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Treatment of pulmonary arterial hypertension (PAH): Updated Recommendations of the Cologne Consensus Conference 2011☆

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ABSTRACT

The 2009 European Guidelines on Diagnosis and Treatment of Pulmonary Hypertension have been adopted for Germany. The guidelines contain detailed recommendations on the diagnosis of pulmonary hypertension (PH). However, the practical implementation of the European Guidelines in Germany requires the consideration of several country-specific issues and already existing novel data. This requires a detailed commentary to the guidelines, and in some aspects an update already appears necessary. In June 2010, a Consensus Conference organized by the PH working groups of the German Society of Cardiology (DGK), the German Society of Respiratory Medicine (DGP) and the German Society of Pediatric Cardiology (DGPK) was held in Cologne, Germany. This conference aimed to solve practical and controversial issues surrounding the implementation of the European Guidelines in Germany. To this end, a number of working groups was initiated, one of which was specifically dedicated to the treatment of pulmonary arterial hypertension (PAH). This commentary describes in detail the results and recommendations of the working group on treatment of PAH which were last updated in October 2011.

Preliminary remarks

This article is part of a supplement of the *International Journal of Cardiology* in which the results of a Consensus Conference on pulmonary hypertension are described that took place in June 2010 in Cologne, Germany, and was organized by the PH working groups of the German Society of Cardiology (Deutsche Gesellschaft für Kardiologie, DGK), the German Society of Respiratory Medicine

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(Deutsche Gesellschaft für Pneumologie, DGP) and the German Society of Pediatric Cardiology (Deutsche Gesellschaft für pädiatrische Kardiologie, DGPK). This conference addressed practical issues surrounding the implementation of the European Guidelines for diagnosis and therapy of pulmonary hypertension in Germany. To this end, a number of working groups was initiated, one of which was specifically dedicated to the treatment of pulmonary arterial hypertension (PAH). The authors were members of this working group. The corresponding articles were initially published in the *Deutsche Medizinische Wochenschrift*, and the information was now updated in October 2011. Below, the corresponding sections of the European Guidelines are described [1–3] whereby comments and additions appear in italics. The information on class of recommendation and level of evidence correspond to the tables listed in the preamble of this supplement.

1. Introduction

In the past few years, treatment of PAH has undergone an extraordinary evolution, which has led to the current approval by regulatory agencies of seven targeted PAH drugs with different routes of administration. The approval of additional drugs is expected in the near future. Modern drug therapy leads to a significant improvement in patients' symptomatic status and a slower rate of clinical deterioration. In addition, a meta-analysis performed on 23 randomized controlled trials (RCTs) in PAH patients (published prior to October 2008) reports a 43% decrease in mortality and a 61% reduction in hospitalizations in patients treated with specific drug therapies vs. patients randomized to placebo [4]. These results, achieved after an average treatment period of 14.3 weeks, support the efficacy of the currently approved PAH treatments. Despite this finding, PAH remains a chronic disease without a cure. In addition, the medical and interventional treatments for more advanced cases are still invasive (e.g. continuous parenteral prostanoid therapy) and prone to significant side effects [1,2].

The therapy of PAH patients cannot be considered as a mere prescription of drugs but is characterized by a complex interdisciplinary strategy which includes the evaluation of severity, supportive and general measures, the assessment of vasoreactivity, the estimation of efficacy, and combination of different drugs plus interventions (e.g. atrial septostomy, transplantation). In any of these steps, the knowledge and experience of the responsible physicians are critical to optimize the available resources [1,2].

Comment:

In light of the high costs of targeted PAH therapies, the consideration of cost efficacy is of relevance. However, when treating patients with a life-threatening disease, medical necessities must always be paramount.

In this context, it is crucial to ensure a proper diagnostic work-up and classification, and to prescribe targeted PAH therapies within the approved indication and meet the requirements of each individual patient. It is the responsibility of PH expert centers to ensure this.

2. General measures

Psychosomatic or psychological as well as social work support are important for patients with PAH as is the case in all chronic diseases. Encouraging patients and their family members to join patients support groups (in Germany "pulmonale hypertonie e.V. [phev]") can have positive effects on coping, confidence, and outlook [1,2].

Although patients should be encouraged to be active within symptom limits, excessive physical activity that leads to distressing symptoms (e.g., severe breathlessness, exertional dizziness, chest pain, syncope, etc.) should be avoided. On the other hand, there is growing evidence for the value of supervised physical training programs in improving exercise performance [5,6]. Physically deconditioned patients may therefore undertake supervised exercise rehabilitation. This should however only take place in facilities that are specially trained in PAH, and this approach requires further scientific exploration [1,2].

Table 1
Recommendations for general measures [1,2].

Statement	Class of recommendation	Level of evidence
It is recommended to avoid pregnancy in patients with PAH	I	C
Immunization of PAH patients against influenza and pneumococcal infection is recommended	I	C
Physically deconditioned PAH patients should be considered for supervised exercise rehabilitation	IIa	B
Psychosocial support should be considered in patients with PAH	IIa	C
In-flight O_2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently less than 8 kPa (60 mmHg)	IIa	C
Epidural anaesthesia instead of general anaesthesia should be utilized, if possible, for elective surgery	IIa	C
Excessive physical activity that leads to distressing symptoms is not recommended in patients with PAH	III	C

Patients with PAH should avoid pregnancy. Appropriate consultation and reliable contraception is necessary whereby pharmacological interactions with PAH drugs that may affect the efficacy of hormonal contraceptives must be pointed out.

Travelling to altitudes above 1,500–2,000 m without supplemental O_2 should be avoided. During air travel, the known physiological effects of hypoxia suggest that in-flight O_2 administration should be considered for patients in WHO functional class III and IV and those with arterial blood O_2 pressure consistently below 8 kPa (60 mmHg). A flow rate of 2 L/min will raise inspired O_2 pressure to values seen at sea level [1,2] (see comment*).

Regular immunizations against influenza and pneumococcal infections are recommended [1,2].

Elective surgery is expected to have an increased risk in patients with PAH. It is not clear as to which form of anaesthesia is preferable but epidural is probably better tolerated than general anaesthesia [1,2].

Comment:

The risk of severe complications during and after pregnancy is particularly high in IPAH/HPAP, and considerable in Eisenmenger's syndrome. The level of endangering depends, among others, on the extent of pulmonary hypertension and may be highest in patients in whom pulmonary artery pressure exceeds half-systemic pressure. Exact cut-off values are not known. In PH due to a left-to-right shunt, the hazard level depends on the size of the shunt, the (dys)function of the affected parts of the heart, and the risk of paradox embolism. In such cases, shunt closure should be considered before pregnancy. The few cases of uncomplicated pregnancies in patients with IPAH/HPAH or with Eisenmenger's syndrome should not be reason to diverge from the general recommendation to avoid pregnancy in women with severe pulmonary hypertension.

Supervised exercise training with adjusted physical strain by a highly qualified team in a specialized rehabilitation center has been evaluated by a German working group and showed a significant improvement of exercise capacity at 3 months [5]. There is also recent

evidence of the safety and long-term efficacy of the training program. However, is has so far not been investigated if a generalization and the safe application outside of these special conditions is warranted. Furthermore, it remains unclear if controlled physical training – beyond its effects on clinical symptoms – leads to an improvement of survival and/or hemodynamics. Prospective studies investigating this are currently under way.

Depression considerably impairs the quality of life of PAH patients, is associated with inadequate patient behavior, and may have a negative effect on adherence and the course of the disease. Psychological comorbidity (especially depression, anxiety and adjustment disorders) should therefore be documented on a routine basis by the use of screening questions or questionnaires. The following two screening questions may be appropriate to appraise the danger to the patient from depression with high sensitivity and specifity [7]:

- *"Did you frequently suffer from feelings of dejection, depression, or hopelessness in the past month?"*
- *"Did you frequently suffer from lack of interest or joylessness in the past month?"*

One available questionnaire is e.g. the German version of the "Hospital Anxiety and Depression Scale" (HADS-D), representing an economic instrument that is especially suited for patients with physical illnesses. Patients should be offered focused psychotherapy and/or pharmacological antidepressive treatment [8].

Elective surgical interventions should always be performed in close cooperation with specialized PH centers. Epidural anaesthesia may lead to loss of vascular tone in the lower extremities which has negative impact on venous return and systemic pressure, and may therefore lead to shunt reversal in the respective patients. Therefore, conduction anesthesia should only be carried out by experienced physicians, and potential complications must always be considered. General anaesthesia may be beneficial in individual cases.

**Air travel: It should be emphasized that the evidence for the recommendations given in the ESC/ERS guidelines is rather low. Patients with shunt-related hypoxemia seem to react less sensitive to hypoxia than those with pulmonary hypoxemia. The sensitivity of hypoxemia caused by pulmonary vascular disease is not known. A recently conducted survey in more than 720 patients in Germany (supported by the German patient organization [phev]) demonstrated good safety (no adverse events) during air travel in patients with stable pulmonary vascular disease. 29 of 57 patients on outpatient oxygen therapy used oxygen during the flight [9]. Further international prospective studies will be required in order to make appropriate recommendations.*

3. Supportive therapy

3.1. Oral anticoagulants

Despite insufficient available data, oral anticoagulation is recommended in PAH patients unless there are contraindications. Evidence in favour of oral anticoagulation is confined to patients with IPAH, HPAH, and PAH due to anorexigens; it is generally retrospective and based on single center experience [1,2]. Hence, a class IIa recommendation is given for oral anticoagulation in IPAH, heritable PAH, and PAH due to anorexigens, and a class IIb recommendation is given for patients with APAH (Table 2). The recommended target INR is 2.0–3.0. (Special recommendations for patients with Eisenmenger's syndrome and portopulmonary hypertension are listed in Tables 7 and 9).

3.2. Diuretics

Although there are no randomized controlled trials of diuretics in PAH, clinical experience shows clear symptomatic benefit in fluid-overloaded patients treated with this therapy. Therefore, diuretics are used according to the clinical situation. Since there is no data for the superiority or inferiority of individual substances, the choice and dose of diuretic therapy may be left to the PAH physician. The addition of aldosterone antagonists should also be considered [1,2].

Table 2
Recommendations for supportive therapy [1,2].

Statement	Class of recommendation	Level of evidence
Diuretic treatment in PAH patients with signs of right ventricular failure and fluid retention	I	C
Continuous long-term oxygen therapy is indicated in PAH patients when arterial blood O_2 pressure is consistently <8 kPa (60 mmHg)[a]	I	C
Oral anticoagulant treatment should be considered in patients with IPAH, heritable PAH, and PAH due to use of anorexigens	IIa	C
Oral anticoagulant treatment can be considered in patients with APAH	IIb	C
Digoxin may be considered in patients with PAH who develop atrial tachyarrhythmias to slow ventricular rate	IIb	C

[a] See also recommendations for PAH associated with congenital cardiac shunts (Table 9).

3.3. Oxygen

The guidance with regard to long-term oxygen therapy in patients with PAH is mainly based on evidence in patients with COPD: When arterial blood O_2 pressure is consistently less than 8 kPa (60 mmHg) patients are advised to take O_2 to achieve an arterial blood O_2 pressure of >8 kPa for at least 15 h/day. Ambulatory O_2 may be considered when there is evidence of symptomatic benefit and correctable desaturation on exercise [1,2]. Since there are no randomized data to suggest that long-term O_2 therapy is beneficial in patients with PAH, the decision for O_2 therapy has to be made on an individual basis.

3.4. Treatment of arrhythmias

The ECS/ERS guidelines include only a brief comment about the use of digoxin for the treatment of atrial tachyarrhythmias to slow ventricular rate. This, however, does not adequately meet the requirements of many patients (see comment).

Comment:

Diuretic therapy may also be indicated for the prevention of right ventricular failure and fluid retention. The indication for the use of diuretics is often based on the central venous pressure measured during right heart catheterization. Furthermore, peripheral edema in the lower extremities, concomitant pleural and/or pericardial effusion as well as ascites represent clinical signs that are indicative for diuretic therapy. While there is no general recommendation as to which class of diuretics should be used, low to moderate doses of aldosterone antagonists are mostly combined with loop diuretics.

The indication for long-term O_2 treatment in Eisenmenger's syndrome is controversial. Adults with Eisenmenger's syndrome usually do not benefit from such treatment, and the risks and side effects (e.g. exsiccosis of the nasal mucosa, tendency to epistaxis, sleep disorders) must be considered. In such cases, O_2 treatment should be limited to individual patients who subjectively benefit from this treatment or to special situations (e.g. pulmonary infections).

While ventricular tachycardia is rather uncommon in patients with PAH, supraventricular tachycardia – especially atrial flutter/fibrillation

– occurs more frequently. Even when the ventricular rate remains normal, such arrhythmias usually lead to significant clinical worsening and progressive right ventricular failure if left untreated [10]. These patients benefit from aggressive therapy, aiming at restoring sinus rhythm. Even though the available data for treating these arrhythmias in PAH is sparse, restoring or maintaining the sinus rhythm should be attempted whenever possible. Medical treatment with amiodarone or interventional techniques (ablation) may be indicated. Although β-blockers and calcium channel blockers bear risks due to their negative inotropic effects, they may be indicated in individual cases.

Current data demonstrate that the presence of anemia and iron deficiency in patients with pulmonary hypertension correlates negatively with disease severity and all-cause mortality [11,12]. Therefore, appropriate replacement therapy may be helpful – similar as reported for patients with left heart failure. However, the available data for patients with pulmonary hypertension should be regarded as preliminary, and further data must be collected, especially with regard to therapeutic consequences.

4. Targeted PAH drug therapy

Regarding targeted PAH drug therapy, only the most important aspects of individual therapies are described in this manuscript. For detailed information please refer to the European guidelines and to specialized literature [1–3,13–27]. The recommended use of the available agents is demonstrated in a treatment algorithm in Fig. 1 [1,2]. The grades of recommendation and the levels of evidence for the individual PAH treatments are also shown in Table 3. Country-specific regulatory approval and labeling for PAH medical treatments are listed in Table 4.

Comment:

The approval for inhaled treprostinil was given in 2009 by the FDA but denied in 2010 by the EMA. Therefore, this drug is currently only available in the USA.

5. Calcium channel blockers

Calcium channel blockers (CCB) are recommended only for PAH patients (not for other forms of PH) who demonstrate a favourable response to acute vasodilator testing at the time of right heart catheterization and meet the defined responder criteria (see article on invasive diagnosis of PH in this Supplement). It is increasingly recognized that one a small number of patients with IPAH meet the responder criteria and do well with CCBs [28,29]. Patients who have not undergone a vasoreactivity study or those with a negative study should not be started on CCBs because of potential severe side effects (e.g. hypotension, syncope, RV failure) [1,2]. Therefore, treatment with CCBs should only be initiated at centers with comprehensive experience with PAH patients, since this therapy may have fatal consequences if not indicated.

The CCBs that have been predominantly used in reported studies are nifedipine, diltiazem, and amlodipine, with particular emphasis on the first two [28,29]. The daily doses of these drugs that have shown efficacy in IPAH are relatively high (120–240 mg for nifedipine, 240–720 mg for diltiazem, up to 20 mg for amlodipine). CCBs should be started at a low dose and up-titrated cautiously to the maximum tolerated dose. Limiting factors for dose increase are usually systemic hypotension and lower limb peripheral edema. If a patient does not show an adequate response (defined as being in WHO functional class I or II and marked hemodynamic improvement), additional PAH therapy should be instituted [1,2].

Comment:

Although most data is available for nifedipine and diltiazem, most PH centers in Germany predominantly use amlodipine. The initial dose

Table 3
Recommendations for the efficacy of specific PAH drug therapy, balloon atrial septostomy, and lung transplantation for PAH (group 1) according to WHO functional class [1,2][#].

Measure		WHO-FC II	WHO-FC III	WHO-FC IV
Calcium channel blockers		I-C[a]	I-C[a]	–
Endothelin receptor antagonists	Ambrisentan	I-A	I-A	IIa-C
	Bosentan	I-A	I-A	IIa-C
Phosphodiesterase type-5 inhibitors	Sildenafil	I-A	I-A	IIa-C
	Tadalafil	I-B	I-B	IIa-C
Prostanoids	Beraprost	–	IIb-B	–
	Epoprostenol (iv)	–	I-A	I-A
	Iloprost (inhaled)	–	I-A	IIa-C
	Iloprost (iv)	–	IIa-C	IIa-C
	Treprostinil (sc)	–	I-B	IIa-C
	Treprostinil (iv)	–	IIa-C	IIa-C
	Treprostinil (inhaled)[b]	–	I-B	IIa-C
Primary combination therapy		–	–	IIa-C
Sequential combination therapy		–	I-C	I-C
Balloon atrial septostomy		–	I-C	I-C
Lung transplantation		–	I-C	I-C

[a] Only in responders to acute vasoreactivity tests. Recommendation class I for idiopathic PAH, heritable PAH, and PAH due to anorexigens; IIa for APAH.
[b] Not approved by the EMA.
[#] Since the ERA sitaxentan has been withdrawn from the market, this compound has been removed from the original ESC/ERS table.

Table 4
Country-specific regulatory approval and labeling for PAH-specific drug therapy [1,2][#].

Treatment	Country	Etiology	WHO-FC
Calcium channel blockers	–	–	–
Ambrisentan	USA, Canada, EU	PAH	II–III–IV
Bosentan[a]	EU	PAH	II–III
	USA, Canada	PAH	II–III–IV
Sildenafil	USA, Canada	PAH	II–III–IV
	EU	PAH	II–III
Tadalafil	USA	PAH	II–III–IV
	EU	PAH	II–III
Beraprost[b]	Japan, Korea	PAH	II–III–IV
Epoprostenol (iv)[c]	EU	PAH	III–IV
Iloprost (inhaled)	EU	IPAH	III
	USA	PAH	III–IV
Iloprost (iv)	New Zealand	IPAH, PAH-CTD, CTEPH	III–IV
Treprostinil (sc)	USA	PAH	II–III–IV
	Canada	PAH	III–IV
	EU[d]	IPAH	III
Treprostinil (iv)	USA[e]	PAH	II–III–IV
Treprostinil (inhaled)[b]	USA	PAH	III

[a] Specifically approved also for PAH associated with congenital left-right shunts and Eisenmenger's syndrome.
[b] Not approved in Europe.
[c] Epoprostenol in Europe has not been centrally approved by the EMA but on a national basis in several European countries *(not in Germany)*.
[d] Treprostinil in Europe has not been centrally approved by the EMA but is approved in France and other countries on a national basis through the mutual recognition process.
[e] In case of intolerance of subcutaneous application.
CTD, connective tissue diseases; CTEPH, chronic thromboembolic pulmonary hypertension; EMA, European Medicines Agency (European Approval Agency); IPAH, idiopathic PAH; PAH: pulmonary arterial hypertension; WHO-FC: WHO functional class.
[#] Since the ERA sitaxentan has been withdrawn from the market, this compound has been removed from the original ESC/ERS table.

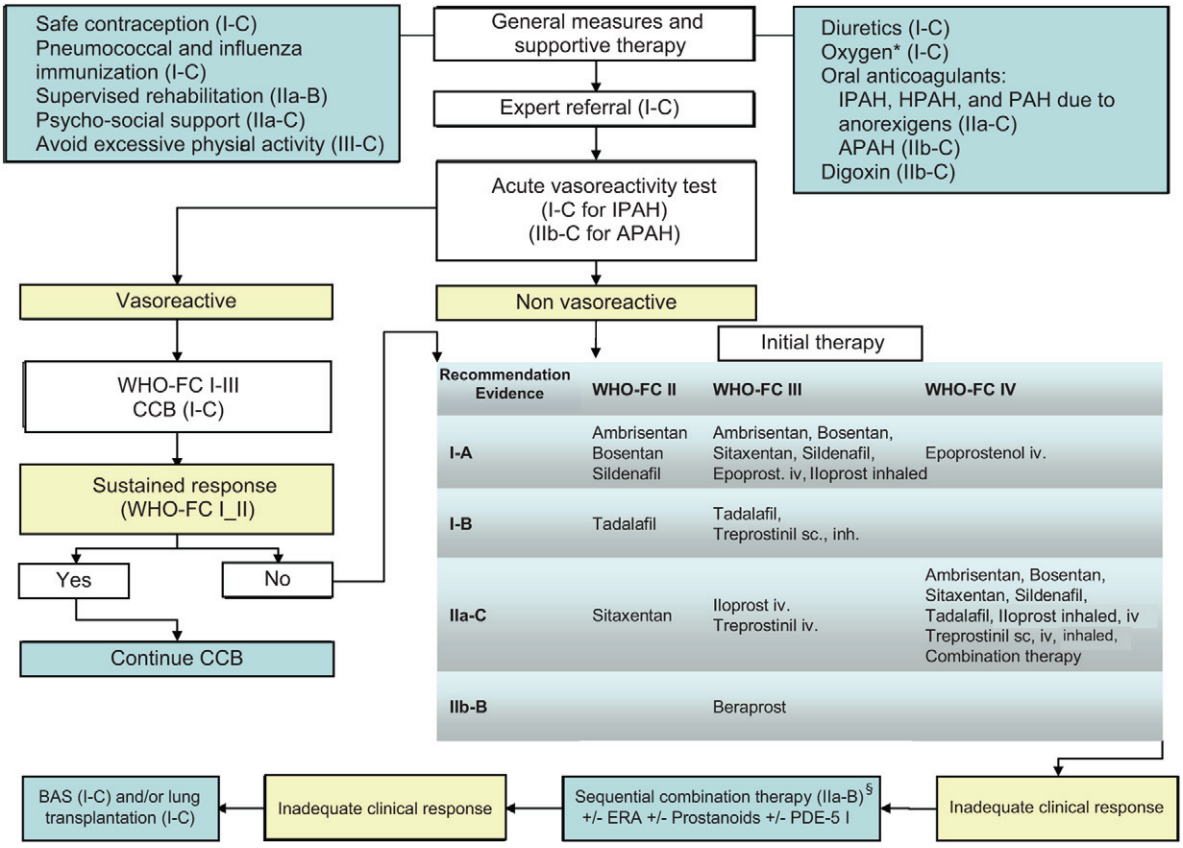

Fig. 1. Evidence-based treatment algorithm for patients with pulmonary arterial hypertension (for group 1 patients only) [1,2]#.
*In order to reach a systemic arterial pO2 ≥8 kPa (60 mmHg) + EMA evaluation is pending. § IIa-C for WHO-FC II. APAH, associated PAH; IPAH, idiopathic PAH; BAS, balloon atrial septostomy; LTX, lung transplantation; CCB, calcium channel blocker; ERA, endothelin receptor antagonist; PDE-5 I, phosphodiesterase type-5 inhibitor; WHO-FC, WHO functional class (corresponds to modified NYHA class). Combination therapy = combination of 2 or more specific PAH therapies.
Since the ERA sitaxentan has been withdrawn from the market, this compound has been removed from the original ESC/ERS treatment algorithm.

is 2.5 mg/day which – under careful monitoring – is increased to the normal target dose of 10–20 mg/day within a few weeks. Currently, it remains unclear how to use CCBs in patients who, although meeting the responder criteria, present with severely compromised right ventricular function (e.g. cardiac index <1.5 l/min/m²) at the time of vasoreactivity testing. Upon initiation of CCB therapy, it is conceivable that these patients could suffer right ventricular failure due to the cardiodepressive potential of CCBs before they may benefit from the desired effect. In such cases, it should be considered to primarily use one of the available targeted PAH therapies, and once right ventricular function has improved and after repeat right heart catheterization with vasoreactivity testing (provided that the responder criteria is still met), to initiate CCB therapy. During up-titration it is recommended to draw special attention to hypotension, obstipation, and any signs of right heart failure. Peripheral edema can mostly be managed with diuretics and/or compression stockings. PVOD patients meeting responder criteria are particularly prone to lung edema on CCBs.

6. Endothelin receptor antagonists (ERA)

All approved compound belonging to this drug class (bosentan, ambrisentan) are presumed potentially hepatotoxic and can only be prescribed by registered prescribers. Regular controls of amino-transferases (in 4-week intervals) are required. The specified target doses for ERAs apply to adult patients; for children or patients <40 kg body weight, it is referred to the respective summary of product characteristics and the section "special aspects concerning children" (see below).

- Bosentan [16,18,22,25] is a dual endothelin-A and -B receptor antagonist and is approved for the treatment of PAH in WHO functional class II and III. The target dose is 125 mg b.i.d. In children, bosentan is approved from the age of 2 years and is also available in a special pharmaceutical form of 32-mg tablets that can be quartered.
- Ambrisentan [21,30] is a selective endothelin-A receptor antagonist and is approved for the treatment of PAH in WHO functional class II and III with a target dose of 5–10 mg once daily.

Comment:

So far only bosentan has been investigated in a randomized controlled study with patients in functional stage II only, and demonstrated significant improvement of hemodynamics as well as a reduced rate of clinical events even though it did not achieve one of the predefined primary endpoints, the improvement of the 6-minute walking distance [22]. The European approval agency EMA evaluated the data from this study as sufficiently solid to also issue an indication for bosentan for the treatment of PAH patients in functional class II. Even if there is no such specific study for ambrisentan, the EMA decided on the basis of subgroup analyses of class II patients from the ARIES studies of ambrisentan, to initially issue approval also for functional class II patients [21]. Data from a postmarketing surveillance in the US showed no evidence of hepatotoxicity with the use of ambrisentan. Accordingly, the FDA has removed the recommendation to perform monthly transaminase controls in patients with ambrisentan therapy.

Sitaxentan [13,14] had also received approval by the EMA for the treatment of PAH in WHO functional class III. However, in december 2010 this compound was withdrawn from the market worldwide because of reported deaths that occurred most likely in association with idiosyncratic liver toxicity. Such effects have not been reported for other ERAs.

7. Phosphodiesterase type-5 (PDE-5) inhibitors

- Sildenafil [20,27] is approved for the treatment of PAH in functional class II and III at a dose of 20 mg t.i.d. In children, sildenafil is approved at the age between 1 and 17 years.
- Tadalafil [19] is approved for the same indication as sildenafil. The target dose for this compound is 40 mg once daily.

Comment:

There is consensus among the German PH experts that the currently approved dose of 20 mg t.i.d. for sildenafil should at times be exceeded during the course of long-term therapy of PAH patients. This is based on the clinical observation that patients, who initially show clinical and hemodynamic improvement on the approved dose may then deteriorate after a variable period of time. It is unclear, however, if this worsening reflects progression of the underlying disease or a beginning tolerance to the treatment with PDE-5 inhibitors. In many cases, an escalation of the sildenafil dose to up to 80 mg t.i.d. results in further improvement of the clinical condition and pulmonary hemodynamics. This observation is supported by published data. For example, the relevant SUPER-1 study demonstrated a clear correlation between the sildenafil dose and the hemodynamic improvement of examined patients (whereby 80 mg sildenafil t.i.d. was most effective) [20]. Furthermore, while there are no long-term efficacy data available for the 20 mg t.i.d. dose, by far most of the available long-term data on sildenafil were collected on PAH patients treated with 80 mg t.i.d. (including 3-year long-term follow-up data from the SUPER-2 study [31]). Similarly, the PACES study, a randomized, controlled trial on the combined use of intravenous prostacyclin and oral sildenafil, demonstrated for the first time a survival benefit in patients receiving combination therapy including sildenafil 80 mg t.i.d. as compared to patients who continued treatment with intravenous prostacyclin "only" [27]. While there is evidence for the use of sildenafil at dosages beyond the approved dose of 20 mg t.i.d. in selected PAH patients, dose increases exceeding 20 mg t.i.d. should only take place at or after consultation with a PH expert center.

For tadalafil, the highest dose (40 mg once daily) tested in a clinical development program (PHIRST study) has been approved [19]. Unlike sildenafil, there is no data in the available literature that would support higher doses for the treatment of PAH patients.

The equivalent oral doses for these two PDE-5 inhibitors are unknown.

A postmarketing surveillance in children with PAH showed increased mortality in those children with doses beyond the approved dose, and a warning letter has been issued. The reasons for the association between elevated doses and elevated mortality are a matter of discussion.

Sildenafil was recently approved by the EMA for intravenous use in patients with PAH who are prescribed oral sildenafil and are clinically and hemodynamically stable, but are temporarily unable to take orally applied medications.

8. Prostanoids

- Inhaled iloprost [24] is approved in Germany for IPAH in WHO functional class III. It is administered via special nebulizers at a dose of 2.5–5 μg, and inhalations have to be performed 6–9 times per day. Intravenous iloprost [32] is not approved in Europe but represents the most widely used intravenous prostanoid in Germany (see comment). Initiation of therapy and continuous dose adjustments should only be carried out in PH expert centers. As with other systemic prostanoids, there is a risk of life-threatening catheter infections and other side effects that typically occur during treatment with prostanoids (including hypotension, flushing, jaw pain and headaches, nausea, diarrhea, etc.).
- Intravenous epoprostenol [15] was recently approved in Germany, but is currently not widely used in this country.
- Treprostinil (inhaled, subcutaneous, intravenous, oral): oral treprostinil and intravenous treprostinil are not approved in Germany. Subcutaneous treprostinil [26] was not approved by the EMA but by the French pharmaceutical regulatory agency. This approval was adopted in Germany. Inhaled treprostinil [33] is approved in the USA but not in Europe. The approval of inhaled treprostinil in Germany is not expected in the near future.

Comment:

While in the ESC/ERS treatment algorithm, intravenous epoprostenol is the only recommended therapy with the highest level of evidence for patients in functional class IV and is also recommended with a high level of evidence for patients in functional class III (besides oral PDE-5 inhibitors, ERAs, and inhaled iloprost), this does not correspond to the established pattern of use in Germany. Historically, this may be explained by the fact that intravenous epoprostenol was only recently approved in Germany (and all other prostanoids are not approved for intravenous use) as well as the experience of local PH centers that even patients who are in advanced stages (WHO functional class IV) may be treated successfully with non-parenteral (usually combination) therapies (see also comment on combination therapies). Intravenous prostanoids (particularly intravenous iloprost) are generally only used in patients with impending or manifest right ventricular failure. Intravenous iloprost is then uptitrated from an initial dose of 0.25–0.5 ng/kg/BW/min to a short- to medium-term target dose of 2–4 ng/kg/min. The use of intravenous prostanoids should strictly be limited to PH expert centers that have appropriate substantial experience with such treatments. The choice of a permanently implanted central venous access varies from center to center (Hickman catheter vs. port systems) as does the preferred pump system. Intravenous prostacyclin (epoprostenol) which is the only approved and preferably administered prostanoid in other countries, is not widely used in Germany due to the comparably high costs, the chemical instability with the need of cooling and protection from light, and the associated limitations in practical application.

Treatment with inhaled iloprost is approved in Europe for patients with primary pulmonary hypertension (equivalent to IPAH and HPAH) in functional class III. This deviates from the recommendations in the ESC/ERS guidelines, the available data from the relevant phase III study (AIR, which enrolled patients with a broader PAH spectrum and patients with non-operable CTEPH) [24] as well as from the pattern of use in Germany. Inhaled iloprost is frequently used analogue to other targeted PAH drugs in patients with PAH. Regarding this indication, there is consensus among the expert group. In light of the elaborate administration as compared oral drugs (inhalation with a special device, the variable duration [6–12 min/inhalation] and high frequency of inhalations [6–9 times per day], inhaled iloprost is often used in sequential combination therapies only after oral ERA and/or PDE-5 inhibitors have already been used and the clinical improvement was not satisfactory (see also section on treatment goals). With regard to the approval situation it should be mentioned that unlike the EMA, the FDA has approved inhaled iloprost for the treatment of PAH in functional class III and IV. In Australia, inhaled iloprost is even approved for patients with non-operable CTEPH, thus representing the only approved PAH drug for this indication in a country with Western health standards.

9. Combination therapy

Since there is currently no cure for PAH, and in the majority of patients the treatment goals as defined below cannot be achieved or maintained by the use of monotherapy, a combination of the above compounds has become the standard of care in many PAH centers, although the long-term safety and efficacy have not

yet been amply explored. Numerous case series have suggested that various drug combinations appear to be safe and effective. In one series, a step-wise use of combination therapy according to predefined treatment goals was associated with an improved outcome compared with a historical control group [34]. Results of a few randomized controlled trials evaluating combination therapy for PAH have been published, most of which have demonstrated improved treatment results with a combination regimen [27,33,35]. The available data on combination therapy are still insufficient and there are many open questions, including the choice of combination agents, the optimal timing (initial combination in naive patients versus sequential combination according to the response to the first drug, when to switch, and when to combine. Therefore, no detailed recommendations can be given at present. When combination therapy is considered, patients should be treated within clinical trials or registries whenever possible [1,2].

Comment:

Combination therapies using compounds from the three approved drug classes, administered either sequentially or initially, constitute the established long-term form of treatment for the majority of patients with PAH. It is currently unclear if initial combination therapy should be preferred to sequential combination therapy, especially in patients with advanced stages of the disease (functional class III and IV). Since there are little data available from randomized controlled trials thus far, sequential combination therapy is mostly preferred in Germany at present. Usually, patients with PAH are initially treated with one of the approved oral targeted PAH drugs, i.e. either an ERA or a PDE-5 inhibitor. If the desired treatment goals are met within 3–6 months (see stage-related treatment goals below), patients will remain on the respective mono-therapy as long as prognostically relevant clinical and hemodynamic values indicate that the disease is stabilized. If, however, important treatment goals are either not met, or the patient improved initially but deteriorates during the course of the treatment, a complementary therapeutic agent will be added. The treatment success will be re-evaluated after 3–6 months, and depending on the test results, appropriate therapeutic decisions are being made. The final step in this common escalation sequence is the addition of intravenous prostanoids (as mentioned above, the most commonly used compound in Germany is intravenous iloprost).

Patients who do not show an adequate response to treatment despite combination therapy should timely be referred to a transplant center whenever possible. If patients are referred too late, and atrial septostomy is considered and/or preparations for heart/lung transplantation are initiated only after all available medical treatment options have been exhausted there is almost no chance of reaching the time of transplantation.

Data from the first randomized controlled trials on the combined use of targeted PAH drugs are available now, e.g. for subgroups in pre-approval studies on inhaled treprostinil and oral tadalafil (mostly pretreatment with an ERA) [19,33] as well as the combination study with intravenous epoprostenol and oral sildenafil (PACES study) which was planned exclusively as a combination therapy trial [27]. The latter study was able to demonstrate a survival benefit in patients receiving combination therapy as compared to monotherapy with intravenous epoprostenol. This has led to a paradigm shift in countries with extensive use of epoprostenol (e.g. USA and France).

The indication for combination therapy must always be determined on an individual basis. It is currently recommended in patients who do not respond adequately to monotherapy. Due to the complex decision making, safety reasons and pharmacoeconomic considerations, the decision to initiate combination therapy should be reserved for expert centers only.

10. Balloon atrial septostomy

Balloon atrial septostomy may improve survival in patients with PAH, although there are no data on the value of this procedure in patients who are treated with targeted PAH drugs, and the impact on long-term survival has not been established in randomized controlled trials. Atrial septostomy should be regarded as palliative or bridging procedure to be performed only by centers with experience in this method [1,2]. It is not indicated in stable patients receiving drug treatment. Its therapeutic window is narrow, since septostomy should also not be performed as emergency procedure in patients with decompensated right heart failure (e.g. right atrial pressure >20 mmHg, arterial O_2 saturation at rest $<80\%$ on room air) [1,2].

Comment:

In Germany, atrial septostomy is currently used as a very rare treatment option in adults with PAH. There is a certain rationale for patients who experience recurring syncopes despite extensive medical therapy, but demonstrate compensated right heart function (e.g. right atrial pressure <15 mmHg, no pericardial effusion, cardiac index >2 l/min/m^2) and a peripheral oxygen saturation $>95\%$ (with or without oxygen therapy). The mortality associated with this procedure depends on the severity of the disease and the experience of the center, but is reported to be up to 30%.

11. Transplantation

Double lung or heart–lung transplantation continues to be an important therapeutic option for suitable patients who do not respond sufficiently to optimized medical therapy. PAH patients with features of a poor prognosis profile despite maximal treatment should be referred for transplant listing well in advance. Patients with PVOD or pulmonary capillary hemangiomatosis should be listed for transplantation at diagnosis. The overall 5-year survival rate following transplantation for PAH is 45–50%, with evidence of continued good quality of life [1,2].

12. Treatment algorithm

An evidence-based treatment algorithm for patients with PAH is provided in Fig. 1 [1,2]. These recommendations do not apply to other forms of PH. The corresponding levels of evidence and grades of recommendation are shown in Table 3 and refer to scientific evidence and not to the approval status (Table 4). The individual drug classes are listed in alphabetic order. Evidence for the individual therapies mainly applies to IPAH and PAH associated with connective tissue disease. Specific details listed below may apply to other forms of PAH.

Comment:

Supervised rehabilitation is listed among supportive therapies. The corresponding evidence was generated in Germany where all applicable patients were treated in a single specialized center [5]. Therefore, the available data does not allow generalization to all rehabilitation facilities.

According to the ESC/ERS guidelines, i.v. epoprostenol is the only recommended treatment for patients in WHO functional class IV. However, epoprostenol has only recently been approved in Germany, and the current level of experience is low, while other compounds (e.g., iloprost) are more frequently used.

13. Drug interactions

Significant drug interactions involving the disease-specific therapies for PAH must be taken into account. In accordance with

Table 5
Potentially significant drug interactions with PAH-targeted therapies (contraindicated or with proven interaction[#].)

PAH drug	Mechanism of interaction	Interacting drug	Interaction
Ambrisentan	OATP inhibitor	Cyclosporine	Ambrisentan AUC increases 2-fold with concomitant administration, therefore maximum administration of 5 mg/d ambrisentan.
	CYP3A4 inhibitor	Ketoconazole	Clinically irrelevant increase of ambrisentan
Bosentan	CYP3A4 inducer OATP inhibitor	Cyclosporine	This combination is contraindicated. Cyclosporine AUC falls 50%, bosentan AUC increases 4-fold.
	CYP3A4 inhibitor	Erythromycin	Bosentan AUC increases; may not require dose adjustment during short co-medication.
	CYP2C9 and CYP3A4 inhibitor	Fluconazole	Increase of bosentan AUC is expected, this combination is potentially contraindicated.
	CYP3A4 inducer + bile salt pump (BSEP) inhibitor	Glibenclamide	Risk of elevated aminotransferases. Potential decrease of the effect of glibenclamide. This combination is contraindicated.
	CYP3A4 inducer	HMG CoA reductase inhibitors	Simvastatin AUC reduces about 50%. Similar effects are expected with lovastatin and atorvastatin. Cholesterol levels should be monitored.
	CYP2C9 and 3A4 inducers	Hormonal contraceptives	Contraceptive AUC reduce about 30% (in individual cases even 60%). Hormonal contraception unreliable.
	CYP3A4 inhibitor	Itraconazole	This combination is potentially contraindicated.
	CYP3A4 inhibitor	Ketoconazole	Bosentan AUC increases 2-fold.
	CYP3A4 inhibitor, Transporter inhibition	Lopinavir/Ritonavir	This combination leads to transient 48-fold increase of bosentan concentration, in steady-state to 5-fold increase. At the same time, protease inhibitor AUCs decrease slightly (14–17%). Intensive monitoring of bosentan effects is necessary.
	Transporter inhibition	Nevirapine	Increase in hepatotoxicity is expected; this combination is not recommended.
	CYP2C9 and 3A4 inducers	Rifampicin	Bosentan AUC decreases by 58%, large variability. Need for dose adjustment likely.
	CYP3A4 inducer, OATP inhibitor	Sildenafil	Sildenafil AUC decreases by 63%, bosentan AUC increases by 50%. Dose adjustment may not be required.
	CYP3A4 inducer	Tadalafil	Tadalafil AUC decreases by 42%. No relevant change of bosentan AUC.
	CYP2C9 inducer	Warfarin	Increases warfarin metabolism; intensified INR monitoring at the start of treatment or adjustment of bosentan dose.
Sildenafil	Vasorelaxation	Alpha blockers (doxazosin, silodosin)	Pronounced reduction in blood pressure.
	CYP3A4 inducer, OATP inhibitor	Bosentan	Sildenafil AUC decreases by 63%, bosentan AUC increases by 50%. Dose adjustment may not be required.
	CYP3A4 inhibitor	Cimetidine	Sildenafil AUC increases by 56%; usually no dose adjustment required.
	CYP3A4 inhibitor	Erythromycin	Sildenafil AUC increases by 183%. Probably no dose adjustment required.
	CYP3A4 inhibitor	Fluvoxamine	Sildenafil AUC increases by 40%, probably no dose adjustment required.
	CYP3A4 inhibitor	HIV protease inhibitors	Ritonavir increases the sildenafil AUC tenfold and is therefore contraindicated. If the effect of saquinavir is less, dose adjustment is required.
	CYP3A4 inhibitor	Itraconazole	This combination is potentially contraindicated.
	CYP3A4 inhibitor	Ketoconazole	Significant increase of sildenafil AUC; this combination is contraindicated.
	Inhibition of cGMP breakdown	Molsidomine, organic nitrates, nicorandil	Significant systemic hypotension. This combination is contraindicated.
	CYP3A4 inhibitor	Ritonavir	Increase of sildenafil AUC by 1100%; this combination is contraindicated.
Tadalafil	CYP3A4 inducer	Bosentan	Tadalafil AUC decreases by 42%. No relevant change of bosentan AUC.
	Vasorelaxation	Doxazosin	Increased reduction in blood pressure
	CYP3A4 inhibitor	Ketoconazole	Twofold to fourfold increase of tadalafil AUC.
	Inhibition of cGMP breakdown	Molsidomine, organic nitrates, nicorandil	Significant systemic hypotension. This combination is contraindicated.
	CYP3A4 inducer	Rifampicin	Tadalafil AUC decreases by 88%.
	CYP3A4 inhibitor	Ritonavir	Twofold increase of tadalafil AUC.
	PDE inhibitors	Theophylline	Slight increase in heart rate.

[#] Since the ERA sitaxentan has been withdrawn from the market, this compound has been removed from the original ESC/ERS table.

the ESC/ERS guidelines, the most important known interactions of targeted PAH drugs are compiled in Table 5 [1,2].

Comment:

In addition to the general approach of this recommendation, an updated table of interactions is shown below that does not only demonstrate already proven interactions and combinations without interactions (Table 6) but also theoretical untested interactions that can be expected and may be clinically relevant (Table 7).

- *The proven interactions between some of the targeted PAH drugs have lead to the definition of definite contraindications.*
- *So far, there are only single recommendations with regard to*

Table 6
Drug combinations for PAH-targeted therapies without interaction[#].

PAH drug	Interacting drug
Ambrisentan	Digoxin
	Ethinylestradiol
	Norethisterone
	Omeprazole
	Sildenafil
	Tadalafil
	Warfarin
Bosentan	Digoxin
	Treprostinil
Sildenafil	Acetylsalicylic acid
	Ambrisentan
	Amlodipine
	Atorvastatin
	Azithromycine
	Ethinylestradiol
	Levonorgestrel
	Magaldrat
	Mg-/Al hydroxide
	Tolbutamide
	Warfarin
Tadalafil	Acetylsalicylic acid
	Ambrisentan
	Amlodipine
	Digoxin
	Enalapril
	Lovastatin
	Metoprolol
	Midazolam
	Tamsulosin
	Warfarin

[#] Since the ERA sitaxentan has been withdrawn from the market, this compound has been removed from the original ESC/ERS table.

possible dose adjustments of individual or several combination partners or specific measures for risk minimization.

- *As a rule, every dose adjustment associated with these (mostly) dose-dependent interactions requires accurate monitoring and, if necessary, a dose modification.*
- *While there are well documented studies on interactions between ERAs and warfarin, there is so far no published data on interactions with phenprocoumon, representing the most commonly used oral anticoagulant in Germany. In general and for the time being, the recommendation regarding the combination of ERAs and phenprocoumon should be equivalent to warfarin.*
- *Supervised coagulation self-control is recommended in suitable patients.*
- *For a number of model compounds, interactions have been investigated on a quality and quantity basis; empirically it is understood that compounds with closely related mechanisms of interaction will also interact even if this may have never been analyzed (Table 7).*
- *The proven pharmacokinetic interactions between targeted PAH drugs have not yet led to a recommendation with regard to dose adjustments of single or several combination partners because so far no evident safety signals have occurred.*

14. Definition of adequate clinical response

The proper assessment of adequate clinical response to medical therapy is essential for therapeutic decisions, particularly with regard to the escalation treatment and the initiation of a combination therapy. According to the ESC/ERS guidelines, recommend the initiation of a sequential combination therapy is recommended if the clinical status of a patient is not satisfactory on monotherapy (see Fig. 1; treatment algorithm). However, the judgement of an unsatisfactory treatment effect may be challenging, and the stage-related definition of inadequate response to therapy as suggested in the ESC/ERS guidelines may be helpful (Table 8). Furthermore, the guidelines recommend regular follow-up visits and specify treatment goals (see article on non-invasive diagnosis in this Supplement).

Comment:

Criteria of adequate clinical response are listed in Table 15 of the original ESC/ERS guidelines (see also Fig. 2, in the article on "non-

Table 8
Definition of inadequate response to PAH treatments [1,2].

Inadequate clinical response for patients who were initially in WHO class II or III:
1. Resulting clinical status defined as stable and not satisfactory
2. Resulting clinical status defined as unstable and deteriorating
Inadequate clinical response for patients who were initially in WHO class IV:
1. No rapid improvement to WHO class III or better
2. Resulting clinical status defined as stable and not satisfactory

Table 7
Drug combinations for PAH-targeted therapies where interactions must be expected.)

PAH drug	Mechanism of interaction	Interacting drug	Interaction
Bosentan	CYP3A inducer	Carbamazepine	Need for dose adjustment likely
	CYP3A4 inducer	Phenobarbital	Need for dose adjustment likely
	CYP3A4 inducer	Phenytoin	Need for dose adjustment likely
	Transporter interaction	Sirolimus	Increase of bosentan AUC is expected, this combination is not recommended.
	Transporter interaction	Tacrolimus	Increase of bosentan AUC is expected, this combination is not recommended.
Sildenafil	CYP3A4 inducer	Carbamazepine	Decrease of sildenafil AUC is expected
	CYP3A4 inducer	St. John's wort	Decrease of sildenafil AUC is expected
	CYP3A4 inducer	Phenobarbital	Decrease of sildenafil AUC is expected
	CYP3A4 inducer	Phenytoin	Decrease of sildenafil AUC is expected
	CYP3A4 inducer	Rifampicin	Decrease of sildenafil AUC is expected
Tadalafil	Vasorelaxation	Antihypertensive	Variable increase in blood pressure reduction
	CYP3A4 inducer	Carbamazepine	Decrease of tadalafil AUC is expected
	CYP3A4 inhibitor	Clarithromycin	Increase of tadalafil AUC is expected
	CYP3A4 inhibitor	Erythromycin	Increase of tadalafil AUC is expected
	CYP3A4 inhibitor	Itraconazole	Increase of tadalafil AUC is expected
	CYP3A4 inducer	St. John's wort	Decrease of tadalafil AUC is expected
	CYP3A4 inducer	Phenobarbital	Decrease of tadalafil AUC is expected
	CYP3A4 inducer	Phenytoin	Decrease of tadalafil AUC is expected
	CYP3A4 inhibitor	Saquinavir	Increase of tadalafil AUC is expected

AUC, area under the concentration–time curve (measure of exposure); cGMP, cyclic guanosine monophosphate; OATP, organic anion transporter protein; BSEP, bile salt efflux pump; CYP, cytochrome P450 isoenzyme.
Potential contraindicated means that the manufacturer does not recommend this combination.

invasive diagnosis" in this Supplement). However, they do not necessarily apply to certain patient groups (e.g. congenital heart disease). Therefore, treatment goals and consequently also adequate response to treatment should be determined and evaluated according to the condition of the individual patient and, if applicable, co-morbidities.

Therapeutic limitations and new developments

Despite the enormous progress that has been achieved in the area of PAH during the last decade, it must be emphasized that this disease is still not curable and that drug therapy for PAH must be continued life-long. Despite the currently available therapies, morbidity and mortality remain unsatisfactory. According to current registry data, the annual mortality rate in PAH remains at approximately 10% [36,37]. Hence, the further improvement of medical treatment in PAH is highly desirable. The German expert centers for PH are decisively involved in the development of new agents, and for many patients enrollment in clinical trials may be an option.

A number of novel agents is currently under clinical investigation. These include stimulators of soluble guanylate cylcase (sGC) and tyrosine kinase inhibitors (TKI). sGC stimulators act independently of NO as well as synergistic with endogenous NO and thereby promote pulmonary vasodilation [38,39]. An open-label phase II study demonstrated that the sGC stimulator riociguat led to an improvement of pulmonary hemodynamics and exercise tolerance in patients with PAH and CTEPH [40]. In contrast to other drug classes, TKIs do not have a vasodilating effect but act purely as antiproliferative agents. They inhibit the activation of growth factor receptors (receptor tyrosine kinases) which play a crucial role in the pathobiology of PAH [41–43]. Current data of phase II and phase III studies indicate that the TKI imatinib is effective in improving exercise tolerance, pulmonary hemodynamics and right ventricular function in patients with severe PAH and inadequate response to established therapies [44,45].

15. Specific PAH populations

15.1. PAH associated with congenital cardiac shunts

The complexity of diagnosis and therapy of patients with congenital cardiac shunts render a detailed presentation impossible at this point so that reference is made to the European guidelines [1,2]. These patients should also be treated in specialized centers. The recommendations are summarized in Table 9.

Comment:

Defined treatment goals for Eisenmenger's syndrome do not exist.

Only bosentan was investigated for the specific indication of Eisenmenger's syndrome (BREATHE-5 study) and showed significant improvements of pulmonary hemodynamics and exercise tolerance without safety concerns [18]. This does not mean that other PAH drugs are less effective or less safe.

Positive effects were also described for sildenafil and epoprostenol in small, uncontrolled studies [46–48], and for tadalafil in a randomized controlled study [49].

Current data from a retrospective analysis of 229 patients with Eisenmenger's syndrome demonstrated that targeted PAH therapy in 68 patients who received either prostanoids and/or endothelin receptor antagonists and/or PDE-5 inhibitors was associated with a significant improvement of survival [50]. Hence, targeted PAH therapy is recommended in patients with Eisenmenger's syndrome, the respective classes of recommendation and levels of evidence are listed in Table 9.

*The available data on **combination therapy** is not sufficient to provide detailed recommendations.*

*The recommendations for **oral anticoagulant treatment** in Eisenmenger's syndrome are controversial. Despite the bleeding tendency of patients with Eisenmenger's syndrome (coagulation disorders and concomitant thrombocytopenia), anticoagulation may be considered in certain situations (e.g. atrial fibrillation, thromboembolic events) if there is no relevant hemoptysis present. In this case, the adjustment of coagulation requires expert knowledge. Specific tests are needed to determine the coagulation parameters in erythrocytosis and a hemoglobin level >65%.*

Table 9
Recommendations for PAH associated with congenital cardiac shunts [1,2].

Statement	Class of recommendation	Level of evidence
The ERA bosentan is indicated in WHO-FC III patients with Eisenmenger's syndrome	I	B
ERAs other than bosentan, PDE-5 inhibitors and prostanoids should be considered in patients with Eisenmenger's syndrome	IIa	C
In the absence of significant hemoptysis, oral anticoagulation treatment should be considered in patients with pulmonary arterial thrombosis or signs of heart failure	IIa	C
The use of supplemental oxygen therapy should be considered in cases in which it produces a consistent increase in arterial oxygen saturation and reduces symptoms	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered usually when hematocrit is >65%	IIa	C
Combination therapy may be considered in patients with Eisenmenger's syndrome	IIb	C
The use of CCBs is not recommended in patients with Eisenmenger's syndrome	III	C

***Phlebotomies** should be avoided in general. The indication for phlebotomy must be determined according to strict specifications. Indications are given almost only in symptomatic erythrocytosis (HCT markedly exceeding 65%) and neurological symptoms if exsiccosis or hypovolemia have been ruled out. It is also important to provide adequate volume replacement. Repeated phlebotomies lead to iron deficiency which may worsen the rheologic properties in the microvascular system. In case of iron deficiency that has been documented through laboratory tests (including the determination of transferrin, ferritin, soluble transferrin receptor), low-dose(!) iron replacement is recommended (caution: exacerbated increase of hemoglobin and hematocrit!).*

16. PAH associated with connective tissue disease

PAH occurs in 5–15% of patients with systemic sclerosis, 5–10% of patients with mixed connective tissue disease, and 2–5% of patients with systemic lupus erythematosus (SLE) [51,52]. Diagnosis and therapy of PAH in these patients largely follows the above-mentioned principles for IPAH, however screening is recommended in asymptomatic patients with systemic sclerosis or mixed connective tissue disease (Table 10). The significance of additional immunosuppressive or immunomodulatory therapies depends on the underlying disease. For PAH associated with scleroderma, this approach is believed to be without effect and is not recommended, while immunosuppressive treatment in SLE and PAH has been reported to be successful. Patients with PAH associated with mixed connective tissue disease usually show the same response as scleroderma patients but, in individual cases, may also benefit from immunosuppressive therapy.

Comment:

In patients with collagenosis (e.g. SLE, MCTD), the possibility of immunosuppressive therapy should be evaluated within the framework

Table 10
Recommendations for PAH associated with connective tissue disease [1,2].

Statement	Class of recommendation	Level of evidence
In patients with PAH associated with CTD, the same treatment algorithm as in patients with IPAH is recommended	I	A
Echocardiographic screening for the detection of PH is recommended in symptomatic* patients with scleroderma spectrum of diseases	I	B
Echocardiographic screening for the detection of PH is recommended in symptomatic* patients with all other CTDs	I	C
Right heart catheterization is indicated in all cases of suspected PAH associated with CTD, in particular if specific drug therapy is considered	I	C
Oral anticoagulation should be considered on an individual basis	IIa	C
Echocardiographic screening for the detection of PH may be considered in asymptomatic* patients with the scleroderma spectrum of diseases	IIb	C

CTD, connective tissue disease; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension (group I).
*Symptoms of pulmonary hypertension or right ventricular failure.

Table 11
Recommendations for PAH associated with portal hypertension [1,2].

Statement	Class of recommendation	Level of evidence
Echocardiographic screening for the detection of PH is recommended in symptomatic patients with liver diseases and/or in candidates for liver transplantation	I	B
In patients with PAH associated with portal hypertension, the same treatment algorithm as in patients with IPAH should be considered, taking into consideration comorbidities	IIa	C
Anticoagulation is not recommended in patients with increased risk of bleeding	III	C
Significant PAH is a contraindication to liver transplantation if mean PAP $\geq$35 mmHg and/or PVR $\geq$250 dyn s cm^{-5}	III	C

of interdisciplinary cooperation. Patients with PAH associated with systemic sclerosis generally do not respond to immunosuppressive therapy.

16.1. PAH associated with portal hypertension

Portopulmonary hypertension (PoPH) is defined as the occurrence of PAH in patients with portal hypertension. The incidence of PoPH in patients with liver cirrhosis is approximately 0.5–1% [1,2]. The recommendations of the ESC/ERS guidelines are summarized in Table 11. Echocardiographic screening to rule out right ventricular load should be performed in patients who are evaluated for liver transplantation, since survival after transplantation depends on the presence and extent of PH. There are no data from controlled studies on the treatment of PoPH. The same treatment algorithm as in IPAH is recommended, however, taking co-morbidities into consideration [1,2].

Comment:

Smaller case studies indicate the efficacy and safety of PAH drugs for the treatment of PAH associated with portal hypertension, but there are no data from a randomized controlled trial. This does not mean that PAH drugs are not effective or unsafe in this case. In patients with Child A cirrhosis, positive experiences with bosentan, sildenafil, and ambrisentan have been published [53–56]. ERAs are contraindicated in advanced liver disease, so that PDE-5 inhibitors and/or prostanoids are mostly used in this situation. In rare individual cases, combined lung–liver transplantation may be considered in treatment refractory cases [57].

In candidates for liver transplantation, it is important to distinguish between portopulmonary hypertension and the hepatopulmonary syndrome. In the latter case, the indication for transplantation may be given if the mean PAP is $\geq$35 mmHg within the scope of hepatic hypercirculation.

Table 12
Recommendations for PAH associated with HIV infection [1,2].

Statement	Class of recommendation	Level of evidence
Echocardiography is indicated in patients with unexplained dyspnea to detect HIV-related cardiovascular complications	I	B
In patients with PAH associated with HIV infection, the same treatment algorithm as in patients with IPAH should be considered, taking into consideration co-morbidities and drug–drug interactions	IIa	C
Anticoagulation is not recommended in patients with increased risk of bleeding	III	C

16.2. PAH associated with HIV infection

Approximately 0.5% of HIV-infected patients develop PAH [58]. In these patients, the diagnostic work-up and treatment strategies are largely based on the above-mentioned recommendations (see Table 12). Positive experiences have been reported with bosentan and sildenafil. In some but not all cases, the use of antiretroviral therapy had a positive effect on the course of PAH. Potential interactions between PAH-specific drugs and antiretroviral therapy must be taken into account (see section on drug interactions). This applies especially to the combination of sildenafil with HIV protease inhibitors (see Table 5).

Comment:

Smaller case studies indicate the efficacy and safety of targeted PAH drugs – especially bosentan [59,60] and sildenafil [61,62]. However, for the specific indication PAH associated with HIV infection, there are no data from randomized controlled trials. This does not mean that PAH drugs are not effective or unsafe in this case.

17. Pulmonary veno-occlusive disease (PVOD)

Since PVOD is usually very difficult to diagnose, one of the most important criteria for the potential presence of PVOD is the insufficient response or clinical worsening on targeted PAH treatment. There is still no medical therapy for PVOD and the prognosis is particularly poor, so that patients should be referred to a transplant center as soon as the corresponding tentative diagnosis is established (Table 13).

18. Specific pediatric aspects

The complexity of diagnosis and therapy in different types of PAH and in different age groups constitutes that children with PAH should be treated exclusively at specialized expert centers. The special aspects in children with PAH are considered in the ESC/ERS guidelines only to the extent that they are valid independent of age. The treatment recommendations currently applicable for

Table 13
Recommendations for patients with pulmonary veno-occlusive disease [1,2].

Statement	Class of recommendation	Level of evidence
Referral of patients with PVOD to a transplant center for evaluation is indicated as soon the diagnosis is established	I	C
Patients with PVOD should be managed only in centers with extensive experience in PAH due to the risk of lung edema after the initiation of PAH-specific drug therapy	IIa	C

Table 14
Recommendations for pediatric PAH [1,2].

Statement	Class of recommendation	Level of evidence
The PH diagnostic work-up proposed for adults should also be considered in children	IIa	C
The PAH therapeutic algorithm proposed for adults should also be considered in children	IIa	C

adults have been largely adopted for the treatment of children with PAH. There is, however, much less available data from randomized controlled studies in children than in adults. Regarding the recommendation to use the same diagnostic and therapeutic algorithms as for adults, there is a class IIA recommendation, and the level of evidence is C (Table 14).

Comment and specific recommendations for children:

- *When the available data from clinical trials and the approval status are considered, the diagnostic and therapeutic algorithms suggested for adults cannot be applied in children without modification. For example, the 6-minute walking test is neither standardized nor has it been prospectively evaluated in children (see article on non-invasive diagnosis in this Supplement).*
- *Chronic thromboembolic disease plays a minor role in children, while congenital heart disease represents the predominant form of PH.*
- *Recent studies have documented that the use of available drug therapies (e.g. i.v. epoprostenol, bosentan, sildenafil) either as mono- or as combination therapy lead to improved survival in children as compared to historical untreated populations [63,64].*
- *The ERA bosentan is approved for children, as it has been specifically investigated in children [65–67]. Based on the available information, bosentan is approved from the age of 2 years and is available in a special pharmaceutical form of 32-mg tablets that can be quartered (initial dose for the first 4 weeks: 2 mg/kg/d in 2 single doses, target dose: 4 mg/kg/d in 2 single doses). This does not mean that other ERAs are less effective or less safe. Because of the available data and the approval status, however, they should only be used in justified exceptions.*
- *The PDE-5 inhibitor sildenafil is also approved in children at the age between 1 and 17 years (1.5–4.5 mg/kg/d in 3 single doses). It may be used as monotherapy or in combination with other PAH drugs. The warning letter addressing higher dosages has been addressed above.*
- *Inhaled iloprost is usually only used in cases of treatment escalation when oral therapies are not sufficiently effective. In Germany, no intravenous prostanoid is currently approved for the use in children. In selected cases, epoprostenol (initial dose 2 ng/kg/min, dose increase according to therapeutic effect) or iloprost (initial dose 0.5 ng/kg/min) may be used.*
- *In children with IPAH who demonstrate a favourable response during acute vasoreactivity testing, CCBs (amlodipine 0.1–0.5 mg/kg/d, nifedipine 1–2 mg/kg/d) are used as in adults. Because of the higher vasoreactivity rate in children that correlates negatively with age and the therapeutic consequences, acute vasoreactivity testing is recommended in children with IPAH.*
- *The treatment of PAH associated with congenital heart disease (postoperative, Eisenmenger's syndrome, etc.) basically equals that of IPAH.*
- *During childhood, there are a number of specific diseases with increased pulmonary vascular resistance for which a targeted PAH therapy may be considered on an individual basis. These include infants with bronchopulmonary dysplasia or children with univentricular heart and passive pulmonary blood flow (Fontan circulation). Since data from clinical studies are lacking for these diseases, treatment decisions have to be based on empiric experience in such cases.*

19. Treatment in referral centers for pulmonary hypertension

Due to the complex issues and often difficult treatment decisions, the ESC/ERS guidelines recommend to refer patients with suspected pulmonary hypertension to a specialized center. This is to ensure the correct diagnosis of patients and the prescription of specific PAH drugs that are appropriate to the indication and meet the needs of the individual patients. PH centers are able to carry out the diagnosis and therapy of all or nearly all forms of PH independently and according to guidelines. The requirements listed in the ESC/ERS guidelines are presented in Table 15.

Comment:

In Germany there is an independent discussion about the definition of a referral center for pulmonary hypertension. To some extent, the criteria are set considerably lower than those stipulated in the European guidelines. The authors believe that the criteria listed in the European guidelines constitute meaningful specifications that help define a PH expert center.

More detailed specifications are required for referral centers managing rare subgroups, such as children and patients with congenital heart disease.

It is recommended to promote the development of network structures aiming at interdisciplinary expertise in PH. This includes the close cooperation with patient organizations (in Germany "pulmonale hypertonie e.V. [phev]") (see general section).

Table 15
Recommendations for a pulmonary hypertension referral center [1,2].

Statement	Class of recommendation	Level of evidence
Referral centersare required to provide care by a multiprofessional team (cardiology and respiratory medicine physicians, clinical nurse specialists, radiologists, psychological and social work support, appropriate on-call expertise)	I	C
Referral centers are required to have direct links and quick referral patterns to other services (such as CTD service, family planning service, PEA service, lung transplantation service, adult congenital heart disease service)	I	C
A referral center should follow at least 50 patients with PAH or CTEPH and should receive at least two new referrals per month with documented PAH or CTEPH	IIa	C
Referral centers should perform at least 20 vasoreactivity tests in PAH patients per year	IIa	C
Referral centers should participate in collaborative clinical research in PAH, which includs phase II and phase III clinical trials	IIa	C

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Conflicts of interest

H.A. Ghofrani: Honoraria for lectures and/or consultation of Actelion, Bayer, Gilead, GSK, Lilly, LungRx, Novartis, and Pfizer.

O. Distler: Honoraria for lectures and/or consultation of Actelion, Biovitrium, BMS, Ergonex, FibroGen, NicOx, and Pfizer.

F. Gerhardt: Honoraria for lectures and/or consultancy for Lilly.

M. Gorenflo: Honoraria for lectures and/or consultancy for Bayer.

E. Grünig: Honoraria for lectures and/or consultancy for Actelion, Bayer, GSK, Lilly, Novartis, Pfizer, and United Therapeutics.

W.E. Haefeli: Honoraria for lectures and/or consultation of Actelion, Bayer, Daiichi-Sankyo, GSK, MSD, Novartis, ONO Pharma, Sanofi-Aventis.

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M.M. Hoeper: Honoraria for lectures and/or consultancy for Actelion, Bayer, Gilead, GSK, Lilly, LungRX, Novartis, and Pfizer.

C.M. Kähler: Honoraria for lectures and/or consultation of Actelion, Bayer, GSK, LungRx/AOP,and Pfizer.

H. Kaemmerer: Honoraria for lectures and/or consultation of Actelion and Pfizer.

H. Klose: Honoraria for lectures and/or consultation of Actelion, Bayer, GSK, Lilly, LungRx, Novartis, Pfizer, and United Therapeutics.

V. Köllner: Honoraria for lectures and/or consultation of Actelion, and Bayer.

B. Kopp: none.

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A. Meyer: none.

O. Miera: Honoraria for lectures and/or consultation of Actelion and Pfizer.

D. Pittrow: Honoraria for lectures and/or consultation of Bayer, Pfizer, and Novartis.

G. Riemekasten: Honoraria for lectures and/or consultation of Actelion, Bayer, and Pfizer.

S. Rosenkranz: Honoraria for lectures and/or consultancy for Actavis, Actelion, Bayer, GSK, Lilly, Novartis, Pfizer and United Therapeutics.

D. Schranz: none.

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