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Chronic Thromboembolic Pulmonary Hypertension

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Since the last World Symposium on Pulmonary Hypertension in 2008, we have witnessed numerous and exciting developments in chronic thromboembolic pulmonary hypertension (CTEPH). Emerging clinical data and advances in technology have led to reinforcing and updated guidance on diagnostic approaches to pulmonary hypertension, guidelines that we hope will lead to better recognition and more timely diagnosis of CTEPH. We have new data on treatment practices across international boundaries as well as long-term outcomes for CTEPH patients treated with or without pulmonary endarterectomy. Furthermore, we have expanded data on alternative treatment options for select CTEPH patients, including data from multiple clinical trials of medical therapy, including 1 recent pivotal trial, and compelling case series of percutaneous pulmonary angioplasty. Lastly, we have garnered more experience, and on a larger international scale, with pulmonary endarterectomy, which is the treatment of choice for operable CTEPH. This report overviews and highlights these important interval developments as deliberated among our task force of CTEPH experts and presented at the 2013 World Symposium on Pulmonary Hypertension in Nice, France. (J Am Coll Cardiol 2013;62:D92–9) © 2013 by the American College of Cardiology Foundation

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially curable cause of pulmonary hypertension (PH). In the previous 4th World Symposium on Pulmonary Hypertension at Dana Point, California, in 2008, this topic was addressed in 2 overlapping task forces: 1) Interventional and Surgical Modalities of Treatment in Pulmonary Hypertension; and 2) Diagnosis, Assessment, and Treatment of Non-PAH Pulmonary Hypertension (1,2). For the current symposium, a separate dedicated task force consisting of experts from both medical and surgical specialties was established to focus on this unique and important cause of PH. The goals of this task force were to provide key updates, reinforce best practice guidelines, and to discuss and stimulate future directions. To facilitate these goals, this panel proposed and explored 4 key clinical topics germane to CTEPH at the present time.

CTEPH Diagnosis

Over the years, there have been numerous and evolving versions of diagnostic algorithms for the evaluation of PH. These algorithms have consistently recommended the use of a radionuclide ventilation/perfusion (VQ) scan to screen for chronic thromboembolic disease (3–6). Despite advances in

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computed tomography (CT) and magnetic resonance imaging (MRI), the VQ scan remains the preferred test for screening for chronic thromboembolic disease, and it should be viewed as an initial step in the diagnosis of CTEPH (Fig. 1). The limitations of using computed tomography pulmonary angiogram (CTPA) for detecting chronic thromboembolic disease were highlighted in the report from Tunariu et al. (7). They reported a sensitivity rate of detecting chronic thromboembolic disease of just 51% with CTPA versus >96% with a VQ scan.

VQ scan remains the preferred test for screening for additional reasons. Compared with CTPA, a VQ scan requires less radiation exposure, avoids potential complications related to intravenous contrast, and offers potential cost benefits with less likelihood for detection of incidental findings (8). In addition, interpretation requires less additional training beyond what is currently demanded for interpreting a VQ scan. In other words, perfusion defects on VQ scan appear identical for either pulmonary embolism or chronic disease (9). However, with CTPA, the defects in chronic disease usually have a different appearance than pulmonary embolism, hence requiring additional training and attention to detect such differences (10). An additional concern regarding reliance on CTPA for screening PH includes false-positive cases from conditions mimicking chronic thromboembolic disease. These conditions include proximal lining thrombi associated with pulmonary arterial hypertension (PAH) or congenital heart defects (11). Pulmonary artery sarcoma can also be mistaken for chronic thrombus (12). Therefore, overreliance on CTPA may lead to a false-positive diagnosis of chronic thromboembolic disease.

Another important concern regarding the reliance on CTPA for screening and diagnosis of CTEPH has to do with operability assessment. CTPA detects chronic thromboembolic disease in vessels often deemed accessible for experienced pulmonary endarterectomy (PEA) surgeons (segmental, lobar, or main pulmonary arteries). Disease confined to the very distal segmental or subsegmental pulmonary arteries (locations more likely to be deemed inoperable) may be missed if screened by using CTPA. Indeed, even with the latest 320-slice CT technology, the sensitivity for detecting chronic disease in the segmental vessels was reportedly lower compared with detection rates for disease found in the main or lobar branches (86% vs. 97%, respectively) (13). Accordingly, for experienced or higher-volume endarterectomy centers, CTEPH diagnosed by using CTPA will often be deemed technically operable. Furthermore, reliance on CTPA for screening alone may miss potentially inoperable patients with CTEPH who should be considered for a trial of medical therapy or could participate in an appropriate clinical investigation.

Underutilization of VQ scans in screening PH invites potential misdiagnosis of PAH. In the recent report from the Pulmonary Arterial Hypertension Quality Enhancement Research Initiative registry, we learned that 43% of patients in the registry with PAH never had a VQ scan leading up to their diagnosis (14). When considering the lower sensitivity of CTPA in detecting CTEPH, some of these patients presumed to have PAH may in fact have CTEPH. The report also disclosed that roughly one-third of these cases without a VQ scan were because the provider reported that the scan was not relevant. Therefore, in addition to the technical and interpretive limitations of CTPA over VQ scans in the screening for CTEPH, there is a need for ongoing physician education and general emphasis of best practice for the evaluation of PH.

These limitations notwithstanding, CTPA has some benefits over conventional pulmonary angiography in the evaluation of CTEPH. With an abnormal screening VQ scan, the next imaging step in diagnostic algorithms recommends pulmonary angiography for disease confirmation (Fig. 1). With improving generations of CT scanners, the higher-resolution images provide additional details such as vascular wall thickness and surrounding structures not appreciated by conventional angiography (15,16). Furthermore, CTPA avoids the need for direct catheter access and the associated expertise and capability to perform selective angiograms. Accordingly, high-quality CTPA, especially at centers experienced with chronic thromboembolic disease, may be a reasonable alternative to pulmonary angiography in the evaluation of CTEPH. CT also has the advantage of revealing associated findings suggestive of chronic thromboembolic disease such as bronchial artery collaterals and a mosaic perfusion pattern, and it may also serve to screen for underlying mediastinal disease or other conditions mimicking chronic thromboembolic disease (17). Lastly, with promising modalities such as dual-energy CT and lung perfusion MRI, the innovation and growth potential in pulmonary vascular imaging seem assured (18,19).

Despite these advances in CT and MRI scans, catheter-based selective pulmonary angiography (particularly incorporating digital subtraction angiography to improve vessel contrast) remains the gold standard for diagnosis and confirmation of chronic thromboembolic disease, and it is the reference technique by which other imaging modalities are compared in CTEPH (20,21). A major advantage with catheter-based pulmonary angiogram is the ability to combine the imaging with assessment of hemodynamic parameters by using right heart catheterization. The

Abbreviations and Acronyms

ACP = antegrade cerebral perfusion
CT = computed tomography
CTEPH = chronic thromboembolic pulmonary hypertension
CTPA = computed tomography pulmonary angiogram
DHCA = deep hypothermic circulatory arrest
ECMO = extracorporeal membrane oxygenation
MRI = magnetic resonance imaging
PAH = pulmonary arterial hypertension
PAP = pulmonary artery pressure
PEA = pulmonary endarterectomy
PH = pulmonary hypertension
PTPA = percutaneous transluminal pulmonary angioplasty
PVR = pulmonary vascular resistance
RCTs = randomized controlled trials
VQ = ventilation/perfusion

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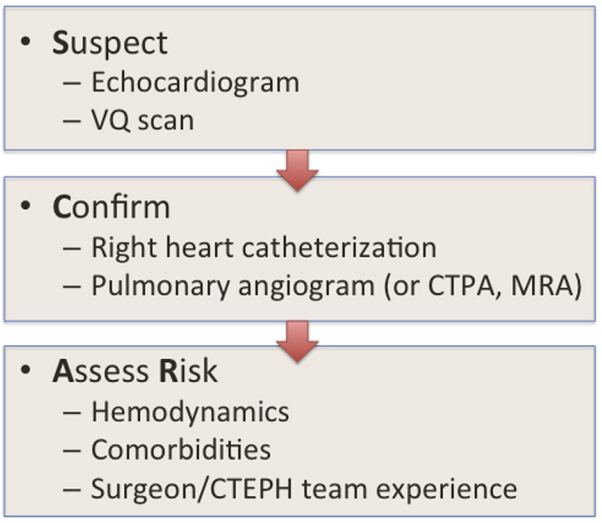

Figure 1 Diagnosis of CTEPH Leads to Operative Assessment

Diagnosis and treatment of CTEPH occur in a stepwise process, starting with an echocardiogram and ventilation-perfusion scan. Diagnostic confirmation requires high quality pulmonary angiogram and right heart catheterization to assess the location of chronic thromboembolism and severity of PH, respectively. The pulmonary endarterectomy operability assessment depends on numerous factors which contribute to overall risk assessment. CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = computed tomography pulmonary angiogram; MRA = magnetic resonance angiogram; VQ = ventilation/perfusion.

amount of contrast can be tailored by using cardiac output measurement to produce optimum image quality while minimizing contrast exposure. The angiographic appearance and distribution, such as subpleural perfusion score (i.e., qualitative measurement of pulmonary angiographic "pruning"), has been associated with postoperative outcomes (22). The comparison of radiographic burden of disease with hemodynamics is a critical exercise in determining operability as well as surgical risk before PEA (23). Ultimately, however, the overall operability assessment also needs to incorporate patient factors such as comorbidities and the experience level of the PEA surgeon and supporting CTEPH team.

Recommendations regarding CTEPH diagnosis are thus as follows:

- VQ scan is the preferred and recommended screening test for chronic thromboembolic disease in patients with PH. CTPA for screening may lead to potential misdiagnosis of PAH and underdiagnosis of CTEPH, including patients with distal disease.
- Pulmonary angiography (digital subtraction angiography) remains the gold standard for confirmation of chronic thromboembolic disease and evaluation of operability.
- High-quality multidetector CTPA may be a suitable alternative to pulmonary angiography in centers with experience in CTEPH.

Updates on Surgical Therapy

The standard surgical technique for PEA has not changed in the last 5 years. It is based on the principles established by the group from San Diego (24). A median sternotomy is essential to approach both lungs and cardiopulmonary bypass and cooling to 20°C to allow arrest of the circulation. Deep hypothermic circulatory arrest (DHCA) is necessary to provide a clear operating field to enable a complete endarterectomy with dissection into subsegmental branches. This technique has proven safe and reproducible and is used at most centers performing PEA surgery. Indeed, the latest series from San Diego reported an in-hospital mortality of 2.2% in the last 500 consecutive patients (25). In the European CTEPH registry, with 17 surgical centers, the in-hospital mortality was 4.7% despite some centers having low volumes and less experience (26). However, there have been a series of reports, from Europe, indicating that PEA is possible without complete DHCA and another recommending multiple episodes of brief DHCA (27–31). These have served to stimulate debate about the technique and question if they can be improved further. Can DHCA be reduced or even avoided? Is there subtle cognitive injury with DHCA, and is there any benefit in attempting to maintain some brain perfusion? More fundamentally, the purpose of the procedure is to reduce pulmonary vascular resistance (PVR), and it is not certain whether a complete endarterectomy is feasible in all patients without DHCA.

The PEACOG (Circulatory Arrest Versus Cerebral Perfusion During Pulmonary Endarterectomy Surgery) study attempted to answer these questions (32). In this prospective controlled trial, patients were randomized to undergo the PEA operation with DHCA or antegrade cerebral perfusion (ACP) with maintained brain blood flow. Cognitive function was assessed with multiple tests by a blinded independent observer before surgery and at 3 months and 1 year after surgery. This trial was the first direct comparison of DHCA and ACP in any surgical procedure, the largest trial involving DHCA in adults, and the most complete evaluation of cognitive function after PEA. Seventy-four patients were randomized to receive treatment, with only 1 death in the hospital (1.4%), and 1-year survival was 96%. The findings with respect to cognitive function were unexpected. At 3 months and 1 year, there was no difference between the groups and, more importantly, the mean scores in both groups for the main parameters actually improved after surgery. This finding was probably a result of improved cardiac output. The results did not change when analyzed on a per-protocol or intention-to-treat basis. Importantly, 9 patients had to cross over from the ACP to the DHCA group to complete the PEA because vision in the operating field was compromised without complete circulatory arrest. Therefore, patients and referring physicians can be reassured that the current PEA procedure is safe and does not cause impairment of cognitive

function despite the long cardiopulmonary bypass times and DHCA. Surgeons can be confident that the standard DHCA procedure is the best technique to allow a complete endarterectomy, and this remains the recommended procedure. Any further modifications should be compared directly with this standard, preferably in a randomized controlled setting.

Despite the improvements in outcome, there are specific complications that account for the majority of deaths after surgery: residual PH and reperfusion lung injury. The 2 are often present in combination, and when severe, conventional therapy has proved ineffective. As the technology of extracorporeal membrane oxygenation (ECMO) support has improved in the last few years, it has been used for PEA patients. Venoarterial ECMO is necessary if there is hemodynamic instability, and the rationale is uniquely appropriate for the pathophysiology. It can be used both centrally with cannulation of the heart or peripherally with cannulation of the femoral vessels. Blood is diverted away from the right heart and lungs, allowing reduction in pulmonary artery pressure, offloading the right ventricle; at the same time, the ECMO circuit provides cardiac output and gas exchange. For reperfusion injury alone, veno-venous ECMO support is sufficient. The important principle for ECMO use is fulfilled as recovery can occur within the time frame of potential support. To date, 3 publications have reported on ECMO after PEA. Some have reserved ECMO for patients with severe reperfusion lung injury who have had a good hemodynamic result from PEA (33). Other groups have used ECMO for hemodynamic support in patients with right ventricular failure (34,35). Average support duration is a median of 5 days in most series, and reported survival is up to 57% (35). In the last 2 years, there have been 4 additional case reports of ECMO use (36–39). It is estimated that many of the patients described in these series would have died without ECMO, and it is therefore recommended as a standard of care for PEA centers to have salvaging ECMO capability for the most severe complications after PEA.

The primary treatment for patients with CTEPH remains surgical. However, since the original publication on percutaneous pulmonary angioplasty in 2001, there had been no further reports until 2012 when 3 reports emerged from Japan (40–43). In total, there are now data published on 127 patients. In some reports, the procedure was reserved for patients who were not felt to be surgical candidates, but in others a surgical opinion was not documented. Some reports indicated that patients had "distal" disease and some had "operable" disease, but comorbidity precluded PEA. Some of the images within the publications demonstrate that the vessels opened were of a size that arguably could be treated surgically with PEA. The patients studied were more likely to be female (>78%), whereas CTEPH typically has no sex predilection, thus suggesting selection bias. Common to all the series is the need for multiple angioplasty procedures within the same patient to achieve beneficial results. The reported hemodynamic results are impressive and represent hemodynamic improvements of the magnitude obtained with PEA by experienced centers. Furthermore, improvements in 6-min walk distance and in World Health Organization functional class have also been observed (43).

However, there are numerous concerns and unanswered questions about this technique for the treatment of CTEPH. First, clarification is needed to address the patient selection process for this therapy over established and potentially curative PEA. This technique also requires multiple procedures, each with risks of complications, the most severe being vessel rupture and reperfusion lung injury. In addition, the procedure is currently limited, with a relatively short follow-up compared with PEA. The durability of the procedure and the risk of restenosis need to be systematically evaluated and established. Hence, based on the evidence to date, the role of percutaneous pulmonary angioplasty in CTEPH remains uncertain and requires further evaluation before it can be recommended as an established treatment for CTEPH.

Recommendations regarding updates on surgical therapy are thus as follows:

- PEA with DHCA remains the standard and recommended operative technique for the treatment of CTEPH.
- ECMO can be helpful as a supportive measure for patients with severe postendarterectomy complications and should be a standard of care in PEA centers.
- The role of percutaneous pulmonary angioplasty needs to be further evaluated and should not replace PEA for the treatment of CTEPH.
- A CTEPH team, consisting of an experienced PEA surgeon and CTEPH physicians, should assess operability before alternative treatments are considered. Close working collaboration between community providers and CTEPH centers is required.

Role of Medical Therapy

There are compelling reasons for considering PAH-targeted therapies in CTEPH. The histopathological examination of distal arteries in CTEPH patients reveals vascular changes similar to those in patients with idiopathic PAH (44). As in PAH, plasma levels of endothelin-1 closely correlate with the hemodynamic and clinical severity of disease (45,46); a significant number of operated patients have persistent PH; and there are CTEPH patients whose condition is inoperable (47). In the large European CTEPH registry, 17% of the patients had persistent PH defined by a mean PAP >25 mm Hg at the last measurement in the intensive care unit, and 37% of patients referred to the participating centers were considered inoperable, mainly because of anatomically peripheral disease deemed inaccessible, comorbidities, and

discrepancy between PH severity and morphological lesions.

There is mounting evidence that PAH-targeted medical therapy may have a role in the treatment of select CTEPH patients. Patients deemed inoperable due to peripheral disease and patients with residual or persistent PH after PEA are in need of effective therapy. Numerous open-label and several randomized controlled trials (RCTs) of 3 to 6 months' duration have reported varying degrees of efficacy with medical therapy (Table 1) (48–60). Recognizing that the treatment of choice and the only potential for cure remains PEA, the 2 largest RCTs to date devoted to CTEPH included an operability adjudication process. The first large-scale RCT in CTEPH was the BENEFiT (Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension) study with bosentan (58). A total of 157 patients with inoperable CTEPH, including 28% with previous PEA, were randomized to receive either placebo or bosentan and were studied for 16 weeks. The study observed mixed results in its 2 co-primary endpoints: 6-min walk distance in meters was unchanged, with a treatment effect of 2 m (95% confidence interval: −22 to 27; $p = 0.5449$), whereas PVR reduction was achieved with a treatment effect of −24% (95% confidence interval: −32 to −16; $p < 0.0001$).

In the most recent and largest RCT of medical therapy in CTEPH to date, the CHEST-1 (Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial-1) study with riociguat became the first to achieve clinically meaningful primary endpoints (60). Riociguat is an oral therapy taken 3 times a day and belongs to a novel class of soluble guanylate cyclase stimulators. In CHEST-1, a total of 261 patients with prospectively adjudicated, inoperable CTEPH, including 27% with previous PEA, were randomized 2:1 to receive either riociguat or placebo, respectively. The study used a cautious drug up-titration scheme to offset systemic vasodilatory effects. At the end of 16 weeks, the treatment group was observed to have a 46-m improvement in the primary endpoint of 6-min walk distance (95% confidence interval: 25 to 67; $p < 0.001$). In addition, PVR was the first in a series of hierarchical secondary endpoints and saw a placebo-adjusted treatment effect of −31% with therapy ($p < 0.001$). Additional positive secondary endpoints included N-terminal pro–B-type natriuretic peptide and World Health Organization functional class. However, no significant effect on time to clinical worsening was observed. In the subgroup analysis, the treatment effects were less pronounced in patients with persistent PH after PEA. The safety profile seems satisfactory even if an increased incidence of hemoptysis was observed in the double-blind period and in the open-label continuation study. Riociguat is approved by the U.S. Food and Drug Administration for PAH and CTEPH patients and is currently undergoing the regulatory approval process by the European Medicines Agency for both indications.

As with previous guidelines, medical therapy in CTEPH should not be considered as a replacement for PEA. The evidence for medical therapy has all specifically focused on a subset of CTEPH patients with either peripheral disease that PEA specialists deemed inoperable or those patients with recurrent or residual PH after PEA. Accordingly, the critical step in the CTEPH treatment algorithm remains the operability assessment by a CTEPH team (Fig. 2). Because the operability assessment remains complex, we recommend that only an experienced CTEPH team should determine that a case of CTEPH is inoperable. Furthermore, recognizing the subjective nature of the operability assessment process, we encourage a re-evaluation of operability by a second experienced CTEPH center, whenever feasible, in cases initially deemed inoperable. In cases of operable CTEPH, medical treatment is associated with delays with PEA, and it adds no

Table 1 Short-Term (3 to 6 Months) Effects of Medical Treatment in CTEPH

	First Author (Ref. #), Year	Study Design	Duration	n	NYHA	6MWD*	Effect	PVR	Effect
Epoprostenol (IV)	Cabrol et al. (48), 2007	–	3 months	23	III–IV	280 ± 112	66	(T) 29 ± 7†	−21%
Treprostinil (SC)	Skoro-Sajer et al. (49), 2007	–	6 months	25	III–IV	260 ± 111	59	924 ± 347	−13%
Iloprost (inh)	Olschewski et al. (50), 2002	RCT	3 months	57	III–IV	NA	NS	NA	NS
Sildenafil (PO)	Ghofrani et al. (51), 2003	–	6 months	12	NA	312 ± 30	54	1,935 ± 228‡	−30%
Sildenafil (PO)	Reichenberger et al. (52), 2007	–	3 months	104	II–IV	310 ± 11	51	863 ± 38	−12%
Sildenafil (PO)	Suntharalingam et al. (53), 2008	RCT	3 months	19	II–III	339 ± 58	18 (NS)	734 ± 363	−27%
Bosentan (PO)	Hoeper et al. (54), 2005	–	3 months	19	II–IV	340 ± 102	73	914 ± 329	−33%
Bosentan (PO)	Hughes et al. (55), 2005	–	3 months	20	II–IV	262 ± 106	45	(T) 1,165 ± 392	−21%
Bosentan (PO)	Bonderman et al. (56), 2005	–	6 months	16	II–IV	299 ± 131	92	712 ± 213	NA
Bosentan (PO)	Seyfarth et al. (57), 2007	–	6 months	12	III	319 ± 85	72	1,008 ± 428	NA
Bosentan (PO)	Jais et al. (58), 2008	RCT	4 months	157	II–IV	342 ± 84	2 (NS)	783 (703–861)	−24%
Riociguat (PO)	Ghofrani et al. (59), 2010	–	3 months	41	II–III	390 (330–441)	55	691 (533–844)	−29%
Riociguat (PO)	Ghofrani et al. (60), 2013	RCT	4 months	261	II–IV	347 ± 80	46	787 ± 422	−31%

*Mean ± SD or median (interquartile range) in meters. Pulmonary vascular resistance (PVR) dyn·s/cm^5 in †Woods unit, dyn·s/cm^5/m^2. This table summarizes the results from published reports of medical treatment effects for select CTEPH patients, including the four randomized controlled trials noted under study design.

CTEPH = chronic thromboembolic pulmonary hypertension; inh = inhaled; IV = intravenous; NYHA = New York Heart Association functional class; 6MWD = 6-min walk distance; NA = not applicable; PO = per os; RCT = randomized controlled trial; SC = subcutaneous; T = total pulmonary resistance (mean ± SD or median).

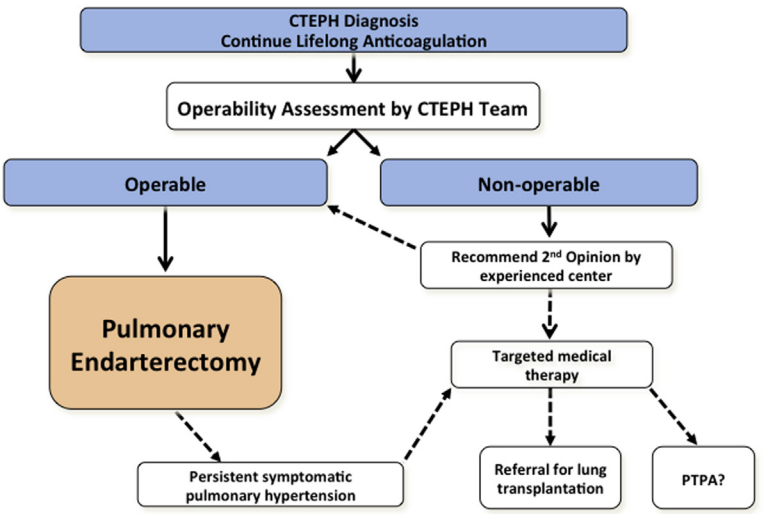

Figure 2 **CTEPH: Treatment Algorithm**

Once the diagnosis of CTEPH is made, all patients should receive life-long anticoagulation therapy unless contraindicated. All patients with CTEPH should be referred for operability assessment by an experienced CTEPH team to determine if the patient is operable and candidate for pulmonary endarterectomy. If a patient is deemed non-operable, we recommend consideration for a second opinion by an experienced CTEPH team. This recommendation is in recognition of operability definition being subjective and dependent on center experience, and mirroring the operability adjudication process utilized in recent randomized controlled trials of medical therapy. For patients deemed non-operable, or patients after pulmonary endarterectomy with persistent symptomatic PH, treatment with PH targeted medical therapy is recommended. Other treatment options in select cases may include lung transplantation or percutaneous transluminal pulmonary angioplasty. PTPA = percutaneous transluminal pulmonary angioplasty; other abbreviations as in Figure 1.

benefit (61). Therefore, PAH-targeted medical therapy in operable cases of CTEPH is not recommended. In addition to the delay for definitive treatment with PEA, the potential effects and risks of PAH-targeted therapies on the chronic thromboembolic material or surgery have not been adequately evaluated.

Recommendations regarding the role of medical therapy are thus as follows:

- The determination of operability is critical in CTEPH and should only be conducted by an experienced CTEPH team.
- For inoperable CTEPH and residual disease after PEA, medical therapy is recommended. Riociguat is the first drug therapy to show positive primary endpoints in an RCT for those indications.
- Operable CTEPH cases should be referred for PEA without delay. The role of bridging with medical therapy has not been sufficiently studied and should be reserved for controlled investigation.

Treatment Outcome Considerations

In the early years of PEA for CTEPH, reasonable alternative treatments did not exist. In addition, PEA operative mortality was significantly higher than seen in the modern era. Accordingly, early or traditional focus has been with immediate postoperative hemodynamic improvement and in-hospital mortality (62). With increases in global awareness and clinical activity in PH, we have witnessed a parallel growth in the science and clinical experience of CTEPH. New centers have begun performing PEA surgery, in part to keep up with a growing demand of patients diagnosed with CTEPH (63). At the same time, the experienced and established centers are performing more surgeries, gaining more experience, and, as a result, are improving their post-operative outcomes (25). In anticipation and recognition of this growth and trend, at the 4th World Symposium on Pulmonary Hypertension in Dana Point, California, the consensus recommendation was for PEA centers to achieve and target a <7% in-hospital mortality rate (1). At this point, we recommend revisiting these targets and endorse additional treatment goals and expectations.

The European CTEPH registry has contributed valuable information to help guide the field of CTEPH going forward (26,47). This registry combined 679 incident cases of CTEPH diagnosed from 1 Canadian center and 26 European centers (including 17 PEA centers). The registry reinforced the importance of PEA in the treatment of CTEPH and improved surgical outcome based on center experience as measured according to PEA cases performed per year. The outcome data after PEA importantly went beyond the typical in-hospital mortality and captured long-term mortality. The difference in observed survival at 3 years was 89% for operated CTEPH versus 70% for the nonoperated group ($p < 0.0001$) (64). Similarly favorable long-term survival rates after PEA

have been reported by Archibald et al. (65), and these results re-emphasize the importance of surgical evaluation and treatment for all patients with CTEPH.

Although long-term survival is of critical importance, it may not be adequate without additional considerations. For the individual patient with CTEPH, efficacy of any treatment should also demonstrate durability of benefit and improved quality of life. For the patient who undergoes PEA, freedom from PAH-targeted therapy, oxygen supplementation, or lung transplantation represents an important measure of treatment success beyond in-hospital or long-term survival. For cases of inoperable CTEPH, both affected patients and treating clinicians want effective treatment alternatives that will improve exercise capacity, quality of life, and prolong survival, while posing minimal adverse effects or risks from the therapy. At this time, the cumulative evidence and experience unequivocally support PEA as the treatment of choice in patients with operable CTEPH. Accordingly, all cases of CTEPH should receive operability assessment by a CTEPH team and PEA if deemed operable.

Recommendations regarding treatment outcome considerations are thus as follows:

- Operable CTEPH patients treated with PEA have a better long-term survival rate than those deemed inoperable and treated with medical therapy.
- Emerging PEA centers should strive to achieve early hemodynamic improvements and low (<7%) in-hospital mortality rates after PEA. However, the definition of success of PEA needs to include long-term outcomes.
- CTEPH centers are encouraged to participate in current and future collaborative studies to resolve uncertainties in the understanding and treatment of CTEPH, and adequately assess long-term outcomes.

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