

# A Treatment Algorithm for Pulmonary Arterial Hypertension

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The treatment algorithm for pulmonary arterial hypertension (PAH) represents graphically a sequence of operations that are needed for the management of patients. The treatment algorithm includes different types of recommendations with varying degrees of scientific evidence. The recommendations are based on information derived from different areas including clinical, hemodynamic, medical, interventional, pharmacological, and regulatory domains.

The current treatment algorithm is divided into 3 main sections: I) general measures, supportive therapy, referral strategy, acute vasoreactivity testing, and chronic treatment with calcium channel blockers; II) initial therapy with approved PAH drugs; III) clinical response to the initial therapy, combination therapy, balloon atrial septostomy, and lung transplantation. The European Society of Cardiology grades of recommendation and levels of evidence are adopted to rank the proposed treatments.

The complexity of the treatment algorithm for pulmonary arterial hypertension (PAH) has progressively increased since the Second 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.<sup>1</sup> Currently 10 drugs from 3 main pharmacological groups (addressing 3 pathways) and 4 different routes of administration (oral, inhaled, subcutaneous, and intravenous) have been officially approved for PAH patients. Although this progress in pharmacotherapy has been associated in different meta-analyses with a reduction of morbidity and mortality observed,<sup>2,3</sup> limiting symptoms and poor outcome still characterize patients with PAH.

The current treatment algorithm as proposed during the Fifth World Symposium on Pulmonary Hypertension<sup>4</sup> is divided into 3 main sections. The first includes 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. The second provides information about the initial therapy and includes drugs approved in PAH in at least one 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. The third section provides indications according to the clinical response to the initial therapy and in case of inadequate results, combination drug therapy and additional interventional procedures such as balloon atrial septostomy (BAS) and lung transplantation are recommended. The European Society of Cardiology grades of recommendation and levels of evidence are adopted to score the proposed treatments.<sup>4</sup> The treatment algorithm is shown in Figure 1.

## GENERAL MEASURES

### Pregnancy

Pregnancy is associated with a substantial mortality rate in PAH. A recent report<sup>5</sup> over a 3-year period documented 26 pregnancies. Three women (12%) died and one (4%) developed right heart failure requiring urgent heart-lung trans-

plantation. 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

Supervised exercise rehabilitation may improve exercise and functional capacity and quality of life in patients with pulmonary hypertension (PH).<sup>6-13</sup> The limitations of this method are based on the gaps in knowledge of the optimal method, intensity, and duration of the training; of the characteristics of the supervision; and of the practical organization in the real world. Despite this, a grade of recommendation class I with a level of evidence A has been granted.

### Supportive Therapy

No changes have been proposed for anticoagulants, diuretics, digitalis, and oxygen. Long-term oxygen therapy is suggested to maintain arterial blood oxygen pressure  $\geq 8$  kPa (60 mm Hg).

### Referral Centers and Vasoreactivity Testing

The recommendation to refer patients to expert centers after PAH diagnosis is maintained, and 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 CCBs. Inhaled nitric oxide (iNO) is the compound of choice for the acute test.

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

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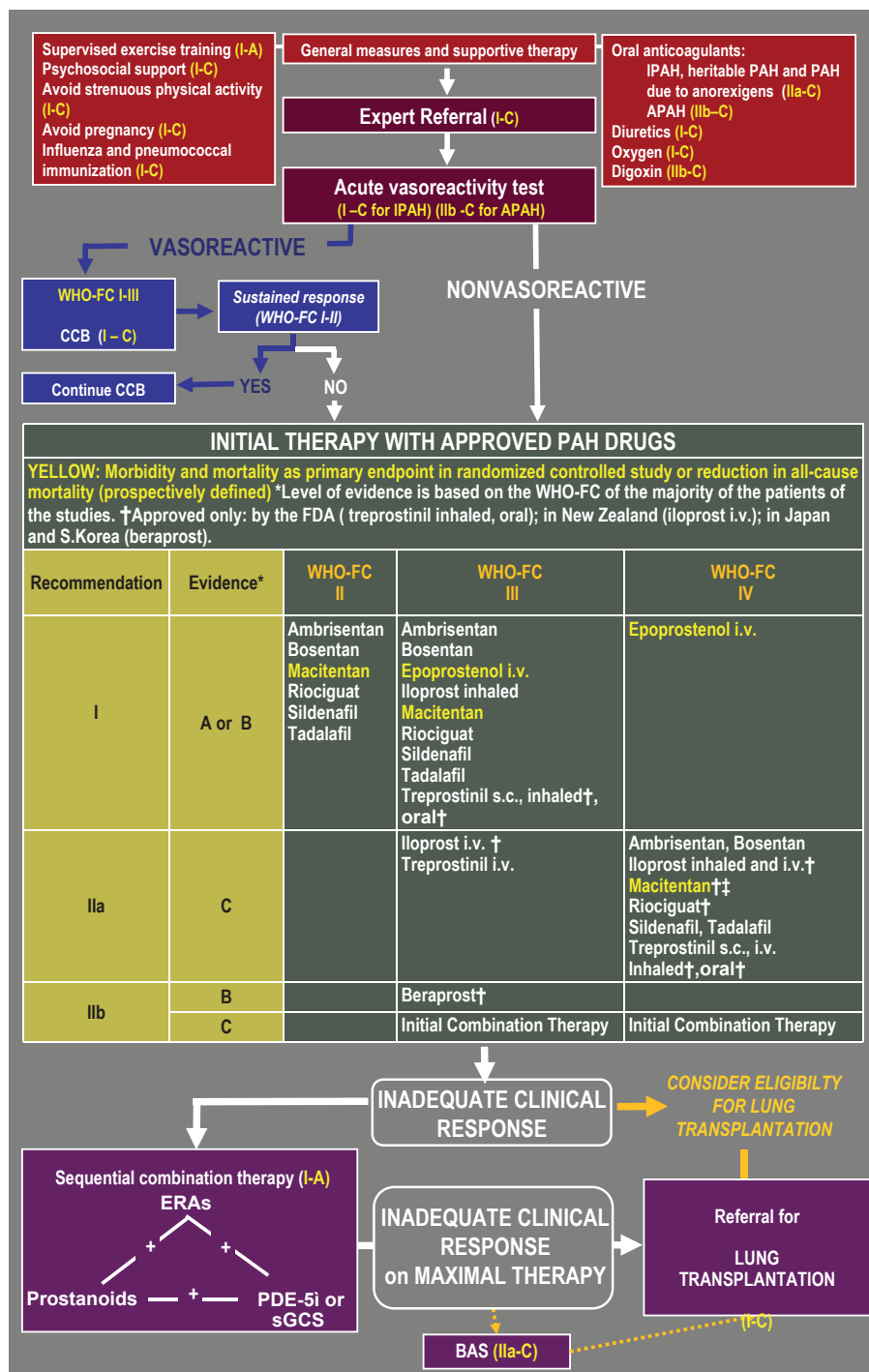


Figure 1: Evidence-Based Treatment Algorithm. Adapted from Galiè N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013; 62(25 Suppl):D60-D72, with permission from Elsevier. Abbreviations: APAH, associated pulmonary arterial hypertension; BAS, balloon atrial septostomy; CCB, calcium channel blockers; ERA, endothelin receptor antagonist; GCS, 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

## INITIAL THERAPY WITH APPROVED PAH DRUGS

Therapy with approved PAH drugs needs to be initiated in PAH patients who are not vasoreactive, or are vasore-

active but not responding appropriately to CCBs (Figure 1). For the initial therapy, drugs are classified according to the grade of recommendation and the level of evidence based on published ran-

domized controlled trials (RCTs). In addition, initial drug therapies are stratified according to WHO-FC.

## INDIVIDUAL COMPOUNDS

Pharmacological classes and drugs are listed in alphabetical order. Only compounds approved for PAH are included in the treatment algorithm and are listed in alphabetical order (Figure 1).

### Endothelin Pathway

Activation of the endothelin system has been demonstrated in both plasma and lung tissue of PAH patients,<sup>14,15</sup> and these data support a prominent role for the endothelin system in the pathogenesis of PAH.<sup>16</sup> Endothelin exerts vasoconstrictor and mitogenic effects.

### Endothelin Receptor Antagonists

**Ambrisentan.** Ambrisentan is a nonsulfonamide, propanoic acid-class, endothelin receptor antagonist (ERA) that is selective for the endothelin-A receptor. Ambrisentan has been evaluated in different studies<sup>17</sup> that 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 (CTD) and HIV infection.<sup>18</sup>

Ambrisentan has been approved for the treatment of WHO-FC II and III patients. The incidence of abnormal liver function tests ranges from 0.8% to 3%, and monthly liver function assessment is not mandated in the United States.<sup>19</sup> An increased incidence of peripheral edema has been reported. Ambrisentan is approved for PAH patients.

**Bosentan.** Bosentan is an oral active dual endothelin A- and B-receptor antagonist and has been evaluated in PAH (idiopathic, associated with CTD and Eisenmenger syndrome) in multiple RCTs, which showed improvement in exercise capacity, functional class, hemodynamics, echocardiographic and Doppler variables, and time to clinical worsening.<sup>20-24</sup> Increases in hepatic aminotransferases occurred in approximately 10% of the subjects, and 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. In the event-driven SERAPHIN study<sup>25</sup> of 742 PAH patients, macitentan significantly reduced a 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 sildenafil. 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. The drug is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for PAH patients.

### **Nitric Oxide Pathway**

Impairment of nitric oxide (NO) synthesis and signalling through the NO-soluble guanylate cyclase-cyclic guanosine monophosphate pathway (cGMP) is involved in the pathogenesis of PH through the reduction of intracellular concentrations of cGMP, a vasodilator and antiproliferative effector.

### **Soluble Guanylate Cyclase Stimulators**

While phosphodiesterase type-5 inhibitors (PDE-5is) such as sildenafil, tadalafil, and vardenafil enhance the NO-cGMP pathway slowing cGMP degradation, soluble guanylate cyclase (sGC) stimulators enhance cGMP production.

**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-1)<sup>26</sup> in 443 PAH patients (44% and 6% on background therapy with ERAs 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 most common serious adverse event in the placebo group and the 2.5 mg group was syncope (4% and 1%, respectively). Hemoptysis was more frequent with riociguat and not observed with placebo. 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.<sup>27</sup> Riociguat is approved by the FDA and EMA for PAH patients.

### **Phosphodiesterase Type-5 Inhibitors**

Inhibition of the PDE-5 results in vasodilatation and antiproliferative effects through the NO/cGMP at sites expressing this enzyme, including the pulmonary vasculature.<sup>28,29</sup> 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, 75–90, and 40–45 minutes, respectively.<sup>30</sup>

**Sildenafil.** Sildenafil is an orally active, potent, and selective inhibitor of PDE-5. Four RCTs in PAH patients treated with sildenafil have confirmed favorable results on exercise capacity, symptoms, and/or hemodynamics.<sup>31–34</sup> The PACES trial addressing the effects of adding sildenafil to epoprostenol showed improvements after 12 weeks in 6-minute walk distance (6MWD) and time to clinical worsening. Of note, 7 deaths occurred in this trial, all in the placebo group.<sup>35</sup> The approved dose of sildenafil is 20 mg tid. Most side effects of sildenafil are mild to moderate and mainly related to vasodilation (headache, flushing, epistaxis).

**Tadalafil.** Tadalafil is a once-daily, selective PDE-5i. An RCT (PHIRST) in 406 PAH patients (53% on background bosentan therapy) treated with tadalafil 2.5, 10, 20, or 40 mg has shown favorable results on exercise capacity, symptoms, hemodynamics, and time to clinical worsening at the highest dose.<sup>36</sup> The side-effect profile was similar to that of sildenafil. Tadalafil is approved for PAH patients.

**Vardenafil.** Vardenafil is a twice-daily PDE-5i. An RCT (EVALUATION) in 66 treatment-naïve PAH patients treated with vardenafil 5 mg has shown favorable results on exercise capacity, hemodynamics, and time to clinical worsening.<sup>37</sup> The side-effect profile was similar to that of sildenafil. Vardenafil is currently not approved for PAH patients.

### **Platelet-Derived Growth Factor Pathway**

Evidence from animal models and human disease suggest that platelet-derived growth factor (PDGF) and c-KIT signalling 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 PDGF 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 approved PAH drugs) have shown positive results on exercise capacity and hemodynamics (data possibly influenced by the dropout rate in the treated group), but failed to show favorable effects on time to clinical worsening.<sup>38,39</sup> 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 vasodilatation of all vascular beds, and in addition is an inhibitor of platelet aggregation and appears to have both cytoprotective and antiproliferative activities.<sup>40</sup>

### **Prostanoids**

**Beraprost.** Beraprost is the first chemically stable and orally active prostacyclin analogue. The RCT ALPHABET<sup>41</sup> in Europe and a second study in the US<sup>42</sup> with this compound have shown an improvement in exercise capacity, which unfortunately persists only up to 3 to 6 months. Beraprost is approved for PAH in Japan and South Korea.

**Epoprostenol.** Epoprostenol (synthetic prostacyclin) has a short half-life (3 to 5 minutes) and is stable at room temperature for only 8 hours requiring cooling, continuous administration by means of an infusion pump, and a permanent tun-



nelled catheter. The efficacy of continuous intravenous administration of epoprostenol has been tested in 3 unblinded RCTs in patients with idiopathic PAH<sup>43,44</sup> and in those with PAH associated with the scleroderma spectrum of diseases.<sup>45</sup> 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<sup>44</sup> and a meta-analysis.<sup>4</sup> 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 by the FDA and EMA.

**Iloprost.** Iloprost is a chemically stable prostacyclin analogue available for intravenous, oral, and aerosol administration. Inhaled iloprost has been evaluated in 1 RCT (AIR) with daily repetitive iloprost inhalations (6 to 9 times).<sup>46</sup> 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 and COMBI) of patients already treated with bosentan have shown conflicting results of the addition of inhaled iloprost.<sup>47,48</sup> Continuous intravenous administration of iloprost appears to be as effective as epoprostenol in a small, uncontrolled series of patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH).<sup>49</sup> Inhaled iloprost is approved for PAH. The intravenous 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 intravenously, as well as subcutaneously and orally. The subcutaneous administration of treprostinil can be accomplished by a micro-infusion 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.<sup>50</sup> Infusion site pain was the most common adverse effect of subcutaneous treprostinil.<sup>50</sup> An RCT was performed with intravenous treprostinil in PAH patients (TRUST), but the enrollment of this trial was closed after 45 (36%) of the planned 126 patients had been randomized because of safety considerations.<sup>51</sup> The data generated from 31 (25%) survivors after the randomized phase (23 active and 8 placebo) are not considered reliable.

An RCT (TRIUMPH) with inhaled treprostinil in PAH patients on background therapy with either bosentan or sildenafil showed improvements in 6MWD by 20 m at peak dose, NT-proBNP, and quality of life measures.<sup>52</sup> Oral treprostinil has been evaluated in 2 RCTs in PAH patients on background therapy with bosentan and/or sildenafil (FREEDOM C1 and C2) and in both the primary endpoint 6MWD did not reach statistical significance.<sup>53,54</sup> An additional RCT in PAH-naïve patients showed improvement in 6MWD by 26 m at peak dose.<sup>55</sup> Subcutaneous treprostinil is approved for PAH. Intravenous treprostinil is approved in the US and EU in patients with PAH who cannot tolerate the subcutaneous administration. Inhaled and oral treprostinil are approved for PAH in the US.

#### *Prostacyclin IP-receptor Agonists*

**Selexipag.** Selexipag is an orally available, selective prostacyclin IP receptor agonist. In a pilot RCT in PAH patients (receiving stable ERA and/or PDE-5i therapy), selexipag reduced PVR after 17 weeks.<sup>56</sup> A large, event-driven Phase 3 RCT (GRIPHON) is ongoing. Selexipag is currently not approved for PAH.

### **CLINICAL RESPONSE, COMBINATION THERAPY, AND INTERVENTIONAL PROCEDURES**

#### *Clinical Response*

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

#### *Combination Therapy*

Combination therapy—using 2 or more classes of drugs simultaneously—is an attractive option for the management of PAH, because 3 separate signalling pathways are known to be involved in the disease: the prostacyclin pathway, the endothelin pathway, and the NO pathway. A recent meta-analysis on 6 RCTs with combination therapy including 858 patients has been published<sup>57</sup>: compared with the control group, combination therapy reduced the risk of clinical worsening.

The patterns to apply combination therapy may be sequential or initial (up front). *Sequential combination therapy* is the most widely utilized strategy both in RCTs and in clinical practice. From monotherapy there is addition of a second and then a 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.<sup>58</sup> A recent study has confirmed a better prognosis in patients achieving these goals as compared with the patients who did not.<sup>59</sup>

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 up-front combination therapy is based on the severity of PAH and with the attempt to “hit early and hit hard.” The evidence for this strategy is still limited.<sup>22,60</sup> 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. An RCT (AMBITION) comparing first-line monotherapy with tadalafil or ambrisentan with initial combination therapy with tadalafil and ambrisentan in de novo WHO-FC II and III PAH patients has been completed recently, and results will be available very soon. In the meantime, 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 intravenous prostanoids.

### Interventional Procedures

**Lung transplantation.** The advent of disease-targeted therapy for severe PAH has reduced and delayed patients' referral to lung transplant programs.<sup>61</sup> The long-term outcomes of medically treated patients remains 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.<sup>62,63</sup> The overall 5-year survival following transplantation for PAH was considered to be 45% to 50%, with evidence of continued good quality of life.<sup>64</sup> More recent data show that survival is increased to 52% to 75% at 5 years and to 45% to 66% at 10 years.<sup>65-67</sup> Given this 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. Currently the vast majority of patients worldwide receive bilateral lungs as evidenced by the International Society for Heart and Lung Transplantation registry figures.<sup>68</sup> Patients with Eisenmenger syndrome due to simple shunts have been treated by isolated lung transplantation and repair of the cardiac defect or by

heart-lung transplantation.<sup>64</sup> Recent reports indicate that venoarterial extracorporeal membrane oxygenation may be employed in awake end-stage PH patients for bridging to lung transplantation.<sup>69</sup>

**Balloon atrial septostomy.** The creation of an interatrial right-to-left shunt can decompress the right heart chambers and increase left ventricle preload and cardiac output.<sup>70,71</sup> In addition, this improves systemic oxygen transport despite arterial oxygen desaturation<sup>70</sup> and decreases sympathetic hyperactivity. The recommended technique is graded BAS, which produces equivalent improvements in hemodynamics and symptoms, but reduced risk compared with the original blade technique. Other techniques are considered experimental.<sup>72</sup> The impact of BAS on long-term survival has not been established in RCTs.<sup>70,71</sup> BAS should be regarded as a palliative or bridging procedure to be performed only by centers with experience in the method.<sup>61</sup>

### TREATMENT ALGORITHM

The treatment algorithm for PAH patients is shown in Figure 1. The treatment algorithm does not apply to patients in other clinical groups, and in particular not to patients with PH associated with Group 2, left heart disease, or with Group 3, lung diseases. Only the compounds officially approved for PAH in at least one country are included. Single compounds are listed by alphabetical order according to 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 labelling, the route of administration, the side-effect profile, patients' preferences, physician experience, and the cost. Drugs with morbidity and mortality as primary end-point in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined) have been highlighted.

The first algorithm section includes the adoption of the general measures, the initiation of the supportive therapy, and referral to an expert center. The

acute vasoreactivity testing should be performed in patients with idiopathic PAH, heritable PAH, and PAH associated with anorexigen use. Vasoreactive patients should be treated with 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; patients in 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 above) for either WHO-FC II or III patients.

Continuous intravenous epoprostenol is recommended as first-line therapy for WHO-FC IV PAH patients because of the survival benefit in this subset. In the absence of intravenous epoprostenol, all other compounds may be utilized. In WHO-FC IV patients, initial combination therapy may 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. 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-5i 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 soon after the inadequate clinical response is confirmed on maximal combination therapy. BAS should be regarded as a palliative or bridging procedure in patients deteriorating despite maximal medical therapy.

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