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Review article

Interventional and pharmacological management of chronic thromboembolic pulmonary hypertension

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ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by obstruction of the pulmonary vasculature, leading to increased pulmonary vascular resistance and ultimately right ventricular failure, the leading cause of death in non-operated patients. This article reviews the current management of CTEPH. The standard of care in CTEPH is pulmonary endarterectomy (PEA). However, up to 40% of patients with CTEPH are ineligible for PEA, and up to 51% develop persistent/recurrent PH after PEA. Riociguat is currently the only medical therapy licensed for treatment of inoperable or persistent/recurrent CTEPH after PEA based on the results of the Phase III CHEST-1 study. Studies of balloon pulmonary angioplasty (BPA) have shown benefits in patients with inoperable or persistent/recurrent CTEPH after PEA; however, data are lacking from large, prospective, controlled studies. Studies of macitentan in patients with inoperable CTEPH and treprostinil in patients with inoperable or persistent/recurrent CTEPH showed positive results. Combination therapy is under evaluation in CTEPH, and long-term data are not available. In the future, CTEPH may be managed by PEA, medical therapy or BPA – alone or in combination, according to individual patient needs. Patients should be referred to experienced centers capable of assessing and delivering all options.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a debilitating, life-threatening form of pulmonary hypertension (PH) caused by obstruction of pulmonary vasculature by residual organized thrombi, leading to increased pulmonary vascular resistance (PVR), progressive worsening PH and right ventricular failure [1,2]. At diagnosis, patients typically have impaired exercise capacity and dyspnea. Other symptoms include chest pain, weight loss, edema, weakness, palpitations and syncope [3]. The physical and emotional burdens of CTEPH significantly affect patients' quality of life [3], and it imposes (or it is associated with) substantial healthcare utilization and economic costs [4,5].

1.1. Incidence of CTEPH

CTEPH is thought to arise as a complication of acute pulmonary embolism (PE) subsequent to venous thromboembolism that fails to resolve [6]. Some patients, however, have no history of PE [6]. In survivors of acute PE there is high variability in the reported incidence of CTEPH [7,8]. A meta-analysis of >4000 patients with PE followed for ~2 years found that the incidence of CTEPH after acute PE was 0.56%, rising to 3.2% in patients alive after 6 months of treatment [9]. Left untreated, CTEPH has a poor prognosis (5-year survival rate ~30%) [10].

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Abbreviations

6MWD	6-min walking distance
AE	Adverse event
BPA	Balloon pulmonary angioplasty
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CT	Computed tomography
CTEPH	Chronic thromboembolic pulmonary hypertension
DSA	Digital subtraction angiography
ERA	Endothelin receptor antagonist
LS	Least-squares
mPAP	Mean pulmonary arterial pressure
N/A	Not available
NO	Nitric oxide
NS	Not significant
NT-proBNP	*N*-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PDE5is	Phosphodiesterase type 5 inhibitors
PE	Pulmonary embolism
PEA	Pulmonary endarterectomy
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
SAE	Serious adverse event
SCR	Satisfactory clinical response
SD	Standard deviation
sGC	Soluble guanylate cyclase
WHO FC	World Health Organization Functional Class

Predisposing risk factors for CTEPH include abnormal fibrinolysis and underlying hematological or autoimmune disorders [11]. It is now recognized that the pathogenesis of CTEPH after pulmonary endarterectomy (PEA) involves small vessel vasculopathy [12], contributing to hemodynamic and functional impairment, disease severity and progression. The molecular processes involved, however, are not fully understood [1,13]. Impairment of the nitric oxide (NO)–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) pathway is central to CTEPH pathogenesis [14]. cGMP production, catalyzed by NO binding to sGC, promotes vasodilation and inhibits smooth muscle proliferation and vascular remodeling [15]. Endothelial dysfunction in CTEPH leads to impaired NO synthesis, resulting in insufficient NO–sGC–cGMP activity [14].

Here we describe treatment options for CTEPH and review recent evidence for the efficacy and safety of approved and investigational therapies for inoperable and persistent/recurrent CTEPH.

2. Diagnosis of CTEPH

Lung ventilation/perfusion scintigraphy (*V/Q* scan) and computed tomography pulmonary angiography are accurate methods for the detection of CTEPH with excellent diagnostic efficacy [16]. *V/Q* scan remains the preferred initial imaging test for CTEPH screening [17,18]. The previous gold standard for characterizing vessel morphology in CTEPH, digital subtraction angiography (DSA), is now challenged by advances in non-invasive modalities. With recent advances in distal PEA and balloon pulmonary angioplasty (BPA), conventional DSA may not be suitable for providing finer detail. Selective direct injection conventional angiography is widely available, although more selective imaging, such as cone-beam computed tomography (CT) and electrocardiogram-gated area detector CT may be more advantageous, particularly in the more distal vessels [19]. However, these newer imaging techniques are not widely available and require expertise for use.

3. Surgical and interventional treatment of CTEPH

3.1. Pulmonary endarterectomy

The standard of care for CTEPH is the surgical procedure PEA. PEA involves removal of all obstructive thromboembolic material from the pulmonary arteries, including the intima and superficial media. The aim is to reduce right ventricular afterload and improve cardiac function, pulmonary hemodynamics and ventilation/perfusion matching. The operation is performed through a median sternotomy incision to approach both pulmonary arteries using extracorporeal circulation and phases of deep hypothermic circulatory arrest [20]. Treatment guidelines recommend that all CTEPH patients should undergo evaluation by an interdisciplinary team for operability at an experienced expert treatment center and PEA for all patients deemed operable following assessment [21,22]. An operable patient is one with sufficient accessible thromboembolic material and a PVR proportional to the degree of obstruction [23]. However, patient selection for PEA in CTEPH is challenging, and assessments of operability and risk/benefit are subjective, with no defined standards [24–26]. Several factors correlate with a good post-surgical outcome. These include a history of PE or deep vein thrombosis, World Health Organization Functional Class (WHO FC) II or III, PVR < 1000 dyn·s·cm^{-5} consistent with the extent of obstructions visible on imaging, bilateral lobe disease that is concordant across images, experience of the surgical team, and lower post-surgical pulmonary artery pulse pressure (<38 mmHg) [22,23,27]. Signs of right heart failure or other comorbidities are associated with higher operative risk, but do not necessarily preclude PEA [20,22,23]. PEA is potentially curative and can result in near normalization of pulmonary hemodynamics [21,23,24,28]. Registry data show that 3-year survival rates are around 90% in patients who undergo surgery compared with 70% in those who do not (Fig. 1) [29]. Data also show that outcomes are significantly better in patients who undergo surgery compared with operable patients who refuse surgery [28].

While proximal lesions (i.e. in the main, lobar and segmental arteries) are generally operable [23], more distal disease may be inaccessible, or accessible only to highly experienced surgeons. Improvements in surgical techniques at PEA expert centers (defined as those carrying out > 50 PEA procedures per year, including surgery at the level of the segmental arteries, with a surgical mortality $< 5\%$) [22] have expanded the pool of patients in whom PEA is possible [23,30–32]. Furthermore, outcomes after PEA are similar between patients with proximal disease and those with more distal disease [31]. Data on long-term outcomes are limited because of the small number of expert centers with experience in the management of CTEPH [24]. Despite these improvements, up to 40% of patients with CTEPH are considered inoperable. Furthermore, while PEA is potentially curative, up to 51% of patients will experience persistent/recurrent CTEPH after surgery [6,27]. Recent evidence from a prospective, pilot, randomized, sham-controlled clinical trial suggests pulmonary artery denervation using remote magnetic navigation may potentially benefit these patients; improvements were seen in PVR (mean difference 109 dyn·s·cm^{-5} [95% confidence interval {CI}, 45 to 171]; $p < 0.001$) and 6-min walking distance (6MWD) (71 m [95% CI, 13 to 129]; $p = 0.03$) for patients receiving this procedure ($n = 25$) versus patients receiving the sham procedure ($n = 25$) [33]. Though promising, these findings need to be confirmed in a larger trial.

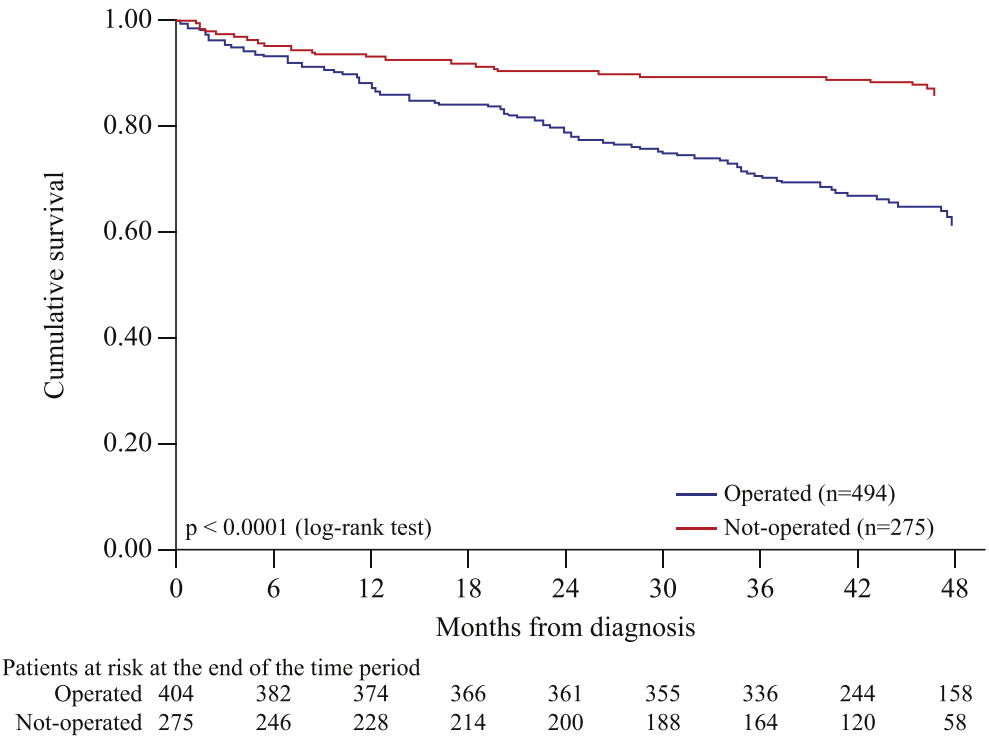

Fig. 1. Kaplan–Meier estimates of survival for patients from the international CTEPH registry who underwent pulmonary endarterectomy and those who did not [29].

3.2. Balloon pulmonary angioplasty

BPA aims to disrupt the organized clot material in the pulmonary arteries, thereby improving pulmonary vascular blood flow [24]. The procedure is less invasive than PEA, involving cannulation of the femoral or jugular veins to allow insertion of guidewires [34]. Numerous studies have now been conducted in patients with inoperable or persistent/recurrent CTEPH after PEA (Table 1). In these studies, those patients who received BPA following PEA achieved a better mean pulmonary arterial pressure (mPAP), WHO FC and 6MWD compared with those who received PEA alone [35]. BPA followed by treatment such as riociguat also improved WHO FC, mPAP and PVR [36]. Hemodynamic benefits of BPA have been demonstrated in observational studies [24]. Although early European studies did not report the same magnitude of efficacy as seen in the original Japanese studies [22,25], possibly for reasons including differences in thresholds for operability, and the characteristics of patients treated, a recent retrospective analysis of 1006 BPA sessions in 184 French patients with inoperable CTEPH showed similar outcomes to the Japanese series. Overall survival after BPA was 97% at 1 year and 95% at 3 years (Fig. 2) [37]. BPA is currently recommended, alone or in combination with riociguat, as a treatment for patients with CTEPH who are technically inoperable or carry an unfavorable risk/benefit ratio for PEA [21,22].

Eligibility criteria for BPA are based on assessment of pulmonary artery anatomy and function, and lung perfusion [38]. This should be based on multiple diagnostic modalities, including selective pulmonary angiogram, intravascular imaging and pressure gradient analysis [22,38,39]. While BPA may be a treatment option for patients with CTEPH who are technically operable but considered unsuitable for surgery or have declined PEA, its role in these patients is yet to be determined.

Table 1
Studies of BPA in patients with CTEPH.

Year	Study	Study type	No. of participants	Medical treatment before BPA (%)
2012	Sugimura et al. [87]	Prospective	12	100
	Kataoka et al. [88]	Prospective	29	100
	Mizoguchi et al. [89]	Observational	68	100
2013	Andreassen et al. [90]	Observational	20	10
2014	Inami et al. [91]	Retrospective	136	85
	Taniguchi et al. [92]	Retrospective	29	100
	Fukui et al. [93]	Retrospective	20	75
2016	Aoki et al. [94]	Prospective	24	92
	Inami et al. [95]	Retrospective	170	91
2017	Roik et al. [39]	Prospective	11	66
	Kurzyna et al. [96]	Observational	56	80
	Ogo et al. [19]	Retrospective	80	61
	Olsson et al. [97]	Prospective	56	Almost all
	Ogawa et al. [98]	Retrospective	308	72
2018	Wiedenroth et al. [36]	Prospective	123	100
	Yanaka et al. [35]	Prospective	10	100
2019	Araszkiewicz et al. [99]	Retrospective	15	100
	Brenot et al. [37]	Retrospective	184	62

BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension.

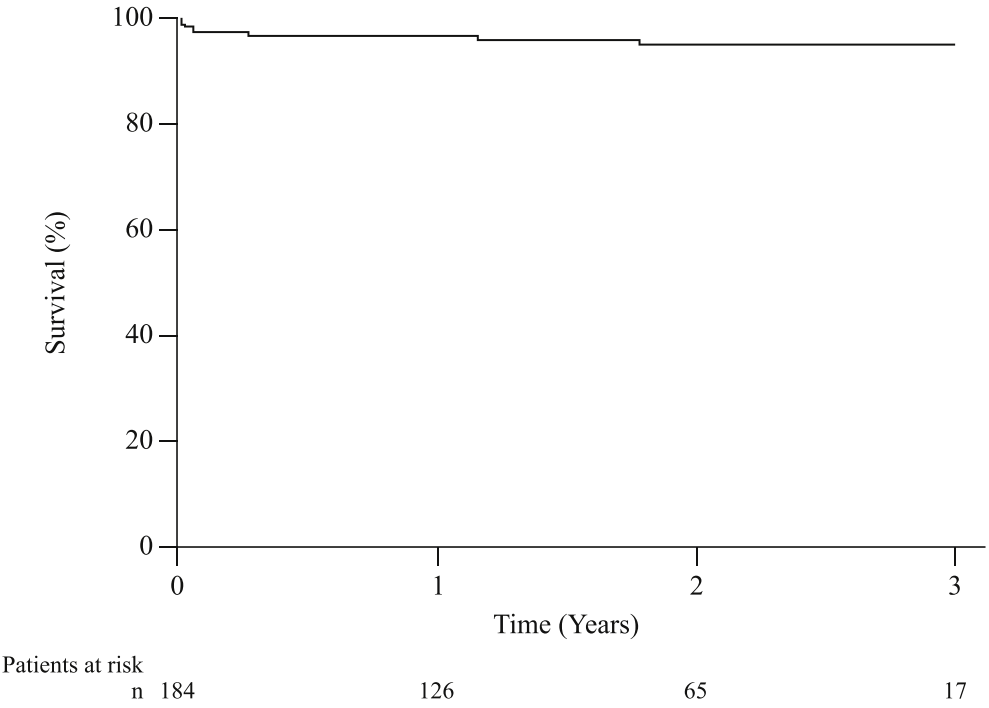

Fig. 2. Kaplan–Meier analysis of survival in patients with inoperable CTEPH who underwent BPA at a French expert center [37].

BPA may be associated with complications, such as vascular injury, which can be accompanied by hemoptysis and/or hypoxemia [38]. Most patients undergoing BPA will require more than one session, as attempting to treat too many lesions in one session can increase the risk of complications [25]. The risk/benefit ratio of BPA is not fully understood, and long-term data are lacking from large, prospective, randomized controlled trials. Furthermore, there is a steep learning curve for any center wishing to include BPA in their treatment options for patients with CTEPH [40]. Therefore, BPA should be performed only at experienced CTEPH centers for patients who are ineligible for PEA as a result of distal chronic thromboembolism or persistent/recurrent PH after surgery [22].

BPA is mostly performed on a background of medical treatment and is often considered complementary to medical therapy (Table 1). The efficacy and safety of BPA compared with riociguat in patients with inoperable CTEPH are being investigated in two randomized controlled trials: the RACE trial (NCT02634203) in approximately 124 patients and a multicenter trial (UMIN000019549) of approximately 60 patients in Japan. Combining PEA with BPA, either sequentially or as a hybrid procedure, is also being investigated [41].

4. Medical treatment of CTEPH

Only three trials in CTEPH – the Phase III CHEST-1 trial (riociguat), the Phase III CTREPH trial (treprostinil) and the Phase II MERIT-1 trial (macitentan) – have met their primary endpoints. No head-to-head trials have been conducted with riociguat versus other medical therapies for the treatment of CTEPH, and direct comparisons between studies are limited by differences in study design. Key differences between CHEST-1, CTREPH and MERIT-1 are that MERIT-1 only enrolled patients with inoperable CTEPH whereas CHEST-1 and CTREPH included patients with inoperable CTEPH and patients with persistent/recurrent CTEPH. Also, MERIT-1 and CTREPH allowed PAH therapy at baseline, whereas CHEST-1 included treatment-naïve patients only [42,43]. Finally, the patients enrolled in CTREPH were older overall and had more severe disease than those in the CHEST-1 and MERIT-1 studies [42–44].

4.1. Riociguat

Current treatment guidelines recommend the sGC stimulator riociguat for the management of inoperable CTEPH and persistent/recurrent CTEPH after PEA [21]. Riociguat has a dual mode of action within the NO–sGC–cGMP pathway, stimulating sGC directly via a NO-independent binding site and stabilizing the binding of NO to sGC [14].

4.2. Riociguat clinical trials

After positive findings from animal models [14,45] and Phase I and II proof-of-concept studies [46–48], a multicenter, open-label, uncontrolled, 12-week Phase II study of riociguat reported favorable safety and significant improvements in exercise capacity, symptoms and pulmonary hemodynamics in patients with pulmonary arterial hypertension (PAH) and inoperable CTEPH [49].

The pivotal Phase III CHEST-1 study evaluated the safety and efficacy of riociguat (individually adjusted up to 2.5 mg three times a day) in 261 patients with inoperable CTEPH (72%) or persistent/recurrent CTEPH after PEA (28%) [42]. After 16 weeks, riociguat significantly improved 6MWD by a least-squares (LS) mean difference of +46 m versus placebo (primary endpoint), as well as improving NT-proBNP (*N*-terminal prohormone of brain natriuretic peptide) (LS mean difference [95% CI] −444 pg/mL [−843 to −45]; $p < 0.001$) and WHO FC [42]. Riociguat also significantly improved hemodynamic parameters including PVR (LS mean difference [95% CI] 246 dyn·s·cm^{-5} [−303 to −190]; $p < 0.0001$) and cardiac index (LS mean difference [95% CI] 0.5 L/min/m^2 [0.3 to 0.6]; $p < 0.0001$) [42,50].

Patients with inoperable CTEPH experienced numerically higher improvements in 6MWD, PVR, cardiac output, cardiac index, mPAP and diastolic pressure gradient compared with patients with persistent/recurrent PH after PEA, although relative changes were generally similar between the subgroups [50]. The LS mean difference (95% CI) in 6MWD at Week 16 in inoperable patients was +54 m (29–78) compared with +26 m (−16 to 68) in the persistent/recurrent subgroup [50]. The LS mean difference (95% CI) in PVR in the inoperable subgroup was −285 dyn·s·cm^{-5} (−357 to −213) ($p < 0.0001$) compared with −131 dyn·s·cm^{-5} (−214 to −48) ($p = 0.0025$) in the persistent/recurrent

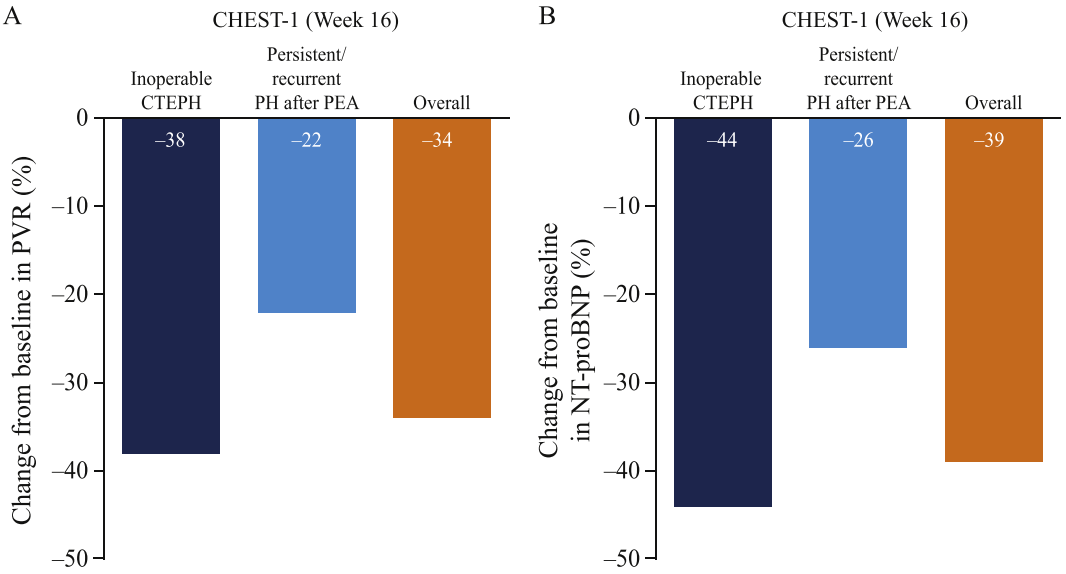

Fig. 3. Mean treatment difference for riociguat versus placebo in percentage change from baseline to Week 16 in (A) PVR (dyn·s·cm^{-5}) and (B) NT-proBNP (pg/mL): reanalysis of CHEST-1 data. An analysis of covariance model was applied with log-transformed baseline value and treatment group as fixed effects. CTEPH, chronic thromboembolic pulmonary hypertension; NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

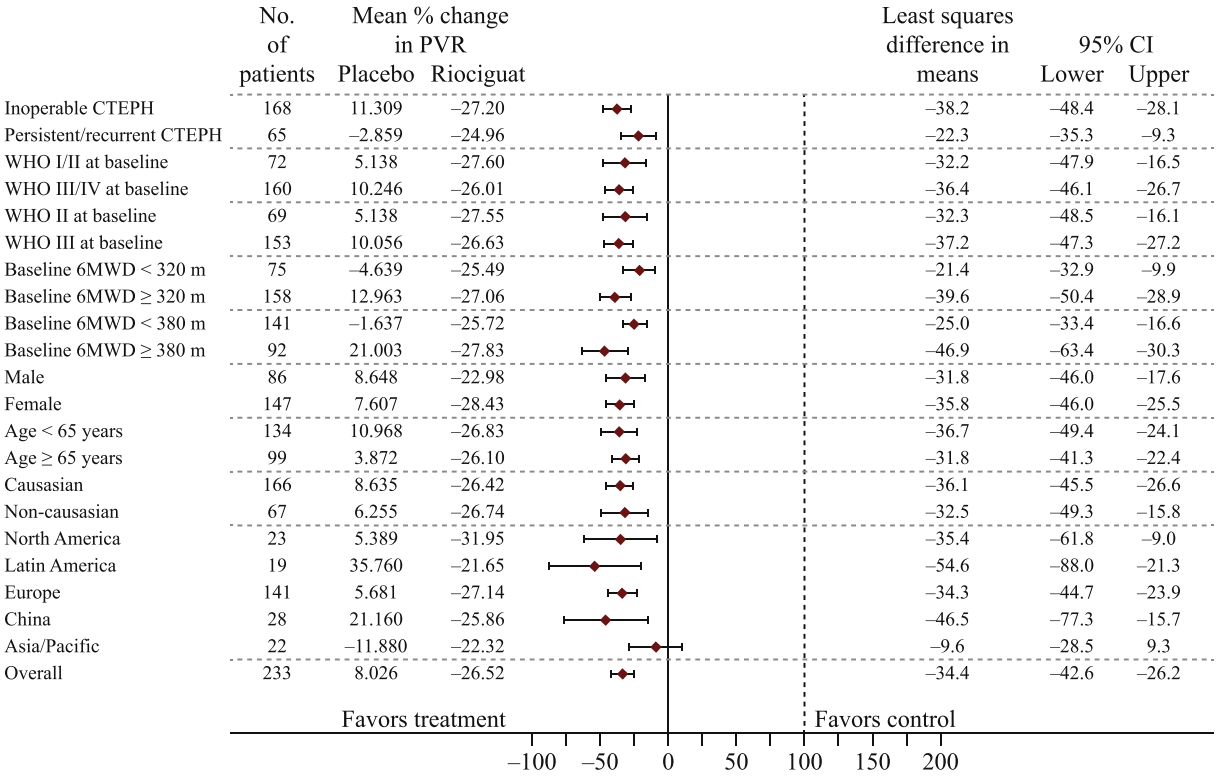

Fig. 4. Mean treatment difference in percentage change from baseline to last visit in PVR (dyn·s·cm^{-5}) by subgroup (intent-to-treat population): reanalysis of CHEST-1 data (data on file). LS estimates and CIs are based on an analysis of covariance model with baseline and treatment effect as fixed effects. Baseline = last observed value before start of study treatment. Last visit = last observed value (not including follow-up) for patients who completed the study or withdrew, except imputed worst value in case of death or clinical worsening without a termination visit. Subgroups with n < 5 were excluded. 6MWD, 6-min walking distance; CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; PVR, pulmonary vascular resistance; WHO, World Health Organization.

subgroup.

In a post hoc analysis of the CHEST-1 PVR data, a placebo-corrected LS mean treatment difference of −38% (95% CI −48 to −28) was observed in patients with inoperable CTEPH versus −22% (−35 to −9) in the persistent/recurrent subgroup (Fig. 3A). Subgroup analysis of PVR was limited to patients with inoperable CTEPH and those with persistent/recurrent PH after PEA. An exploratory reanalysis of the data by additional subgroups (CTEPH type, WHO FC, baseline 6MWD, gender,

age, race and geographical region) demonstrated a consistent treatment effect across all subgroups (Bayer, data on file) (Fig. 4).

Reanalysis of the CHEST-1 NT-proBNP data at Week 16 (analysis of covariance with log-transformed baseline value and treatment group as fixed effects) revealed a 39% reduction in NT-proBNP with riociguat versus placebo (Bayer, data on file) (Fig. 3B). The treatment effect in inoperable CTEPH was 0.56 (0.43–0.74), a 44% reduction, and 0.74 (0.47–1.17) in persistent/recurrent CTEPH (26% reduction) [42].

Of 243 patients completing CHEST-1, 237 (98%) entered the long-term extension CHEST-2 [51]. Improvements in 6MWD and WHO FC were sustained at 2 years (mean ± standard deviation [SD] 6MWD +52 ± 66 m at 1 year, +50 ± 68 at 2 years; WHO FC improved / stabilized / worsened: 40 / 57 / 4% at 1 year) [51,52]. At 2 years, overall survival was 93% (Fig. 5) and clinical worsening-free survival was 82% [52].

Riociguat was well tolerated in CTEPH clinical studies [42,51,53]. Adverse events (AEs) related to study treatment were generally mild to moderate, self-limiting and rarely required discontinuation of treatment [54]. During 2 years of treatment in CHEST-2 there was a lower exposure-adjusted frequency of common AEs than in CHEST-1 [52]. Serious adverse events (SAEs) in the CHEST studies were generally related to underlying disease progression or the mode of action of riociguat [42,51].

Several responder threshold criteria have been identified for patients with PAH, which provide an indication of response to treatment [55]. These include 6MWD ≥380 m, WHO FC I/II, cardiac index ≥2.5 L/min/m^2, venous oxygen saturation ≥65% and NT-proBNP < 1800 pg/mL. A post hoc analysis of CHEST-1 showed that riociguat treatment increased the proportion of patients achieving these thresholds compared with placebo [55]. A composite satisfactory clinical response (SCR) endpoint has also been used to evaluate the effect of achieving SCR components on clinical worsening-free survival [56]. SCR was defined as ≥ 10% improvement from baseline in 6MWD and improvement to (or maintenance of) WHO FC I/II in the absence of clinical worsening. Compared with placebo, riociguat increased the proportion of patients who met SCR criteria at Week 16 in CHEST-1 and patients achieving the WHO FC and 6MWD components had improved clinical worsening-free survival in CHEST-2 compared with those not achieving these endpoints [56].

4.3. Investigational therapies for CTEPH

Since riociguat is not tolerated or efficacious in all patients, and is not curative, there remains an unmet need for alternative therapies for CTEPH. Two investigational therapies, macitentan and treprostinil, have reported positive clinical trial data and represent potential future therapeutic options for CTEPH. Histological similarities between CTEPH and PAH provide a rationale for off-label use of PAH-specific medical therapies (phosphodiesterase type 5 inhibitors [PDE5is], endothelin receptor antagonists [ERAs] and prostacyclin analogs) to target the microvascular component of CTEPH [13,21,57], and such treatment is common among patients with inoperable or persistent/recurrent CTEPH after PEA. This is often related to reimbursement, reluctance of physicians and/or patients to consider surgery [4,6,58], or the availability of only unapproved treatments. Clinical trial evidence supporting the efficacy of these therapies in CTEPH is, however, scarce. Several small retrospective and open-label trials of bosentan [59–61], treprostinil [62], epoprostenol [63–65] and sildenafil [66] (reviewed by Hoeper [67]) were limited by small patient cohorts, lack of randomization and blinding, or absence of a control arm [57,67]. Evidence from randomized controlled trials of medical therapies in patients with CTEPH is summarized in Table 2. The AIR study evaluated inhaled iloprost in a mixed population of patients with primary PH and selected forms of non-primary PH, including inoperable CTEPH, and demonstrated the efficacy of iloprost compared with placebo in the overall population [68]. In the BENEFiT study, a significant difference between bosentan and placebo was observed for PVR after 16 weeks in 157 patients with inoperable or persistent/recurrent CTEPH, but there was no corresponding effect on 6MWD, the other co-primary endpoint (Table 2) [69]. A small study in 19 patients with inoperable or persistent/recurrent CTEPH receiving sildenafil showed no significant benefit on the primary endpoint of 6MWD at Week 12 compared with placebo, although there was a significant benefit for PVR (Table 2) [70]. The AMBER-1 study of ambrisentan versus placebo in patients with inoperable CTEPH was terminated early because of difficulties in enrollment (ClinicalTrials.

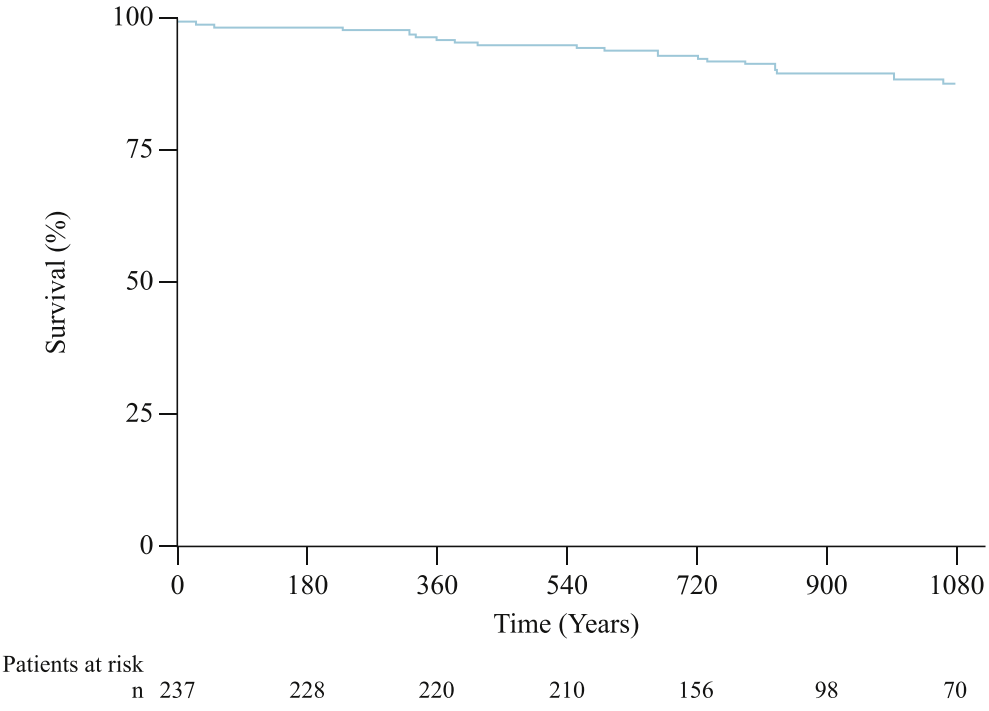

Fig. 5. Kaplan–Meier analysis of survival in patients with inoperable or persistent/recurrent CTEPH who received long-term riociguat in the CHEST-2 study [52].

Table 2
Randomized controlled trials of medical therapies in patients with CTEPH.

	Study						
	BENEFiT [69]	Suntharalingam et al. [70]	MERIT-1 [43]	CHEST-1 [100]	AMBER-1* [71]	CTREPH [44]	AIR [68]
Design	Multicenter, randomized, double-blind, placebo controlled	Randomized, double-blind, placebo controlled	Phase II, randomized, double-blind, placebo controlled	Phase III, randomized, double-blind, placebo controlled	Randomized, double-blind, placebo controlled, parallel group	Phase III, randomized, double-blind, controlled	Randomized, double-blind, placebo controlled
Duration	16 weeks	12 weeks	24 weeks	16 weeks	16 weeks	24 weeks	12 weeks
Study drug/ control	Bosentan/placebo	Sildenafil/placebo	Macitentan/ placebo	Riociguat/ placebo	Ambrisentan/ placebo	Treprostinil (high- vs. low-dose)	Iloprost/placebo
No. of patients	157	19	80	261	33	105	203
Study population	Inoperable CTEPH (n = 96); persistent/ recurrent PH after PEA (n = 41)	Inoperable CTEPH (n = 10); persistent/ recurrent PH after PEA (n = 9)	Inoperable CTEPH (n = 80)	Inoperable CTEPH (n = 189); persistent/ recurrent CTEPH (n = 72)	Inoperable CTEPH (n = 33)	Inoperable CTEPH (n = 105)	PH (n = 203), including inoperable CTEPH (n = 57)
Primary endpoint	Change in PVR as % of baseline and 6MWD from baseline to Week 16 (co-primary endpoints)	Change in 6MWD from baseline to Week 12	Resting PVR at Week 16	Change in 6MWD from baseline to Week 16	Change in 6MWD from baseline to Week 16	Change in 6MWD from baseline to Week 24	≥10% increase in 6MWD and an improvement in the NYHA functional class in the absence of a deterioration in the clinical condition or death during the 12 weeks of the study
Primary endpoint (s) met?	No	No	Yes	Yes	No	Yes	Yes
Treatment effect on PVR, mean (95% CI)	−24.1% (−31.5 to −16.0); p < 0.0001	−197 dyn·s·cm^{-5} (−389 to −6); p = 0.044	0.84 dyn·s·cm^{-5}† (0.70–0.99); p = 0.041	−34% (−43 to −26)‡	−130 dyn·s·cm^{-5} (−502.0 to 78.0)§	[Mean (SD) change from baseline: high-dose, 214 (324) dyn·s·cm^{-5} low-dose, 73 (285) dyn·s·cm^{-5}; p < 0.00001 for high- vs. low-dose]	[Mean (SD) change from baseline: iloprost, −239 (279) dyn·s·cm^{-5}; p < 0.001 vs. baseline placebo, +96 (322) dyn·s·cm^{-5}; p < 0.05 vs. baseline]
Treatment effect on 6MWD, m, mean (95% CI)	+2.2 (−22.5 to 26.8); p = NS	+17.5 (−23.9 to 58.8); p = NS	+34.0 (2.9–65.2); p = 0.033	+46 (25–67); p < 0.001	[Mean (SD) change from baseline: ambrisentan, 28.3 ± 41.7 m placebo, 6.8 ± 67.5 m]	+41 (16–66); p = 0.0016 for high- vs. low-dose	+36 (N/A); p = 0.004

*The AMBER-1 study (ClinicalTrials.gov: NCT01884675) was terminated early due to low numbers enrolled. †Ratio of geometric means, which corresponds to a 16% reduction; PVR decreased by 206 dyn·s·cm^{-5} in the macitentan group and by 86 dyn·s·cm^{-5} in the placebo group. ‡Least-squares mean difference based on an analysis of covariance model with baseline value and treatment effect as fixed events. §Not statistically analyzed. 6MWD, 6-min walking distance; CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; N/A, not available; NS, not significant; NYHA, New York Heart Association; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SD, standard deviation.

gov: NCT01884675) [71]. Other potential treatments for CTEPH that are currently under investigation include the prostacyclin receptor agonist selexipag in persistent/recurrent and inoperable CTEPH (the Phase III SELECT study; NCT03689244) and the inhaled sGC activator BAY1237592 in patients with CTEPH or PAH (the Phase I ATMOS study; NCT03754660).

4.3.1. MERIT-1

The Phase II MERIT-1 trial evaluated the efficacy and safety of the dual ERA macitentan versus placebo in 80 patients with inoperable CTEPH [43]. At baseline, 61% of patients were receiving PAH therapy (primarily PDE5is); no patient was receiving riociguat. The primary endpoint was change in resting PVR from baseline to Week 16.

At Week 16, a significant decrease in geometric mean PVR was observed to 73% of baseline in the macitentan group (mean decrease 206 dyn·s·cm^{-5}) and 87% of baseline in the placebo group (mean decrease 86 dyn s cm^{-5}; placebo-corrected treatment difference −16% [p = 0.041] (Fig. 6A) [43]. The treatment effect was consistent in all prespecified subgroups (sex, geographical region, WHO FC and PAH medications at baseline). The decrease in PVR of 206 dyn·s·cm^{-5} in macitentan-treated patients was similar in magnitude to that previously observed with other treatments in inoperable patients (−257 dyn·s·cm^{-5} in CHEST-1 and −127 dyn·s·cm^{-5} in BENEFiT) [42,43,69].

In MERIT-1, changes in 6MWD and NT-proBNP were measured at Week 24 (Week 16 in CHEST-1). At Week 24, an improvement in mean ± SD for 6MWD of 35 ± 52.5 m was observed for inoperable patients, with a 21% reduction in NT-proBNP versus placebo (p = 0.040) (Fig. 6B) [43]. Improvements in PVR and exercise capacity were consistent, irrespective of background therapy, suggesting that macitentan might be beneficial when used in combination with other PAH therapies acting on different pathways [43]. Combination therapy is the standard of care for PAH, and data from MERIT-1 support this approach in CTEPH [72]. It is important to note, however, that MERIT enrolled only 80 patients. Larger randomized controlled studies over a longer duration are required to validate the use of combination therapy in CTEPH. Improvements observed with macitentan in MERIT-1 were maintained at up to 6 months of the long-term extension MERIT-2 [73].

4.3.2. CTREPH

Treprostinil is a stable prostacyclin analog with acute hemodynamic effects that has been shown to be efficacious and tolerable in patients with PAH and CTEPH. The Phase III CTREPH trial evaluated the efficacy and safety of low-dose (3 ng/kg/min) versus high-dose (30 ng/kg/min) treprostinil administered subcutaneously in 105 patients with persistent, recurrent or inoperable CTEPH, 30% of whom were receiving background therapy with either bosentan, sildenafil, riociguat,

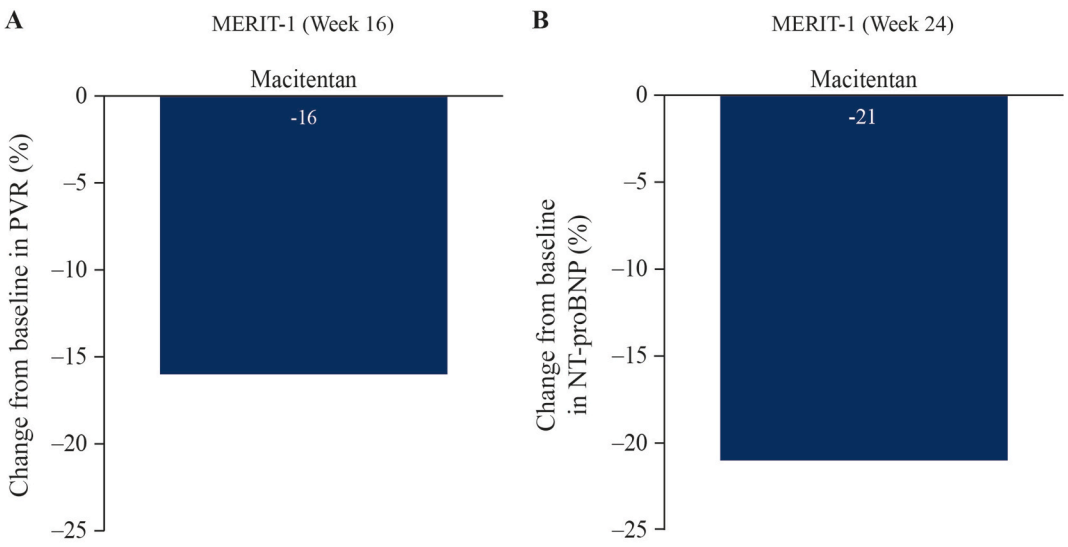

Fig. 6. Mean treatment difference for macitentan versus placebo in percentage change from baseline in (A) PVR (dyn·s·cm^{-5}) at Week 16 and (B) NT-proBNP at Week 24. An analysis of covariance model was applied with log-transformed percentage of baseline value including treatment and log-transformed baseline values as covariates. NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PVR, pulmonary vascular resistance [43].

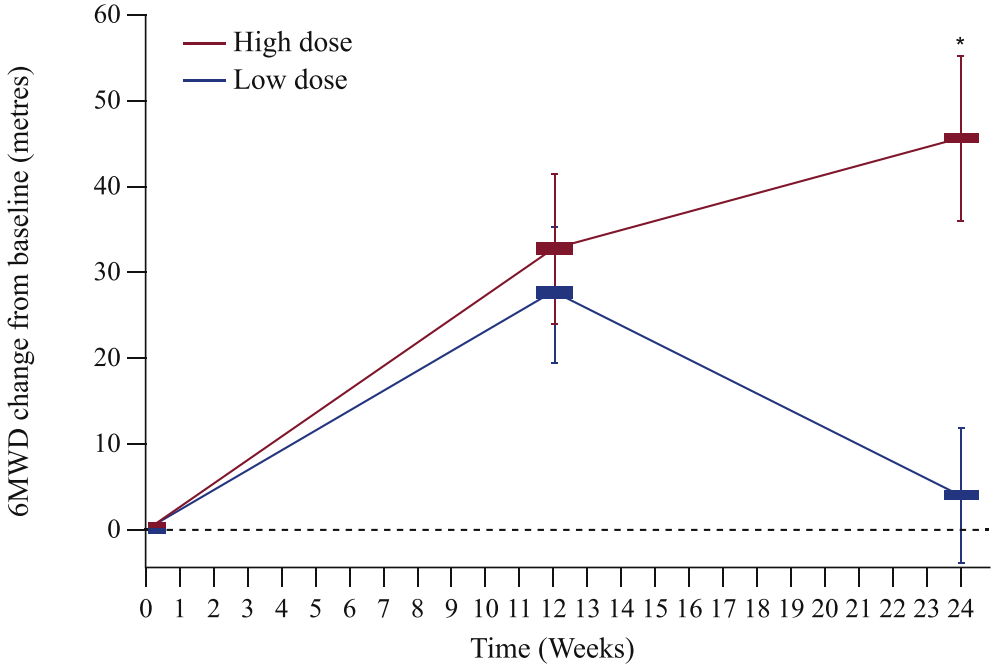

Fig. 7. Mean (standard error) changes from baseline in 6-min walking distance in patients receiving high- or low-dose treprostinil during the 24-week CTREPH study [44]. *p < 0.05.

macitentan or a combination [44]. The primary endpoint was change from baseline in 6MWD at Week 24. The use of subcutaneous treprostinil prevents the need for intravenous lines, which may reduce the likelihood of thromboembolism.

At Week 24, mean 6MWD had improved by 44.98 m in the high-dose group and by 4.29 m in the low-dose group (Fig. 7). Improvements in WHO FC were observed in 27 (50.9%) patients in the high-dose group and 9 (17.3%) patients in the low-dose group. PVR decreased from baseline by 214.2 dyn·s·cm^{-5} in the high-dose group and by 73 dyn·s·cm^{-5} in the low-dose group. The results also showed that treprostinil was associated with a significant improvement in mPAP and cardiac output. SAEs were experienced by 9 patients (17%; 16 events) in the high-dose group and by 10 patients (19%; 12 events) in the low-dose group, with significantly more patients in the high-dose group experiencing diarrhea, headache and pain in extremity [44]. The safety profile was similar to that previously shown in PAH [74].

5. Bridging therapy

One potential application of medical therapies in CTEPH is as a bridge to PEA or BPA. However, data on bridging therapy are limited and observational studies have yielded conflicting results [75,76]. Notably, medical bridging could lead to delayed referral and worse outcomes. The PEA Bridging Study (NCT03273257) is an ongoing, randomized, double-blind, Phase II trial in which patients with high pre-operative PVR will receive riociguat or placebo for 3 months before

undergoing PEA. Study completion is scheduled for July 2020.

6. Anticoagulation

Recurrent venous thromboembolism is central to the pathophysiology of CTEPH, and treatment guidelines therefore recommend lifelong anticoagulation [21]. Vitamin K antagonists (VKAs) have been the mainstay of anticoagulation therapy in patients with CTEPH, but more recently non-vitamin K antagonist oral anticoagulants (NOACs) such as apixaban, edoxaban, rivaroxaban, and dabigatran have been developed to overcome the limitations of VKAs. For example, VKAs such as warfarin can increase the risk of bleeding and have a pharmacokinetic profile that is commonly affected by food and other drugs [77,78]. As a result, patients receiving VKAs must be closely monitored. Meta-analyses of clinical trials in patients with VTE-associated conditions other than CTEPH have shown that NOACs are as effective as VKAs in preventing VTE and cardiovascular events, with similar rates of hemorrhages [79–81]. Data on the efficacy and safety of VKAs and NOACs in CTEPH are, however, limited. A recent retrospective case review in the UK assessed outcomes and complication rates in 1000 patients with operable CTEPH receiving VKAs or NOACs after PEA [82]. The results showed that functional and hemodynamic outcomes were similar between the two groups after PEA, although rates of recurrent VTE, while low overall, were significantly higher in patients receiving NOACs compared with VKAs. The incidence of major bleeding events was similar between the VKA and NOAC groups. Further data regarding the use of VKAs and NOACs in CTEPH have been reported from the EXPERT study (EXPosurE Registry RiociguaT in patients with pulmonary hypertension), an international, multicenter, prospective, non-interventional registry assessing the safety of riociguat in clinical practice. Preliminary data from 844 patients with PAH or CTEPH who received riociguat with concomitant NOACs or VKAs [83] showed that serious hemorrhages and embolic/thrombotic events were uncommon, and their frequency was similar in patients receiving concomitant NOACs or VKAs at baseline. Further data are needed to allow anticoagulation strategies to be optimized in patients with CTEPH.

7. Risk assessment in patients with CTEPH

In PAH, multiple choices of medical therapy are available and treatment guidelines recommend using risk assessment to aid treatment decisions [21]. Until recently, however, the only treatment options for CTEPH were PEA or riociguat for patients with inoperable or persistent/recurrent disease. The advent of BPA, either combined with medical therapy or alone, has increased the number of treatment options. Risk prediction tools are currently not established in CTEPH and the tools established in PAH cannot be directly applied to CTEPH due to the differences in therapies. While risk prediction may not be relevant for patients eligible for PEA, it may be of value in patients who are candidates for pharmacotherapy, and several risk assessment tools have been explored in this setting. These include the REVEAL risk score calculator [84], and three abbreviated models of the European Society of Cardiology/European Respiratory Society risk assessment (French registry invasive, French registry non-invasive and COMPERA/Swedish registry) [85,86]. These models have shown that improved risk status in CTEPH is associated with improved survival and clinical worsening-free survival [86]. These initial results in inoperable or persistent/recurrent CTEPH suggest that further evaluation of risk prediction is warranted in this population.

8. Conclusions

CTEPH is a debilitating, life-threatening condition associated with a substantial physical, psychological, social and emotional burden. The standard of care is PEA, but many patients are ineligible for surgery or have persistent/recurrent CTEPH after surgery. For patients with inoperable CTEPH, BPA and/or medical therapy are the recommended options. Riociguat is the only medical treatment approved for use in CTEPH, and the Phase III CHEST studies demonstrated the short- and long-term efficacy and tolerability of treatment in inoperable patients and those with persistent/recurrent CTEPH after PEA. Other PAH therapies, including PDE5is, ERAs and prostanoids, are used off label in routine practice, although only macitentan and treprostinil have shown favorable clinical effects in randomized controlled studies. Several tools are being investigated for risk assessment and stratification of patients to provide optimal therapy. Today, CTEPH management is becoming truly multimodal. While PEA remains the gold standard, there is increasing evidence for the efficacy and reproducibility of BPA, particularly in combination with medical therapy. Complementary to interventional therapies, there is a continued need for targeted medical therapies in patients with inoperable or persistent/recurrent CTEPH after PEA, particularly in those with distal disease.

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Author contributions

All authors were involved in reviewing each draft and approving the final manuscript.

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Hossein-Ardeschir Ghofrani. Conceptualization; resources; investigation; writing – review & editing; supervision; approval of final draft for submission.

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Gérald Simonneau. Conceptualization; investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Patient consent

Not required.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Hossein-Ardeschir Ghofrani has received personal fees for advisory board work payment for lectures including service on speaker bureaus from Actelion, Bayer AG, GlaxoSmithKline, Novartis and Pfizer; consultancy fees from Actelion, Bayer AG, Bellerophon Pulse Technologies, GlaxoSmithKline, MSD, Novartis and Pfizer; and grants from Deutsche Forschungsgemeinschaft (DFG). **Andreas D'Armini** has received fees for organizing Masters-level courses, lecture fees and writing assistance from Bayer AG and Merck; and fees for serving on steering committees from Actelion. **Nick Kim** has received personal fees for consultancy, steering committee work and speakers' bureau membership from Actelion and Bayer AG; personal fees for consultancy from Merck; and is a board member of the International CTEPH Association, CTEPH.com. **Eckhard Mayer** has received personal speaker's and consulting fees from Actelion, Bayer, and MSD. **Gérald Simonneau** has received grants, personal fees and non-financial support from Actelion, Bayer Healthcare, Merck and GlaxoSmithKline.

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