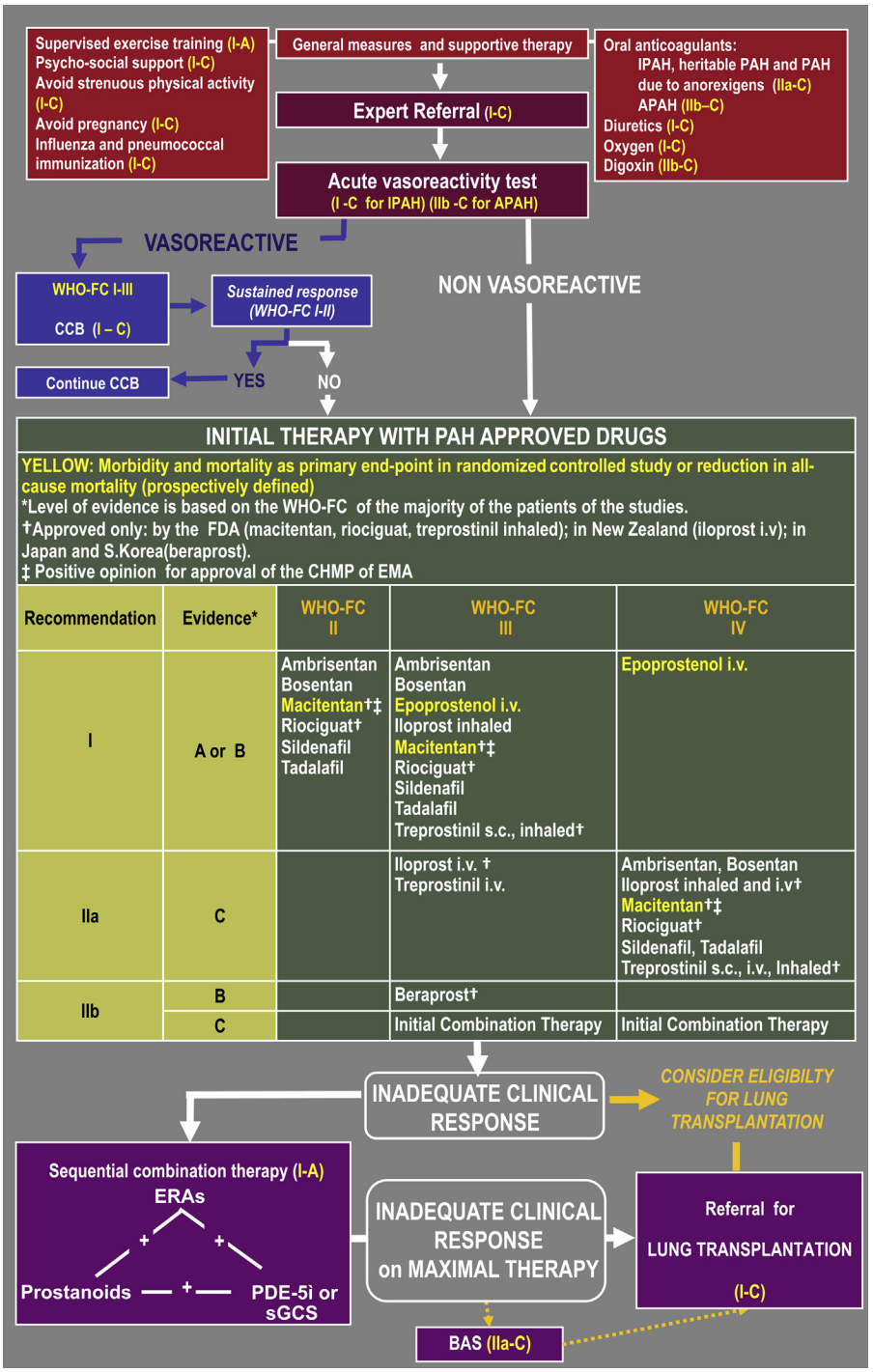

Figure 1 Evidence-Based Treatment Algorithm

APAH = associated pulmonary arterial hypertension; BAS = balloon atrial septostomy; CCB = calcium channel blockers; ERA = endothelin receptor antagonist; sGCS = soluble guanylate cyclase stimulators; IPAH = idiopathic pulmonary arterial hypertension; i.v. = intravenous; PDE-5i = phosphodiesterase type-5 inhibitor; s.c. = subcutaneous; WHO-FC = World Health Organization functional class.

in 2 large RCTs (ARIES [Ambrisentan in pulmonary arterial hypertension, Randomized, double-blind, placebo-controlled, multicentre, Efficacy Study]-1 and -2), which have demonstrated efficacy on symptoms, exercise capacity, hemodynamics, and time to clinical worsening of patients with idiopathic PAH and PAH associated with connective tissue disease and human immunodeficiency virus infection (24). Ambrisentan has been approved for the treatment of

JACC Vol. 62, No. 25, Suppl D, 2013
December 24, 2013:D60–72

Table 3 Characteristics of Randomized Controlled Trials With Pulmonary Arterial Hypertension Drugs Interfering With the Endothelin Pathway (See Text for References)

Drug(s) Tested	Study	Background	Primary Endpoint	Outcome (Secondary Endpoint)	Duration (weeks)	No. of Patients
Ambrisentan	ARIES-1	No	6MWD	TTCW (NS)	12	202
	ARIES-2	No	6MWD	TTCW	12	192
Bosentan	Study-351	No	6MWD	TTCW	12	32
	BREATHE-1	No	6MWD	TTCW	16	213
	BREATHE-2*	No	PVR	—	12	33
	EARLY	No Sildenafil (16%)	PVR, 6MWD	TTCW	24	185
	BREATHE-5	No	SaO_2, PVR	—	12	54
Macitentan†	SERAPHIN	No, PDE5i or Inhal iloprost	TTCW	Safety	100	742

*Bosentan + epoprostenol versus placebo + epoprostenol. †Approved by the FDA for PAH patients and has obtained at the time of printing the positive opinion of the Committee for Medicinal Products for Human Use of the the EMA for this indication.

6MWD = 6-min walk distance; inhal = inhalation; NS = not statistically significant; PDE5i = phosphodiesterase type-5 inhibitors; PVR = pulmonary vascular resistance; SaO_2 = finger oxygen saturation; TTCW = time to clinical worsening.

WHO-FC II and III patients. The incidence of abnormal liver function tests range from 0.8% to 3%. No tendency for development of abnormal liver function tests was observed in patients who had previously demonstrated abnormalities while on other ERA, and monthly liver function assessment is not mandated in the United States (25). An increased incidence of peripheral edema has been reported with ambrisentan use. Ambrisentan is approved for PAH patients.

BOSENTAN. Bosentan is an oral active dual endothelin-A and -B receptor antagonist and the first molecule of its class to be synthesized. Bosentan has been evaluated in PAH (idiopathic, associated with connective tissue disease and Eisenmenger's syndrome) in 5 RCTs (Study-351, BREATHE [Bosentan Randomised trial of Endothelin Antagonist THErapy]-1, BREATHE-2, BREATHE-5, and EARLY [Endothelin Antagonist tRial in mildLY symptomatic pulmonary arterial hypertension patients]), which showed improvement in exercise capacity, functional class, hemodynamics, echocardiographic and Doppler variables, and time to clinical worsening (26–30). Increases in hepatic aminotransferases occurred in approximately 10% of the subjects but were found to be dose-dependent and reversible after dose reduction or discontinuation. For these reasons, liver function testing should be performed monthly in patients receiving bosentan. Bosentan is approved for PAH patients.

MACITENTAN. The dual ERA macitentan was developed by modifying the structure of bosentan to increase efficacy and safety. Macitentan is characterized by sustained receptor binding and enhanced tissue penetration. In the event-driven SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome) study (31), 742 PAH patients were treated with 3 or 10 mg macitentan as compared with placebo for an average of 100 weeks. The primary endpoint was the time from the initiation of treatment to the first occurrence of a composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of PAH. Macitentan significantly reduced this composite endpoint of morbidity and mortality among patients with PAH and also increased exercise capacity. Benefits were shown both for patients who had not received treatment previously and for those receiving background therapy for PAH. While no liver toxicity was shown, reduction in blood hemoglobin $\leq$8 g/dl was observed in 4.3% of patients receiving 10 mg of macitentan. Macitentan is approved by the U.S. Food and Drug Administration (FDA) for PAH patients and has obtained at the time of printing the positive opinion of the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) for this indication.

Table 4 Characteristics of Randomized Controlled Trials With Pulmonary Arterial Hypertension Drugs Interfering With the Nitric Oxide Pathway (See Text for References)

Drug(s) Tested	Study	Background	Primary Endpoint	Outcome (Secondary Endpoint)	Duration (weeks)	No. of Patients
Soluble Guanylate Cyclase Stimulators						
Riociguat*	PATENT	No bosentan or prostanoids	6MWD	TTCW	12	443
Phosphodiesterase Type-5 Inhibitors						
Sildenafil	SUPER-1	No	6MWD	TTCW (NS)	12	277
	Sastry	No	TT	—	12	22
	Singh	No	6MWD	—	6	20
	PACES	Epoprostenol	6MWD	TTCW	16	264
	Iversen	Bosentan	6MWD	—	12	20
Tadalafil	PHIRST	No or bosentan (54%)	6MWD	TTCW	16	405
Vardenafil†	EVALUATION	No	6MWD	TTCW	12	66

*Approved by the FDA for PAH and CTEPH patients and is currently undergoing the regulatory approval process by the EMA for both indications. †Not approved for pulmonary arterial hypertension.

TT = treadmill test; other abbreviations as in Table 3.

Table 5 Characteristics of Randomized Controlled Trials With Pulmonary Arterial Hypertension Drugs Interfering With the Platelet-Derived Growth Factor Pathway (See Text for References)

Drug(s) Tested	Study	Background	Primary Endpoint	Outcome (Secondary Endpoint)	Duration (weeks)	No. of Patients
Tyrosine kinase inhibitor imatinib*	Phase 2	Bosentan and/or sildenafil and/or prostanoids	6MWD (NS)	—	24	59
	IMPRES	Bosentan and/or sildenafil and/or prostanoids	6MWD	TTCW (NS)	24	202

*Not approved for pulmonary arterial hypertension.
Abbreviations as in Table 3.

Nitric oxide pathway. Impairment of NO synthesis and signaling through the NO–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) pathway is involved in the pathogenesis of pulmonary hypertension.

Soluble guanylate cyclase stimulators. While PDE-5is, such as sildenafil, tadalafil, and vardenafil, enhance the NO–cGMP pathway, slowing cGMP degradation, sGC stimulators enhance cGMP production and are potentially effective also in conditions in which endogenous NO is depleted (32). Pre-clinical studies with sGC stimulators have shown antiproliferative and antiremodeling properties in various animal models.

RIOCIGUAT. Riociguat has a dual mode of action, acting in synergy with endogenous NO and also directly stimulating sGC independent of NO availability. An RCT (PATENT [Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial]-1) (33) in 443 PAH patients (44% and 6% on background therapy with ERA or prostanoids, respectively) treated with riociguat up to 2.5 mg 3 times daily has shown favorable results on exercise capacity, hemodynamics, WHO-FC, and time to clinical worsening. The increase in exercise capacity was also demonstrated in patients on background therapy. The most common serious adverse event in the placebo group and the 2.5 mg group was syncope (4% and 1%, respectively). The combination of riociguat and PDE-5i is contraindicated due to hypotension and other relevant side effects detected in the open-label phase of the PATENT-plus study (34). Riociguat is approved by the FDA for PAH and chronic thromboembolic pulmonary hypertension (CTEPH) patients and is currently undergoing the regulatory approval process by the EMA for both indications.

PDE-5is. Inhibition of the cyclic guanosine monophosphate degrading enzyme PDE-5 results in vasodilation through the NO/cGMP pathway at sites expressing this enzyme. Because the pulmonary vasculature contains substantial amounts of PDE-5 the potential clinical benefit of PDE-5ì has been investigated in PAH. In addition, PDE-5i exerts antiproliferative effects (35,36). All 3 PDE-5is approved for the treatment of erectile dysfunction, sildenafil, tadalafil, and vardenafil cause significant pulmonary vasodilation with maximum effects observed after 60, 75 to 90, and 40 to 45 min, respectively (37).

SILDENAFIL. Sildenafil is an orally active, potent, and selective PDE-5i. Five RCTs in PAH patients treated with sildenafil have confirmed favorable results on exercise

Table 6 Characteristics of Randomized Controlled Trials With Pulmonary Arterial Hypertension Drugs Interfering With the Prostacyclin Pathway (See Text for References)

Drug(s) Tested	Study	Background	Primary Endpoint	Outcome (Secondary Endpoint)	Duration (weeks)	No. of Patients
Prostanoids						
Beraprost	ALPHABET	No	6MWD	—	12	130
	Barst	No	CW (NS)	—	52	116
Epoprostenol	Rubin	No	6MWD	—	12	23
	Barst	No	6MWD	Survival	12	81
	Badesch	No	6MWD	—	12	111
Iloprost	AIR	No	6MWD and FC	—	12	203
	STEP	Bosentan	6MWD	TTCW	12	67
	COMBI	Bosentan	6MWD (NS)	—	12	40
Treprostinil	SC- Simonneau	No	6MWD	—	12	470
	Inhal TRIUMPH	Bosentan or Sildenafil	6MWD	—	12	235
	PO- Freedom M	No	6MWD	—	16	185
	PO- Freedom C1	Bosentan and/or sildenafil	6MWD (NS)	—	16	354
	PO- Freedom C2	Bosentan and/or sildenafil	6MWD (NS)	—	16	310
Prostacyclin IP-receptor Agonists						
Selexipag*	Phase 2	Bosentan and/or sildenafil	PVR	6MWD (NS)	17	43

*Not approved for pulmonary artery hypertension.
CW = clinical worsening; FC = Functional Class; inhal = inhalation; PO = oral; SC = subcutaneous; other abbreviations as in Table 3.

JACC Vol. 62, No. 25, Suppl D, 2013
December 24, 2013:D60–72

Table 7 Survival After Lung Transplantation in Patients With Pulmonary Arterial Hypertension

	1 year	5 years	10 years
Pittsburgh (Toyoda et al., 2008 [74])	86	75	66
Paris (Fadel et al., 2010 [75])	79	52	43
Toronto (de Perrot et al., 2012 [76])	78	60	45
Vienna (Klepetko, unpublished data, 2011)	73	71	—

capacity, symptoms, and/or hemodynamics (38–41). The PACES (Pulmonary Arterial hypertension Combination study of Epoprostenol and Sildenafil) trial addressing the effects of adding sildenafil to epoprostenol showed improvements after 12 weeks in 6MWD and time to clinical worsening. Of note, 7 deaths occurred in this trial, all in the placebo group (42). The approved dose of sildenafil is 20 mg three times daily. Most side effects of sildenafil are mild to moderate and mainly related to vasodilation (headache, flushing, epistaxis). On the basis of pharmacokinetic data an intravenous formulation of sildenafil (43) has been approved by the FDA and EMA as a bridge for PAH patients on long-term oral treatment who are temporarily unable to ingest tablets. Sildenafil is approved for PAH patients.

TADALAFIL. Tadalafil is a once daily dispensed, selective PDE-5i. An RCT (PHIRST [Pulmonary arterial Hypertension and ReSponse to Tadalafil] trial) in 406 PAH patients (53% on background bosentan therapy) treated with tadalafil 2.5, 10, 20, or 40 mg once daily has shown favorable results on exercise capacity, symptoms, hemodynamics, and time to clinical worsening at the highest dose (44). The side effect profile was similar to that of sildenafil. Tadalafil is approved for PAH patients.

VARDENAFIL. Vardenafil is a twice daily dispensed PDE-5i. An RCT (EVALUATION [Efficacy and Safety of Vardenafil in the Treatment of Pulmonary Arterial Hypertension]) in 66 treatment naive PAH patients treated with vardenafil 5 mg twice daily has shown favorable results on exercise capacity, hemodynamics, and time to clinical worsening (45). The side effect profile was similar to that of sildenafil. Vardenafil is currently not approved for PAH patients.

Platelet-derived growth factor pathway. Proliferation of endothelial cells and vascular smooth muscle cells with narrowing or occlusion of the vessel lumen is a histopathological hallmark of the distal pulmonary arteries in PAH patients. Evidence from animal models and human disease suggest that platelet-derived growth factor and c-KIT signaling are important in vascular smooth muscle cell proliferation and hyperplasia.

Tyrosine kinase inhibitors. IMATINIB. Imatinib is an antiproliferative agent developed to target the Bcr-Abl tyrosine kinase in patients with chronic myeloid leukemia. In addition, the inhibitory effects of imatinib on platelet-derived growth factor receptors and c-KIT suggest that it may be efficacious in PAH. Two RCTs on PAH patients treated with imatinib (all of them on background therapy with at least 2 PAH-approved drugs) have shown positive results on exercise capacity and hemodynamics (data possibly influenced by the drop-out rate in the treated group), but failed to show favorable effects on time to clinical worsening (46,47). In addition, an increased incidence of subdural hematoma was observed in PAH patients treated with both imatinib and oral anticoagulants. Regulatory consideration of imatinib for the PAH indication has recently been halted.

Prostacyclin pathway. Prostacyclin is produced predominantly by endothelial cells and induces potent vasodilation of all vascular beds and in addition is an inhibitor of platelet aggregation and it also appears to have both cytoprotective and antiproliferative activities (48). Dysregulation of the prostacyclin metabolic pathways has been shown in patients with PAH as assessed by reduction of prostacyclin synthase expression in the pulmonary arteries and of urinary metabolites of prostacyclin (49,50).

Prostanoids. The clinical use of prostacyclin in patients with PAH has been extended by the synthesis of stable analogues.

BERAPROST. Beraprost is the first chemically stable and orally active prostacyclin analogue. The RCT ALPHABET (Arterial Pulmonary Hypertension And Beraprost European Trial) (51) in Europe and a second study in the United States (52) with this compound have shown an improvement in exercise capacity, which unfortunately persists only up to 3 to 6 months. There were no hemodynamic benefits. The most frequent adverse events were headache, flushing, jaw pain, and diarrhea. Beraprost is approved for PAH in Japan and South Korea.

EPOPROSTENOL. Epoprostenol (synthetic prostacyclin) has a short half-life (3 to 5 min) and is stable at room temperature for only 8 h requiring cooling, continuous administration by means of an infusion pump and a permanent tunneled catheter. The efficacy of continuous intravenous (IV) administration of epoprostenol has been tested in 3 unblinded RCTs in patients with idiopathic PAH (53,54) and in those with PAH associated with the scleroderma spectrum of diseases (55). Epoprostenol improves symptoms, exercise capacity, and hemodynamics in both clinical conditions, and is the only treatment shown to reduce mortality in idiopathic PAH in a randomized study (54). The meta-analysis for total mortality of the 3 epoprostenol RCTs (53–55) performed with the Mantel–Haenszel and the Peto fixed-effect methods showed a relative risk (RR) reduction of 70% ($z = 2.35$, $p = 0.019$, heterogeneity $p = 0.182$) and 68% ($z = 2.52$, $p = 0.012$, heterogeneity $p = 0.153$), respectively (Fig. 2). Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction, and sepsis. Intravenous epoprostenol is approved for PAH patients. A thermostable formulation of epoprostenol is approved in the United States, Canada, Japan and in most of the European

countries and does not require cooling packs to maintain stability beyond 8 to 12 h.

ILOPROST. Iloprost is a chemically stable prostacyclin analogue available for intravenous, oral, and inhaled administration. Inhaled iloprost has been evaluated in 1 RCT (AIR [Aerosolized Iloprost Randomized] study) in which daily repetitive iloprost inhalations (6 to 9 times, 2.5 to 5 μg/inhalation, median 30 μg daily) were compared with placebo inhalation in patients with PAH and CTEPH (56). The study showed an increase in exercise capacity and improvement in symptoms, pulmonary vascular resistance (PVR) and clinical events in enrolled patients. Two additional RCTs (STEP [Safety and pilot efficacy Trial of inhaled iloprost in combination with bosentan for Evaluation in Pulmonary arterial hypertension] and COMBI [COMbination therapy of Bosentan and aerosolized Iloprost in idiopathic pulmonary arterial hypertension]) of patients already treated with bosentan have shown conflicting results of the addition of inhaled iloprost (57,58). Overall, inhaled iloprost was well tolerated with flushing and jaw pain being the most frequent side effects. Continuous IV administration of iloprost appears to be as effective as epoprostenol in a small uncontrolled series of patients with PAH and CTEPH (59). Inhaled iloprost is approved for PAH. The IV formulation is approved for PAH in New Zealand.

TREPROSTINIL. Treprostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability to be administered at ambient temperature. These characteristics allow administration of the compound by the IV as well as the subcutaneous and oral route. The subcutaneous administration of treprostinil can be accomplished by a microinfusion pump and a small subcutaneous catheter. The effects of treprostinil in PAH were studied in an RCT and showed improvements in exercise capacity, hemodynamics, and symptoms (60). Infusion site pain was the most common adverse effect of treprostinil, leading to discontinuation of the treatment in 8% of cases on active drug and limiting dose increase in an additional proportion of patients (60). An RCT was performed with intravenous treprostinil in PAH patients (TRUST [Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Compared Continuous IV Treprostinil to Placebo in PAH Patients]) but the enrollment of this trial was closed after 45 (36%) of the planned 126 patients had been randomized because of safety considerations (61). The data generated from 31 (25%) survivors after the randomized phase (23 active and 8 placebo) are not considered reliable and the study is not included in Table 6.

An RCT (TRIUMPH [inhaled TReprostInil sodiUM in Patients with severe Pulmonary arterial Hypertension]) with inhaled treprostinil in PAH patients on background

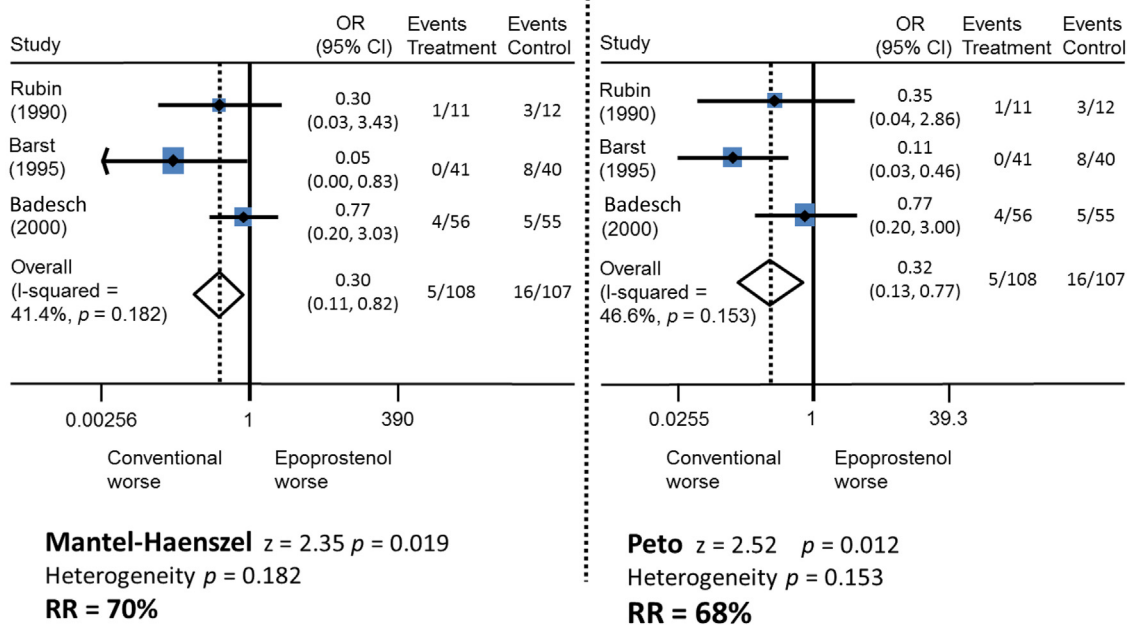

Figure 2 **Meta-Analysis of Published Randomized Controlled Studies (Identified by First Author and Year of Publication) With Epoprostenol in Pulmonary Arterial Hypertension by Mantel–Haenszel and Peto Methods**

The analysis included 215 patients in 3 trials. The figure shows the cumulative relative risk (RR) estimate of death in active treatment groups when compared with control groups. An overall reduction of the risk of mortality of 70% (p = 0.019) and 68% (o = 0.012) is shown with Mantel–Haenszel and Peto methods, respectively. CI = confidence interval; OR = odds ratio.

therapy with either bosentan or sildenafil showed improvements in 6MWD by 20 m at peak dose, N-terminal pro–B-type natriuretic peptide (NT-proBNP) and quality-of-life measures (62).

Oral treprostinil has been evaluated in 2 RCTs in PAH patients on background therapy with bosentan and/or sildenafil (FREEDOM [Multicenter, Double-101 Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of Oral treprostinil Sustained Release Tablets in Subjects With Pulmonary Arterial Hypertension] C1 and C2) and in both the primary endpoint 6MWD did not reach statistical significance (63,64). An additional RCT in PAH naive patients showed improvement in 6MWD by 26 m at peak dose (65). Subcutaneous treprostinil is approved for PAH. Intravenous treprostinil is approved in the United States and European Union in patients with PAH who cannot tolerate the subcutaneous administration (based on bioequivalence). Inhaled treprostinil is approved for PAH in the United States. Oral treprostinil is currently not approved for PAH.

Prostacyclin IP-receptor agonists. SELEXIPAG. Selexipag is an orally available, selective prostacyclin IP receptor agonist. Although selexipag and its metabolite have modes of action similar to that of endogenous prostacyclin (IP receptor agonism), they are chemically distinct from prostacyclin with a different pharmacology. In a pilot RCT in PAH patients (receiving stable ERA and/or a PDE-5i therapy) selexipag reduced PVR after 17 weeks (66). A large event-driven phase 3 RCT (GRIPHON [Prostocyclin (PGI2) Receptor Agonist in Pulmonary Arterial Hypertension] trial) is currently ongoing. Selexipag is currently not approved for PAH.

Clinical Response, Combination Therapy, and Interventional Procedures

After initial therapy, the next steps are based on the clinical response, which is usually reassessed at 3 to 6 months after treatment start.

The clinical response is based on the evaluation of different parameters including WHO-FC, exercise capacity, cardiac index, right atrial pressure, NT-proBNP plasma levels, echocardiographic parameters, and perceived need for additional/change of therapy. The exact definition of clinical response is addressed in another paper of this supplement and is beyond the scope of this paper.

If the clinical response is considered not adequate, combination therapy is considered.

Combination therapy. Combination therapy—using 2 or more classes of drugs simultaneously—has been used successfully in the treatment of systemic hypertension and heart failure. It is also an attractive option for the management of PAH, because 3 separate signaling pathways are known to be involved in the disease: the prostacyclin pathway, the endothelin pathway, and the NO pathway.

In Tables 3 to 6, 13 (43%) of the RCTs performed in PAH patients included at least 1 subgroup treated with combination therapy. The experience with combination therapy is therefore growing and a recent meta-analysis on 6 RCTs with combination therapy including 858 patients has been published (67): compared with the control group, combination therapy reduced the risk of clinical worsening (RR: 0.48; 95% confidence interval: 0.26 to 0.91; $p = 0.023$), increased the 6MWD significantly by 22 m, and reduced mean pulmonary arterial pressure, right atrial pressure, and PVR. The incidence of serious adverse events was similar in the 2 groups (RR: 1.17; 95% confidence interval: 0.40 to 3.42; $p = 0.77$). The reduction on all-cause mortality was not statistically significant. However, the incidence of mortality in RCTs with PAH medications is relatively low and to achieve statistical significance a sample size of several thousands of patients may be required (67).

The patterns to apply combination therapy may be sequential or initial (upfront).

Sequential combination therapy is the most widely utilized strategy both in RCTs (12 of 13 of the RCTs with combination therapy) (Tables 3 to 6) and in clinical practice: From monotherapy there is addition of a second and then third drug in cases of inadequate clinical results or in cases of deterioration. A structured prospective program to evaluate the adequacy of clinical results is the so-called "goal-oriented therapy," a treatment strategy that uses known prognostic indicators as treatment targets. The therapy is considered adequate only if the targets are met. The key difference between goal-oriented therapy and nonstructured approaches is that patients who are stabilized, or even those who improve slightly, can still receive additional therapy if treatment goals are not met. The goal-oriented treatment strategy has been endorsed by recent PAH guidelines proposing different targets including WHO-FC I or II and the near normalization of resting cardiac index and/or of NT-proBNP plasma levels (4). A recent study has confirmed a better prognosis in patients achieving these goals as compared with the patients who did not (68). Sequential combination therapy has been allocated a grade of recommendation I and level of evidence A in PAH patients with inadequate clinical response to initial monotherapy.

The rationale for initial or upfront combination therapy is based on the known mortality of PAH that is reminiscent of many malignancies and the fact that malignancies and critical medical illnesses (heart failure, malignant hypertension) are not treated with a stepwise approach to therapy but rather with pre-emptive combination therapy. The experience on RCTs with initial combination therapy is limited to the small BREATHE-2 study, which failed to demonstrate any significant difference between patients treated initially with the combination epoprostenol and bosentan as compared with epoprostenol alone (28). In a more recent experience, 23 treatment naive PAH patients were treated with the initial combination of epoprostenol and bosentan and compared with a matched historical control group treated with epoprostenol (69). The study

showed a statistically significantly greater decrease in PVR in the initial combination therapy group but this hemodynamic benefit did not translate into a statistically significant difference in survival, or in transplant-free survival. A multicenter, multinational blinded placebo controlled trial (AMBITION [A Randomized, Multicenter Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension]) comparing first line monotherapy with tadalafil, monotherapy with ambrisentan and combination therapy with tadalafil and ambrisentan in de novo WHO-FC II and III PAH patients was underway at the time of this publication to address the efficacy to safety ratio of initial combination therapy. Initial combination therapy has been allocated a grade of recommendation IIb and level of evidence C in WHO-FC IV PAH patients in case of nonavailability of IV prostanoids.

Interventional procedures. LUNG TRANSPLANTATION. The advent of disease targeted therapy for severe PAH has reduced and delayed patients referral for lung transplant programs (70). The long-term outcomes of medically treated patients remain uncertain and transplantation should continue to be an important option for those who fail on such therapy and remain in WHO-FC III or IV (71,72). Delayed referral in combination with the length of the waiting time, due to the shortage of organ donors, may increase the mortality on the waiting list and clinical severity at the time of transplantation.

The overall 5-year survival following transplantation for PAH was considered to be 45% to 50% with evidence of continued good quality of life (73). More recent data show that survival is increased to 52% to 75% at 5 years and to 45% to 66% at 10 years (Table 7) (74–76).

Considering together the previous information, it seems reasonable to consider eligibility for lung transplantation after an inadequate clinical response to the initial monotherapy and to refer the patient soon after the inadequate clinical response is confirmed on maximal combination therapy (Fig. 1).

Also the etiology of PAH may help the decision making because the prognosis varies according to the underlying condition. In fact, PAH associated with connective tissue disease has a worse prognosis than idiopathic PAH even when treated with prostanoids, while patients with PAH associated with congenital heart disease have a better survival. The worst prognosis is seen in patients with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis because of the lack of effective medical treatments and these patients should be listed for transplantation at diagnosis.

Both heart-lung and double-lung transplantation have been performed for PAH, although the threshold for unrecoverable right ventricle systolic dysfunction and/or left ventricle diastolic dysfunction is unknown. Currently the vast majority of patients worldwide receive bilateral lungs as evidenced by the International Society for Heart and Lung Transplantation Registry figures (77). Patients with Eisenmenger's syndrome due to simple shunts have been treated by isolated lung-transplantation and repair of the cardiac defect or by heart-lung transplantation (73).

While registry data initially supported a survival benefit of heart-lung transplantation for patients with pulmonary hypertension associated with a ventricular septal defects (78) experience with isolated bilateral lung transplantation has grown and more recent data supports a role for this approach combined with repair of the defect (79).

Recent reports indicate that venoarterial extracorporeal membrane oxygenation may be employed in awake end-stage PH patients for bridging to lung transplantation (80).

BALLOON ATRIAL SEPTOSTOMY. The creation of an interatrial right-to-left shunt can decompress the right heart chambers, and increase left ventricle pre-load and cardiac output (81,82). In addition, this improves systemic O_2 transport despite arterial O_2 desaturation (81) and decreases sympathetic hyperactivity. The recommended technique is graded balloon dilation atrial septostomy, which produces equivalent improvements in hemodynamics and symptoms but reduced risk compared with the original blade technique. Other techniques are considered experimental (83).

A careful pre-procedure risk assessment ensures reduced mortality. Balloon atrial septostomy (BAS) should be avoided in end-stage patients presenting with a baseline mean right atrial pressure of >20 mm Hg and O_2 saturation at rest of <85% on room air. Patients should be on optimal medical therapy, which may include preconditioning with IV inotropic drugs, prior to considering BAS. Published reports suggest a benefit in patients who are in WHO-FC IV with right heart failure refractory to medical therapy or with severe syncopal symptoms (81,82). It may also be considered in patients awaiting transplantation or when medical therapy is not available. Studies show improvements in cardiac index and decreases in right atrial pressure with improvement in 6MWD (81,82). The impact of BAS on long-term survival has not been established in RCTs (81,82). BAS should be regarded as a palliative or bridging procedure to be performed only by centers with experience in the method (70).

Treatment algorithm principles and description.

PRINCIPLES.

- The treatment algorithm for PAH patients is shown in Figure 1. The definitions of the grades of recommendation and the levels of evidence are reported in Tables 1 and 2.
- The different treatments have been evaluated by RCTs mainly in idiopathic PAH, heritable PAH, PAH due to anorexigen drugs, and in PAH associated with connective tissue disease or with congenital heart disease (surgically corrected or not). The grades of recommendation and levels of evidence for the other associated PAH conditions may be lower. However, the treatment algorithm is applicable to associated PAH conditions without substantial changes.

- PAH is a rare disease and regulatory agencies may require only 1 RCT with pre-specified characteristics (e.g., size, duration, endpoint, level of statistical significance) to grant the approval for the use. For these reasons approved drugs with level of evidence A (more than 1 RCT or meta-analysis) and approved drugs with Level of Evidence: B (1 RCT) have been grouped together.
- The treatment algorithm does not apply to patients in other clinical groups, and in particular not to patients with PH associated with left heart disease (group 2) or with lung diseases (group 3).
- Only the compounds officially approved for PAH or under regulatory approval process in at least 1 country are included. Single compounds are listed by alphabetical order according with the pharmacological name.
- As head-to-head comparisons among different compounds are not available, no evidence-based first-line treatment can be proposed. In this case the choice of the drug may depend on a variety of factors including the approval status, the labeling, the route of administration, the side effect profile, patients preferences, physician experience, and the cost.
- A 4-level hierarchy for endpoints in RCT has been proposed by experts according to level of evidence regarding efficacy (84,85): Level 1 is a true clinical efficacy measure; Level 2 is a validated surrogate (for a specific disease setting and class of interventions); Level 3 is a nonvalidated surrogate, yet 1 established to be reasonably likely to predict clinical benefit (for a specific disease setting and class of interventions); and Level 4 is a correlate that is a measure of biological activity but that has not been established to be so at a higher level. All-cause death and morbidity and mortality endpoints for PAH have been included in Level 1 (84) whereas 6MWD is not considered a validated surrogate in PAH (86) and it may be included either at Level 3 or 4. According to this hierarchy, drugs with morbidity and mortality as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined) have been highlighted.

DESCRIPTION.

- The suggested initial approach after the diagnosis of PAH is the adoption of the general measures, the initiation of the supportive therapy, and referral to an expert center.
- Acute vasoreactivity testing should be performed in all patients with PAH (group 1), although patients with idiopathic PAH, heritable PAH, and PAH associated with anorexigen use are the most likely to exhibit an acute positive response and to benefit from high-dose CCB therapy. Vasoreactive patients should be treated with high and optimally tolerated doses of CCBs; adequate response should be confirmed after 3 to 4 months of treatment.
- Nonresponders to acute vasoreactivity testing who are in WHO-FC II should be treated with an oral compound.
- Nonresponders to acute vasoreactivity testing, or responders who remain in (or progress to) WHO-FC III, should be considered candidates for treatment with any of the approved PAH drugs.
- As head-to-head comparisons among different compounds are not available, no evidence-based first-line treatment can be proposed (see previous) for either WHO-FC II or III patients.
- Continuous IV epoprostenol is recommended as first-line therapy for WHO-FC IV PAH patients because of the survival benefit in this subset. In absence of IV epoprostenol all other compounds may be utilized.
- Although ambrisentan, bosentan, and sildenafil are approved in WHO-FC IV patients in the United States, only a small number of these patients were included in the RCTs of these agents. Accordingly, most experts consider these treatments as a second line in severely ill patients.
- In WHO-FC IV patients initial combination therapy may also be considered.
- In case of inadequate clinical response, sequential combination therapy should be considered. Combination therapy can either include an ERA plus a PDE-5i or a prostanoid plus an ERA or a prostanoid plus a PDE-5i. Upon regulatory approval the sGC stimulator riociguat can be considered as a potential alternative to PDE-5i in the different types of double combinations. The combination of riociguat and PDE-5is is contraindicated.
- In case of inadequate clinical response with double combination therapy, triple combination therapy should be attempted.
- It seems reasonable to consider eligibility for lung transplantation after an inadequate clinical response to the initial monotherapy and to refer the patient for lung transplantation soon after the inadequate clinical response is confirmed on maximal combination therapy.
- Balloon atrial septostomy should be regarded as a palliative or bridging procedure in patients deteriorating despite maximal medical therapy.

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Key Words: endothelin receptor antagonists ■ guanylate cyclase stimulators ■ hypertension, pulmonary ■ lung transplantation ■ phosphodiesterase type-5 inhibitors ■ prostanoids ■ pulmonary.