Risk stratification and medical therapy of pulmonary arterial hypertension

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ABSTRACT Pulmonary arterial hypertension (PAH) remains a severe clinical condition despite the availability over the past 15 years of multiple drugs interfering with the endothelin, nitric oxide and prostacyclin pathways. The recent progress observed in medical therapy of PAH is not, therefore, related to the discovery of new pathways, but to the development of new strategies for combination therapy and on escalation of treatments based on systematic assessment of clinical response. The current treatment strategy is based on the severity of the newly diagnosed PAH patient as assessed by a multiparametric risk stratification approach. Clinical, exercise, right ventricular function and haemodynamic parameters are combined to define a low-, intermediate- or high-risk status according to the expected 1-year mortality. The current treatment algorithm provides the most appropriate initial strategy, including monotherapy, or double or triple combination therapy. Further treatment escalation is required in case low-risk status is not achieved in planned follow-up assessments. Lung transplantation may be required in most advanced cases on maximal medical therapy.

Introduction

Pulmonary arterial hypertension (PAH) remains a severe clinical condition despite the publication of 41 randomised clinical trials (RCTs) in the past 25 years and the regulatory approval of multiple drugs active by four routes of administration (*i.v.*, *s.c.*, oral and inhaled) [1, 2]. Currently approved therapies target three main pathways important in endothelial function: the prostacyclin and nitric oxide (NO) pathways, which are underexpressed in PAH patients, and the endothelin pathway, which is overexpressed in PAH patients (see the Task Force article by HUMBERT *et al.* [3] in this issue of the *European Respiratory Journal*). This imbalance in vasoactive mediators plays a critical role in the development and progression of the obstructive proliferative pathological changes of the distal pulmonary arteries [3], which, when untreated, will lead to heart failure and premature death (see the Task Force article by VONK NOORDEGRAAF *et al.* [4] in this issue of the *European Respiratory Journal*). Prostacyclin analogues (PCAs) and prostacyclin receptor agonists, phosphodiesterase type 5 inhibitors (PDE5is) and guanylate cyclase stimulators, and endothelin receptor antagonists (ERAs) are intended to correct the dysfunction of the prostacyclin, NO and endothelin pathways, respectively. Interestingly, drugs targeting the three pathways were already approved and included in the treatment algorithm for PAH patients proposed in 2003 at the 3rd World Symposium on Pulmonary Hypertension (WSPH) held in Venice, Italy [5]. The progress observed in medical therapy of PAH patients over the past 15 years is not, therefore, related to the discovery of new pathways, but to the evolution and testing of new drugs and strategies for combination therapy, and on escalation of treatments based on systematic assessment of clinical response [1, 2]. In fact, in the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines the treatment strategy was intimately linked to the baseline severity of the newly diagnosed PAH patient and recommendations for subsequent treatment escalation were founded on the patient's conditions after a pre-specified period of therapy [1, 2]. Both the baseline assessment and the treatment response were based on a multiparametric approach to stratify the patients in low-, intermediate- or high-risk groups for 1-year mortality. The "risk" table included clinical, functional, exercise, right ventricular function and haemodynamic parameters.

This central connection between methodical risk assessment and treatment strategy in PAH patients has been recently validated by retrospective analyses of three independent registries, showing a clear prediction of survival or event-free survival based on this multiparametric approach at baseline and at follow-up [6–9].

This article will provide an updated analysis of risk stratification and its relationship with different treatment strategies available for PAH patients, including general measures, supportive therapies, monotherapy, initial and sequential combination therapy, and interventional therapies.

Risk stratification

The assessment of the prognosis of patients with PAH has been considered an important part of care since the publication of the first US National Institutes of Health idiopathic PAH (IPAH) registry nearly three decades ago [10]. Over time, different baseline and follow-up parameters, including clinical, functional, exercise, non-invasive and invasive variables, have been utilised individually or combined in formulas or calculators to predict outcome: the French Pulmonary Hypertension Network (FPHN) registry risk equation [11, 12], the PH connection equation [13, 14], the Scottish composite score [15], the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk equation [16] and risk score [17, 18], and the 2015 ESC/ERS PH guidelines risk table [1, 2]. Table 1 shows the characteristics of four registries testing the PAH risk stratification strategy of the REVEAL score and of the 2015 ESC/ERS PH guidelines risk table [6–9, 17–19].

The REVEAL equation [16] and the subsequent score [17, 18], derived from a cohort of 2716 PAH patients and using 12 modifiable and non-modifiable parameters measured at baseline, provided the 12-month likelihood of survival (five strata) in incident and prevalent IPAH and associated PAH patients. If utilised at follow-up, the equation can predict outcome at 1 additional year [18]. The risk score calculator was validated internally in 504 newly diagnosed PAH patients, externally in registries and in clinical trials datasets [20, 21]. Survival up to 5 years has been reported according to baseline REVEAL score data, but not at follow-up reassessment [22]. REVEAL survival up to 5 years has also been provided for a subgroup of 1426 patients and based only on repeated high *versus* low brain natriuretic peptide (BNP) plasma level assessments [23]. The REVEAL registry also demonstrated the prognostic value of renal dysfunction at baseline and follow-up measurements of estimated glomerular filtration rate (eGFR) [24].

The REVEAL 2.0 risk score calculator is a refinement of the original REVEAL risk score calculator; it includes all-cause hospitalisations within the previous 6 months and eGFR, both of which have been shown to impact mortality [24, 25].

TABLE 1 Summary of four registries assessing risk scores

	REVEAL [17–19]	Swedish PAH Register [6]	COMPERA [7]	French Pulmonary Hypertension Network [8][#]
Required variables n	12–14	8	8	4
Patients at baseline n	2716	530	1588	1017
Patients at follow-up n	2529	383	1094	1017
Associated PAH included	Yes	Yes	Yes	No
Definition of low risk	⩽6 REVEAL score	<1.5 average score	<1.5 average score	3–4 out of 4 low-risk criteria
1-year mortality by risk group (low/intermediate/high) %	⩽2.6/7.0/⩾10.7	1.0/7.0/26.0	2.8/9.9/21.2	1.0/NA/13.0–30.0

PAH: pulmonary arterial hypertension; NA: not available. [#]: incident patients only.

The REVEAL 2.0 risk score calculator (14 variables) has been compared [19] with the strategies utilised in the FPHN registry [8] and in the Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry [7]. In this experience the data showed that, based on the 12-month mortality, the correspondences between the low-, intermediate- and high-risk groups as defined by the 2015 ESC/ERS PH guidelines and the REVEAL 2.0 calculator (14 variables) were as follows: low risk=REVEAL score ⩽6, intermediate risk=REVEAL score 7 and 8, and high risk=REVEAL score ⩾9. The authors propose a more discriminating risk stratification provided by the REVEAL score, although it is not clear how this translates to the approach to treatment [7].

The limitations of the REVEAL score include the relatively short prediction period (1 year) when assessed at follow-up and the large number of variables required (from 12 to 14 variables). Simplified versions of the REVEAL score utilising high-yield variables seem to have a similar predictive value as the original version [26].

The 2015 ESC/ERS PH guidelines have recommended a flexible approach to PAH patient risk assessment: using a multidimensional stratification according only to modifiable clinical, functional, exercise, biochemical, echocardiographic and haemodynamic variables with known prognostic significance (ESC/ERS PH guidelines Table 13 Risk assessment in PAH). Patients were categorised as low, intermediate or high risk based on expected 1-year mortality [1, 2]. Recently, a retrospective analysis of three major registries (total of 3135 patients) provided an independent validation of this approach and showed a clear difference in 5-year survival or transplantation-free survival, depending on risk stratification category at both baseline and first follow-up [6–8]. In addition, post hoc analysis of the SERAPHIN haemodynamic substudy has shown a reduction in the morbidity and mortality end-point if low-risk haemodynamics thresholds included in the 2015 ESC/ERS PH guidelines were reached after 6 months of treatment with macitentan [27].

Interestingly, the risk stratification strategies have varied significantly among the registry studies: in the Swedish PAH Registry (SPAHR) [6] and COMPERA [7] studies (both including IPAH and associated PAH patients), individual risk was calculated at baseline and at the first follow-up by assigning a score of 1, 2 or 3 to each criterion (1=low risk, 2=intermediate risk and 3=high risk according with the 2015 ESC/ERS PH guidelines) and rounding to the mean of the available variables. In the FPHN registry [8], risk assessment was performed in incident IPAH patients according to the presence of four low-risk criteria: World Health Organization (WHO)/New York Heart Association Functional Class (FC) I or II, 2) 6-min walk distance (6MWD) >440 m, 3) right atrial pressure (RAP) <8 mmHg and 4) cardiac index ⩾2.5 L·min^{-1}·m^{-2}. Patients were classified according to the number of low-risk criteria present at baseline (i.e. at the time of PAH diagnosis) or at the time of re-evaluation. As exploratory analyses, the additive value of BNP <50 ng·L^{-1} or N-terminal pro-BNP (NT-proBNP) <300 ng·L^{-1} plasma levels or mixed venous oxygen saturation (SvO_2) >65% as low-risk criteria was assessed in the subsets of patients for whom these data were available.

Recently, the FPHN non-invasive risk assessment strategy using three dichotomised low-risk criteria (FC, 6MWD and NT-proBNP or BNP plasma levels) has been applied to the COMPERA cohort at baseline and at the first follow-up: the authors conclude that the FPHN risk assessment strategy provides a more accurate identification of patients with an excellent long-term survival than the approach of averaging risk scores [9].

Interestingly, the variables with the highest yield in the registriy analyses are similar, i.e. FC, 6MWD, NT-proBNP or BNP plasma levels, cardiac index, RAP and SvO_2 [6–8]. These variables are appropriate at

both baseline and first follow-up, and the fulfilment of low-risk criteria in three or four parameters represents a clinical response to the treatment that portends a good prognosis [8, 9]. A new risk stratification strategy based on four criteria and using these six variables has recently been proposed [28].

The limitations of the 2015 ESC/ERS PH guidelines risk table are related to the presence of "overlap patients" with prognostic parameters belonging to more than one risk designation [1, 2]. This problem has been addressed in the registry analyses with both the "score and average" method of the SPAHR and COMPERA registries and the "low-risk focused" method of the FPHN study. These methods may prove to be difficult to utilise in clinical practice, particularly for the exact distinction between intermediate- and high-risk status in individual patients. In addition, the simplified approach does not include non-modifiable or partially modifiable prognostic parameters such as age, sex, PAH type and comorbidities (renal insufficiency, diabetes mellitus, coronary artery diseases, *etc.*).

There are several limitations present in all risk assessment methods, including the retrospective nature of the validating analyses even when applied to prospective observational registries. In addition, data collection was not standardised in all published registries, and significant missing data and numbers of patients lost to follow-up were reported. Other important prognostic variables such as echocardiographic, cardiac magnetic resonance imaging and cardiopulmonary exercise test data were not collected systematically or analysed. Life-threatening complications such as haemoptysis, pulmonary artery aneurismal dilatation with chest organ compression, arrhythmias, *etc.*, are not included in the current risk stratification tools. The exact influence of these parameters on the risk level designation and on the consequent treatment decisions need to be clarified in future and prospective studies. These data should be considered as part of a comprehensive risk assessment strategy which, of course, should also include clinical judgement [29].

Clinical trials in PAH

Figure 1 shows the time-course of the 41 RCTs performed in 9061 PAH patients and published so far [30–70]. 21 RCTs tested monotherapy *versus* placebo, 18 RCTs included patients already treated and tested sequential combination therapy *versus* background therapy plus placebo, and finally two RCTs enrolled treatment-naive patients and tested initial monotherapy *versus* initial double combination therapy. The different treatment strategies adopted and compared, and the diverse background therapies of enrolled PAH patients, has allowed evidence to be collected on efficacy and safety for the multiplicity of conditions encountered in clinical practice.

An important evolution in PAH RCT design is the shifting of the primary end-point from a short-term correlate such as 6MWD to a long-term true clinical efficacy measure such as clinical worsening [60, 68, 69] or clinical failure [67]. Interestingly, this change in strategy was recommended by the Task Force on Clinical Trials Design at the 4th WSPH held in Dana Point, CA, USA, in 2008 [71]. This shift has supported an increase in the level of evidence of the efficacy of the tested PAH drugs according with the scale adopted by experts [72, 73].
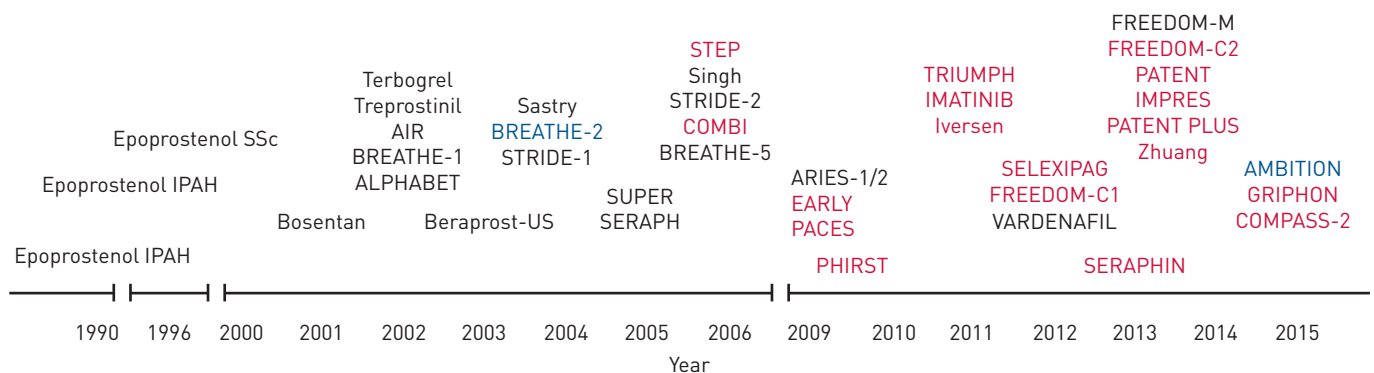
FIGURE 1 Time-course of completed randomised controlled trials (RCTs) in pulmonary arterial hypertension (PAH) (n=41) according to treatment strategy. SSc: systemic sclerosis; IPAH: idiopathic PAH. Reproduced and modified from [70] with permission.

The effect of PAH drugs on mortality was explored in a meta-analysis of 3839 patients enrolled in 25 RCTs testing monotherapy *versus* placebo in treatment-naive patients and reporting a risk reduction of 44% (p=0.016) in the 14 weeks of the average treatment comparison time [70, 74]. An additional meta-analysis was performed in 4095 patients enrolled in 17 RCTs that compared sequential combination therapy with monotherapy [75]: in this analysis, sequential therapy was associated with a significant risk reduction for clinical worsening (−35%; p<0.0001), but not mortality (−14%; p=0.09). The potential reasons for the lack of apparent mortality benefit include reduced statistical power of this meta-analysis for mortality as well as an overall reduced number of fatal events linked also to a short duration of the treatment comparison period [75].

In summary, based on global experience collected in the RCTs on PAH patients, the following comments can be proposed:

- *In treatment-naive PAH patients, initial monotherapy* is able to improve exercise capacity, haemodynamics and outcome compared with untreated patients [70, 74].
- *In treatment-naive and newly diagnosed (incident) PAH patients, initial combination therapy* is able to improve symptoms, exercise capacity and outcome compared with initial monotherapy [67, 76].
- *In already treated (prevalent) PAH patients, sequential combination therapy* is able to improve exercise capacity, haemodynamics and outcome compared with patients continuing with their background therapy [60, 69, 75].

General measures and supportive therapy

No major advances have been reported on general measures and supportive therapy since the publication of the 2015 ESC/ERS PH guidelines, and the recommendations included in the 2015 ESC/ERS PH guidelines *Table 16 Recommendations for general measures* and *Table 17 Recommendations for supportive therapy* can be referred to [1, 2]. In particular, oral anticoagulant therapy is not recommended in associated forms of PAH, while in IPAH, heritable PAH (HPAH) and drug-induced PAH the data on efficacy is more conflicting. Therefore, in this subgroup, the decision about anticoagulation has to be made on a case-by-case basis after an individual risk–benefit analysis. The 2015 ESC/ERS PH guidelines suggest that PAH patients should be advised to be active within symptom limits, but to avoid excessive physical exertion if this causes symptoms. Physically deconditioned patients who are stable on targeted medication are also advised to undertake supervised exercise training. Recently, two further RCTs and meta-analyses have been published in this regard, confirming the positive effect of training in PAH [77, 78].

Treatment algorithm

The recommended treatment algorithm for PAH patients is shown in figure 2.

The PAH treatment algorithm does not apply to patients in other clinical groups, and in particular it does not apply to patients with PH associated with group 2 (left heart disease) or group 3 (lung diseases). In addition, the different treatments have been evaluated by RCTs mainly in IPAH, HPAH, PAH due to drugs and in PAH associated with connective tissue disease, with Eisenmenger syndrome or with corrected congenital heart disease. The haemodynamic inclusion criteria in the majority of the RCTs were as follows: pulmonary arterial wedge pressure ⩽15 mmHg, mean pulmonary arterial pressure ⩾25 mmHg and pulmonary vascular resistance >3 Wood Units (>5 Wood Units in some RCTs). *It is not clear if the efficacy/safety ratio of the PAH drugs is favourable when used in patients not fulfilling the above criteria.* There is insufficient evidence to make recommendations in group 5 patients.

Since the release of the 2015 ESC/ERS PH guidelines no new RCTs leading to the approval of new PAH treatments have been published; we refer to the tables of these guidelines for the classes of recommendations and the level of evidence of the approved PAH treatments [1, 2]. In particular, the guidelines tables of interest are: *Table 1 Classes of recommendations*, *Table 2 Level of evidence*, *Table 19 Recommendations for efficacy of drug monotherapy*, *Table 20 Recommendations for efficacy of initial drug combination therapy*, *Table 21 Recommendations for efficacy of sequential drug combination therapy*, and *Table 22 recommendations for efficacy of intensive care unit management, balloon atrial septostomy and lung transplantation*. Amendments to these tables are required only for approvals granted by regulatory agencies after the 2015 ESC/ERS PH guidelines as follows: selexipag has been approved by the European Medicines Agency in patients with WHO FC II either as double or triple combination with an ERA and/ or a PDE5i, or as monotherapy in patients who are not candidates for these therapies.

The 2015 ESC/ERS PH guidelines tables provide the necessary evidence for alternative evidence-based therapeutic strategies recognising that the therapeutic approach to PAH may vary depending on local availability (and expertise) of therapeutic options in various hospitals and clinical settings. In these tables, only the compounds officially approved for PAH or under regulatory approval process in at least one
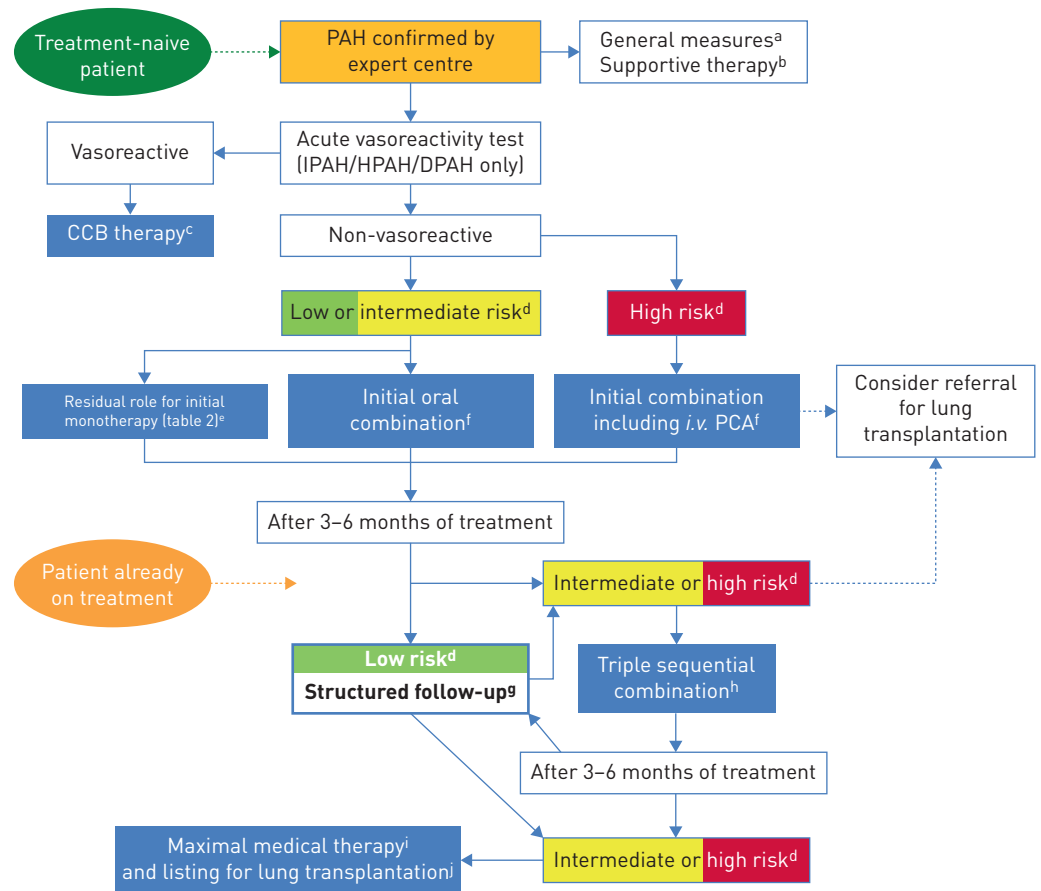
FIGURE 2 Treatment algorithm. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; DPAH: drug-induced PAH; CCB: calcium channel blocker; PCA: prostacyclin analogue; PH: pulmonary hypertension. [a]: 2015 ESC/ERS PH guidelines *Table 16*; [b]: 2015 ESC/ERS PH guidelines *Table 17*; [c]: 2015 ESC/ERS PH guidelines *Table 18*; [d]: 2015 ESC/ERS PH guidelines *Table 13*; [e]: 2015 ESC/ERS PH guidelines *Table 19*; [f]: 2015 ESC/ERS PH guidelines *Table 20*; [g]: 2015 ESC/ERS PH guidelines *Table 14*; [h]: 2015 ESC/ERS PH guidelines *Table 21*; [i]: maximal medical therapy is considered triple combination therapy including a *s.c.* or an *i.v.* PCA (*i.v.* preferred in high-risk status); [j]: 2015 ESC/ERS PH guidelines *Table 22*.

country are included. A four-level hierarchy for end-points in RCT has been proposed by experts based on level of evidence regarding efficacy [72, 73]. According to this hierarchy, drugs or combination of drugs with outcome as the primary end-point in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined) have been highlighted with a footnote in the 2015 ESC/ERS PH guidelines *Tables 19–21*.

Treatment algorithm description
See the treatment algorithm in figure 2.

Initial approach

- After confirmation of the diagnosis of the treatment-naive PAH patient in an expert centre, the suggested initial approach is the adoption of *general measures* and the initiation of *supportive therapy* (2015 ESC/ERS PH guidelines *Tables 16* and *17*).
- *Acute vasoreactivity testing* should be performed to predict response to calcium channel blocker (CCBs) only in patients with IPAH, HPAH, and PAH associated with drugs and toxin use. Vasoreactive patients (see the Task Force article by SIMONNEAU *et al.* [79] in this issue of the *European Respiratory Journal*) should be treated with *high doses (progressively titrated) of CCBs*; adequate response should be confirmed after 3–6 months of treatment (2015 ESC/ERS PH guidelines *Table 18*). *Adequate treatment response to high doses of CCBs* is considered WHO FC I/II with sustained haemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only. Vasoreactive patients without an adequate treatment response to high doses of CCBs

TABLE 2 Potential role for initial monotherapy in specific pulmonary arterial hypertension (PAH) subsets
IPAH, HPAH and drug-induced PAH patient responders to acute vasoreactivity tests and with WHO FC I/II and sustained haemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only
Long-term-treated historical PAH patients with monotherapy (>5–10 years) stable with low-risk profile
IPAH patients >75 years old with multiple risk factors for heart failure with preserved LVEF (high blood pressure, diabetes mellitus, coronary artery disease, atrial fibrillation, obesity)
PAH patients with suspicion or high probability of pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis
Patients with PAH associated with HIV infection or portal hypertension or uncorrected congenital heart disease, as they were not included in RCTs of initial combination therapy
PAH patients with very mild disease (*e.g.* WHO FC I, PVR 3–4 WU, mPAP <30 mmHg, normal right ventricle at echocardiography)
Combination therapy unavailable or contraindicated (*e.g.* severe liver disease)

IPAH: idiopathic PAH; HPAH: heritable PAH; CCB: calcium channel blocker; PAP: pulmonary arterial pressure; PVR: pulmonary vascular resistance; LVEF: left ventricular ejection fraction; RCT: randomised controlled trial; WHO: World Health Organization; FC: Functional Class; WU: Wood Units; mPAP: mean PAP.

should be treated with approved PAH medications according to the non-vasoreactive patients' treatment strategy.

- *Non-responders to acute vasoreactivity testing who are at low or intermediate risk* should be treated with *initial oral combination therapy with an ERA and a PDE5i* (2015 ESC/ERS PH guidelines *Table 20*) [76, 80, 81].
- Some specific PAH subsets in which the efficacy/safety ratio of initial combination therapy is not established (table 2) should be treated with initial monotherapy.

Recommendations for initial monotherapy are reported in the 2015 ESC/ERS PH guidelines *Table 19*.

- If initial monotherapy is chosen, as head-to-head comparisons among different compounds are not available, no evidence-based first-line monotherapy can be proposed. The choice of drug may depend on a variety of factors, including approval status, labelling, route of administration, side-effect profile, potential interaction with background therapies, patient preferences, comorbidities, physician experience and cost.
- *In non-vasoreactive and treatment-naive patients at high risk*, initial combination therapy including *i.v.* PCAs is recommended (2015 ESC/ERS PH guidelines *Table 20*). Intravenous epoprostenol receives the strongest recommendation as it has reduced the 3-month rate of mortality in high-risk PAH patients also as monotherapy (2015 ESC/ERS PH guidelines *Table 19*) [82]. Alternative types of initial combination therapy may be considered (2015 ESC/ERS PH guidelines *Table 20*). Referral for lung transplantation should also be considered.

Follow-up therapy

- *When the initial treatment approach results in a low-risk status* within 3–6 months, the therapy should be continued and structured follow-up established (2015 ESC/ERS PH guidelines *Table 14*).
- *When the initial treatment approach results in an intermediate-risk statu*s, escalation to triple combination therapy is recommended according to the 2015 ESC/ERS PH guidelines *Table 21* or to double combination in case monotherapy has been chosen. The combinations of macitentan and sildenafil [60], riociguat and bosentan [61], and selexipag and ERA and/or PDE5i [69] have the highest recommendation and evidence. PCAs should also be considered. The combination of riociguat and PDE5i is contraindicated [62]. Referral for lung transplantation should also be considered.
- *When the initial treatment approach results in a high-risk status*, maximal medical therapy including *i.v.* PCAs is recommended (2015 ESC/ERS PH guidelines *Table 20*). Referral for lung transplantation should also be considered.
- *When the second treatment step results in the low-risk status* within 3–6 months, the therapy should be continued and structured follow-up continued (2015 ESC/ERS PH guidelines *Table 14*). Referral for lung transplantation should also be considered according to local rules for organ allocation and average waiting time in the list.
- *When the second treatment step results in an intermediate- or high-risk status*, escalation to maximal medical therapy is recommended according to the 2015 ESC/ERS PH guidelines *Table 21*. *Maximal medical therapy is considered to be triple combination therapy* including a *s.c.* or an *i.v.* PCA (*i.v.* preferred in high-risk status). For patients on intermediate-risk status on double combination therapy with an ERA and a PDE5i or riociguat, the addition of selexipag should be considered [69]. For

patients on triple combination therapy including selexipag who remain in the intermediate-risk group or progress to high risk, the substitution with *s.c.* or *i.v.* PCAs should be considered. Referral for lung transplantation should also be considered.

- *Patients on follow-up with low-risk status who deteriorate* to the intermediate- or high-risk group should be treated with double, triple or maximal combination therapy depending on the initial background treatment.
- We recommend consideration of lung transplantation in all patients on maximal triple combination therapy, with priority for those in intermediate- and high-risk groups, in accordance with local rules for organ allocation and average waiting time in the list (2015 ESC/ERS PH guidelines *Table 22*) (see the Task Force article by HOEPER *et al.* [83] in this issue of the *European Respiratory Journal*).
- Advanced treatments for patients in severe right ventricular failure who are admitted to intensive care units are reported by HOEPER *et al.* [83].
- Balloon atrial septostomy should be regarded as a palliative or bridging procedure in patients deteriorating despite maximal medical therapy.

Transitions of PAH therapies

Clinicians might consider transitioning from one PAH-specific therapy to another for a number of reasons, including improvement of the side-effect profile and convenience or compliance with therapy. In patients who are not meeting treatment goals, transitions are considered to escalate therapy and improve patient status. Occasionally, patients have an extraordinary response to therapy and transition to a less invasive therapy is considered. As much of the literature on this topic is retrospective, prospective but observational or prospective randomised but open label, we do not recommend this approach except in rare circumstances and under close expert care. One study showed that, in carefully selected patients, the transition from *i.v.* epoprostenol to *i.v.* treprostinil was achievable around 80% of the time [84]. Transition from parenteral epoprostenol to the thermostable form was generally achievable [84].

There have been conflicting outcomes in the transition from parenteral prostacyclins to inhaled or oral prostacyclins [84]. When discontinuation of bosentan is necessary due to liver function test elevations, transitioning to ambrisentan [85] or macitentan is safe.

In case of lack of efficacy, transition from selexipag or non-parenteral PCAs to *s.c.* or *i.v.* PCAs is recommended.

There is insufficient evidence to recommend transition from sildenafil or tadalafil to riociguat for improving efficacy [86]. An additional open-label, randomised study is currently ongoing on this issue (ClinicalTrials.gov identifier NCT02891850).

PAH complications

PAH-related hospitalisations which usually are associated with different types of complications are predictive of mortality in *post hoc* analyses of the SERAPHIN and GRIPHON studies [87]. Recommendations for the diagnosis and treatment of arrhythmias, haemoptysis and mechanical complications related to the dilatation of the pulmonary artery are already reported in the 2015 ESC/ERS PH guidelines [1, 2]. Recently, a study has reported a large series of PAH patients with angina or angina-like symptoms who underwent percutaneous coronary interventions with stenting due to severe left main coronary artery stenosis by extrinsic compression from a dilated pulmonary artery [88]. The favourable acute and long-term results of this procedure suggest increased awareness for this important and potentially catastrophic complication.

Conclusions

Assessment of the severity of the newly diagnosed PAH patient by a multiparametric risk stratification approach is utilised for defining a low-, intermediate- or high-risk status. According to the risk status, the multiple drugs approved for PAH, interfering with the endothelin, NO and prostacyclin pathways, can be utilised with different strategies including monotherapy or combination therapies. Further treatment escalation is required in case low-risk status is not achieved in planned follow-up assessments. Low-risk patients should continue with the chosen therapy and be assessed accurately in a structured follow-up to timely identify possible deteriorations. Triple combination therapy and lung transplantation may be required in most advanced cases.

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