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Targeted therapy of pulmonary arterial hypertension: Updated recommendations from the Cologne Consensus Conference 2018

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ABSTRACT

In the summer of 2016, delegates from the German Respiratory Society, the German Society of Cardiology and the German Society of Pediatric Cardiology met in Cologne, Germany, to define consensus-based practice recommendations for the management of patients with pulmonary arterial hypertension (PAH). These recommendations were built on the 2015 European Pulmonary Hypertension guidelines and included new evidence, where available. The treatment algorithm for PAH was modified based on the observation that there are now many patients diagnosed with IPAH who are at an advanced age and have significant cardiopulmonary comorbidities. For patients newly diagnosed with classic forms of PAH, i.e. younger patients without significant cardiopulmonary comorbidities, the consensus-based recommendation was to use initial combination therapy as the standard approach. The use of monotherapies was no longer considered appropriate in such patients. The choice of treatment strategies should be based on the risk assessment as proposed in the European guidelines. In patients presenting with a low or intermediate risk, oral combination therapy with endothelin receptor antagonists and phosphodiesterase-5 inhibitors or soluble guanylate cyclase stimulators, respectively, should be used. In high-risk patients, triple combination therapy including a subcutaneous or intravenous prostacyclin analogue should be considered. For patients who suffer from PAH and significant cardiopulmonary comorbidities, initial monotherapy is recommended and the use of combination therapies should be considered on an individual basis. The latter recommendations are based on the scarcity of evidence supporting the use of combination therapy and the higher risk of drug-related adverse events in such patients.

1. Introduction

The 2015 Guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) [1,2] base the therapeutic approach to patients with pulmonary arterial hypertension (PAH) on individualized risk stratification (Fig. 1). Since publication of these

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Prognostic parameter (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5-10%)	High risk (>10%)
Clinically overt right heart failure	No	No	Yes
Progression of symptoms	No	Slow	Rapid
Syncope	None	Occasional, orthostatic syncope or syncope during brisk physical exertion	Repeated, even during mild physical exertion
WHO functional class	I/II	III	IV
6-minute walk distance	>440 m	165-440 m	<165 m
Spiroergometry	• Peak VO_2 >15 ml/min/kg (>65% of target value) • VE/VCO_2 slope <36	• Peak VO_2 11-15 ml/min/kg (>65% of target value) • VE/VCO_2 slope 36-44	• Peak VO_2 <11 ml/min/kg (>65% of target value) • VE/VCO_2 slope >44
BNP serum concentration	<50 ng/L	50-300 ng/L	>300 ng/L
NT-proBNP serum concentration	<300 ng/L	300-1400 ng/L	>1400 ng/L
Cardiac imaging (echocardiography, cMRI)	• RA area <18 cm^2 • No pericardial effusion	• RA area 18-26 cm^2 • No/minimal pericardial effusion	• RA area >26 cm^2 • Pericardial effusion
Haemodynamics	• RA <8 mmHg • CI > 2.5 L/min/m^2 • SvO_2 >65%	• RA 8-14 mmHg • CI 2.0-2.4 L/min/m^2 • SvO_2 60-65%	• RA >14 mmHg • CI <2.0 L/min/m^2 • SvO_2 <60%

Fig. 1. Risk stratification for patients with PAH [1,2]. Legend: BNP, brain natriuretic peptide; CI, cardiac index; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; peak VO_2, maximum rate of oxygen consumption; RA, right atrium; SvO_2, mixed venous oxygen saturation; VE/CO_2 slope, ventilatory equivalent for CO_2.

guidelines, this risk stratification strategy has been validated by three independent studies [3–5]. In addition, the European guidelines emphasize the role of combination therapy, mainly because several long-term studies published since 2013 have demonstrated improved event-free survival in patients receiving combination therapy [6–8]. In addition, a recent meta-analysis confirmed the positive effect of combination

Table 1
Distinct phenotypes of patients fulfilling the diagnostic criteria for idiopathic pulmonary hypertension but presenting with clinically relevant cardiopulmonary comorbidities.

Parameter	Criteria
Haemodynamic profile	The same as for the other forms of PAH, i.e. precapillary PH with increased pulmonary vascular resistance
Phenotypical features	Often, but not exclusively elderly patients; risk profile and comorbidities the same as for patients with left heart or lung disease
Left heart phenotype	≥3 of the following risk factors: • Arterial hypertension • Coronary heart disease, • Diabetes mellitus • Obesity (BMI >30 kg/m^2) • Other features (including enlargement of the left atrium, atrial fibrillation)
Pulmonary phenotype	• Normal or almost normal body plethysmography • Chest CT scan without clinically relevant lung parenchymal abnormalities • DLCO <45% of the predicted value • Profound hypoxemia

Abbreviations: BMI, body mass index; CT, computed tomography; DLCO, diffusion capacity of the lungs for carbon monoxide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

therapies on 6-min walk distance (6MWD), World Health Organization functional class (WHO FC), PAH-related hospitalizations and event-free survival [9].

However, increasing discrepancies are becoming evident, particularly in the USA and Europe, between the PAH patients included in clinical studies and the patients who are diagnosed with, and treated for, PAH in everyday clinical practice. In Germany, Switzerland and Sweden, the median age of newly diagnosed PAH patients was last reported to be about 65 years, or higher [10–12], whereas it was 50 years or less in recently completed international studies [6–8,13]. Elderly patients with PAH often present with several comorbidities and share clinical features of patients with left heart disease or lung disease [14]. Distinct phenotypes of patients have been emerging as summarized in Table 1 [15–17]. These phenotypes have not yet been fully characterized and merely provide a reference point for describing patient populations that share important clinical features and may respond differently to PAH targeted therapies [18]. Practically all controlled studies of PAH medications have included predominantly younger patients with "classic" PAH. This should be taken into consideration when interpreting data and selecting therapeutic strategies.

The following recommendations are based on a German consensus conference sponsored by the German Societies of Cardiology (DGK), Pediatric Cardiology (DGPK) and Pneumology (DGP) that took place in June 2016 in Cologne, Germany. Proceedings from this conference have been published previously [19], and the current manuscript presents an updated version of these recommendations taking into account the most recent evidence in the field.

2. Vasoreactivity testing and calcium channel blockers (CCB)

The 2015 European PH guidelines recommend pulmonary vasoreactivity testing to identify potential responders to CCB therapy only in patients with idiopathic PAH (IPAH) and related disorders, i.e. hereditary PAH (HPAH) and drug-associated PAH. Vasoreactivity testing in patients with other forms of PAH has no predictive value and may be misleading, as these patients almost never benefit from therapy with CCBs [20]. This same is true for other forms of pulmonary hypertension (PH), where vasoreactivity testing to identify candidates for therapy with CCBs is obsolete. If vasoreactivity testing is performed as part of an initial diagnostic work-up, i.e. when the exact classification is not yet known, CCB therapy should be initiated only if the final diagnosis is idiopathic, hereditary or drug-associated PAH and not if other forms of PH or PAH are diagnosed.

Vasoreactivity testing should be performed exclusively at experienced PH centers. Inhaled nitric oxide (NO), inhaled iloprost, and intravenous epoprostenol are suitable vasoreactivity testing agents. The formerly recommended intravenous adenosine should be avoided because of relatively poor tolerance [21]. The responder criterion remains – independently of the test substance selected – a drop in mean pulmonary arterial pressure (mPAP) of >10 mmHg from baseline to an absolute value of <40 mmHg, while cardiac output is unchanged or increased [1,2].

Treatment with high-dose CCBs in PAH is potentially dangerous and should only be initiated and supervised at experienced PH centers. Only dihydropyridines should be utilized and amlodipine (usually 15–20 mg per day) is the most frequently used substance in Germany, despite the absence of randomized clinical trials. It is obsolete to administer CCB therapy to patients with PAH without prior vasoreactivity testing.

3. Targeted therapy with PAH medications

At present, the following substances are authorized for the treatment of PAH in European countries:

- Phosphodiesterase-5 (PDE5) inhibitors: sildenafil and tadalafil
- Soluble guanylate cyclase (sGC) stimulator: riociguat
- Endothelin receptor antagonists (ERAs): ambrisentan, bosentan and macitentan
- Prostacyclin analogues: iloprost (inhaled), epoprostenol (intravenous), treprostinil (subcutaneous and intravenous)
- Prostacyclin (IP) receptor agonist: selexipag.

For a more detailed discussion of these compounds, the interested reader is referred to current review articles [22,23]. The levels of evidence and levels of recommendation for the individual compounds are presented in detail in the ESC/ERS guidelines [1,2].

Targeted PAH therapy should be initiated by experienced PH centers. Suitable therapeutic options should be selected primarily based on the data from randomized, controlled clinical studies, in particular long-term outcome data. Combination therapies are now the primary treatment option for patients with PAH, at least for those with a "classic" presentation. The essential data on combination therapy are summarized in Tables 2 and 3.

3.1. PDE-5 inhibitors

The PDE5 inhibitors sildenafil and tadalafil are used in the treatment of PAH. Sildenafil is approved at a dose of 20 mg three-times daily and improves hemodynamics, 6MWD and WHO FC [24]. There are no data from controlled studies on the long-term effects of sildenafil, and most of the open-label extension studies following the randomized studies were performed with a target dose of 80 mg three times daily [25,26]. The question of whether the approved sildenafil dose is the most effective dose remains to be answered. In the authorization study, sildenafil at a three-times daily dose of 80 mg led to a significantly greater reduction in pulmonary vascular resistance (PVR) than 20 mg three times daily, while the effect on 6MWD was practically identical [24]. Still, administration of sildenafil at dosages other than 20 mg three times daily constitutes an off-label usage.

Tadalafil is used at a dose of 40 mg given once daily. The authorization data were comparable with those of sildenafil [27]. However, tadalafil demonstrated positive long-term clinical effects in the AMBITION study, where it was used in an initial combination therapy regimen with ambrisentan (see below) [6].

3.2. Soluble guanylate cyclase stimulators

To date, the only substance available from this group is riociguat. Therapy generally begins with doses of 1.0 mg three times a day, followed by a gradual increase until a target dose of 2.5 mg three times a day is reached. In the 12-week authorization study, PATENT-1, riociguat showed favorable effects on 6MWD, WHO FC, hemodynamics and time to clinical worsening [13]. These effects were demonstrated in treatment-naïve patients as well as in patients who received background treatment with ERAs, predominantly bosentan, or non-intravenous prostacyclin analogues. However, riociguat should not be combined with PDE5 inhibitors, because no efficacy signals were detected in a small ($n = 18$) controlled study, while in the follow-up phase cumulative adverse events occurred, particularly discontinuations of therapy as a result of hypotension, as well as three deaths [28]. At present, long-term data on riociguat are available from the open-label extension study PATENT-2 [29,30], but not from controlled studies.

3.3. Endothelin receptor antagonists

Three ERAs are currently approved for PAH, i.e. bosentan, ambrisentan and macitentan. Bosentan is the oldest of the three available ERAs and has been authorized since 2001. In controlled short-term studies, bosentan demonstrated improvements in clinical symptoms, hemodynamics and time to clinical worsening [31,32]. In the

Table 2
Randomized, controlled short-term studies on combination therapy in patients with PAH.

Study	Duration	n[a]	Design	Key results
PACES [68]	16 weeks	267	Sildenafil in patients previously treated with epoprostenol	Significant improvement in 6MWD, haemodynamics and time to clinical deterioration
STEP [40]	12 weeks	67	Inhaled iloprost in patients previously treated with bosentan	• Increase in 6MWD with marginal statistical significance ($p = 0.051$) • Significant improvement in FC and time to clinical deterioration
COMBI [41]	12 weeks	40	Inhaled iloprost in patients previously treated with bosentan	Study prematurely ended after interim analysis, no clinical improvement observed
TRIUMPH [69]	12 weeks	255	Inhaled treprostinil in addition to sildenafil or bosentan	• Significant improvement in 6MWD • No improvement in FC and time to clinical deterioration
FREEDOM-C [70]	16 weeks	350	Oral treprostinil in addition to ERAs and/or PDE-5 inhibitors	No significant improvement in 6MWD, FC or time to clinical deterioration
FREEDOM-C2 [71]	16 weeks	310	Oral treprostinil in addition to ERAs and/or PDE5 inhibitors	No significant improvement in 6MWD, FC or time to clinical deterioration
PHIRST [27]	16 weeks	216	Subgroup analysis of patients who were given tadalafil + bosentan	• No significant improvement in 6MWD (+23 m, 95% CI: −2 to 48 m) • No improvement in FC and time to clinical deterioration in patients previously treated with bosentan
Selexipag phase II [72]	17 weeks	43	Selexipag in addition to ERAs and/or PDE5 inhibitors	Significant improvement in PVR, no significant improvement in 6MWD and NT-proBNP
IMPRES [73]	24 weeks	202	Imatinib in addition to dual or triple combination therapy	• Significant improvement in 6MWD, PVR and NT-proBNP • No effect on time to clinical deterioration • High dropout rate because of adverse effects • Unexpectedly high rate of subdural hematoma
PATENT [13]	12 weeks	222	Riociguat in addition to ERAs and/or prostacyclin analogues	Significant improvement in 6MWD and PVR in previously treated patients
PATENT-plus [28]	12 weeks	18	Riociguat in addition to sildenafil	No change in systolic blood pressure (primary endpoint), no efficacy signals, increased hypotensive episodes in the extension phase of the study
Pfizer combination study (NCT00323297)	12 weeks	103	Sildenafil in addition to bosentan	No improvement in 6MWD, FC or time to clinical deterioration

Abbreviations: 6MWD, 6-min walk distance; ERA, endothelin receptor antagonist; FC, functional class; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; PVR, pulmonary vascular resistance.
[a] Relates exclusively to patients who received combination therapy in the studies named above.

COMPASS-2 study, however, bosentan had no significant effect on the course of the disease in patients who were already treated with sildenafil [33]. A pharmacokinetic drug interaction has been discussed as a possible reason for these unexpected results, because bosentan accelerates the clearance of sildenafil through induction of cytochrome P450 3A4 [34,35]. In addition, bosentan has hepatotoxic potential. In COMPASS-2, increased transaminase levels (>3× the upper range of normal) occurred during a mean follow-up period of 38 months in 21.8% of patients on bosentan [33]. Because of the unfavorable long-term data [33] as well as the hepatotoxicity and potentially clinically relevant drug interactions, bosentan is no longer considered a first-choice ERA for patients with newly diagnosed PAH.

Ambrisentan is approved at daily doses of 5 mg and 10 mg for the treatment of PAH. Both dosages were equally effective in the authorization studies [36]. Furthermore, ambrisentan (daily target dose: 10 mg) in an initial combination with tadalafil in the AMBITION study exerted

Table 3
Event-driven studies on combination therapy in patients with PAH.

Study	n[a]	Design	Key results
COMPASS-2 [33]	334	Bosentan in addition to sildenafil	• No significant improvement in progression-free survival (primary endpoint) • Significant improvement in 6MWD and NT-proBNP after 16 weeks
SERAPHIN [7]	471	Macitentan in previously treated patients (predominantly with PDE5 inhibitors)	• Significant improvement in progression-free survival (HR 0.62; $p = 0.009$) • Significant improvement in 6MWD, FC and PVR after 6 months
AMBITION [6]	500	Initial combination therapy with ambrisentan and tadalafil versus monotherapy with one of these substances	• 50% risk reduction in time to therapy failure with initial combination therapy • Significant improvement in 6MWD and NT-proBNP after 6 months
GRIPHON [8]	925	Selexipag in addition to ERAs and/or PDE5 inhibitors	• 40% reduction in risk for disease progression, almost independently of pre-existing therapy • No improvement in FC

Abbreviations: 6MWD, 6-min walk distance; ERA, endothelin receptor antagonist; FC, functional class; HR, hazard ratio; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; PVR, pulmonary vascular resistance.
[a] Relates exclusively to patients who received combination therapy in the studies named above.

a favorable effect on exercise capacity and long-term outcomes compared with monotherapy with either of the two substances [6]. No hepatotoxic effects or clinically relevant drug interactions are known for ambrisentan.

Macitentan is used at a daily dose of 10 mg. Its approval is based on the SERAPHIN study, in which macitentan demonstrated a favorable effect on the course of PAH, both as a monotherapy and in patients who were receiving other PAH medications as background therapy, mostly sildenafil [7]. As with ambrisentan, there are no known hepatotoxic effects or clinically relevant drug interactions for macitentan.

3.4. Intravenous epoprostenol

Intravenous epoprostenol is still the only substance for which a reduction in PAH mortality has been demonstrated; however, this was achieved in an open, controlled study in which the control group received supportive therapy only [37]. The effects of intravenous epoprostenol in patients previously treated with other PAH medications have not been studied. Epoprostenol has to be administered continuously via a permanent central venous access. Its half-life is only a few minutes, which means that even short interruptions in therapy can have deleterious consequences. A recently approved thermostable version of epoprostenol has a similar profile [38].

3.5. Inhaled iloprost

Inhaled iloprost, given as monotherapy, was shown to improve exercise capacity in the AIR-1 study [39]. Data on its efficacy in combination with other drugs are contradictory [40,41]. There is a lack of long-term outcome data from controlled studies.

3.6. Subcutaneous and intravenous treprostinil

In Europe, treprostinil is approved for subcutaneous and intravenous administration. However intravenous therapy, according to the authorization text, should be reserved for patients with substantial side effects on subcutaneous therapy.

Subcutaneous therapy is administered with micro-infusion pumps via subcutaneously inserted needles. As monotherapy, subcutaneous treprostinil showed a modest increase in 6MWD compared with placebo; however, this was at relatively low dosages [42]. At higher doses, the substance is considered to be equipotent to epoprostenol [43]; however, this has not been demonstrated in controlled studies. The main side effect of subcutaneous treprostinil is infusion site pain, which occurs in >80% of patients and cannot always be satisfactorily treated [42]. According to a small, uncontrolled study, rapid uptitration to clinically effective dose and proactive infusion site pain management seemed to be better tolerated and improved exercise capacity and haemodynamics after 16 weeks [44].

Treprostinil can also be administered intravenously, either via a central venous catheter or via a fully implantable pump [45–47]. These pumps are generally implanted into the abdominal wall. The drug is administered via a subcutaneously tunneled central venous catheter. In this way, the pain associated with subcutaneous administration is avoided, while at the same time the infection risk appears to be markedly reduced compared with administration via a tunneled venous catheter or port [47].

3.7. Selexipag

Selexipag is not a prostacyclin analogue but an orally available IP receptor agonist. In the GRIPHON study, selexipag delayed disease

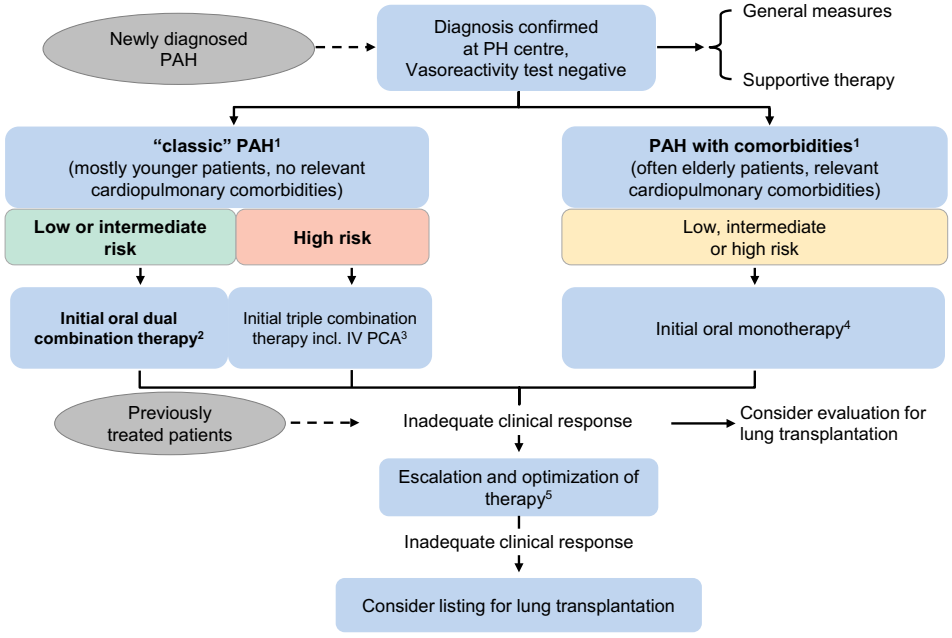

Fig. 2. Treatment algorithm for patients with PAH modified from [1,2]. Abbreviations: PH, pulmonary hypertension; PAH, pulmonary arterial hypertension. [1] Phenotype defines classification as "classic", i.e. younger patients without significant cardiopulmonary comorbidities versus PAH in elderly patients with significant cardiopulmonary comorbidities; Age alone is not a sufficient criterion but the risk of comorbidities and risk factors for cardiopulmonary disease (including hypertension, coronary heart disease, diabetes, obesity, smoking) become more relevant with increasing age [2] Initial, meaning immediate, combination therapy with endothelin receptor antagonists plus phosphodiesterase-5 inhibitors or soluble guanylate cyclase stimulators. [3] Initial triple combination therapy with endothelin receptor antagonists plus phosphodiesterase-5 inhibitors or soluble guanylate cyclase inhibitors plus an intravenous or subcutaneous prostacyclin derivate. [4] In these frequently elderly patients with cardiac and/or pulmonary comorbidities, the efficacy and tolerability of the PAH medicines have been less well investigated and the risk of drug-related side effects may be increased; this also applies to combination therapies, which is why monotherapy is recommended as initial treatment. [5] Individual adjustment of therapy in "typical" PAH, if necessary further escalation of the combination therapy including prostacyclin analogues; consider SC/IV prostacyclin; consider changing from phosphodiesterase-5 inhibitors to stimulators of soluble guanylate cyclase; decide on a case-by-case; for all patients, optimization of supportive therapy, including rehabilitation.

progression compared with placebo both in therapy-naïve patients and in patients who had been previously treated with PDE5 inhibitors and/or ERAs [8]. In patients pre-treated with other agents however, no clinically relevant improvement was observed in 6MWD and WHO FC. The dose of selexipag starts low and is increased gradually with the aim of reaching the maximum tolerated dose for each individual. The maximal approved dose of selexipag is 1600 μg twice daily. Side effects are similar to those observed with prostacyclin analogues, predominantly headache, nausea and diarrhea. In the GRIPHON study, 14.3% of patients discontinued selexipag therapy because of side effects, as opposed to 7.1% of patients on placebo [8].

4. Treatment strategies in PAH

The treatment algorithm recommended in the current ESC/ERS guidelines was developed for patients with "classic" PAH, i.e. predominantly younger patients without clinically relevant cardiopulmonary comorbidities. This treatment algorithm was amended at the Cologne Consensus Conference taking into account the varying phenotypes of patients diagnosed with PAH in Western countries. This relates primarily to the high number of elderly patients with PAH who have relevant cardiopulmonary comorbidities (Fig. 2).

4.1. Therapy in patients with newly diagnosed PAH at low/intermediate risk

Patients with newly diagnosed "classic" PAH who present at low or intermediate risk should be treated with dual oral combination therapy consisting of ERAs and PDE5 inhibitors or sGC stimulators, respectively. Monotherapies are no longer considered appropriate for these patients, unless individual considerations suggest otherwise.

The recommendation of initial combination therapy is predominantly supported by the AMBITION study, in which ambrisentan and tadalafil were used [6,48]. In addition, upfront combination therapy with ambrisentan and tadalafil showed positive effects in an open-label study in patients with PAH associated with systemic sclerosis [49]. Therefore, initial combination therapy with ambrisentan and tadalafil was given the highest level of recommendation in the ESC/ERS guidelines [1,2]. Initial combination therapy with other ERAs or PDE5 inhibitors may also be considered; however, the only data available on this at present are uncontrolled data from case series [50]. No data are currently available on an initial combination therapy with an ERA and riociguat. Still, this combination has been included in the recommendations from the Cologne Consensus conference to reflect the reality of treatment in some large PH centers.

4.2. Therapy in patients with newly diagnosed PAH at high risk

The ESC/ERS guidelines recommend initial combination therapy including an intravenous prostacyclin analogue in high-risk PAH patients [1,2]. This recommendation is based essentially on a single-center series of 19 high-risk patients who were treated immediately after diagnosis with bosentan, sildenafil and intravenous epoprostenol [51]. Despite the small number of cases and the uncontrolled, retrospective design, these data are considered relevant, because the improvements observed in hemodynamics, symptoms and survival rates were superior to those observed to date in patients on monotherapy or dual combination therapy [37,51,52].

The Cologne Consensus Conference has slightly modified the ESC/ERS recommendations. Triple upfront combination therapy consisting of (i) an intravenous or subcutaneous prostacyclin analogue, (ii) an ERA and (iii) a PDE5 inhibitor, is recommended for these patients.

Of note, the abovementioned recommendations apply only to patients with "classic" PAH. Initial dual or triple combination therapy is not recommended for elderly patients with PAH and cardiopulmonary comorbidities. PAH treatment in these patients should begin as monotherapy with consideration of sequential combination therapy on an individual basis. Data from COMPERA show that these patients are predominantly treated with PDE5 inhibitors. Sequential combination therapy tends to be used with caution throughout the disease course [18]. The reluctance to recommend initial combination therapy in these patients is based on the lack of efficacy data as well as on safety concerns, as registry data have shown a high rate of drug discontinuations due to adverse events in these patients [53].

4.3. Treatment considerations in patients at low risk while receiving PAH medications

If patients are at low only risk while receiving PAH therapy, the selected treatment strategy should be continued [3]. However, a combination regimen with ERAs should be considered for low-risk patients who are receiving PDE5 inhibitor-monotherapy as they benefited, in the long-term, from combination therapy in the SERAPHIN study [7].

4.4. Treatment considerations in patients at intermediate risk while receiving PAH medications

Therapy escalation, in the form of dual and triple combination therapy, is recommended for patients that are at an intermediate risk despite existing PAH therapy. Oral therapy is initially preferred, i.e. patients on monotherapy with PDE5 inhibitors or sGC stimulators are also given an ERA and vice versa.

Therapy can be expanded with the addition of selexipag, particularly in patients that are already being treated with a combination of ERA and PDE5 inhibitors and/or sGC stimulators, respectively [8]. Inhaled, subcutaneous or intravenous prostacyclin analogues may be considered as well.

In future, another therapeutic option could be switching from a PDE5 inhibitor to a sGC stimulator. This approach was investigated in the RESPITE study [54]. RESPITE was an open-label, uncontrolled study in which patients who were still at intermediate risk, despite existing therapy with PDE5 inhibitors (and ERAs if applicable), were switched to riociguat. After 6 months, most of these patients had shown improvements in exercise capacity, WHO FC, NT-proBNP and hemodynamics. However, given a relatively high drop-out rate and the uncontrolled, open-label design of RESPITE, this approach needs to be further investigated [55].

4.5. Treatment considerations in patients at high risk while receiving PAH medications

Patients who fall into the high-risk category while receiving PAH therapy need therapy optimization wherever possible. In the first place, this should include subcutaneous or intravenous prostacyclin therapy if these have not already been initiated. A switch from PDE5 inhibitors to riociguat can be considered, with the caveat discussed above that this is used as a supplementary treatment rather than an alternative to parenteral prostacyclin therapy.

4.6. Lung transplantation

Lung transplantation remains an important, but underused, therapeutic option for patients with treatment-refractory PAH. A recent analysis of the COMPERA registry included a total of 209 patients with IPAH who were younger than 65 years, 25 of whom died during the observation period [56]. In the same period, only three patients from this group underwent transplantation.

Because the course of disease is difficult to predict in patients with PAH, it is recommended that potentially suitable candidates are referred to a transplant center if they are at intermediate or high risk despite optimized therapy [57]. In the first instance, this evaluation serves to clarify whether transplantation is possible and considered a potential option by the patient. An early evaluation is generally recommended, allowing for a quick response in case of unforeseen clinical deterioration. In general, patients should be definitively listed for transplantation

when high risk persists despite optimized therapy, including the use of subcutaneous or intravenous prostacyclin analogues [57]. Today, the standard procedure in PAH is bilateral lung transplantation, which has a 1-year survival rate of >90% when performed at experienced centers [58]. The right ventricle recovers rapidly after transplantation [58,59]. Today, combined heart-lung transplantation is required only in cases where non-correctable congenital heart defects underlie the PAH or when patients also have serious left heart disease.

4.7. PAH therapy in children

The currently available data on PAH therapy in childhood are limited by the lack of randomized controlled clinical studies; therefore, specific treatment recommendations are mainly derived from the guidelines for adults. In Europe, sildenafil is one of the few drugs approved for the treatment of pediatric PAH. STARTS-1 and -2 [60,61] were the first randomized, placebo-controlled pediatric trials conducted in therapy-naïve children with PAH, which in 2011 led to the EMA authorization of sildenafil for children with PAH after the first year of life. The manufacturer recommends doses of 3 × 10 mg/day in children with a bodyweight of 8–20 kg, 3 × 20 mg/day in children with a bodyweight above 20 kg and 1 mg/kg in smaller children. Higher doses should be avoided, because they may be associated with increased mortality [61].

In Europe, bosentan is available as a 32-mg effervescent tablet that is easily divisible (known as the pediatric formulation), which was authorized by the EMA for use in children after the first year of life, on the basis of the data from the BREATHE-3 and FUTURE-1 studies [62,63]. Monthly monitoring of liver function is recommended; however an increase in transaminases appears to be more common in adults and children ≥12 years (7.8%), than in children under 12 years of age (2.7%) [64].

Randomized controlled studies with tadalafil, riociguat, ambrisentan, macitentan and selexipag in children with PAH are currently underway or being prepared.

If satisfactory therapeutic success cannot be achieved on a PDE5 inhibitor or ERA monotherapy, sequential combination therapy can be considered. When this should be initiated is not yet clear. To date, the effects of combination therapy have been rarely studied in childhood; prospective studies are needed to provide robust recommendations on combination therapy in pediatric patients with PAH.

Intravenous or subcutaneous prostacyclin therapy should be considered in patients with severe, advanced PAH (WHO FC III-IV), with an unfavorable risk profile and if there has been an inadequate response to oral combination therapy.

New interventional and operative therapeutic procedures aimed at the decompression of the right ventricle have become a promising alternative to lung transplantation, particularly in children and adolescents with severe, treatment-refractory PAH. To this end, a shunt is created between the pulmonary and systemic circulations; at the atrial level in percutaneous atrioseptostomy or at the arterial level in the Potts shunt. The right-to-left shunt that is created acts as a "pressure relief valve" and leads to decompression of the right ventricle and improvement of left-ventricular filling, thus improving the function of both ventricles.

The Potts shunt is a surgically created anastomosis between the left pulmonary artery and the descending aorta [65]. The advantage of this method is that, in contrast to an interatrial shunt, the resulting hypoxemia is limited to the lower half of the body, while completely saturated blood is retained for coronary and cerebral perfusion. This method can be applied if suprasystemic systolic and above all diastolic PAPs are present. There are case reports involving valved Potts anastomosis in PAPs that are just sub-systemic to avoid intermittent left-to-right shunting [65]. In children with a ductus arteriosus that is still patent, this can be augmented by ductal stenting and used in the same way as a modified Potts shunt [66]. Initial experiences with interventional insertion of a Potts shunt were published recently [67].

5. Summary and outlook

PAH continues to be an incurable disease. The principal aim of therapy is disease control, i.e. long-term stabilization of the patient at a good clinical performance level with the least possible impairment in right-heart function. Reaching and maintaining WHO FC I or II with a 6MWD >440 m and NT-proBNP levels <300 ng/L has been associated with excellent long-term survival rates [3–5]. Current treatments are particularly successful in patients with "classic" PAH, especially through the early use of combination therapies. A proactive approach is increasingly replacing the former strategy of initiating targeted PAH therapy as monotherapy and escalating to combination therapy only if the response is insufficient or if clinical deterioration occurs. The optimal combination therapy has not yet been determined. At present, combinations of ERAs and PDE5 inhibitors are preferred; in high-risk patients, these are used together with subcutaneously or intravenously administered prostacyclin analogues. The question of whether sGC stimulators may be more effective than PDE5 inhibitors in the long term has not yet been answered. It also remains to be studied if upfront triple combination therapy yields better long-term survival than less aggressive approaches. Finally, treatment strategies for elderly patients with PAH and cardiopulmonary comorbidities need to be further investigated.

Conflicts of interest/author declarations

MMH received fees for consulting and/or lectures from Actelion, Bayer, Gilead, GSK, Merck and Pfizer.

CA received fees for lectures from Actelion.

EG received fees for lectures and/or consulting from Actelion, Bayer, GSK, MSD, Novartis, Pfizer and United Therapeutics. Research funding from GSK, Actelion and Bayer.

MH received fees for consulting and/or lectures and conference sponsorship from Actelion, Bayer, Gilead, GSK, Merck, Novartis, OMT and Pfizer.

RE received fees for consulting and/or lectures from Actelion, Pfizer, Bayer, GSK, UT and Merck and research support from Actelion and Pfizer.

HKae received fees for consulting and/or lectures, and conference sponsorship from Actelion, Bayer and Bristol Myers Squibb. His institution received research funding from Actelion, Deutsche Stiftung für Herzforschung, and Deutsche Herzstiftung.

HJK received fees and reimbursement for travel/conference expenses from the companies Actelion, Bayer, GSK and Pfizer.

CMK received fees for consulting and/or lectures and conference sponsorship from Actelion, AOP, Bayer, GSK, Novartis and Pfizer.

HKlo received fees for lectures and/or consulting and conference expenses from Actelion, Bayer, MSD, GSK, UT, Novartis, OMT and Pfizer and research funding from GSK, Actelion and Bayer.

HL received fees for consulting and/or lectures from Actelion, Bayer, GSK, Merck and Pfizer.

SU receives research funding from the Swiss National Fund and the Zürich Lung League. She received fees and uncommitted research funding from Actelion, Bayer and Orpha-Swiss.

KMO received fees for consulting and/or lectures from Actelion, Bayer, GSK, Pfizer and United Therapeutics.

OD had consultancy relationship and/or has received research funding from Actelion, Bayer, Boehringer Ingelheim, ChemomAb, espeRare foundation, Genentech/Roche, GSK, Inventiva, Lilly, medac, MedImmune, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Sanofi, Sinoxa and UCB in the area of potential treatments of scleroderma and its complications. In addition, Prof. Distler has a patent mir-29 for the treatment of systemic sclerosis licensed.

SR received fees for consulting and/or lectures from Actelion, Bayer, Gilead, GSK, Merck, Novartis, Pfizer and United Therapeutics. His institution received research funding from Actelion, Bayer, Novartis and United Therapeutics.

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