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General measures and supportive therapy for 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 aiming at their practical implementation, considering country-specific issues, and including new evidence, where available. To this end, a number of working groups was initiated, one of which was specifically dedicated to general measures (*i.e.* physical activity/supervised rehabilitation, pregnancy/contraception, elective surgery, infection prevention, psychological support, travel) and supportive therapy (*i.e.* anticoagulants, diuretics, oxygen, cardiovascular medications, anaemia/iron deficiency, arrhythmias) for PAH. While the European guidelines provide detailed recommendations for the use of targeted PAH therapies as well as supportive care, detailed treatment decisions in routine clinical care may be challenging, and the relevance of supportive care is often not sufficiently considered. In addition, new evidence became available, thus requiring a thorough reevaluation of specific recommendations. The detailed results and recommendations of the working group on general measures and supportive therapy for PAH, which were last updated in the spring of 2018, are summarized in this article.

1. General measures

Patients with pulmonary hypertension (PH) need detailed recommendations about their activities of daily living. They have to adapt to the challenges that are associated with a progressive, chronic and life-threatening disease. This diagnosis usually results in a certain degree of social isolation. Encouraging patients and their family members to join support groups can have positive effects on coping with the disease, self-confidence and perspectives. The recommendations for general measures are listed in Table 1 and Fig. 1.

2. Physical activity and supervised rehabilitation

According to the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines, PAH patients should be advised to be active within symptom limits, but to avoid excessive physical exertion if this causes symptoms [1]. Physically deconditioned patients are also advised to undertake supervised exercise training.

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Table 1
Recommendations for general measures for patients with pulmonary arterial hypertension (PAH) (modified from [1]).

Recommendation	Recommendation class	Level of evidence
Patients with PAH should avoid pregnancy	**I**	**C**
Immunization of PAH patients against influenza and pneumococcal infection is recommended.	**I**	**C**
Psychological support is recommended in patients with PAH.	**I**	**C**
Exercise training *supervised by an expert centre* should be considered in PAH patients receiving pharmacological therapy.	***I****	***A***
In-flight oxygen (O_2) administration should be considered for arterial blood O_2 partial pressure consistently below 8 kPa (60 mm Hg) at rest.	**IIa**	**C**
For elective surgery, regional anaesthesia rather than general anaesthesia should be prefered whenever possible.	**IIb**	**C**
Excessive physical activity that results in overexertion and worsening of symptoms should be avoided.	**III**	**C**

*Recommendations in italics are the authors' suggestions for further discussion, not guideline recommendations.
PAH = pulmonary arterial hypertension.

These recommendations were initially based on a randomised controlled trial that demonstrated improvement in exercise capacity and quality of life (QoL) for patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH) [2]. Several uncontrolled studies with different training modalities have been conducted since then that support this concept [3–7]. Two additional randomised controlled trials showed that trained PAH patients reached higher levels of physical activity, had less fatigue, and showed improvements in 6-minute walk distance, cardiorespiratory function, and QoL compared to the respective control groups [8,9]. The sample sizes of all these studies are quite small (ranging from 19 to 183 patients) and all or the initial training was highly supervised and in some instances conducted in an inpatient setting. These recommendations are limited by gaps in the knowledge about the optimal method of exercise rehabilitation and the intensity and duration of the training. In addition, the characteristics of optimal supervision and the mechanisms by which symptoms, physical and functional capacity are improved are unclear, as are the potential effect on prognosis. Exercise training programmes should only be implemented by centres experienced in both PAH patient care and rehabilitation of compromised patients. In addition, patients should be treated with the best standard of pharmacological treatment and in stable clinical condition before embarking on a supervised rehabilitation programme.

Comments: *Since the publication of the ESC/ERS guidelines, another randomised controlled trial* [10] *and several meta-analyses have been published* [11–13] *that confirm the positive effect of training in PH. Therefore, the evidence level should be upgraded from IIa B to I A, with the caveat that the involvement of a PH expert centre should be considered mandatory* (Table 1).

3. Pregnancy, contraception and post-menopausal hormone therapy

In female patients with PAH, pregnancy remains associated with an increased mortality rate, so the current guidelines continue to give a class I-C recommendation, meaning that patients with PAH should avoid getting pregnant [1]. However, a recent report indicates that the outcome of pregnancies in PAH patients has improved, at least

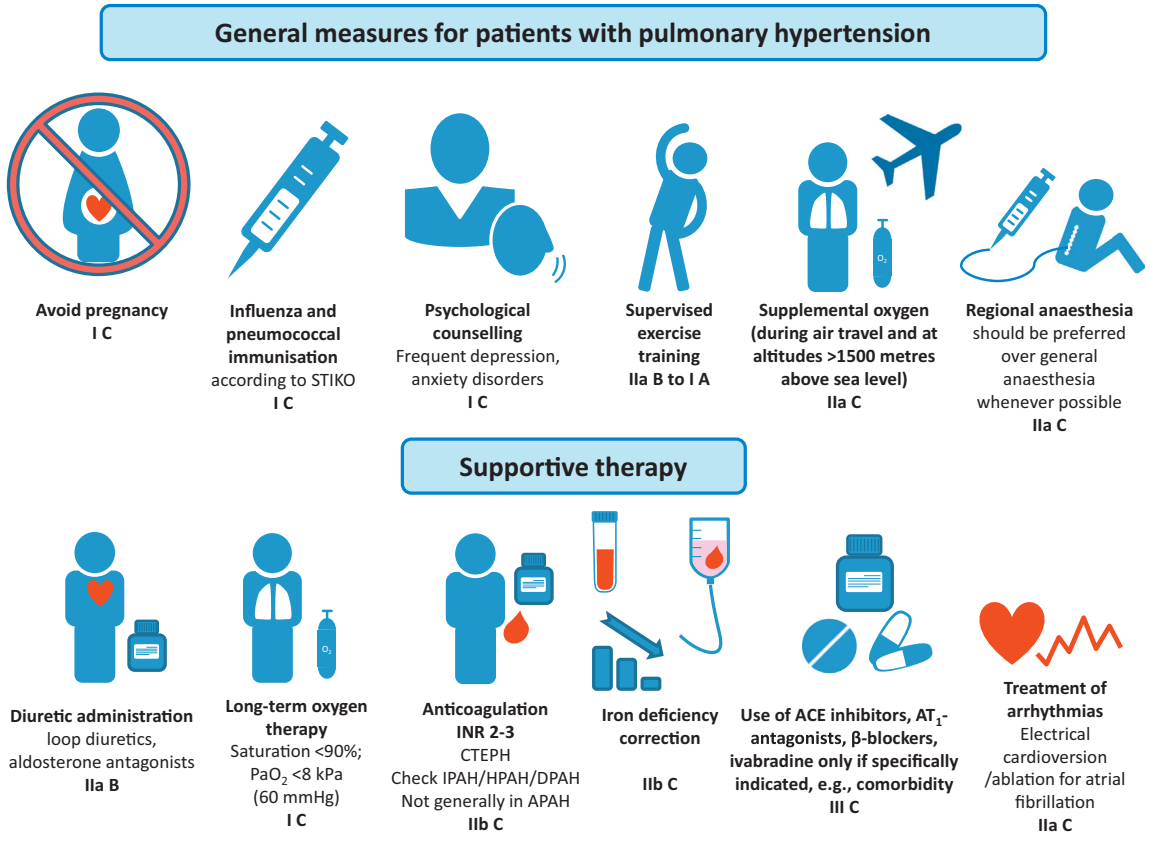

Fig. 1. Recommendations for general measures and supportive therapy in PAH. STIKO: Germany's Standing Immunization Committee ACE = angiotensin converting enzyme; APAH = PAH associated with other conditions; AT_1 = angiotensin receptor; CTEPH = chronic thromboembolic pulmonary hypertension; DPAH = PAH due to anorexigenic use; HPAH = hereditary PAH; INR = international normalised ratio; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; PaO_2 = partial pressure of oxygen.

when PAH is well controlled and monitored. This is particularly true in long-term responders to calcium channel blocker (CCB) therapy [14]. During a 3-year observation period, 26 pregnancies were reported in 13 participating centres. Three women (12%) died and one developed severe right heart failure requiring urgent heart–lung transplantation. There were eight abortions; two spontaneous and six medically induced. Sixteen of the pregnancies (62%) were successful, and the mothers delivered healthy babies without complications. In a study from five American centres, three female patients (17%) died between 1999 and 2008 [15]. These findings must be confirmed by larger sample sizes before the general recommendation for all female patients with PAH to avoid pregnancy can be reconsidered.

There is less consensus relating to the most appropriate methods of birth control. Barrier contraceptive methods are safe for the patient, but with an unpredictable effect. Progesterone-only preparations such as medroxyprogesterone acetate and etonogestrel are effective approaches to contraception and avoid the potential issues of oestrogens such as those associated with the old-generation mini-pill [16]. The levonorgestrel-releasing intrauterine coil is also effective but may rarely lead to a vasovagal reaction when inserted, which may be poorly tolerated in severe PAH. A combination of two methods may also be utilized. When prescribing oral contraceptives, it is worth considering that the endothelin receptor antagonist (ERA) bosentan may reduce the efficacy of oral contraceptives. The patient who becomes pregnant should be informed of the high risk of pregnancy and termination of the pregnancy should be discussed. Those patients who choose to continue pregnancy should be treated with disease-targeted therapies, planned elective delivery and effective close collaboration between obstetricians and the PAH team.

Comments: *Despite improvement in outcome, recent data from the Registry Of Pregnancy And Cardiac Disease of the European Society of Cardiology confirmed that maternal and fetal mortality remain high especially in women with iPAH* [17]*. Therefore, every patient who gets pregnant should be offered personalised counselling and a risk assessment at a PH centre* [18]*. Pregnant patients with PAH should be closely monitored at a centre with expertise in PAH, as well as physicians with experience in managing high-risk pregnancies and in critical care using extracorporeal procedures. Patients, especially those with Eisenmenger's syndrome, are particularly at risk not only during pregnancy and delivery, but particularly also in the immediate post-partum period* [19].

CCBs, phosphodiesterase-5 inhibitors and prostacyclin analogues are considered safe, but ERAs are contraindicated because of their teratogenic effects in animal experiments. To minimize the haemodynamic risks of an uncontrollable and painful birth, PAH patients should schedule a preterm delivery via Caesarean section at 32–36 weeks [20–22].

With regard to oral contraceptives, the Cologne Consensus Conference recommends a combination of oestrogen and progestogen (combined oral contraceptive [COC]) with a low risk of thrombosis (levonorgestrel, norgestimate, norethisterone). Alternatively, intrauterine devices (IUDs) coated with progestogen can be used if low-dose progestogen is not contraindicated. In patients who are not at risk of developing endocarditis, IUDs not coated with hormones (e.g., copper T-type IUDs) can also be used. If a product containing ethinyl-estradiol is contraindicated, the minipill containing desogestrel is an appropriate alternative. A progestin implant with etonogestrel or the three-month progestin depot injection with medroxyprogesterone acetate can also be used. Etonogestrel is available on the German market as a subcutaneously implanted progesterone system. Sterilisation can also be considered in individual cases but the potential risk of general anaesthesia has to be taken into consideration.

4. Elective surgery

Elective surgery is associated with a higher risk in patients with PAH. To date, it is unclear which form of anaesthesia should be used, but epidural anaesthesia seems to be better tolerated than general anaesthesia [23–25]. Patients who are usually treated with oral PAH therapies may require a temporary conversion to intravenous (i.v.) or nebulised forms of treatment until they are able to both receive and absorb oral drugs again.

Comments: *There are detailed comments on this topic in the "Decompensated right heart failure, intensive care and perioperative management in patients with PH" article in this supplement.*

5. Infection prevention

Patients with PAH are at higher risk of developing pneumonia, which is the cause of death in 7% of cases. [26]. Although no controlled trials have been conducted on this issue, vaccination against influenza and pneumococci is recommended.

Comments: *If transplantation is imminent, patients should get or update their recommended vaccines including hepatitis A/B. If patients receiving i.v. prostacyclin therapy develop a fever or signs of infection or experience a sudden clinical deterioration, a catheter-related infection must be ruled out.*

6. Psychological support

PH is a disease with a significant impact on the psychological, social (including financial), emotional and spiritual well-being of patients and their families [27]. Multimodal teams managing these patients should have the skills and expertise to assess and manage issues in all of these domains. For patients with severe psychosocial problems, the teams should have close links to colleagues in relevant disciplines, such as psychiatry, clinical psychology, welfare and social work. Patient support groups may also play an important role and patients should be advised to join such groups.

PH is generally associated with a clear reduction in life expectancy. Therefore, in addition to psychological and social support, there should be proactive advanced care planning with referral to specialist palliative care services when appropriate and necessary.

Comments: *As impairment worsens, patients often develop depression and anxiety, which are found in 25–40% of PAH patients in WHO functional class (FC) III-IV* [28–30]*. These significantly reduce PAH patients' QoL and may also have a negative impact on both treatment adherence and the disease course. Therefore, screening questions or questionnaires should be used routinely to detect psychological comorbidities (primarily depressive symptoms, anxiety, and adjustment disorders)* [31]*. Treating physicians can estimate the patient's risk of a depressive disease with good sensitivity and specificity by asking two screening questions* [32]*:*

- *"Are you sleeping well?"*
- *"In the last month, have you experienced feelings of despondency, depression or hopelessness?"*

An example of a screening questionnaire is the German version of the Hospital Anxiety and Depression Scale (HADS-D). Affected patients should be offered focused psychotherapeutic therapies and/or pharmacological antidepressant treatment [33,34].

7. Travel

To date, there are no studies using flight simulation to determine the need for supplemental O_2 during long-distance flights in patients with

PAH. The known effects of hypoxia suggest that O_2 administration during flights should be considered for patients in WHO FC III and IV and those with arterial blood O_2 partial pressure consistently <8 kPa (60 mm Hg) at rest [35]. A flow rate of 2 L/min will increase O_2 concentrations to sea level values. Similarly, hypoxemic patients should avoid spending time at altitudes of >1500–2000 m without supplemental O_2. Patients should be advised to travel with written information about their disease and be told how to contact local expert centres at their destination.

Comments: *Air travel-induced hypoxaemia in PAH patients is likely comparable with that in other lung diseases* [36]. *A flow rate of 2 L*/min *supplemental oxygen might be appropriate for PAH patients with no pre-existing PaO2 < 60 mm Hg at sea level. A recent study showed a progression of pulmonary arterial systolic pressure during simulated short-term hypoxia, while right heart function was not impaired* [37].

8. Supportive therapies

The ESC/ERS guideline recommendations on supportive therapies are summarized in Table 2. More recent data are now available on diuretic therapy, anticoagulation, and antiarrhythmic therapy. Recommendations from the Cologne Consensus Conference that exceed those of the guideline recommendations are added in italics in Table 2.

9. Oral anticoagulants

Post-mortem examination of patients with idiopathic PAH (IPAH) has shown a high prevalence of vascular thrombotic lesions [38]. Abnormalities in coagulation and fibrinolysis have also been reported [39–41]. This, together with the increased non-specific risk factors for venous thromboembolism, including heart failure and immobility, represents the rationale for oral anticoagulation in PAH. Evidence in favour of oral anticoagulation is limited to patients with IPAH, hereditary PAH (HPAH), and PAH associated with other conditions (APAH) and is based on retrospective research at single centres [38,42]. Registry data and the results of randomised controlled studies reveal heterogeneous, inconclusive data [43–45]. The potential benefits of oral anticoagulation in APAH are even less clear. Generally patients with PAH receiving therapy with long-term i.v. prostaglandins are anticoagulated in the absence of contraindications due in part to the additional risk of catheter-associated thrombosis. The role of the new oral anticoagulants in PAH is unknown. The use of anticoagulation in patients with Eisenmenger's syndrome is the subject of considerable debate. Anticoagulation may be considered for patients with specific indications such as heart failure, arterial or venous thromboembolisms or atrial arrhythmias with no haemoptysis.

Comments: *In a prospective Australian cohort-study (n = 132) with incident systemic sclerosis associated PAH anticoagulation had a survival advantage compared with no anticoagulation* [46]. *In contrast, recent registry data (COMPERA, REVEAL) suggest that APAH patients have poorer survival rates when taking anticoagulant therapy* [43]. *Thus, anticoagulant therapy currently cannot be generally recommended in patients with APAH (see Table 3). Contradictory are also data of patients with IPAH/HPAH/PAH due to drug use (DPAH): While an analysis from the COMPERA registry indicated a positive effect on survival, this was not confirmed in analyses of the REVEAL registry, in an open-label extension study of PAH patients treated with subcutaneous treprostinil* [47] *or in large treatment studies (SERAPHIN, GRIPHON). Therefore, also in IPAH/HPAH/DPAH the decision about anticoagulation should be made on a case-by-case basis after an individual risk-benefit analysis. Established indications for anticoagulant therapy, e.g., atrial fibrillation or venous thromboembolism are not affected by these considerations.*

In patients with severe PAH associated with congenital heart defects (in particular Eisenmenger's syndrome), cyanosis-related disturbances in blood clotting, i.e., increased bleeding tendency, must be considered. It should be noted that in the presence of erythrocytosis the international normalised ratio should be calculated according to the patients' haematocrit levels.

Table 2
Recommendations for supportive therapies for PAH (modified from [1]).

Statement	Recommendation class	Level of evidence
Treatment with diuretics is recommended in PAH patients with signs of RV failure and fluid retention.	I	C
Continuous long-term O_2 therapy is recommended in PAH patients in whom arterial blood O_2 partial pressure is consistently below 8 kPa (60 mm Hg).	I	C
Oral anticoagulant therapy may be considered in patients with IPAH, HPAH and anorexigen-induced PAH.	IIb	C
Correction of anaemia and/or iron deficiency may be considered in patients with PAH.	IIb	C
The use of ACE inhibitors, angiotensin-1 receptor antagonists, beta-blockers and ivabradine is not recommended in patients with PAH unless required by existing co-morbidities (*i.e.*, high blood pressure, coronary artery disease or heart failure)	III	C
In PAH patients with right heart failure mineralocorticoid antagonists may be considered (NB: renal function, hyperkalemia)	*IIa**	*B*
In patients with PAH associated with congenital heart defects, oral anticoagulation should be considered only if specific indications such as arterial or venous thromboembolisms or atrial arrhythmias are present and there are no signs of haemoptysis.	*IIa**	*C*

*Recommendations in italics are the authors' suggestions for further discussion, not guideline recommendations.
PAH = pulmonary arterial hypertension; RV = right ventricle; O_2 = oxygen; IPAH = idiopathic PAH; HPAH = hereditary PAH; ACE = angiotensin converting enzyme.

10. Diuretics

Decompensated right heart failure leads to fluid retention, raised central venous pressure, hepatic congestion, ascites, and peripheral oedema. Although there are no randomised controlled trials on the use of diuretics in PAH, clinical experience shows clear symptomatic benefit in fluid overloaded patients treated with this therapy. The choice and dose of diuretic therapy may be left to the PAH physician [48].

The addition of aldosterone antagonists should also be considered together with systematic assessments of electrolyte plasma levels. It is important with diuretic use to monitor renal function and blood biochemistry in patients to avoid hypokalaemia and the effects of decreased intravascular volume leading to pre-renal failure.

Comments: *For fluid retention, hepatic congestion, peripheral edema up to and including ascites, thiazides, thiazide-like diuretics, loop diuretics, and aldosterone antagonists can be used. For spironolactone, there is some evidence that its use in PAH possibly improves outcome* [49]. *There are no reliable data on the use of vasopressin antagonists* [50].

11. Oxygen

Although O_2 administration has been demonstrated to reduce the PVR in patients with PAH, there are no randomised data to suggest that long-term O_2 therapy is beneficial. Most patients with PAH, except

Table 3
Recommendations for anticoagulation in PH according to various guidelines.

	American guidelines from 2009 and revised algorithm from the fifth World Conference in Nice, 2013		European guidelines 2015		
PAH aetiology	Recommendation class/Level of evidence	Target INR	Recommendation class/Level of evidence		Target INR
IPAH	IIa/C	1.5–2.5	IIb/C		2.0–3.0
Heritable	IIa/C		IIb/C		
Due to anorexigenics	IIa/C		IIb/C		
APAH					
Connective tissue disease	IIb/C		Anticoagulant therapy may be considered in patients with a thrombophilic predisposition	IIb/C	
HIV			Not recommended due to a lack of data	III/C	
Portal hypertension			Not recommended	III/C	
Congenital heart defect			Consider for patients with specific indications such as heart failure, arterial or venous thromboembolisms or atrial arrhythmias with no haemoptysis	IIb/C	

PAH = pulmonary arterial hypertension, INR = international normalised ratio, IPAH = idiopathic PAH, APAH = associated PAH, HIV = human immunodeficiency virus.

those with CHD and pulmonary-to-systemic shunts, have minor degrees of arterial hypoxaemia at rest unless they have a patent foramen ovale. There are data showing that nocturnal O_2 therapy does not modify the natural history of advanced Eisenmenger syndrome [51]. Recommendations may be based on evidence in patients with chronic obstructive pulmonary disease. When arterial O_2 partial pressure is consistently <8 kPa (<60 mm Hg; alternatively, < 91% of arterial O_2 saturation), patients are advised to use O_2 to achieve an arterial blood O_2 pressure > 8 kPa. [35]. Ambulatory O_2 may be considered when there is evidence of symptomatic benefit and correctable desaturation on exercise.

Comments: *The goal should be to achieve O_2 saturation values of > 90% at rest, during exercise and when sleeping* [52,53]. *It has been shown that supplemental O_2 at night improved not only sleep-associated breathing difficulties, but also exercise performance during the day as well as cardiac repolarisation* [54]. *Adverse reactions, such as dehydration of the nasal mucosa, epistaxis tendency, and sleep disturbances should be monitored. A recent randomised-controlled trial has shown that O_2 given during cardiopulmonary exercise significantly improves maximal work rate and endurance* [53]. *Whether these positive effects of O_2 supplementation during exercise would translate into long-term improvements in daily activity or training is not known to date.*

12. Digitalis and other cardiovascular medications

Digoxin has been shown to acutely improve cardiac output in IPAH patients, although its efficacy is unknown when administered chronically [55]. It may also be given to slow down the ventricular rate in PAH patients who develop atrial tachyarrhythmias. To date, no convincing data are available on the benefit and safety of angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers or ivabradine in patients with PAH.

Comments: *Beta-blockers and CCBs may be harmful in patients with PAH because of their negative inotropic properties, but may be indicated in individual cases* [56]. *Digitalis can, if necessary, be recommended for heart rate control, when rhythm control is not possible.*

13. Anaemia and iron deficiency

Iron deficiency is common in patients with PAH and has been reported with the following prevalence: IPAH: 43%, PAH associated with systemic sclerosis: 46%, PAH with Eisenmenger's syndrome: 56% [57–59]. For all of these aetiologies, it has been shown that iron deficiency may be associated with reduced exercise capacity, and perhaps also with a higher mortality, independent of the presence or severity of anaemia [57,58,60,61]. Based on these data, regular monitoring of the iron status should be considered in patients with PAH and detection of an iron deficiency should trigger a search for potential reasons. Iron substitution should be considered in patients with iron deficiency. Some studies suggest that oral iron absorption is impaired in patients with PAH, so i.v. iron administration may be preferable [57,60,62]. However, controlled trials on this topic are lacking.

Comments: *Two uncontrolled trials demonstrated a positive effect of intravenous iron supplementation in patients with PAH and iron deficiency, demonstrating improvements of the 6-min walking distance, exercise capacity, and QoL* [62,63]. *Further trials are currently under way.*

In patients with erythrocytosis secondary to a pulmonary-to-systemic shunt defect (in particular in Eisenmenger's syndrome), assessing the erythrocyte indices alone is insufficient to detect iron deficiency. In each case, the usual parameters such as transferrin, ferritin, transferrin saturation, soluble transferrin receptor, etc. should be considered [64].

14. Arrhythmias

Management of arrhythmias is described in the current ESC/ERS PH guidelines in the "Diagnosis and treatment of PAH complications" (Section 1). However, because arrhythmias in PAH are common, recommendations for the treatment of arrhythmias are provided in the supportive therapy section of this article.

Arrhythmias are a relevant clinical problem in patients with PAH. In particular, symptomatic atrial arrhythmia can lead to a poorer prognosis [65]. In contrast to left heart disease, malignant ventricular arrhythmias such as ventricular tachycardia, ventricular flutter and ventricular fibrillation are rare in PAH. In a report of 132 confirmed cardiac arrests in PAH patients, ventricular fibrillation was documented in only 8% of the cases [66]. Another study in 231 patients with PAH or CTEPH who were observed over a 6-year period did not report any cases of malignant ventricular arrhythmia [65]. In that study, the annual incidence of supraventricular tachyarrhythmias was 2.8%.

Atrial flutter and atrial fibrillation were equally common and both arrhythmias invariably led to clinical deterioration with signs of right heart failure. Treatment of atrial flutter was generally more successful than treatment of atrial fibrillation. Restoration of a stable sinus rhythm was associated with favourable long-term survival, while persistent atrial fibrillation was associated with a 2-year mortality >80% [65]. Supraventricular arrhythmias were an indication for oral anticoagulation with vitamin K antagonists or direct oral anticoagulants. Both electric cardioversion and radiofrequency ablation have been shown to be effective in refractory cases [67].

Table 4
Recommendations for treatment of arrhythmias in patients with PAH.

Statement	Recommendation class	Level of evidence
In atrial flutter, the aim should be restoration and maintenance of sinus rhythm	*IIa**	*C*
In atrial flutter catheter ablation is recommended	*IIa**	*C*
In atrial fibrillation, the aim should be restoration and maintenance of sinus rhythm	*IIb**	*C*
In atrial fibrillation, electrical cardioversion may be recommended; amiodarone therapy can be considered for relapse prophylaxis	*IIb**	*C*
Digoxin may be considered in PAH patients with atrial tachyarrhythmia if the aim is heart rate control	*IIb**	*C*

*Recommendations in italics are the authors' suggestions for further discussion, not guideline recommendations.

Although prospective and controlled studies are lacking, these data suggest that a stable sinus rhythm after cardioversion should be considered as an important treatment goal in PAH patients. In order to achieve a stable sinus rhythm, prophylaxis with antiarrhythmic drugs without negative inotropic effects, such as oral amiodarone, should be considered, even if specific data regarding the efficacy of this therapy are lacking.

Comments: *To date relevant ventricular arrhythmias in PAH have been described as a rare event* [66]. *In a prospective study of 92 PH patients receiving targeted PAH therapy, short-term ventricular tachycardia was seen on the 72-hour ECG in 13% of patients* [68]. *Increased sympathetic nervous system activity, a prolonged corrected QT interval and right ventricular myocardial ischaemia may play a role* [69]. *The predictive significance of these findings is not yet known. Further research is needed.*

PH patients with the presence of atrial fibrillation showed larger right atrial size and pressures [70]. *P-wave duration > 0.11 s was associated with shorter survival in this analysis. In another retrospective study persistent atrial fibrillation was associated with worsening of hemodynamic and functional parameters and predicted adverse outcome* [71]. *In patients presenting with atrial flutter of right atrial origin, cavo-tricuspid isthmus ablation to create sinus rhythm is a valuable option* [72].

On the basis of the current data, the Cologne Consensus Conference suggests to consider the following additional recommendations (Table 4).

Conflict of interest

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

NB: received speaking fees from Actelion and Bayer.

UK: received speaking fees from Actelion and Bayer.

HK: received Sponsorship/Honoraria from Actelion, Bayer Healthcare, Bristol Myers Squibb. He is Steering Board member of the COMPERA International Steering Board, and had Research grant from Deutsche Stiftung für Herzforschung and Deutsche Herzstiftung

SH: no conflict of interest

KMO: received speaker fees from Actelion, Bayer, GSK, Pfizer und United Therapeutics.

SU: received grants from the Swiss Science Foundation and the Zurich Lung league. She received fees for talks and consulting from Actelion, MSD and Orpha Swiss.

FG: Personal fees for lectures from Actelion; research grants to institution from Actelion

CN: received honoraria for talks and/or consulting from Actelion, Bayer, GSK and United Therapeutics

AS: no conflict of interest

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

AMM: received speaking fees from Bayer.

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

GT: no conflict of interest

KGF: no conflict of interest

HK: received fees for talks and/or consulting work from Actelion, Bayer, MSD, GSK and Pfizer; research funding from GSK, Actelion and Bayer.

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