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Chronic thromboembolic pulmonary hypertension (CTEPH): Updated Recommendations of the Cologne Consensus Conference 2011☆

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ABSTRACT

In the 2009 European Guidelines on the diagnosis and treatment of pulmonary hypertension (PH), one section covers aspects of pathophysiology, diagnosis and treatment of chronic thromboembolic pulmonary hypertension (CTEPH). The practical implementation of the guidelines for this disease is of crucial importance, because CTEPH is a subset of PH which can potentially be cured by pulmonary endarterectomy (PEA). Nowadays, CTEPH is commonly underdiagnosed and not properly managed. Any patient with unexplained PH should be evaluated for the presence of CTEPH, and a ventilation/perfusion (V/Q) lung scan is recommended as screening method of choice. If the V/Q scan or CT angiography reveals signs of CTEPH, the patient should be referred to a specialized center with expertise in the medical and surgical management of this disease. Every case has to be reviewed by an experienced PEA surgeon for the assessment of operability. In this updated recommendation, important contents of the European guidelines were commented, and more recent information regarding diagnosis and treatment was added.

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 (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 treatment of pulmonary hypertension in Germany. To this end, a number of working groups was initiated, one of which was specifically dedicated to the diagnosis and treatment of chronic thromboembolic pulmonary hypertension (CTEPH). 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 summarized [1–3] whereby comments and additions appear in italics. The information on class of recommendation and level of

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evidence correspond to the tables listed in the preamble of this supplement.

1. Definition and pathogenesis

CTEPH is defined as pre-capillary PH as assessed by right heart catheterization (mean PAP $\geq$25 mmHg, PCWP $\leq$15 mmHg) in the presence of multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental) after at least three months of effective anticoagulation [1,2]. CTEPH is thought to result from isolated or recurrent pulmonary thromboembolism and represents one of the most prevalent forms of PH. Although most patients with pulmonary embolism (PE) do not develop CTEPH [4], the disease appears to be more prevalent than previously assumed [5]. Two prospective cohort studies demonstrated a cumulative incidence of symptomatic CTEPH of 3.8% [6] and 1.5% [7] after acute PE, respectively. Nevertheless, it is almost impossible to determine the overall prevalence of CTEPH since not all of these patients have a history of acute PE. In fact, CTEPH is frequently found in patients without any previous clinical episode of acute PE or deep venous thrombosis (up to 50% in different series) [8].

The pathogenesis of CTEPH is complex and has not been fully understood [8]. The most important pathobiological process is non-resolution of acute embolic masses which later undergo fibrosis, thus leading to mechanical obstruction of pulmonary arteries [1,2]. Unlike in acute PE, there is no linear correlation between a compromised hemodynamic state and the mechanical obstruction of pulmonary arteries. Pulmonary thromboembolism or *in situ* thrombosis may be initiated or aggravated by abnormalities in either the clotting cascade, endothelial cells, or platelets, all of which interact in the coagulation process [5]. Thus, coagulation and fibrinolytic disorders are thought to contribute to the development of the disease. In addition, other factors such as abnormal fibrinogen and immunological, inflammatory, or infectious mechanisms trigger pathological remodeling of major and small pulmonary vessels as a response to misguided thrombus resolution (Fig. 1).

Platelet abnormalities and biochemical features of a procoagulant environment within the pulmonary vasculature support a potential role for thrombus formation in initiating the disease in some patients. In most cases, it remains unclear whether thrombosis and platelet dysfunction are a cause or consequence of the disease. Inflammatory infiltrates are commonly detected in the pulmonary endarterectomy (PEA) specimens [1,2].

While acute PE may be clinically silent [9], there is accumulating evidence that CTEPH may also develop in the absence of previous PE [8]. In these cases, the disease is probably initiated by thrombotic or inflammatory lesions in the pulmonary vasculature. Once vessel obliteration is sufficient to cause increases in the PAP, a process of pulmonary vascular remodeling is started which self-perpetuates the progression of PH, even in the absence of further thromboembolic events [1,2].

Pathological lesions are characterized by organized thrombi tightly attached to the pulmonary arterial medial layer in the elastic pulmonary arteries, replacing the normal intima. These may completely occlude the lumen or form different grades of stenoses, webs, and bands [4]. Interestingly, in the non-occluded areas, a pulmonary arteriopathy indistinguishable from that of PAH (including plexiform lesions) can develop [10]. Obstructive lesions observed in the distal pulmonary arteries of non-obstructed areas may be related to a variety of factors, such as shear stress, pressure, inflammation, and the release of cytokines and vasculopathic mediators. Collateral vessels from the systemic circulation (from bronchial, costal, diaphragmatic and coronary arteries) can grow to reperfuse at least partially the areas distal to complete obstructions [1,2].

2. Thrombophilia and CTEPH

Traditional risk factors for venous thromboembolism (VTE) include antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden, plasminogen deficiency, and anticardiolipin antibodies [9]. However, in 147 consecutive patients with CTEPH, the prevalence of hereditary thrombotic risk factors (antithrombin mutations, protein S, protein C, factor II or factor V Leiden) was not increased when compared to 99 consecutive patients with IPAH or to 100 control patients (Table 1) [11].

Thrombophilia studies have shown that lupus anticoagulant may be found in ~10% of CTEPH patients, and 20% carry antiphospholipid antibodies, lupus anticoagulant, or both [12]. A recent study has demonstrated that the plasma level of factor VIII, a protein associated with both primary and recurrent VTE, is elevated in 39% of patients with CTEPH [12]. No abnormalities of fibrinolysis have been identified [1,2]. Blood groups type A, B, and AB were found to be significantly more common in patients with CTEPH compared to patients with PAH (88% vs. 56%) [13].

Plasma lipoprotein levels (a) (Lp(a)), a subgroup of the low density lipoprotein with high atherogenic potency, were significantly higher in patients with CTEPH than in patients with PAH and control subjects, indicating an overlap of venous and arterial thrombotic risk factors [14].

3. Factors that are associated with the development of CTEPH

In addition to thrombophilia, certain conditions are associated with an increased risk for CTEPH [1,2], including previous splenectomy, the presence of a ventriculo-atrial (VA) shunt for the

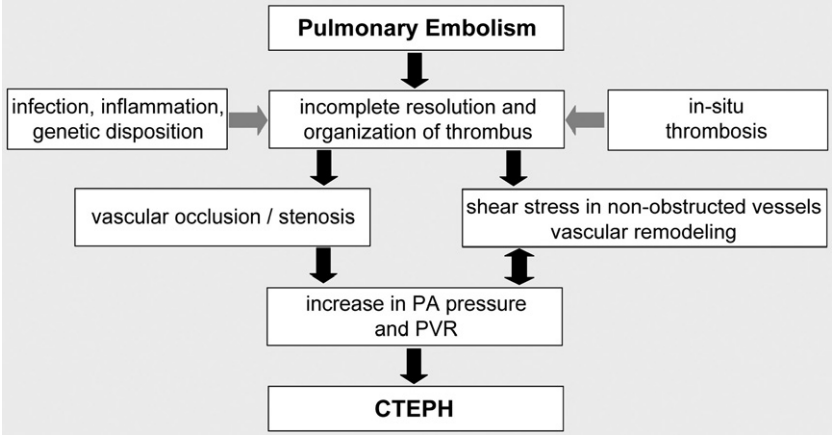

Fig. 1. Current hypothesis for the pathobiology of CTEPH (according to [5,8].)

Table 1
Risk factors for CTEPH [6,11–15].

Independent clinical risk factors for CTEPH
- Splenectomy
- Ventriculo-atrial (VA) shunts
- Pacemaker leads
- Indwelling central venous catheters (e.g. Port, Hickman catheter)
- Chronic inflammatory diseases (osteomyelitis, inflammatory bowel diseases)
- Malignant diseases
- Thyroid hormone replacement therapy

Risk factors associated with CTEPH after symptomatic PE
- Previous pulmonary embolism
- Young age
- Large perfusion defect
- Idiopathic PE at presentation

Plasmatic risk factors associated with CTEPH
- Elevated factor VIII levels >250%
- APA/LAC
- Combined coagulation defects
- Fibrinogen mutations

APA, antiphospholipid antibodies; LAC, lupus anticoagulans.

treatment of hydrocephalus, myeloproliferative disorders, infected intravenous lines, and chronic inflammatory disorders, such as osteomyelitis and inflammatory bowel diseases [14–16]. While these associated conditions have a negative impact on survival [17], the mechanism(s) linking these conditions to CTEPH have not been fully explored, but chronic inflammation or chronic blood stream infection may play a critical role [13].

4. Diagnostic procedures

Any patient with unexplained PH should be evaluated for the presence of CTEPH. Suspicion should be high when the patient presents with a history of previous venous thromboembolism. Survivors of acute PE should be followed after the acute episode to detect signs and symptoms of CTEPH. Patients with acute PE showing signs of PH or RV dysfunction at any time during their hospital stay should receive a follow-up echocardiography after discharge (usually after 3-6 months) to determine whether or not PH has resolved [1,2].

In patients with unexplained PH, a ventilation/perfusion lung scan (*comment: planar images on at least 6 views + SPECT*) is recommended to exclude CTEPH [18,19], since the sensitivity is greater than that of computed tomography [20]. While a normal ventilation/perfusion lung scan rules out CTEPH, unmatched perfusion defects can also occur in other conditions (see Table 2).

Multidetector-row CT angiography is indicated when the ventilation/perfusion lung scan is indeterminate or reveals perfusion defects (see specific recommendations of the working group). Even in the era of modern multirow CT scanners, there is not yet enough evidence to suggest that a normal CT angiography excludes the presence of operable CTEPH [1,2]. Nevertheless, CT angiography may show complete obstruction, stenoses, strictures, or intimal irregularities [21,22]. Parenchymal lesions and hypertrophic bronchial collaterals are visualized.

Once perfusion/ventilation scanning and/or CT angiogram show signs compatible with CTEPH, the patient should be referred to a center with expertise in the medical and surgical management of these patients [1,2]. To determine the appropriate therapeutic strategy, invasive tools including right heart catheterization and traditional pulmonary angiography are usually required [4]. Coronary angiography is indicated in candidates for PEA and risk factors for coronary heart disease. In order to minimize risks and repeated procedures, these investigations should be performed at an expert center rather than at the referring hospitals [23].

Table 2
Differential diagnosis of CTEPH (by localization of the lesion).

1. **Pre-capillary**
   - acute pulmonary embolism
   - PAH
   - in situ thrombosis in congenital heart disease
   - mediastinal fibrosis
   - vasculitis
   - sarcoidosis
   - pulmonary artery sarcoma
   - non-thrombotic embolism
     - tumor
     - parasites
     - histoplasmosis
     - foreign bodies (talcum)
   - Osler's disease
   - pulmonary atresia
   - Swyer James syndrome
   - Recklinghausen's disease
   - hemoglobinopathy
2. **Capillary**
   - capillary hemangiomatosis
3. **Post-capillary**
   - pulmonary veno-occlusive disease (PVOD)
   - mediastinal fibrosis
   - schistosomiasis

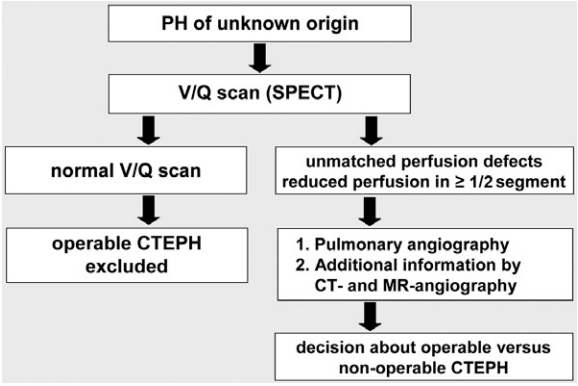

Fig. 2. Diagnostic algorithm for CTEPH.

The final diagnosis of CTEPH is based on the presence of pre-capillary PH as assessed by right heart catheterization (mean PAP ≥25 mmHg, PCWP 15 mmHg, PVR >2 Wood units) in patients with mutiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental) [1,2]. Furthermore, the decision about potential PEA is made by reviewing the patient history and functional class, ventilation/perfusion lung scan, selective pulmonary angiography, CT angiography, and right heart catheterization (Fig. 2, Table 3). Blood group and thrombophilia screening including AT III, lupus anticoagulant, and anti-cardiolipin antibodies should be performed.

Comments:

The diagnostic tools to assess the severity of CTEPH are the same as for PAH. There is, however, less available data for patients with CTEPH than for patients with PAH.

Table 3
Diagnostic criteria in CTEPH.

The final diagnosis of CTEPH is based on the presence of:
1. Symptomatic PH
2. PAPm ≥25 mmHg, PAWP ≤15 mmHg, or non-measurable PAWP
3. With chronic/organized thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, or subsegmental level)
4. After at least three months of effective anticoagulation.

Other imaging procedures such as MRI [24] and angioscopy [25] are not mentioned in the ESC/ERS guidelines but may be applied depending on the experience of the respective center.

In order to determine the therapeutic strategy for patients with CTEPH, one study suggested that vasoreactivity testing may be used within the scope of right heart catheterization [26], although the consequences of such testing remain unclear. Analysis of the pressure decay curves in right heart catheterization during pulmonary arterial occlusion can help identify a distal component of vasculopathy [27].

Specific recommendations of the working group:

1. *(a) Patients with persistent dyspnea after acute PE should be followed up, and the presence of CTEPH should be included into the spectrum of differential diagnoses.*
   (b) Stable patients with signs of significant PH at the time of the thromboembolic event should undergo assessment for the presence of CTEPH three months after the event during which the patient should have received effective anticoagulation.
   (c) The diagnostic work-up should include echocardiography, perfusion scanning, CT angiography, right heart catheterization, and, if necessary, pulmonary angiography.
2. *CT alone is not sufficient to refute the diagnosis or inoperability of a patient with CTEPH. In fact, it is a common observation in PEA centers that CTEPH patients are referred late, after previous misdiagnoses that were based on "negative" CT-scans. Pulmonary angiography is the standard procedure for the evaluation of operability. Selective pulmonary angiography in at least two planes is mandatory and allows visualization of the morphology of segmental and subsegmental arteries, as well as visualization of parenchymal perfusion. CT and MRI currently constitute valuable adjunctive imaging modalities (see Fig. 2).*

5. Treatment of CTEPH

Patients with CTEPH should receive life-long anticoagulation, usually with vitamin K antagonists adjusted to a target INR between 2.0 and 3.0.

The decision on how to treat patients with CTEPH should be made at an expert center based upon interdisciplinary discussion among internists, radiologists, and expert surgeons. Pulmonary endarterectomy (PEA) is the treatment of choice for patients with CTEPH as it is a potentially curative treatment option. As a rule, a patient should not be considered inoperable as long as the case has not been reviewed by an experienced PEA surgeon. Detailed pre-operative patient evaluation and selection, surgical technique and experience, and meticulous post-operative management are essential prerequisites for success after this intervention [21]. The selection of patients for surgery depends on the extent and location of the organized thrombi in relation to the degree of PH, and taking into consideration age and co-morbidities. Proximal organized thrombi represent the ideal indication, while more distal obstructions may complicate or prevent a successful procedure. After an effective intervention, a dramatic drop of pulmonary vascular resistance can be expected with a near normalization of pulmonary hemodynamics. A center can be considered to have sufficient expertise in this field if it performs at least 20 PEA operations per year with a mortality rate $<10\%$ [1,2].

Specific PAH drug therapy has thus far not proven effective in CTEPH. However, targeted treatments may be considered in selected patients with CTEPH, mainly for three different scenarios: (i) if patients are not considered candidates for surgery; (ii) if pre-operative treatment is deemed appropriate to improve hemodynamics, and (iii) if patients present with symptomatic residual/recurrent PH after PEA or develop PH once more after PEA had been performed [1,2]. Several uncontrolled clinical studies suggest that prostanoids, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors may exert hemodynamic and clinical benefits in patients with CTEPH, regardless of whether these patients were considered operable or inoperable [28–35]. The only randomized, placebo-controlled clinical trial that has so far addressed the safety and efficacy of targeted medical treatment was the BENEFIT study (*Bosentan Effects in inoperable Forms of chronic thromboembolic pulmonary hypertension*), which investigated the effects of bosentan in patients with inoperable CTEPH for a 16-week period [36]. This study revealed a significant drop in PVR in the bosentan group but no change in the 6-minute walking test, WHO functional class, or time to clinical worsening [1,2].

Given these limited data, further studies are necessary to obtain reliable long-term data on the effect of medical therapies in patients with CTEPH, and these patients should be treated within clinical trials whenever possible. For the present time, no medical therapy has been approved for CTEPH in Europe or the USA. Bilateral lung transplantation is an option for advanced cases that are not suited to PEA. The recommendations of the ESC/ERS guidelines for CTEPH are summarized in Table 4 [1,2] and included in the specific recommendations of the working group.

Table 4
Recommendations of the ESC/ERS guidelines for CTEPH [1,2].

Recommendation	Class of recommendation	Level of evidence
The diagnosis of CTEPH is based on the presence of pre-capillary PH (mean PAP $\geq$25 mmHg, PCWP $\leq$15 mmHg, PVR $>$2 Wood units) in patients with multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental), persisting after effective anticoagulation over a minimum period of three months.	I	C
In patients with CTEPH, lifelong anticoagulation is indicated.	I	C
Surgical pulmonary endarterectomy (PEA) is the recommended treatment for patients with CTEPH.	I	C
Once perfusion scanning and/or CT angiography shows signs compatible with CTEPH, the patient should be referred to a center with expertise in surgical pulmonary endarterectomy.	IIa	C
The selection of patients for surgery should be based on the extent and location of the organized thrombi, on the degree of PH, and on the presence of co-morbidities.	IIa	C
PAH-specific drug therapy may be indicated in selected CTEPH patients such as patients who are not candidates for surgery or patients with residual PH after pulmonary endarterectomy.	IIb	C

Comment:

A PEA center is defined as an institution which performs $\geq$ 20 PEA surgeries per year with a mortality rate $<$10% [1,2]. Due to the location of stenoses and occlusions of the pulmonary artery branches at the segmental and subsegmental level as well as the variable texture of obstructive material, the intervention is regarded to be technically challenging. Complete disobliteration of the vessels is necessary for maximal RV after-load reduction. Phases of deep hypothermic circulatory arrest allow a better view of the pulmonary arterial branches, and PEA has therefore to be carried out under a considerably limited amount of time. In a recent randomized study, circulatory arrest for PEA surgery has been shown to be a safe procedure with regard to neurocognitive function [37].

Contraindications for PEA include severe left ventricular systolic

dysfunction, advanced lung disease (e.g. COPD, pulmonary fibrosis), and malignant tumors with significantly limited prognosis. Advanced age per se is no contraindication for surgery.

To evaluate surgical accessibility, it is highly recommended to obtain the expert opinion of a second PEA surgeon if in doubt.

The best surgical results are achieved with complete endarterectomy and early postoperative reduction of PVR to <500 dyn s cm^{-5} (6.25 Wood units). The surgical technique (phases of circulatory arrest to ensure a blood-free operating field with adequate brain protection) was first described by the group in San Diego [38]. This group redefined the concept of non-operability by institutional rather than anatomical limitations. For example, there is no definition for "distal obstructions". Instead, "distal" depends on the experience of the surgeon.

Even though the results of PEA in patients with CTEPH have not been assessed in randomized studies, the long-term results with regard to survival, WHO functional class, exercise capacity, quality of life, right ventricular function, hemodynamics, and gas exchange are reported to be excellent for most patients. Recently, the results two prospective large series have been published [39,40]. First results of an international CTEPH registry, that included 386 consecutive patients with newly diagnosed CTEPH (from February 2007 to January 2009) undergoing surgery at 26 centers in Europe and 1 center in Canada, showed a highly significant and sustained decrease in PVR from 736 to 248 dyn s cm^{-5} (95% confidence limit, 702–827 and 230–263, respectively) at the end of intensive care, that was accompanied by substantial improvements of WHO functional class and exercise capacity (increase in 6MWD from 362 to 459 m; 95% CL, 340–399 and 440–473, respectively) at 1 year [39]. In line with these results, a decrease in the PVR from 805 ± 365 to 301 ± 232 dyn s cm^{-5}, and an increase of the 6MWD from 269 ± 119 to 367 ± 108 m was reported in 314 patients who underwent PEA in a continuous national series (1997–2007) in the UK [40]. The reported rates of residual PH after PEA (mean PAP >30 mmHg) were 16.7% and 31%, respectively [39,40].

Recent evidence implicates that PEA may also be successfully performed in pediatric patients (reported age 8–18 years) [41]. In 17 reported cases, there were significant improvements in the mean PAP (45.5 ± 20.7 to 27.3 ± 13.0 mmHg), PVR (929 ± 844 to 299 ± 307 dyn s cm^{-5}), and CO (3.8 ± 1.1 to 5.6 ±1.6 l/min), and long-term survival (5+ years) was achieved in 87.5%. However, the rate of rethrombosis appeared to be significantly higher in children (38%) as compared to adults (1–4%) [41].

The concept of PEA which was originally developed in San Diego was adopted by approximately 20 larger centers worldwide. In 2008, a perioperative mortality rate of 4.7% after PEA in 1,100 surgeries was reported in an international prospective registry [38]. More recently, they even reported a surgical mortality rate of 2.2%. Similarly, early mortality after PEA was reported to be era-dependent in the UK series (25% for 1997–2002; 2.7% for 2006–2007) [40]. With increasing experience, PEA centers worldwide should achieve perioperative mortality rates <10%. This goal may be achieved by education and training at the experienced centers, since the results are subject to a learning curve. The impact of experience and surgical case volume on the mortality rate have been confirmed by the data of the international CTEPH registry: In-hospital mortality at centers with less than 10 PEA operations per year was 7.4% whereas the mortality rate at expert centers with more than 50 operations per year was 3.5% [39].

In order to detect persistent or recurrent PH, systematic follow-up investigations are necessary. Right heart catheterization is recommended 6–12 months after PEA.

The inherent danger of initiating medical therapy without consulting a PEA surgeon is that potentially operable patients are not referred to a PEA center at all or only after delays, and they are therefore denied a potentially curative therapy or are presented for surgery only at a very advanced stage which is associated with a significantly increased risk for surgery. The availability of medical therapy should not imply that operable patients are no longer referred for PEA. Corresponding treatment decisions should therefore only be made at experienced centers (see specific recommendations of the working group).

Specific recommendations of the working group

1. *Operable patients:*
   These patients should undergo surgery (PEA) without delay. For high-risk patients, the decision about the time of surgery and a potential medical therapy prior to surgery should be made together with a PEA surgeon.
2. *Operable patients not undergoing surgery for various reasons (comorbidities, patient refusal):*
   The decision not to operate on such patients may only be taken at expert centers together with the responsible PEA surgeon. If surgery is not an option, medical therapy with targeted PAH drugs may be considered.
3. *Technically non-operable patients:*
   The decision against surgery may only be taken at expert centers together with the responsible PEA surgeon. If surgery is not an option, medical therapy with targeted PAH drugs may be considered.
4. *Persistent and recurrent PH after PEA:*
   The indication for repeated surgery should be reviewed at a PEA center. If re-PEA is not indicated, medical therapy with targeted PAH drugs may be considered.

Medical therapy of CTEPH:

There are no randomized, controlled studies that demonstrate clinical efficacy of targeted PAH drugs in patients with CTEPH [42,43]. Accordingly, no drug has so far been approved for this disease in Europe. However, "PAH drugs" should not be denied to selected patients who may benefit from them. This applies especially to patients with inoperable CTEPH who, in some cases, cannot be clearly distinguished from PAH. The working group believes that the following recommendations regarding medical treatment of these patients are acceptable:

- *Targeted treatment with PAH drugs should only be initiated at experienced centers (definition according to the European guidelines, see Table 4).*
- *The use of medical treatment requires comprehensive diagnostic procedures according to the recommendations of the guidelines, including the referral to a PEA surgeon, to ensure that the patients are non-operable and that other causes of PH are excluded.*
- *Before these patients are treated with a targeted PAH therapy, it should be assessed if they are eligible for a clinical study. Large PH centers as well as PH self-support groups (in Germany: phev) can provide further information about on-going clinical trials.*
- *Unlike in PAH, it is not yet known if PAH drugs have a positive effect on disease progression in patients with CTEPH. It should therefore be considered to attempt initial treatment over a limited period of time such as 6 months, and to subsequently decide after careful re-evaluation if an objective clinical improvement justifying continuation of therapy was achieved. Otherwise the treatment may be discontinued. This procedure and potential therapeutic goals should be determined and documented together with the patient prior to initiation of treatment.*

Conflicts of interest

H. Wilkens: Honoraria for lectures and/or consultancy for Actelion, Bayer, GSK, Lilly, Pfizer and United Therapeutics.

I. Lang: Honoraria for lectures and/or consultancy for Actelion, AOPOrphan Pharm, AstraZeneca, Bayer, GSK, Lilly, LungRX, Pfizer and United Therapeutics.

J. Behr: Honoraria for lectures and/or consultancy for Actelion, Bayer, Gilead, GSK, Lilly, and Pfizer.

T. Berghaus: Honoraria for lectures and/or consultancy for Actelion, Boehringer-Ingelheim, Novartis, and Pfizer.

C. Grohe: Honoraria for lectures and/or consultancy for Actelion, Bayer, Lilly, and Pfizer.

S. Guth: Honoraria for lectures and/or consultancy for Actelion, Bayer, GSK, and Pfizer.

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

T. Kramm: none.

U. Krüger: Honoraria for lectures for Pfizer.

F. Langer: none.

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

H.-J. Schäfers: none.

M. Schmidt: none.

H.-J. Seyfarth: Honoraria for lectures and/or consultancy for Actelion, Bayer, and GSK.

T. Wahlers: none.

H. Worth: Honoraria for lectures and/or consultancy for Actelion, and Lilly.

E. Mayer: Honoraria for lectures and/or consultancy for Actelion, Bayer, and GSK.

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