Diagnosis of Chronic Thromboembolic Pulmonary Hypertension: A Canadian Thoracic Society Clinical Practice Guideline Update

Doug Helmersen, MD, FRCPC[a], Steeve Provencher, MD, MSc, FRCPC[b], Andrew M Hirsch MD, FRCPC[c], Carole Dennie, MD, FRCPC[d], Marc De Perrot, MD, MSc[e], Lisa Mielniczuk, MD[f], Naushad Hirani, MD FRCPC[g], George Chandy, MD, MSc, FRCPC[h], John Swiston, MD, MPH, FRCPC[i], Dale Lien, MD, FRCPC[j], Nick H Kim, MD[k], Marion Delcroix, MD[l], Sanjay Mehta, MDCM, FRCPC, FCCP[m]

[a]University of Calgary, Pulmonary Hypertension Clinic, Division of Respiratory Medicine, Peter Lougheed Hospital, Calgary, Alberta, Canada; [b]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université de Laval, Quebec, Quebec, Canada; [c]Centre for Pulmonary Vascular Disease, Sir Mortimer B Davis Jewish General Hospital, McGill University, Montreal, Quebec, Canada; [d]Thoracic and Cardiac Imaging Sections, The Ottawa Hospital Cardiac Radiology, University of Ottawa Heart Institute, University of Ottawa, Ottawa Ontario, Canada; [e]Toronto Pulmonary Endarterectomy Program, University of Toronto, Division of Thoracic Surgery, Toronto General Hospital, Toronto, Ontario, Canada; [f]University of Ottawa Heart Institute Pulmonary Hypertension Clinic, Cardiology Division, University of Ottawa, Ottawa, Ontario, Canada; [g]University of Calgary, Pulmonary Hypertension Clinic, Division of Respiratory Medicine, Peter Lougheed Hospital, Calgary, Alberta, Canada; [h]University of Ottawa Heart Institute Pulmonary Hypertension Clinic, Respirology Division, The Ottawa Hospital, University of Ottawa, Ottawa, Ontario, Canada; [i]Pulmonary Hypertension Program, Respirology Division, Vancouver General Hospital, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [j]University of Alberta Pulmonary Hypertension Clinic, University of Alberta, Edmonton, Alberta, Canada; [k]Pulmonary Vascular Medicine, University of California, La Jolla, California, United States; [l]Centre for Pulmonary Vascular Diseases, Department of Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium; [m]Southwest Ontario Pulmonary Hypertension Clinic, London Health Sciences Centre, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada.

ABSTRACT

Background: An important and common cause of pulmonary hypertension (PH) is chronic thromboembolic PH (CTEPH). Many care gaps exist in the evaluation of CTEPH including lack of awareness of the diagnosis, failure of clinicians to routinely consider CTEPH in patients at risk, and misguided diagnostic assessment practices including those which may be incomplete or unnecessary.

Methods: A representative multidisciplinary panel of expert physicians undertook a formal clinical practice guideline development process. A total of 4 key clinical issues were defined according to the Patient/problem, Intervention, Comparison, Outcome (PICO) approach. The panel performed an evidence-based, systematic literature review, assessed and graded the relevant evidence, and made 4 recommendations.

Results: Patients should not be routinely screened for the presence of CTEPH (using echo or pulmonary vascular imaging) following an acute pulmonary embolism (PE). Risk factors for CTEPH following acute PE have been established, and patients in these higher risk groups may merit closer attention during clinical follow-up. Routine screening for CTEPH following acute PE has not as of yet been demonstrated in prospective controlled trials to improve patient outcomes.

In patients with PH, clinicians should perform nuclear ventilation/perfusion V/Q lung scanning as a screening test to rule out CTEPH. Either planar or single photon emission computed tomography (SPECT) V/Q are acceptable forms of V/Q lung scanning. A normal perfusion scan effectively rules out the possibility of CTEPH. A negative CTPA does not rule out CTEPH.

In patients with suspected CTEPH, CT pulmonary angiography (CTPA) should be performed to confirm the presence and assess the anatomic extent and location of chronic thromboembolic material. A positive CTPA, confirming chronic thromboembolism, should prompt referral to an expert PH centre where a formal diagnosis can be established. A negative, indeterminate or technically poor CTPA does not exclude CTEPH and should also prompt referral to an expert PH centre for further testing.

Magnetic resonance pulmonary angiography is not currently recommended for routine assessment in patients with suspected CTEPH.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension

Pulmonary hypertension (PH) is a serious condition of the pulmonary blood vessels characterized by increased pulmonary arterial pressure (PAP), and is often associated with progressive right ventricular (RV) failure and a high risk of death. PH is increasingly recognized as an important cause of dyspnea and exercise limitation in many patients. As per the current WHO PH classification updated at the Sixth World Symposium on Pulmonary Hypertension held in 2018 in Nice, France (Table 1), PH can be associated with underlying disorders of the heart and lungs or be due to intrinsic disease of the small pulmonary arteries, known as pulmonary arterial hypertension (PAH).

Table 1 – Updated clinical classification of pulmonary hypertension (PH)(1)

1 PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH (table 3)
1.4 PAH associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers (table 4)
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
1.7 Persistent PH of the newborn syndrome
2 PH due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH
3 PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
4 PH due to pulmonary artery obstructions (table 6)
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
5 PH with unclear and/or multifactorial mechanisms (table 7)
5.1 Haematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

Table 2 – Pulmonary hypertension (PH) due to pulmonary artery obstructions(1)

4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
4.2.1 Sarcoma (high or intermediate grade) or angiosarcoma
4.2.2 Other malignant tumours
Renal carcinoma
Uterine carcinoma
Germ cell tumours of the testis
Other tumours
4.2.3 Non-malignant tumours
Uterine leiomyoma
4.2.4 Arteritis without connective tissue disease
4.2.5 Congenital pulmonary artery stenoses
4.2.6 Parasites
Hydatidosis

A very important and common cause of PH is chronic thromboembolic PH (CTEPH). CTEPH is a result of pulmonary vascular obstruction characterized by recurrent, unresolved pulmonary emboli (PE) and/or progressive pulmonary vascular thrombosis and scarring. In the present document, CTEPH is defined as follows:

1. A mean PAP (mPAP) of 25 mmHg or greater and pulmonary vascular resistance (PVR) of 3 Wood units (240 dyne•s/cm^5) or greater.
2. Persistent pulmonary arterial thrombotic obstruction despite at least three months of effective, uninterrupted anticoagulation.

The potential differential diagnoses for CTEPH include a range of pulmonary vascular diseases including: (i) PAH/COPD with secondary, central thrombus; (ii) Pulmonary artery sarcoma; (iii) Extrinsic vascular compression such as from fibrosing mediastinitis; (iv) Pulmonary veno-occlusive disease; (v) Large vessel pulmonary vasculitis; and (vi) Congenital PA branch stenosis.

Clinical recognition of CTEPH is important for several reasons. First, CTEPH is believed to be one of the more common causes of PH. Second, CTEPH is a serious, progressive and often fatal disease. Patients with untreated CTEPH experience significantly increased mortality. Historical observational studies (2,3) have estimated the median survival rate in severe untreated CTEPH patients to be as low as 10-20% at 2-3 years. Contemporary registry data(4) also illustrates the mortality of CTEPH, with 3 year survival rates in some subpopulations as low as 70%, even with access to with modern era therapies. Third, CTEPH is potentially curable with pulmonary endarterectomy (PEA) surgery. Finally, CTEPH patients may also benefit from treatment with balloon pulmonary angioplasty (BPA), PAH-targeted medications and/or other interventions.

The objective of the present guideline is to inform and provide evidence-based recommendations in the following areas:

Sections	Clinical Questions
Section 1 – Screening for CTEPH	Should patients be screened for CTEPH (using echo and/or pulmonary vascular imaging with ventilation/perfusion (V/Q) lung scan or CT pulmonary angiography (CTPA)) following an acute pulmonary embolism to increase the rate of diagnosis or improve clinical outcomes of CTEPH?
Section 2 – Assessment for CTEPH	Should patients with PH be assessed for CTEPH?
Section 3 – Diagnosis of CTEPH	In patients with suspected CTEPH, should CTPA be used to establish the diagnosis and assess anatomic extent and location of chronic thromboembolic material? In patients with suspected CTEPH, should magnetic resonance pulmonary angiography (MRPA) be used to establish the diagnosis and assess the anatomic extent and location of chronic thromboembolic material?

Differences from prior guideline published in 2010

This clinical practice guideline (CPG) represents an update from an earlier guideline published in 2010 by the Canadian Thoracic Society (CTS) (5). Changes from the prior guideline include the following:

- This CPG is focused on case finding and the diagnostic evaluation of CTEPH. CTEPH treatments are not within the scope of this document (but will be included in a subsequent CPG publication focused on CTEPH management).
- A graphical diagnostic algorithm is provided.
- Guideline applicability and implementability have been considered throughout the CPG development process.
- Updated reviews of CTEPH epidemiology and incidence are not provided.
- A comprehensive update on all CTEPH risk factors is not provided. Table 5 from our 2010 guidelines (5) contains this prior comprehensive list, which includes important CTEPH risk factors such as antiphospholipid antibodies and splenectomy. In this CPG we have reviewed the updated literature for only those CTEPH risk factors identified in patients following post-acute PE (see table 4, section 1).
- The population within the question on screening for CTEPH following acute PE has been broadened from asymptomatic patients to now include all patients following acute pulmonary embolism, irrespective of symptoms. This change was felt by the panel to lead to a recommendation which would be more actionable by clinicians, after consideration of the practical challenges which often arise in attempting to define normal versus abnormal symptoms following PE.

Target patient population

The current clinical practice guideline applies to all adult individuals with prior acute PE, undifferentiated PH, and suspected CTEPH.

Target Users

The present clinical practice guideline is intended for use by the health care teams that care for individuals with venous thromboembolic disease, PH and CTEPH. Specifically, family practitioners and specialist physicians (respirologists, cardiologists, hematologists, internists, cardiac and thoracic surgeons, and radiologists), and other health care professionals who

suspect or currently care for patients with deep vein thrombosis (DVT)/PE, PH and/or CTEPH can use these guidelines to help improve their clinical practice.

Guideline panel composition

The CTEPH guideline panel was comprised of clinicians and health care professionals with content expertise. The panel was chaired by one author and included 10 respirologists (2 international experts), one cardiologist, one radiologist specializing in cardiac and thoracic imaging and one thoracic surgeon. All author conflicts of interests are posted on the CTS website at https://cts-sct.ca/guideline-library/. Patient and caregiver input were not sought in the development of this guideline which is a weakness of the current guideline and will be corrected in the next update of this document.

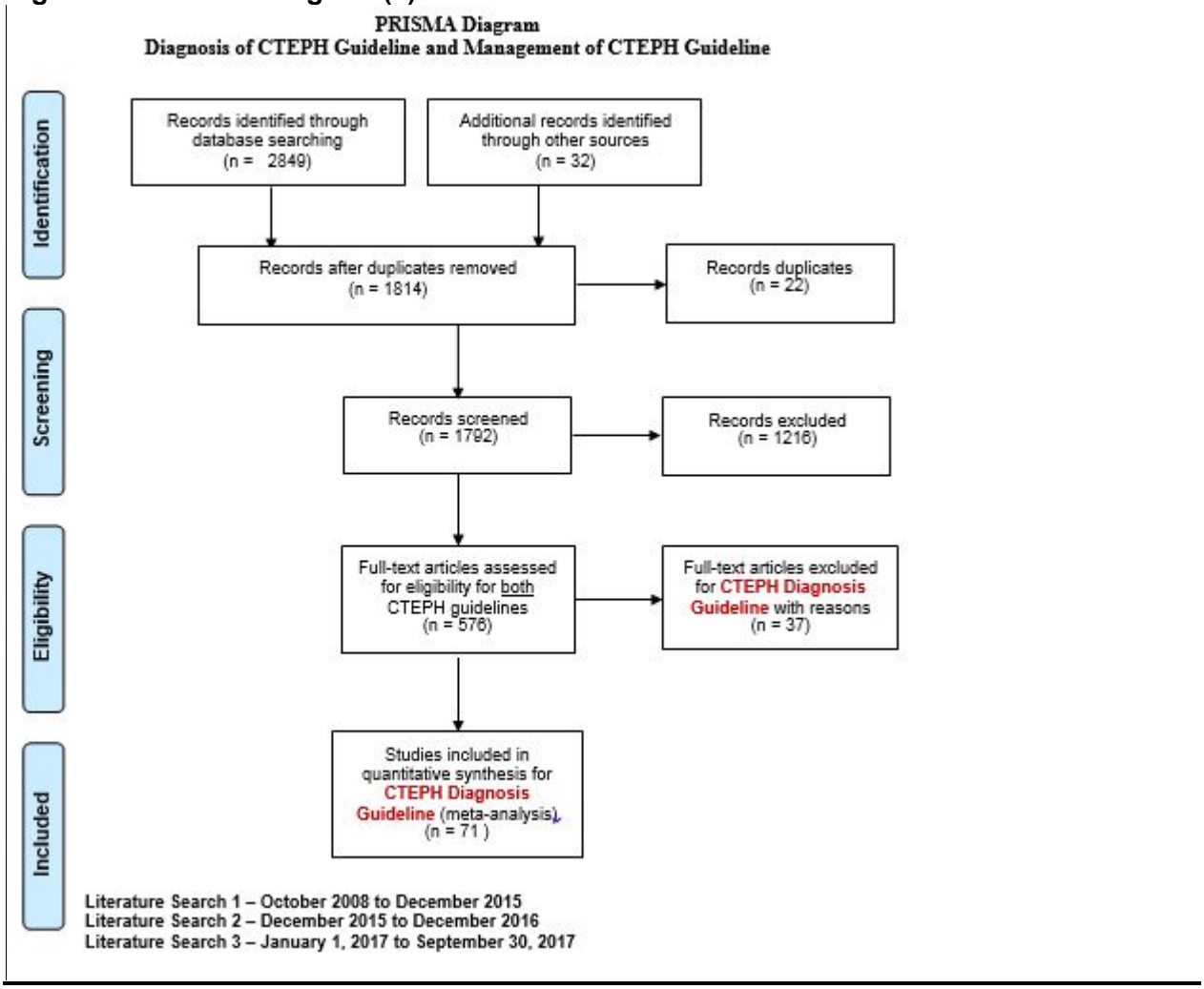
Methodology

This clinical practice guideline was developed in accordance with CTS guideline development process.(6) The CTS Pulmonary Vascular Disease (PVD) guideline panel was comprised of individuals with content expertise in respirology, cardiology, cardiac and thoracic surgery, and chest radiology. The panel utilized the AGREE II checklist to guide the development of this guideline.(7)

Formulation of key clinical questions: The panel determined key clinical questions in the areas of screening and/or case finding, assessment and diagnosis of CTEPH. Questions were crafted with consideration of those disease areas where the panel felt there to be substantial current knowledge-to-care gaps : for example existing clinical practices contributing to cases of CTEPH being missed. The PICO method was used taking into consideration the Patient group or groups that should be addressed, the Intervention or interventions that should be examined, the Comparison groups that should be part of the studies of the various interventions and the Outcome or outcomes of interest (Appendix 1). In the second part of the PICO process, panel members were asked to consider issues that influence implementability, when choosing PICO questions: including the magnitude of the knowledge-to-care gap; target audience(s); known barriers and supports to implementation; possible implementation strategies; societal impact; and measurability of any implementation program.

Literature search and screening of abstracts: An initial literature search was completed current to December 14, 2015 using MEDLINE (OVID); Embase (OVID); HealthStar; the Cochrane Library: the Canadian Medical Association InfoBase; and the National Guideline Clearinghouse. The second literature search was conducted through to March 10, 2017 and a third search from January 1, 2017 to September 30, 2017 was also conducted to include the most recent literature. Additional articles were found by review of the references in the articles accepted. Details of the search strategy are outlined in Appendix 1. A graphical representation of the flow of citations and articles reviewed are shown in Figure 1. The abstracts were assessed by panel members for inclusion or exclusion and conflicts were resolved by discussion between panel members.

Figure 1 – PRISMA Diagram (8)



Footnote: The CTS CTEPH guideline panel are working on two guidelines: 1) Diagnosis of CTEPH and 2) Management of CTEPH. Simultaneous literature searches were conducted for both guidelines. Out of the 576 articles assessed for eligibility for both guidelines, 108 articles were assessed for the Diagnosis of CTEPH guideline. From the 108 articles assessed, 37 studies were excluded with reasons and 71 studies were included.

Study selection criteria: Following abstract screening, the full text articles were retrieved and reviewed (Figure 1). Articles were selected for inclusion in the systematic review of the evidence if they reported data on CTEPH diagnosis. Animal studies, pathology or preclinical studies, clinical images, isolated hemodynamic reports, letters, editorials, duplicate publications without original data, reviews, studies published in a language other than English, and studies of uniquely pediatric populations were excluded.

Critical appraisal of identified studies: Data from all articles relevant to each PICO question were abstracted into tables by each section and are found on the CTS website and as a supplement to the manuscript. During discussion of each question via webinars held in 2017 and 2018, the data were reviewed by the panel, and evidence addressing each clinical question was assessed according to the components of the GRADE (9) (Table 2) criteria.

Table 3 – Strength of the Recommendations Grading System(9)

Grade of Recommendation		Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence	1A	Benefits clearly outweigh risk and burdens or vice versa.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence	1B	Benefits clearly outweigh risk and burdens or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low- or very-low-quality evidence	1C	Benefits clearly outweigh risk and burdens or vice versa.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence	2A	Benefits closely balanced with risks and burden.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate effect.
Weak recommendation, moderate-quality evidence	2B	Benefits closely balanced with risks and burden.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Best action may differ depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low- or very-low-quality evidence	2C	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.

***Synthesis of evidence-based clinical judgment of risk versus clinical benefit*:** For each clinical question, the panel considered the strength and directness of the published evidence supporting an intervention or treatment approach. The panel discussed the potential health benefit to patient, the overall impact on the population burden of morbidity and mortality of CTEPH, and issues of risk, burden on a patient to adhere, and cost effectiveness of an intervention or treatment. These discussions and the resulting synthesis of clinical judgement are presented for each recommendation.

Good practice points are included in association with each clinical question and are intended to offer short pieces of advice to the target user. Some of these good practice points may not have an evidence base, but are viewed as good clinical practice by the expert panel. All good practice points were arrived at by consensus, based on the clinical experience of the guideline panel members.

Formulation of recommendations and classification: Following the open and extensive discussions and review for each PICO question, a draft recommendation was proposed. The strength of the recommendation was based on consideration both of the GRADE quality of evidence, and the expert panel's synthesis of clinical judgment. The recommendations were then vetted by the CTS Canadian Respiratory Guidelines Committee Chair to optimize the language of each recommendation to ensure implementability. The recommendation consensus process was done by electronic survey using a six-point voting scale (Table 3), whereby it was defined a priori that a recommendation would only be accepted if each panel member voted for option 1, 2 or 3. For a recommendation to be accepted, it had to be voted on by 75% of the eligible panel members and achieve ratings of wholeheartedly agree, agree or can support by 80% of the voting panelists. Agreement was achieved by 80% to 100% of those voting in the current recommendations. No panel member was excluded from voting. In the event of a failure to reach a majority (80%) of votes for these first three options, another period of discussion ensued, whereby dissenting opinions were heard and considered. The recommendation was revised and followed by a second round of voting by electronic survey using a three-point scale, for which acceptance of a recommendation required a majority (80%)

for option 1 or 2. Through this process, all recommendations achieved acceptance, with a second round of voting required for only one recommendation.

Table 4 – Voting scales for assessing consensus on draft recommendations

First round of voting	1. Wholeheartedly agree
	2. Agree
	3. Can support
	4. Reservations – would like more discussion
	5. Serious concerns – needs more discussion
	6. Cannot participate – block it
Second round of voting	1. Agree
	2. Can support
	3. Cannot support – block it
For a recommendation to be accepted, it had to be voted on by 75% of the eligible panel members and achieve ratings of wholeheartedly agree, agree or can support by 80% of the voting panelists. If this was not achieved, additional discussion ensued and revision of the recommendation was made, after which the second round of voting proceeded using a three-point scale, for which acceptance of a recommendation required a majority (80%) for option 1 or 2.	

Applicability

Recommendations were formulated with the aim of being clear and actionable by clinicians within the user group. For example, precise criteria were utilized in defining patient populations and diagnostic tests results, wherever possible. Lack of access to key modalities (i.e. echocardiogram, pulmonary vascular imaging) could represent a barrier to guideline applicability in some jurisdictions. A graphical diagnostic algorithm is provided as a tool for clinicians to aide in implementing recommendations into practice. The potential resource implications of applying the recommendations from this CPG were considered. This includes the possible need for increased diagnostic tests to be performed in order to improve patient outcomes via effective screening and/or case finding of CTEPH as well through more precise diagnostic evaluation. Our goal is to monitor the impact of the CPG recommendations through their ability to correct knowledge gaps within the target user group (a pre and post guideline survey project is underway) as well as tracking of characteristics of CTEPH cases and their frequency of diagnosis at the expert PH centres (a Canadian PH database project is underway, including enrollment of CTEPH patients).

Review and approval process: In accordance with the CTS guideline review and approval process, before completion, CTS staff distributed the guideline for formal review by: 1) two external (non-CTS) content experts (one from the primary target audience and one national or international expert); and 2) two internal (CTS) reviewers with one reviewer performing an AGREE assessment of the guideline. The authors were blinded to the identities of the reviewers. The lead author provided responses to the comments and made corresponding changes to the manuscript. These reviews and the AGREE II scoresheet were provided to the CTS Canadian Respiratory Guidelines Committee for review. Upon acceptance, the CRGC recommended approval of the guideline to the CTS Executive Committee. All reviews and author responses are posted, along with author conflicts of interests on the CTS website at https://cts-sct.ca/guideline-library/

Living guideline/future updates: The Diagnosis of CTEPH guideline PICO questions will be uploaded in the CTS/McMaster Database. The authors will use the continuously updated McMaster Plus database to review new articles published in top journals starting in October 2017. The studies are indexed according to the PICO questions, and made available to the guideline panel on a dedicated software platform for manual assignment to individual reviews. This evidence service will prompt guideline updates and facilitate year end reviews.

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Diagnosis of CTEPH Algorithm

Placeholder for Diagnosis of CTEPH Algorithm

SUMMARY OF EVIDENCE

Section 1 – Screening for CTEPH

PICO 1: Should patients be screened for CTEPH (using echo and/or pulmonary vascular imaging with V/Q lung scan or CTPA) following an acute pulmonary embolism to increase the rate of diagnosis or improve clinical outcomes of CTEPH?

Introduction

Following diagnosis of acute PE and appropriate systemic anticoagulant therapy, only a small proportion of patients develop CTEPH. CTEPH has a significant impact on patients, including a poor prognosis for survival if undiagnosed or untreated. Given the availability of effective treatment approaches, screening for CTEPH in patients after an episode of acute PE could be of clinical value. Moreover, some evidence suggests better clinical outcomes in patients diagnosed with CTEPH at a less advanced stage with milder RV dysfunction.(1,2)

BOX 1 – Screening for CTEPH

PICO 1: Should patients be screened for CTEPH (using echo and/or pulmonary vascular imaging with V/Q lung scan or CTPA) following an acute pulmonary embolism to increase the rate of diagnosis or improve clinical outcomes of CTEPH?

Recommendation:

1. We recommend against routine screening for the presence of CTEPH following an acute pulmonary embolism. (GRADE 1C)

Key Evidence

A systematic review of the literature found no RCTs or controlled studies of the effectiveness of CTEPH screening in improving the diagnosis of CTEPH or clinical outcomes in patients post-acute PE, nor in any specific high-risk subgroups. Many uncontrolled studies have followed patients post-acute PE, “screening” for the presence of PH by echo in all patients or selectively in patients with symptoms suggestive of CTEPH, as reviewed in a meta-analysis (3) of 21 published studies.(4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24) Several studies found a higher prevalence of CTEPH in patients with residual symptoms following 3-6 months of effective anticoagulation post-acute PE (e.g., dyspnea, exercise limitation, chest pain), although the vast majority of these symptomatic patients did not have CTEPH.(7,11,12,13,16,25) Moreover, most studies suggest that echo screening can identify a number of patients with PH post-acute PE, but with highly variable criteria and not consistent with recommendations for echo detection of PH (e.g., RVSP thresholds from 30 to 50mmHg). Moreover, there was often limited formal diagnosis of the presence or the cause of PH by RHC, and only infrequent definitive CTEPH diagnosis in many of these studies.

In the above meta-analysis (3), of 14 studies which confirmed CTEPH by RHC (4,7,8,11,12,13,14,15,16,18,19,21,23,26), 9 studies had screened all included patients with echo (8,11,12,14,15,16,18,21,26), whereas echo was only performed in patients reporting dyspnea in 4 other studies.(4,7,13,23) Overall, systematic screening did not increase CTEPH

detection rate, as the incidence of CTEPH was the same whether all patients were screened post-PE or only symptomatic patients were investigated.

Thus, the recommendation informing this question is based upon the lack of direct evidence, and the indirect evidence (case series, cohort studies) for lack of benefit of screening, as well as the consensus of the expert panel.

Expert Panel Synthesis of Clinical Judgment

The panel recognized the lack of any direct evidence to address the specific question of whether screening increases the rate of diagnosis of CTEPH or results in improved CTEPH outcomes. Other relevant factors in screening for CTEPH were considered, including the moderate likelihood of significant direct benefit to the individual patient, the low burden of adherence but moderate potential adverse effects of pursuing screening and subsequent further work-up. In addition, the panel expected low overall impact on morbidity and mortality of the population of patients post-acute PE. There are no cost-effectiveness data available, but the panel strongly felt that routine screening for CTEPH was unlikely to be cost-effective.

Patient values and preferences

No studies were found that assessed patient values or preferences with regards to screening for CTEPH. It was the panel's consensus that most patients with acute PE would be willing to undergo clinical and non-invasive assessments if they were effective in diagnosing CTEPH sooner and especially in improving clinical outcomes.

Good Practice Points

The panel emphasized that the negative recommendation for routine screening of patients post-acute PE may not apply to certain subpopulations. The panel recognized the importance of clinically based follow-up in higher risk groups but emphasized that this clinical follow-up should be tailored to the specific situation and does not always need to include a follow-up echocardiogram and/or pulmonary vascular imaging. Specific subpopulations which warrant closer follow-up post-acute PE include:

1. *Patients with acute PE who may already have CTEPH at the time of initial presentation*. At the time of diagnosis of acute PE, some patients may already have CTEPH that had not previously been recognized or diagnosed (12). Clues to the presence of CTEPH at the time of presentation with acute PE include longstanding/progressive symptoms, evidence for more severe, longstanding PH (e.g., RVSP >60 mmHg, presence of RV hypertrophy), and imaging features of CTEPH on CTPA (e.g., mural defects, intraluminal webs/bands). Such patients merit appropriate clinical and investigational follow-up to reassess the persistence and severity of PH following at least 3 months of effective, uninterrupted anticoagulation.

2. *Patients with acute PE who are at higher risk to develop CTEPH*. The panel recognized that some patients with acute PE are at higher risk for developing CTEPH, based on reported risk factors. These include demographic and clinical factors, as well as features of the clinical presentation at the time of diagnosis of acute PE, including the hemodynamic severity of PH, and CT pulmonary vascular imaging features (Table 4). For example, the risk of CTEPH is higher in patients with recurrent PE compared to first PE (4,17,25), with OR of 3 - 12.1. Although not yet validated in prospective, controlled trials, patients post-acute PE with these risk factors for development of CTEPH may merit closer clinical attention during follow-up, most importantly, clinical monitoring for symptoms (e.g., dyspnea) and functional limitation, as well as echocardiography (e.g. elevated RVSP, secondary signs of PH such as RV

enlargement and/or systolic dysfunction). Routine follow-up pulmonary vascular imaging (VQ lung scan or CTPA) is not recommended in this subgroup.

3. *Patients with acute PE who remain symptomatic despite 3 months of effective anticoagulation*. Persistent symptoms or low HRQoL scores are common in patients with acute PE despite appropriate anticoagulation.(15,27,28) Unexplained dyspnea and functional limitation which persist following at least 3 months of effective anticoagulation can suggest the presence of CTEPH. Such patients merit appropriate clinical and diagnostic investigation for common conditions which may contribute to these persisting symptoms including the "post PE syndrome"(27) and other types of lung or heart diseases, as well as CTEPH.

4. *Other clinical indications for follow-up pulmonary vascular imaging*. The panel recognized that there may be other clinical indications to perform follow-up pulmonary vascular imaging (V/Q lung scan or CTPA) in selected patients post-acute PE, e.g., to decide on duration of anticoagulation, to assess risk of recurrent PE, or to establish a baseline before ongoing surveillance for recurrent PE.

Table 4. Risk factors for CTEPH in patients' post-acute pulmonary embolism

Parameter	*References*
1. Demographic	
• Older age (***Ribeiro Age > 70 OR. 4.1 Klok Age >60 OR 2.9 etc.***)	Ribeiro 1999 (22), Barros 2013 (29), Casazza 2014 (30), Yang 2015 (31), Klok 2016 (32)
• Younger age (*OR 1.49 univariate OR 1.79 multivariate per decade of decreasing age*)	Pengo 2004 (4)
• Male gender	Tosun 2016 (33)
• Females > 70 years old	Otero 2013 (34)
2. Co-morbid medical conditions	
• Higher BMI >30 kg/ m2	Barros 2013 (29)
• Atrial Fibrillation	Otero 2013 (34)
• Chronic Heart/Lung Disease	Otero (2013) (34)
• Hypothyroidism	Klok (2016) (32)
• Varicose veins	Yang 2015 (31), Otero 2013 (34)
3. Clinical / Laboratory features at time of PE diagnosis	
• Previous venous thromboembolism event	Tosun 2016 (33), Guerin 2014 (12), Abul 2014 (6), Korkmaz 2012 (17), Marti 2010 (18), Pengo 2004 (4)
• Unprovoked PE	Pesavento 2017 (35), Klok 2016 (32), Pengo 2004 (4)
• Symptom onset >14 days before PE diagnosis	Klok 2016 (32)
• NYHA functional class III or IV	Berghaus 2011 (8), Dentali 2009 (9)
• Severe PE	Otero 2011 (20), Pengo 2004 (4)
• Intermediate risk PE	Yang 2015 (31)
• Thrombolytic use for submassive PE	Sharifi 2013 (36), Sharma 2000 (37)
• Shorter duration of anticoagulation	Giuliani 2014 (11)
• PaO2 < 80 mmHg	Tosun 2016 (33)
• Elevated RDW % >15%	Abul 2014 (6), Xi 2014 (38)
4. Pulmonary vascular imaging	
Extent of pulmonary vascular obstruction:	
• Large perfusion defects (62.6±12.9)	Pengo 2004 (4)
• Vascular obstruction index >50%	Miniati 2006 (19)
• CT obstruction index >30%	Yang 2015 (31)
• CTPER-index value ≥4	Vavera 2015 (26)
• Qanadli Score ≥42.5%	Serra 2016 (39)
Proximal PE	Guerin 2014 (12)
5. Severity of PH / RV failure	
• RV dilation	Gong 2015 (40), Park 2017 (41)
• SPAP > 50 mmHg	Yang 2015 (31), Guerin 2014 (12), Korkmaz 2012 (17)

• RV Dysfunction	Klok 2016 (32), Gong 2015 (40)
• Septal flattening, RV hypertrophy, or W-pattern in the RV outflow curve	Klok 2015 (16)
• Elevated NT-proBNP	Klok 2015 (16), Guerin 2014 (12)

Areas for Future Research

Given the clinical importance of CTEPH, and the significant benefits of available treatment approaches, research to better identify asymptomatic patients post-acute PE who have an elevated risk of developing CTEPH would be helpful.

There is furthermore a need for future studies to further identify and assess the magnitude of risk factors for CTEPH in the range of populations reflective of clinical practice, including symptomatic and asymptomatic patients as well as those with comorbid conditions. There may be benefit to the development of scoring systems which combining multiple risk factors to define a composite or overall CTEPH risk and thereby identify which subpopulations of patients post-acute PE might benefit from structured CTEPH screening.

Further research should focus on clinical benefit, cost-effectiveness, and patient preferences around screening approaches for CTEPH, ideally within prospective controlled trials.

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Section 2 - Assessment for CTEPH

PICO 2: Should patients with PH be assessed for CTEPH?

Introduction

CTEPH is a common and important cause of PH, with a distinct management strategy. The possibility of CTEPH should be considered in all patients with PH, and appropriate testing performed to confirm or refute the diagnosis of CTEPH.

History alone is insufficient to confirm or exclude CTEPH.(1) Physiologic tests such as cardiopulmonary exercise testing also lack the required high sensitivity to screen for CTEPH.(2,3)

Pulmonary vascular imaging is required for CTEPH screening. The three most commonly proposed imaging modalities for screening of CTEPH in PH patients are nuclear V/Q lung scanning, CTPA and lung perfusion MRI. There have been technical innovations in all of these imaging modalities since our prior guideline recommendations in 2010.

Box 2 – Assessment for CTEPH

PICO 2: Should patients with PH be assessed for CTEPH?

Recommendation:

1. In patients with PH, we recommend that clinicians perform nuclear V/Q lung scanning as a screening test to rule out CTEPH. (GRADE 1C)

Clinical Remarks:

Either Planar or SPECT nuclear V/Q are acceptable modalities to screen for CTEPH.

A normal perfusion (Q) scan effectively rules out the possibility of CTEPH.

A negative CTPA does NOT effectively rule out CTEPH

Key Evidence

Our review found no RCTs or other direct evidence addressing the effect of screening for CTEPH in patients found to have PH. Thus, the recommendation addressing this question is based upon indirect evidence from several cohort studies, as well as the consensus of the expert panel.

Planar V/Q

Our previous 2010 guideline(4) recommended nuclear VQ for CTEPH screening in patients with PH. This recommendation was significantly influenced by one single centre retrospective study(5) in which 227 patients with PH referred to a tertiary centre were screened for CTEPH. Conventional pulmonary angiography was used as the reference standard technique. Planar V/Q was compared with 4-8 detector CTPA in assessing for CTEPH. Large vessel CTEPH was detected by V/Q with a sensitivity of 97.4 % and a specificity of 90%. CTPA had a sensitivity of only 51% but a specificity of 99%.

A cohort study by He et al.(6) assessed 114 patients with suspected CTEPH who all underwent planar V/Q scan, 16 or 64 detector CTPA and conventional pulmonary angiography. Fifty-one patients were diagnosed with CTEPH, 60 with idiopathic PAH and 3 with an atrial septal defect. Conventional pulmonary angiography was used as the reference standard technique. CTEPH was detected by V/Q with a sensitivity of 100% and a specificity of 93.7%. CTPA had a sensitivity 92.2% and specificity of 95.2%. To explain the higher sensitivity of CTPA in this study in comparison to Tunariu et al. (5) it is proposed that there may be that there was a lower proportion of subsegmental PE in the cohort evaluated by He et al. and/or improvements related to the wider detector CT scanners used.

SPECT V/Q

SPECT nuclear V/Q scanning represents the state of the art of perfusion scintigraphy and has emerged as being more sensitive than planar scintigraphy for the diagnosis of acute PE.(7,8) Many centres in the world, including those within Canada, have replaced planar V/Q equipment with SPECT V/Q as the standard of care.

No studies were found which specifically evaluate SPECT V/Q as a screening tool for CTEPH.

A single centre prospective blinded cohort study(9) compared planar VQ in comparison to SPECT V/Q for a clinical question indirectly related to screening; the assessment of extent and location of chronic thromboembolic material in 17 patients with CTEPH. The reference standard involved an evaluation of the PEA surgical specimen as a "mold" of the obstructed pulmonary vasculature. Obstructed segments were detected by SPECT VQ with a sensitivity of 63.5% and specificity of 62.6%. Planar V/Q had a sensitivity of 42.7% and specificity of 76. 8%. These differences in sensitivity were statistically significant (P <0.01). This small study suggests that SPECT VQ might be more sensitive than planar VQ in detecting the obstructed pulmonary vessels characteristic of CTEPH.

A subsequent cohort study from the same authors(10) compared SPECT V/Q to 4- and 64-detector CTPA in 9 patients with CTEPH undergoing PEA surgery. The reference standard again involved an evaluation of anatomic distribution of chronic thrombotic material in the removed PEA specimen. SPECT V/Q had a sensitivity of 62% and specificity of 72% for detecting the obstructed pulmonary arteries. CTPA had significantly lower sensitivity of 47.8% (p<0.03), and similar specificity of 80%. This study suggests that SPECT V/Q may be more sensitive than 4 and 64 detector CTPA in detecting the obstructed pulmonary vessels characteristic of CTEPH.

DE-CTPA

Dual energy CTPA (DE-CTPA) is a novel CT angiographic technology which maps the iodine content of the lung microcirculation to provide information about pulmonary vessel obstruction and its downstream functional consequences.

A cohort study of 51 patients with established CTEPH(11) evaluated DE-CTPA in comparison to SPECT V/Q as the reference standard. The sensitivity of DE-CTPA was high (96%) with a lower specificity (76%). In some of the DE-CTPA cases, the lung segments containing perfusion defects (8.3%) could not be evaluated due to artefacts.

Another single centre prospective cohort study using DE-CTPA(12) assessed 40 patients referred with PH, of whom 14 were diagnosed with CTEPH. The reference standard for CTEPH diagnosis in this study was also based on planar VQ (the presence of at least once segmental

perfusion defect). This study compared planar VQ to ≥64 detector CTPA and DE-CTPA. The sensitivity of DE-CTPA and CTPA were both reported at 100%. The specificities were 92% for DE-CTPA and 96% for CTPA. In the subgroup of CTEPH patients, 7.9% of lung segments were of non-diagnostic quality on DE-CTPA iodine maps due to artefact. There was better agreement between DE-CTPA and V/Q (k=0.44) than between CTPA and V/Q (k=0.09-0.31) at the segmental level.

Giordano et al.(13) evaluated DE-CTPA in a pre-selected group of patients without emphysema and with either PAH (n=13) or "peripheral type" CTEPH (n=9). There was a high concordance (100%) between VQ and DE-CTPA in the peripheral type CTEPH group, with all studies showing defects. In the PAH group there were a number of false positive perfusion defects (3/13=23%) identified with DE-CTPA.

In summary, the body of evidence pertaining to DE-CTPA fails to establish superiority in comparison to VQ (since VQ was used as the gold standard technique in all of the studies) and also demonstrates imaging artefacts which may limit interpretation of the DE-CTPA perfusion defects.

Access to DE-CTPA as well as expertise in its diagnostic interpretation remains limited. DE-CTPA has complex image acquisition and post processing needs, which require appropriate expertise.

DCE Lung Perfusion MRI

Cardiac MRI is an important tool to assess the right ventricle in patients with PH. Cardiac MRI should be distinguished from dynamic contrast enhanced (DCE) Lung perfusion MRI which is a time-resolved form of MR pulmonary angiography designed to assess distal lung perfusion.

The PH centre in Papworth UK has extensive experience using 3D DCE lung perfusion MRI in the evaluation of patients referred for assessment of suspected CTEPH.(14) In a cohort of 132 patients referred (78 diagnosed with CTEPH), Lung perfusion MRI was reported to have test characteristics (sensitivity 97%, specificity 92%) similar to nuclear Q scanning (sensitivity 96%, specificity 90%). No invasive pulmonary angiography was performed in this cohort. The reference standard for the diagnosis of CTEPH was based on a multidisciplinary meeting involving data from CTPA, MRI and nuclear V/Q scanning.

A single centre blinded retrospective cohort study using lung perfusion MRI(15) enrolled 74 patients undergoing evaluation for CTEPH. Within this cohort, 36 patients were diagnosed with CTEPH, 10 patients with CTED (chronic thromboembolic disease without PH) and 28 patients had chronic thromboembolic disease excluded. The reference standard for the diagnosis of CTEPH was based on a multidisciplinary meeting using V/Q and CT data. SPECT V/Q was compared to 3 dimensional DCE lung perfusion MRI. The lung perfusion MRI demonstrated similar sensitivity (100%) and specificity (81%) to SPECT V/Q (sensitivity 97%, specificity 81%) for the diagnosis of chronic thromboembolism.

No studies were found which suggest the superiority of lung perfusion MRI over nuclear V/Q scanning in the assessment of CTEPH.

Access to Lung perfusion MRI technology as well as expertise in its diagnostic interpretation are currently limited in most centres worldwide. Lung perfusion MRI has complex image acquisition and post processing needs, which require appropriate expertise.

Table 5 Key Evidence – Assessment for CTEPH in patients with PH

Reference	N	Population (% CTEPH)	Reference Standard	Imaging Modality (sensitivity)	Imaging Modality (sensitivity)	Comments
Tunariu 2007(5)	227	Mixed PH (34%CTEPH)	Conventional DSA	Planar V/Q (97.4%)	4-8 detector CTPA (51%)	
He (2012) (6)	114	Mixed PH(45% CTEPH)	Conventional DSA	Planar VQ (100%)	16-64 detector CTPA	Both low probability and normal V/Q scans were considered negative
Soler 2011 (9)	17	CTEPH undergoing PEA (100%)	Disease extent including surgical specimen	SPECT V/Q (63.5 %)	Planar V/Q (42.7%)	Lower sensitivity relates to imaging underestimating the full anatomic extent of obstructed segments, using this robust gold standard
Soler 2012 (10)	9	CTEPH undergoing PEA (100%)	Disease extent including surgical specimen	SPECT V/Q (62%)	4-64 detector CTPA (47.8%)	Same as above
Nakazawa 2011(11)	51	CTEPH, treatment not specified (100%)	SPECT V/Q	SPECT V/Q (100%)	DE-CTPA (96%)	8.3 % of DECT images couldn't be assessed due to artefact
Dournes 2014(12)	40	Mixed PH and CTED (35% CTEPH)	Planar V/Q	Planar V/Q (100%)	DE-CTPA (100%)	7.9% of DECT images couldn't be assessed due to artefact
Giordano 2016(13)	31	PAH and peripheral CTEPH (39% CTEPH)	Planar V/Q	Planar V/Q (100%)	DE-CTPA (100%)	Patients with emphysema excluded from cohort
Johns 2017 (15)	74	Mixed PH and CTED (49% CTEPH)	Multidisciplinary meeting incl. CTPA, MRI and V/Q	SPECT V/Q (97%)	MRI (100%)	1 CTEPH patient not identified by SPECT V/Q had "mild inoperable CTEPH" on CTPA and MRI
Rajaram 2013(14)	132	PH referred to expert CTEPH centre (59% CTEPH)	Multidisciplinary meeting incl. CTPA, MRI and V/Q	Q (96%)	MRI (97%)	

Other imaging technologies

While ECG-gated multidetector CT(16,17), Cone beam CT angiography(17) and 320 detector CTPA(18) have been used in the assessment of CTEPH, these particular studies have focused on establishing the diagnosis and assessing the anatomical extent/location of chronic thromboembolic disease (reviewed in PICO Q#3) rather than as screening tests for CTEPH in populations of patients referred with PH.

Expert Panel Synthesis of Clinical Judgement

The panel graded the body of evidence as low. The higher sensitivity of V/Q and lower sensitivity of CTPA in screening PH patients for CTEPH was consistent with the clinical experience of panel members. The lack of evidence for superiority of either DE-CTPA or DCE Lung perfusion MRI in comparison to V/Q was also considered. The panel emphasized the significant potential for direct health benefit to the patient with accurate screening and subsequent diagnosis of CTEPH. The minimal adverse effects and minimal burden on the patient to adhere to the recommendation was considered. The panel considered the possible medium to high impact on morbidity and mortality for the population of PH patients as a whole with the recommended approach. The panel emphasized the lack of cost effectiveness data, leading to the inconclusive economic benefits of the recommended approach.

Patient Values and Preferences

No studies were found that assessed patient values or preferences with regards to screening for CTEPH in patients with PH. It was the panel's consensus that most patients with PH would be willing to undergo V/Q lung scanning as a screening test, particularly if this led to a more accurate diagnostic approach with fewer missed cases of CTEPH.

Good Practice Points

- In patients with PH who are not anticoagulated, consider testing for acute pulmonary embolism according to clinical probability score.(19,20) Acute PE can be an easily missed contributor to PH, particularly in patients with co-existing lung and heart diseases. Omitted or delayed anticoagulation could have severe consequences for patients with occult PE.

- Screening for CTEPH should be the default recommendation in patients found to have PH (following the ESC/ERS guidelines: we define echocardiographic PH as tricuspid regurgitant velocity >2.8 m/s or the presence of other echo PH signs (i.e. RV enlargement, flattening of interventricular septum etc.)(21)

- The panel recognized that in some selected patients with PH, screening for CTEPH may not be necessary, and these patients may be excluded from upfront screening for CTEPH according to clinical judgement. Examples include:

  a) Patients with PH due to left heart disease (WHO group 2 PH). Some patients with left heart disease as a cause of PH (e.g. those with overt pulmonary edema) can have resolution or marked improvement in PH after treatment of the left heart disease. In these cases, CTEPH screening can be deferred with initial treatment focussed on the left heart disease. However, patients with persistent "unexplained" PH following treatment of left heart disease should be considered for subsequent screening for the possibility of coexisting CTEPH.

  b) Patients with PH due to lung disease (WHO group 3 PH). Some patients with untreated hypoxemia and/or lung disease may similarly manifest PH, which can resolve or markedly improve following oxygen or other treatments for the lung disease. In these patients, initial treatments should focus on the lung disease and hypoxemia and CTEPH screening can be deferred. However, patients with PH "unexplained" by the existing lung disease should be considered for subsequent screening for the possibility of coexisting CTEPH.

  - A diagnosis of pulmonary arterial hypertension (PAH) cannot be confirmed until testing has been completed to exclude CTEPH

  - Patients diagnosed with PAH or CTEPH should be referred to an expert PH centre (Canadian local pulmonary hypertension expert centres listed on www.phacanada.ca)

Discussions/Areas for future research

The panel identified the need for future randomized, controlled trials of CTEPH screening in patients with PH. Future trial designs need to consider the varying incidence of CTEPH in different populations of patients(22) and should focus upon populations which are most reflective of clinical practice. Future studies should include patients with a broad range of characteristics, including those with and without co-existing parenchymal lung disease. Further study is required to fully define the test characteristics of V/Q when used to screen for CTEPH in

the setting of an abnormal chest Xray. Future studies should be designed to guide the practices of both tertiary and community care centre physicians.

Multistep screening algorithms may increase the precision of CTEPH assessment. A recently published study(23) has demonstrated the utility of an algorithm starting with a structured symptom questionnaire and followed by diagnostic imaging. The panel suggests ongoing research into multi-modality screening algorithms for CTEPH.

There is a need for prospective trials to assess the impact of testing algorithms for the diagnosis of acute PE in non-anticoagulated patients presenting with undifferentiated PH.

The panel emphasized the need for clinical research to maintain pace with the rapid development of new imaging technology. As new screening tools are developed, prospective controlled trials should be conducted which include robust gold standard definitions of CTEPH as well as meaningful clinical endpoints (Appendix 1). Future trials should consider the long-term impact of screening protocols, not just upon those patients in whom CTEPH is confirmed, but also upon those patients ultimately diagnosed with other causes of PH.

The clinical importance of mild abnormalities on VQ lung scans (especially in the case of SPECT VQ) remains uncertain. Future studies are needed in order to define significance of low probability VQ abnormalities, particularly as it relates to their negative predictive value for a diagnosis of CTEPH.

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SECTION 3 – DIAGNOSIS OF CTEPH

PICO 3: In patients with suspected CTEPH:

a) **Should CTPA be used to establish the diagnosis and assess anatomic extent and location of chronic thromboembolic material?**
b) **Should magnetic resonance pulmonary angiography (MRPA) be used to establish the diagnosis and assess the anatomic extent and location of chronic thromboembolic material?**

Introduction

Establishment of a diagnosis of CTEPH requires confirmation of the presence of chronic thromboembolic lesions typical of this condition by at least one form of pulmonary angiography. (1,2)

Angiography is also necessary to characterize the anatomic extent and location of chronic thromboembolic material, to assess for the most appropriate therapy; including accessibility for surgical pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty (BPA).

Several pulmonary angiographic modalities exist. Traditionally, conventional, invasive digital subtraction angiography (DSA) has been considered the reference standard angiographic technique for CTEPH. Conventional pulmonary angiography is performed using contrast injections through catheters placed directly within the pulmonary arteries to provide detailed images of the pulmonary arterial tree. Conventional pulmonary angiography requires significant center specific experience to obtain the most accurate results.

CT pulmonary angiography (CTPA) can also provide detailed assessment of the pulmonary arteries. CTPA has the advantages of being less invasive (contrast injections are given through peripheral iv) and more widely available than conventional angiography. There are important technical issues to consider in optimizing detection of chronic thromboembolism using CTPA.

Some centers have used MR pulmonary angiography (MRPA) with peripheral gadolinium contrast injection to assess the anatomic extent and location of chronic thromboembolism.(3)

It has been unclear if CT or MRI pulmonary angiography can routinely be used to establish a diagnosis of CTEPH, and whether these modalities provide adequate image quality to properly evaluate chronic thromboembolic lesions for consideration of specific interventional therapies (e.g. PEA, BPA).

Box 3 – Diagnosis of CTEPH

PICO 3a): In patients with suspected CTEPH, should CTPA be used to establish the diagnosis and assess anatomic extent and location of chronic thromboembolic material?

Recommendation:

1. We recommend that clinicians perform CTPA to confirm the presence and assess the anatomic extent and location of chronic thromboembolic material in patients with suspected CTEPH. (GRADE 1B)

Clinical remarks:

A positive CTPA, confirming chronic thromboembolism, should prompt a referral to an expert PH centre for establishment of a formal diagnosis of CTEPH, and assessment of most appropriate treatment.

A negative, indeterminate, or technically poor CTPA does not exclude CTEPH. Patients with these non-positive CTPA results and suspected CTEPH should be referred to an expert PH centre for further diagnostic testing, such as conventional pulmonary angiography.

Key Evidence

Our review found no RCTs or other direct evidence assessing the use of CTPA in the diagnosis and/or assessment of anatomic extent of CTEPH. Specifically, there are no RCTs comparing CTPA to conventional pulmonary DSA. The recommendation informing this question is therefore based upon indirect evidence from one meta-analysis, several medium and small sized cohort studies, and the consensus of the expert panel.

Dong et al.(4) published a meta-analysis based on systematic review of literature published between 1990-2015 assessing the diagnostic accuracy of CTPA in patients with CTEPH. Eleven articles met inclusion criteria (including a total of 712 patients). Some but not all reports used DSA as a gold standard, and there were minimal details provided on the DSA technique. Pooled analysis showed CTPA to have a sensitivity and specificity of 95% and 96% for main/lobar pulmonary artery disease, and of 88% and 89% for segmental disease, respectively. Subsegmental disease was not assessed.

A small cohort study by Sugiura et al.(5) compared 320-detector CTPA to DSA in 44 patients with CTEPH and reported sensitivity and specificity for main/lobar disease of 97% and 97% and for segmental disease 86% and 95%. Subsegmental disease was not assessed.

Another small cohort study by Reichelt et al.(6) used 64-slice CTPA in comparison to DSA in the assessment of 27 patients (CTEPH confirmed in 24 and excluded in 3). Sensitivity and specificity of CTPA for main/lobar disease was 98% and 95% and for segmental disease 94% and 93%.

A medium sized cohort study by He et al.(7) assessed 114 patients referred with PH, of whom 51 were diagnosed with CTEPH. Several analyses were performed in this study, including an assessment of 16 and 64-slice CTPA images in comparison to DSA. Sensitivity and specificity of CTPA for the diagnosis of CTEPH were 92% and 95%. No information was presented on the anatomic extent of the disease.

Grgic et al.(8) used rigidly interpreted CTPA (using vascular obstruction index) and SPECT VQ (using percentage of vascular obstruction index) to predict PEA operability in 49 patients with CTEPH. CTPA performed well in depicting the central thromboembolic material, however, the extent of perfusion abnormalities was better depicted on the functional SPECT VQ examination. CTPA and SPECT VQ were therefore thought to provide complementary information in assessment of operability for PEA.

Three retrospective cohort studies published by the group in Hannover, Germany(9,10,11) have evaluated a novel form of invasive pulmonary angiography utilizing cone beam CT images instead of digital subtraction angiography. Cone beam invasive angiography revealed high resolution images of the pulmonary arteries, including some to the subsegmental level, with potential superior intermodality agreement and delineation of distal CTEPH lesions in comparison to 64-detector CTPA(10) or DSA(9).

Expert Panel Synthesis of Clinical Judgment

The panel graded the body of evidence as moderate. The evidence for the high specificity of CTPA in confirming the diagnosis of CTEPH was recognized, and this was consistent with the clinical experience of panel members. There was concern CTPA may not be sensitive enough to exclude CTEPH, particularly in patients with segmental disease as well as situations where the CTPA is performed or interpreted in less experienced centres. The panel emphasized the limited published evidence supporting CTPA when used for defining anatomic extent of CTEPH to plan PEA or BPA. But several panel members described their own clinical experience using CTPA to plan PEA. It was recognized that wider detector scanners (i.e. 320 slice) tend to provide superior image quality for chronic thromboembolic lesions. However, it was also noted that the bulk of the evidence informing this recommendation was obtained from studies which used 64 detector scanners. The panel had some concerns about the extent to which the evidence directly addressed the clinical question. The potential significant health benefit to the individual patient from a confirmed diagnosis of CTEPH was recognized. The panel also considered the minimal risk of harm to patient with CTPA, the minimal burden on the patient to adhere and the potential high impact on morbidity and mortality for the target population as a whole. Due to the lack of cost effectiveness data, the panel felt it was inconclusive as to whether the recommendation would be cost effective.

Box 4 – Diagnosis of CTEPH

PICO 3b):
In patients with suspected CTEPH, should MRPA be used to establish the diagnosis and assess the anatomic extent and location of chronic thromboembolic material?

Recommendation:
1. We do not recommend the routine use of MRPA to establish the diagnosis and/or to assess the anatomic extent and location of chronic thromboembolic material in patients with suspected CTEPH. (GRADE 1C)

Clinical remarks:
There are few centres with MRPA experience in CTEPH.

MRPA should be distinguished from cardiac MRI protocols used for the assessment of pulmonary hemodynamics and right ventricular function in various types of PH, including CTEPH.

Key Evidence

Our review found no RCTs or other direct evidence assessing the use of MRPA in the diagnosis and/or assessment of anatomic extent of CTEPH. Specifically, there are no RCTs comparing MRPA to conventional invasive pulmonary angiography. The recommendation informing this question is therefore based upon the experience of the expert panel and indirect evidence from the following two retrospective cohorts.

The PH centre in Papworth, UK have used 3D DCE MRI for the confirmation of CTEPH and planning of PEA surgery. In a retrospective cohort(12) of 106 patients (53 with CTEPH, including 22 with segmental level disease), MRPA had high sensitivity of 98% and specificity of 94% in diagnosing CTEPH and was superior to 64-detector CTPA in depicting stenoses and post-stenotic dilatations. The addition of an unenhanced proton MR technique improved the detection of proximal disease. A subsequent research letter(13) described the results with this cohort expanded to 132 patients, showing similar results for MRPA for the diagnosis of CTEPH (97% sensitivity, 92% specificity). There were no comparisons with any forms of invasive pulmonary angiography in this cohort, either via DSA or cone beam CT.

Ley et al.(14) published a small retrospective cohort of 24 patients with CTEPH who underwent contrast enhanced MRPA, 40 to 64-detector CTPA and invasive DSA. Unfortunately, there were challenges with the DSA image quality in this study, with only half of the patients having DSA images rated excellent or good. Sensitivity and specificity for the diagnosis of main/lobar pulmonary arterial disease were highest with CTPA (100% and 100%), followed by MRPA (83%, 99%) and DSA (66%, 100%). For the detection of segmental arterial disease the sensitivities and specificities were: CTPA (100% and 99%), MRPA (88%, 98%) and DSA (75%, 100%).

Expert Panel Synthesis of Clinical Judgement

The panel graded the body of evidence as low. The body of evidence was thought to only indirectly address the clinical question. MRPA was considered to have potentially minimal health benefit to the individual patient in comparison to the more widely available and more studied

techniques of CTPA and invasive pulmonary angiography. The panel also considered the minimal burden of adherence and minimal harm to the patient with MRPA, as well as its anticipated low impact on the morbidity or mortality of the target population. The panel emphasized the lack of cost effectiveness data but felt that MRPA was unlikely to be cost effective. The panel acknowledged the limited access to MRPA technology and emphasized the lack of widespread experience or expertise in MRPA assessment of CTEPH.

Patient values and preferences (3a and 3b)

No studies were found that assessed patient values or preferences with regards to CTPA, MRPA or invasive pulmonary angiography. It was the panel's consensus that most patients would be willing to undergo CTPA, and then be referred to a local expert PH centre and perhaps subsequently a PEA/BPA centre for additional investigations and treatments.

Good Practice Points (3a and b)

- CTPA images may be non-diagnostic or suboptimal due to technical issues. Specific recommended technical criteria include a short breath hold acquisition 3-5 sec) as well as thin collimation and thin-slice reconstruction (≤1 mm) in axial, coronal and sagittal planes. 3-dimensional surface-shaded reconstructions may improve depiction of vessel cut-off.(15) Maximum intensity projections and oblique reconstructions along the long axis of the left and right pulmonary arteries may also be helpful.

- Evaluation for CTEPH in patients with contrast allergy or renal dysfunction can represent a clinical challenge. These cases should be discussed with a PH expert centre.

- Pulmonary angiographic and V/Q imaging data can be complementary when used for the planning of CTEPH treatments.

- Most types of pulmonary vascular imaging can underestimate the true anatomic extent of CTEPH, when compared to intraoperative evaluation at the time of PEA.

- Conventional DSA is the traditional reference standard, but like all imaging techniques can be suboptimal due to technical issues. Regular DSA quality control efforts should be undertaken at expert PH centers, to optimize the techniques of image acquisition.

Areas for Future Research (3a and 3b)

Future studies using newer generations of CT scanners may help further define the role of CTPA, both in ruling out CTEPH and in more effectively assessing the anatomic extent and location of chronic thromboembolic material.

The panel highlighted the need for clinical research to maintain pace with the rapid development of new imaging technology. As new forms of CTPA are developed, prospective trials should be conducted in comparison to the traditional reference standard of a high quality DSA, such as DSA performed in an experienced and high-volume PH expert centre.

There remains only a small body of evidence to support CTPA or other non-invasive imaging techniques aimed at the evaluation of subsegmental level chronic thromboembolic material. Future studies on subsegmental disease which compare a variety of imaging techniques in comparison to DSA are required. Further study of imaging techniques for segmental and more distal levels of disease may reveal important insights, particularly as it relates to assessment of potential candidates for BPA.

Cone beam CT represents a novel form of imaging during invasive pulmonary angiography, but there are only single-centre reports thus far. Potential future clinical use will require multi-centre validation studies.

Similarly, ongoing research into MRPA techniques may allow MRPA to expand beyond its current use in only a few selected centres worldwide.

The panel emphasized the importance of ongoing research regarding optimizing technical best practices for imaging techniques as well as future knowledge translation of such practices.

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IMPLEMENTATION

The first recommendation within this CPG is a negative recommendation aimed at reducing unnecessary routine testing in patients following acute PE. This could be a cost saving initiative if successfully implemented. Enablers to implementation could include knowledge translation efforts targeting those users that routinely evaluate patients following acute PE (i.e. Thrombosis clinics) and in possible partnership with the Choosing Wisely Canada initiative.

An abridged online and electronic copy "quick reference" guide and diagnostic algorithm with reference link to the full document will be circulated to all 13 expert PH centres in Canada. It may be of further benefit to define (and audit practices of) PH centres of excellence. Such an initiative could include peer review of the technical adequacy and the performance of readers for key imaging technologies pertinent to CTEPH including V/Q, CTPA and conventional pulmonary angiography. Such an initiative might be possible in collaboration with the Pulmonary Hypertension Association of Canada.

Implementation strategies for the non-PH expert clinicians (the target users of this CPG) are of the key importance. One anticipated barrier to implementation of the CPG recommendations at the level of the non-PH expert is uncertainty surrounding the types and magnitude of existing knowledge gaps. These knowledge gaps are currently being assessed in urban and rural respirologists and urban internists/hematologists with a pre and post guidelines survey)). Further research to assess knowledge gaps affecting rural and remote clinicians would be of benefit. A second anticipated barrier to implementation of the CPG recommendations is the possible lack of access to key diagnostic technology (i.e. echocardiography and/or V/Q scan) and/or expert interpretation of these tests. Clinicians working in rural or remote areas are likely have unique implementation needs. Knowledge translation tools designed to address the needs of all the non-PH experts are planned to include an abridged and on-line "quick reference guide", continuing medical education including a standard CTEPH diagnosis slide set developed by the CTS pulmonary vascular committee, and the possible development of more detailed CTEPH training and quality improvement programs for clinicians, radiologists and health systems.

Our goal is to monitor the impact of the CPG recommendations through their ability to correct knowledge gaps within the target user group well as tracking of the incidence and geography of CTEPH cases at the expert Canadian PH centres (work is underway on a Canadian PH database project).

SUMMARY

Table 6 – Diagnosis of CTEPH: Summary of Recommendations

Screening for CTEPH		
Clinical (PICO) Question	**Recommendation**	**GRADE**
Should patients be screened for CTEPH (using echo and/or pulmonary vascular imaging with V/Q lung scan or CTPA) following an acute pulmonary embolism to increase the rate of diagnosis or improve clinical outcomes of CTEPH?	1. We recommend against routine screening for the presence of CTEPH following an acute pulmonary embolism.	1C
Assessment for CTEPH		
Clinical (PICO) Question	**Recommendation**	**GRADE**
Should patients with PH be assessed for CTEPH?	1. In patients with PH, we recommend that clinicians perform nuclear V/Q lung scanning as a screening test to rule out CTEPH. **Clinical remarks:** *Either Planar or SPECT nuclear V/Q are acceptable modalities to screen for CTEPH.* *A normal perfusion (Q) scan effectively rules out the possibility of CTEPH.* A negative CTPA does NOT effectively rule out CTEPH	1C
Diagnosis of CTEPH		
Clinical (PICO) Questions	**Recommendations**	**GRADE**
In patients with suspected CTEPH: a) Should CTPA be used to establish the diagnosis and assess anatomic extent and location of chronic thromboembolic material?	1. We recommend that clinicians perform CTPA to confirm the presence and assess the anatomic extent and location of chronic thromboembolic material in patients with suspected CTEPH. **Clinical remarks:** *A positive CTPA, confirming chronic thromboembolism, should prompt a referral to an expert PH centre for establishment of a formal diagnosis of CTEPH, and assessment of most appropriate treatment.* *A negative, indeterminate, or technically poor CTPA does not exclude CTEPH. Patients with these non-positive CTPA results and suspected CTEPH should be referred to an expert PH centre for further diagnostic testing, such as conventional pulmonary angiography.*	1B
In patients with suspected CTEPH: b) Should magnetic resonance pulmonary angiography (MRPA) be used to establish the diagnosis and assess the anatomic extent and location of chronic thromboembolic material?	1. We do not recommend the routine use of MRPA to establish the diagnosis and/or to assess the anatomic extent and location of chronic thromboembolic material in patients with suspected CTEPH. **Clinical remarks:** *There are few centres with MRPA experience in CTEPH.* *MRPA should be distinguished from cardiac MRI protocols used for the assessment of pulmonary hemodynamics and right ventricular function in various types of PH, including CTEPH.*	1C

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EDITORIAL INDEPENDENCE

The CTS PVD Clinical Assembly is accountable to the CTS Canadian Respiratory Guidelines Committee and the CTS Board of Directors. The CTS PVD Clinical Assembly is functionally and editorially independent from any funding sources of the CTS and does not receive any direct funding from external sources. The CTS receives unrestricted grants which are combined into a central operating account to facilitate the knowledge translation activities of the CTS Clinical Assemblies. No funders played a role in the collection, review, analysis or interpretation of the scientific literature or in any decisions regarding the key messages presented in this document.

DISCLOSURES

Members of the CTS CTEPH Guideline Panel declared potential conflicts of interest at the time of appointment and these were updated throughout the process in accordance with the CTS Conflict of Interest Disclosure Policy. Individual member conflict of interest statements are posted at https://cts-sct.ca/guideline-library/.

Appendix 1 - Summary of PICO questions and search strategy

Study design	Any. To be as inclusive as possible, priority will be given to RCTs if enough RCTs are identified. Trials evaluated according to the GRADE methodology (Guidelines, Meta-analysis; Systematic review; Randomized controlled trial; Cohort study; Case control study; Case series or Case report)
Data Sources	MEDLINE®, Cochrane Central®, Cochrane Database of Systematic Reviews, EMBASE®. An extensive grey literature search included systematic searches of relevant citations of Web sites: Canadian Medical Association InfoBase, and the National Guideline Clearinghouse, Clinical Trial Registries (ClinicalTrial.gov, WHO Clinical Trials), Any potentially relevant citations will be cross-checked with our citation database and any that are new will be retrieved and screened as full text. In addition, a targeted environmental scan of international guideline developers' websites and key organizations for evidence-based clinical practice guidelines will be searched.
Publication date	2008 to September 2017
Target Users	Health care providers who care for individuals with venous thromboembolic disease, PH, CTEPH and medical conditions that predispose to CTEPH. Specifically, family practitioners and specialist physicians (respirologists, cardiologists, hematologists, internists, cardiac and thoracic surgeons, radiologists), and other health care professionals who currently care for patients with deep vein thrombosis (DVT)/PE, PH, and/or CTEPH can use these guidelines to help inform their clinical practice.
Scope of this CPG	The diagnostic approach to CTEPH in patients with a history of PE or who present with PH. This document does not address the health economics of the management of CTEPH and does not cover the clinical management of patients with acute PE or with PH due to causes other than CTEPH. This CPG also does not serve as a technical guide to PEA or the peri-operative care of CTEPH patients.
Language Criteria	All publications in English and French will be reviewed and considered for inclusion.
General/main terminology or key words	1. pulmonary hypertension 2. thromboemboli* or thrombo-emboli* or CTEPH or CTPH or VTE or pulmonary embolism or deep vein thrombosis or DVT 3. 1 and 2 4. Clinical outcomes, Survival, Mortality, Hospitalization, PH clinical progression/worsening, pulmonary hemodynamics, RV failure, WHO Functional Class, NYHA Functional Class, Health related quality of life, functional/exercise capacity
Specific key words	We accepted all key words from the 2010 guideline and added in relevant keywords for new PICO questions in this guideline update.

Clinical Questions	PICO	Additional Question Specific Key Words
Q1: Should patients be screened for CTEPH (using echo and/or pulmonary vascular imaging with V/Q lung scan or CTPA) following an acute pulmonary embolism to increase the rate of diagnosis or improve clinical outcomes of CTEPH?	**P:** Patients at least 3 months post-acute VTE event **I:** Echo, imaging (VQ lung scan, CTPA) **C:** Routine Clinical assessment **O:** 1. Survival / mortality 2. Hospitalization 3. PH Clinical progression / worsening 4. Pulmonary hemodynamics 5. RV failure 6. Health-related quality of life 7. Functional / exercise capacity 8. Diagnosis of CTEPH	Screening, Detection, Ventilation Perfusion Lung Scan, VQ lung scan, CT Pulmonary angiography, CTPA, Echocardiogram, Transthoracic echo, Diagnosis
Q2: Should patients with PH be assessed for CTEPH?	**P:** All patients with PH **I:** Specific assessment for CTEPH: Clinical, imaging (VQ scan or CTPA) **C:** No specific assessment for CTEPH **O:** 1. Survival / mortality 2. Hospitalization 3. PH Clinical progression / worsening 4. Pulmonary hemodynamics 5. RV failure 6. Health-related quality of life 7. Functional / exercise capacity 8. Diagnosis of CTEPH	Same as above
Q3: In patients with suspected CTEPH: a) Should CTPA be used to establish the diagnosis and assess anatomic extent and location of chronic thromboembolic material? b) Should magnetic resonance pulmonary angiography (MRPA) be used to establish the diagnosis and assess the anatomic extent and location of chronic thromboembolic material?	**P:** Patients with suspected CTEPH **I:** Conventional pulmonary angiography **C:** CTPA or MRA **O:** Resectability, PEA surgery, BPA	pulmonary angiogra*, digital subtraction angiogra*, CT angiogra*, CTPA, Magnetic resonance angiogra*, Pulmonary thromboendarterectomy, pulmonary endarterectomy, PEA, balloon pulmonary angioplasty, BPA, resectability