

Diagnosis of chronic thromboembolic pulmonary hypertension: A Canadian Thoracic Society clinical practice guideline update

Doug Helmersen^a, Steeve Provencher^b, Andrew M. Hirsch^c, Anne Van Dam^d, Carole Dennie^e, Marc De Perrot^f, Lisa Mielniczuk^g, Naushad Hirani^a, George Chandy^h, John Swistonⁱ, Dale Lien^j, Nick H. Kim^k, Marion Delcroix^l, and Sanjay Mehta^m

^aPulmonary Hypertension Program, Division of Respiratory Medicine, Peter Lougheed Centre, University of Calgary, Calgary, Alberta, Canada; ^bInstitut Universitaire de Cardiologie et de Pneumologie de Québec, Université de Laval, Québec, Québec, Canada; ^cCentre for Pulmonary Vascular Disease, Sir Mortimer B Davis Jewish General Hospital, McGill University, Montreal, Québec, Canada; ^dCanadian Thoracic Society, Ottawa, Ontario, Canada; ^eThoracic and Cardiac Imaging Sections, The Ottawa Hospital Cardiac Radiology, University of Ottawa Heart Institute, University of Ottawa, Ottawa, Ontario, Canada; ^fDivision of Thoracic Surgery, Toronto General Hospital, Toronto Pulmonary Endarterectomy Program, University of Toronto, Toronto, Ontario, Canada; ^gUniversity of Ottawa Heart Institute Pulmonary Hypertension Clinic, Cardiology Division, University of Ottawa, Ottawa, Ontario, Canada; ^hUniversity of Ottawa Heart Institute Pulmonary Hypertension Clinic, Respiriology Division, The Ottawa Hospital, University of Ottawa, Ottawa, Ontario, Canada; ⁱPulmonary Hypertension Program, Respiriology Division, Vancouver General Hospital, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; ^jUniversity of Alberta Pulmonary Hypertension Clinic, University of Alberta, Edmonton, Alberta, Canada; ^kPulmonary Vascular Medicine, University of California San Diego, California, U.S.A.; ^lCentre for Pulmonary Vascular Diseases, Department of Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium; ^mSouthwest 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 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 initial testing 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 computed tomography pulmonary angiogram (CTPA) does not rule out CTEPH.

In patients with suspected CTEPH, 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.

DISCUSSION: The foundation of CTEPH diagnosis remains clinicians' consideration of this possibility in patients at risk. Future research is required to identify the specific diagnostic tests and/or algorithms which will perform best in formal screening protocols for CTEPH. The current diagnosis of CTEPH will until then continue to rely on clinician led case finding, with diagnostic investigations arranged during the course of clinical care. Once case finding investigations have been initiated, an approach which follows the recommendations and sequence of testing outlined in this guideline may improve the rate of diagnosis of CTEPH and potentially the outcomes in these patients.

This guideline will be reviewed every three years or sooner, in accordance with the Canadian Thoracic Society Living Guideline Model.

KEYWORDS

Chronic thromboembolic pulmonary hypertension; diagnosis; risk factors; acute pulmonary embolism; ventilation perfusion scan; computed tomography pulmonary angiogram

This official Canadian Thoracic Society guideline was endorsed by the Canadian Society of Thoracic Radiology in November 2018.

CONTACT Doug Helmersen  doug.helmersen@albertahealthservices.ca  Foothills Hospital, 1403, 29th ST NW, Calgary, AB, T2N2T9.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/ucts.

RÉSUMÉ

CONTEXTE: L'hypertension pulmonaire thromboembolique chronique (HPTEC) constitue une cause importante et fréquente de l'hypertension pulmonaire (HP). L'évaluation de l'HPTEC présente de nombreuses lacunes, dont la méconnaissance du diagnostic, le défaut des cliniciens à envisager l'HPTEC de façon routinière chez les patients à risque, et des pratiques de diagnostic erronées, y compris certaines pratiques incomplètes ou inutiles.

MÉTHODES: Un comité multidisciplinaire représentatif constitué de médecins experts a entrepris un processus d'élaboration de lignes directrices de pratique clinique. Un total de quatre problèmes cliniques clés ont été définis selon la méthode patient/problème, intervention, comparaison, issue clinique (PICO). La comité a effectué une revue systématique de la littérature fondée sur les données probantes, a évalué et noté les données probantes pertinentes et a fait quatre recommandations.

RÉSULTATS: Les patients ne devraient pas faire l'objet d'un dépistage systématique de l'HPTEC (par échographie ou imagerie thoracique) suite à une embolie pulmonaire aiguë. Les facteurs de risque pour l'HPTEC suite à une embolie pulmonaire aiguë ont été établis, et les patients faisant partie de ces groupes à plus haut risque pourraient devoir faire l'objet d'une attention plus soutenue pendant le suivi clinique. Il n'a pas encore été démontré dans le cadre d'essais prospectifs contrôlés que le dépistage de routine pour l'HPTEC après une embolie pulmonaire améliore les issues cliniques des patients.

Chez les patients atteints d'HP, les cliniciens devraient effectuer une scintigraphie pulmonaire de perfusion/ventilation nucléaire (V/Q), afin d'éliminer la possibilité d'un HPTEC. Une scintigraphie pulmonaire planaire ou une tomographie informatisée d'émission à un seul photon (SPECT) sont des formes acceptables de scintigraphie pulmonaire V/Q. Une scintigraphie par perfusion normale permet d'exclure un diagnostic d'HPTEC. Une angiographie pulmonaire par tomodensitométrie négative n'élimine pas la possibilité d'HPTEC.

Lorsqu'un diagnostic d'HPTEC est suspecté, une angiographie pulmonaire par tomodensitométrie devrait être effectuée afin de confirmer la présence du matériau thromboembolique chronique et en évaluer l'emplacement, ainsi que l'étendue anatomique. Une angiographie pulmonaire par tomodensitométrie positive confirmant la présence d'une thromboembolie chronique devrait donner lieu à une référence vers un centre spécialisé en HP où un diagnostic officiel pourra être établi. Une angiographie pulmonaire par tomodensitométrie négative, indéterminée ou techniquement déficiente n'exclut pas l'HPTEC et devrait également donner lieu à une référence vers un centre spécialisé en HP pour que d'autres tests soient effectués.

L'angiographie pulmonaire par résonance magnétique n'est pas recommandée actuellement pour une évaluation de routine pour les patients qu'on soupçonne être atteints d'HPTEC.

DISCUSSION: D'autres études sont nécessaires pour connaître avec plus de précision les tests diagnostiques ou les algorithmes qui seront les plus efficaces dans le dépistage systématique de l'HPTEC. D'ici là, le diagnostic de l'HPTEC continuera de reposer sur la détection clinique par des investigations ciblées par les cliniciens. Un diagnostic d'HPTEC devrait donc être considéré par les cliniciens en présence d'un patient à risque d'HPTEC ou présentant des symptômes compatibles. Lors de l'investigation, une approche qui suit les recommandations et la séquence de tests décrite dans ces lignes directrices pourrait améliorer le diagnostic de l'HPTEC et possiblement les issues cliniques de ces patients.

Cette ligne directrice sera révisée tous les trois ans ou plus tôt, conformément au modèle de lignes directrices évolutives de la Société canadienne de thoracologie.

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 World Health Organization (WHO) PH classification updated at the Sixth World Symposium on Pulmonary Hypertension held in 2018 in Nice, France (Tables 1 and 2), 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).

A very important and common¹ 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 has been 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/cm⁵) or greater; and
2. Persistent pulmonary arterial thrombotic obstruction despite at least three months of effective, uninterrupted anticoagulation.

Table 1. Updated clinical classification of pulmonary hypertension (PH).²

1. PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug – and toxin-induced PAH
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
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
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
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
5. PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

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

Table adapted from: Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2018;1801913.

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

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 tumors
Renal carcinoma
Uterine carcinoma
Germ cell tumors of the testis
Other tumors
4.2.3 Nonmalignant tumors
Uterine leiomyoma
4.2.4 Arteritis without connective tissue disease
4.2.5 Congenital pulmonary artery stenoses
4.2.6 Parasites
Hydatidosis

Table adapted from: Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2018;1801913.

It is of note that following completion of the evidence review and recommendations for this guideline document, the WHO hemodynamic definition of PH² was revised to include mPAP > 20 mmHg, pulmonary artery wedge pressure (PAWP) of 15 mmHg or less and a PVR 3 Wood units or greater. This revised hemodynamic definition was not used in this document but will be considered in future guideline updates.

The potential differential diagnosis for CTEPH includes a range of pulmonary vascular diseases such as: (i) central pulmonary artery thrombosis in the setting of dilated pulmonary arteries secondary to PAH, emphysema or congenital heart disease (ii) pulmonary artery sarcoma; (iii) extrinsic vascular compression such as from fibrosing mediastinitis;

(iv) pulmonary veno-occlusive disease (PVOD); (v) large vessel pulmonary artery vasculitis; and (vi) congenital pulmonary artery 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, affecting approximately 3% of patients following PE.^{1,3} Second, CTEPH is a serious, progressive and often fatal disease. Patients with untreated CTEPH experience significantly increased mortality. Historical observational studies^{4,5} have estimated the median survival rate in severe untreated CTEPH patients to be as low as 10–20% at 2–3 years. Contemporary registry data⁶ also illustrate the significant mortality of CTEPH, with 3-year survival rates in some subpopulations as low as 70%, even with access to modern era therapies. Third, CTEPH is potentially curable with pulmonary endarterectomy (PEA) surgery. Finally, CTEPH patients may also benefit from other treatments such as 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 computed tomography pulmonary angiography (CTPA)) following an acute pulmonary embolism to increase the rate of diagnosis or improve clinical outcomes of CTEPH?
Section 2: Initial Testing for CTEPH	How should patients with PH be tested 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).⁷ 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.

- In this CPG, we have reviewed the updated literature for only those CTEPH risk factors identified in patients following post-acute PE (see [Table 5](#), Section 1). A comprehensive update on all CTEPH risk factors is not provided. [Table 5](#) from our 2010 guidelines⁷ contains a comprehensive list of CTEPH risk factors, which includes important independent CTEPH risk factors such as anti-phospholipid antibodies and splenectomy.
- In Section 1 on screening for CTEPH following acute PE, the specific patient population has been broadened from asymptomatic patients to now include all patients following acute PE, irrespective of symptoms. This change was felt by the panel to lead to a recommendation that would be more actionable by clinicians and made with consideration of the practical challenges which can arise in attempting to define normal versus abnormal symptoms following acute PE.

Target patient population

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

Target users

The present CPG 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. This document should also be useful to patients and patient advocates. Finally, health care decision makers may also use this guideline in policy processes to inform coverage decisions.

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 (DH) and included 10 respirologists (2 international experts), one cardiologist, one radiologist specializing in cardiothoracic imaging and one thoracic surgeon. All author conflicts of interests are posted on the CTS website at <https://cts-sct.ca/guideline-library/>.

Methodology

This CPG was developed in accordance with CTS guideline development process.⁸ The panel utilized the AGREE II checklist to guide the development of this guideline.⁹

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: these include 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, across the same databases. 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 title and abstracts of each article were scrutinized by two panel members to decide whether the article was relevant. Where there was a difference of opinion, the panel members endeavored to reach consensus. When a consensus was reached on the list of relevant abstracts, copies of the articles of all relevant and possibly relevant articles were obtained. The chosen inclusion and exclusion criteria were noted at the abstract and full text review stages.

Study selection criteria

Articles selected for inclusion in the systematic review of the evidence 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 French, and studies of uniquely pediatric populations were excluded. Studies were evaluated in detail by pairs of reviewers who did the data extraction to ensure that selection criteria were met and agreed upon.

Critical appraisal of identified studies

Data from all articles relevant to each PICO question were compiled into tables by each section and are found on the CTS website. During discussion of each question via

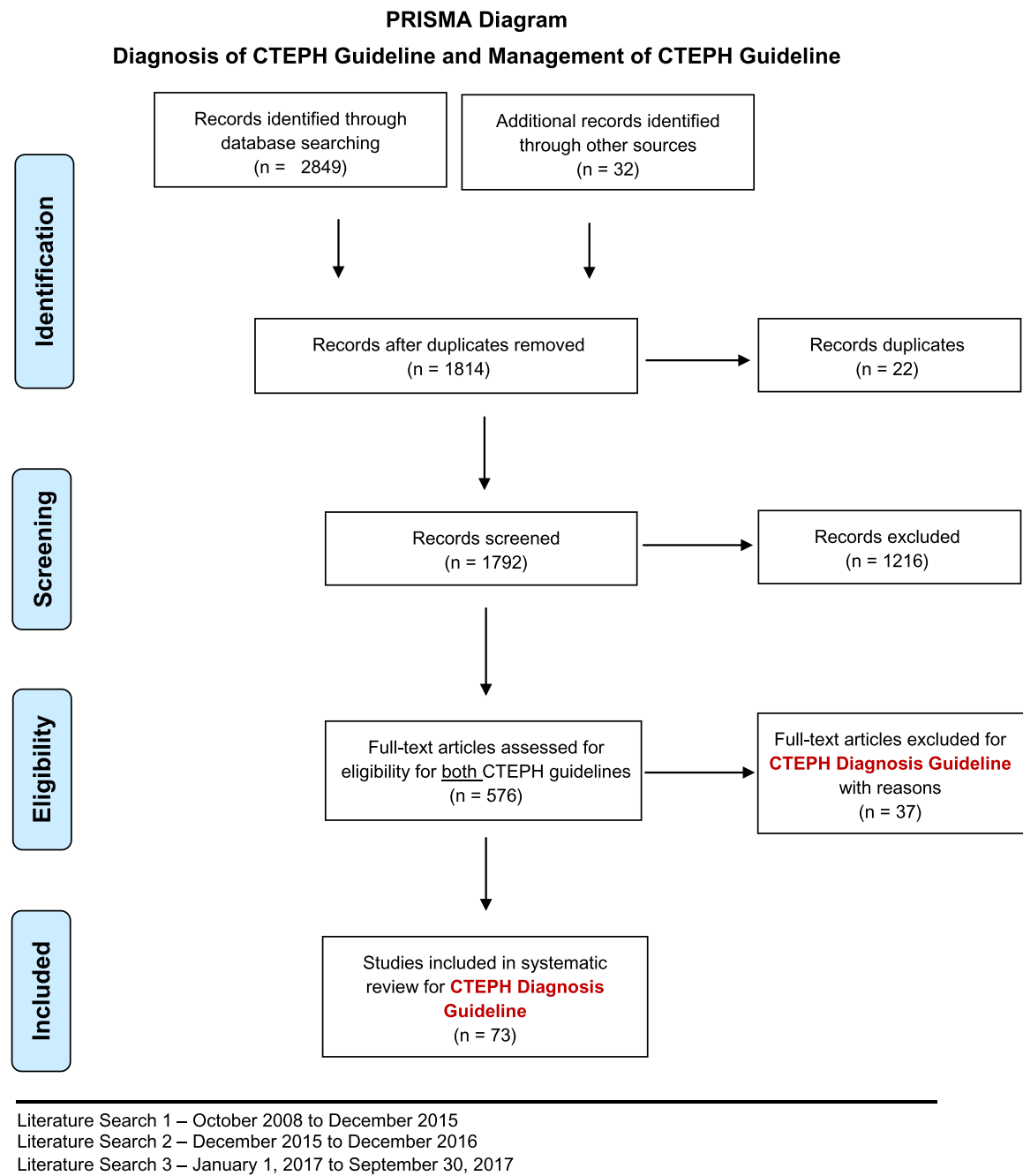


Figure 1. PRISMA Diagram.¹⁰

Footnote: The Canadian Thoracic Society chronic thromboembolic pulmonary hypertension (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, 110 articles were assessed for the Diagnosis of CTEPH guideline. From the 110 articles assessed, 37 studies were excluded with reasons and 73 studies were included.

webinars held in 2017 and 2018, all data were reviewed by all members of the panel, and group consensus was established regarding the quality of the evidence addressing each clinical question, according to the components of the GRADE criteria¹¹ (Table 3).

Synthesis of evidence-base and clinical judgment of risk versus 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 (implementability factors categorized under the “Contextualizations and Deliberations” domain of guidelines¹²). These discussions and the resulting synthesis of evidence and summary clinical judgement are presented for each recommendation.

Table 3. Strength of the recommendations grading system.¹¹

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.

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 by the entire group. 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 (CRGC) Chair to optimize the language of each recommendation to ensure implementability. The recommendation consensus process was completed by electronic survey using a six-point voting scale (Table 4), whereby it was defined a priori that a recommendation would only be accepted if each panel member voted for option 1, 2 or 3 (wholeheartedly agree, agree or can support). For a recommendation to be accepted, it had to be voted on by 75% of the eligible panel members and achieve ratings of 1, 2 or 3 by 80% of the voting panelists. No panel member was excluded from voting. In the event of a failure to reach 80% of votes with ratings of 1, 2 or 3, 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

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.

electronic survey using a three-point scale, for which acceptance of a recommendation required a majority (80%) of panelists to choose option 1 or 2 (Table 4). Through this process, all recommendations achieved acceptance, with a second round of voting required for only one recommendation.

Applicability/implementability

Recommendations were formulated with the aim of being clear and actionable by clinicians within the user group, in accordance with best principles for guideline language and format.¹³ 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 algorithm addressing assessment of CTEPH in patients with

PH is provided as a tool for clinicians to aid in implementing recommendations. 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 and through more precise diagnostic evaluation. Our goal is to monitor the impact of these 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 to track characteristics and frequency of CTEPH cases 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, the CTS independently invited formal review of the guideline by: two external (non-CTS) international content experts and two internal (CTS) reviewers. One of the internal reviewers performed an AGREE assessment of the guideline. The draft guideline was reviewed by the Canadian Society of Thoracic Radiology Executive Committee. The Pulmonary Hypertension Association (PHA) of Canada coordinated a patient review of the draft 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 CRGC for review. Two members of the CRGC then completed a review of the guideline and these documents and provided further feedback for consideration by authors. Upon acceptance, the CRGC recommended approval of the guideline to the CTS Executive Committee. All reviews and author responses are posted 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 Plus database. The authors will use the continuously updated McMaster Plus database to review new articles published in top journals starting from the last date of the literature conducted for this CPG. 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 reviewers. This evidence service will prompt guideline updates and facilitate reviews. The guideline will be formally reviewed every three years or sooner to determine the need for and nature of any updates, in accordance with the CTS Living Guideline Model (details available at www.cts-sct.org/guidelines).

References

- Ende-Verhaar YM, Cannegieter SC, Vonk N, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J*. 2017;49(2):1601792.
- Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2018;53:1801913.
- Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med*. 2004;350(22):2257–2264.
- Riedel M, Stanek V, Widimsky J, et al. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest* 1982; 81(2):151–158.
- Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest* 2001;119(3):818–823.
- Delcroix M, Lang I, Pepke-Zaba J, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *Circulation* 2016;133(9):859–871.
- Mehta S, Helmersen D, Provencher S, et al. Diagnostic evaluation and management of chronic thromboembolic pulmonary hypertension: a clinical practice guideline. *Can Respir J*. 2010; 17(6):301–334.
- Canadian Thoracic Society Guideline Development Process and Methodology. <https://cts-sct.ca/guideline-library/methodology/>.
- Brouwers M, Kho ME, Browman GP, et al. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *Can Med Assoc J*. 2010;182(18):E839–E842.
- Moher D, Liberati A, Tetzlaff J, The PRISMA Group, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. www.prisma-statement.org.
- Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American college of chest physicians task force. *Chest* 2006;129(1):174–181.
- Brouwers M, Makarski J, Kastner M, et al. The Guideline Implementability Decision Excellence Model (GUIDE-M): a mixed methods approach to create an international resource to advance the practice guideline field. *Implement Sci*. 2015;10:36.
- Gupta S, Rai N, Bhattacharria O, et al. Optimizing the language and format of guidelines to improve guideline uptake. *CMAJ*. 2016;188(14):E362–E368.

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 randomized controlled trials (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-analysis³ of 21 published studies.^{4–24} 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.^{7,11–13,16,25} Although most studies suggest that echo screening can identify a number of patients with PH post-acute PE, these studies are limited by highly variable criteria that were not consistent with recommendations for echo detection of PH (e.g., right ventricular systolic pressure (RVSP) thresholds from 30 to 50 mmHg). Moreover, there was often limited formal diagnosis of the presence or the cause of PH by right heart catheterization (RHC) and only infrequent definitive CTEPH diagnosis in many of these studies.

In the aforementioned meta-analysis,³ of the 14 studies which confirmed CTEPH by RHC,^{4,7,8,11–16,18,19,21,23,26} 9 studies had screened all included patients with echo,^{8,11,12,14–16,18,21,26} 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 crafted in the absence of any direct evidence, and is based on indirect evidence (case series, cohort studies) showing no clear benefit of screening, as well as the consensus of the expert panel.

Expert panel synthesis of evidence-base and clinical judgment of risk versus benefit

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 for 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. None of the three tests of echocardiogram, V/Q scanning or CTPA fulfilled the WHO /Wilson’s^{27,28} requirements for good screening tests, when used to screen for CTEPH.

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 noninvasive assessments if they were effective in diagnosing CTEPH sooner and especially if they were effective 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 initial hemodynamic severity of PH and initial CT pulmonary vascular imaging features (Table 5). For example, the risk of CTEPH is higher in patients with recurrent PE compared to first PE,^{4,17,25} with Odds Ratio (OR) of 3 - 12. Age may be a weak risk factor for CTEPH. Low quality evidence suggests the possibility of a higher risk of developing CTEPH following acute PE in older age groups (variably defined as >60 to >70 years) in several studies,^{12,18,22,31,32,34}

although conversely, a single study suggested a higher risk of CTEPH in younger patients.⁴ Although not yet validated in prospective controlled trials, patients post-acute PE with risk factors for CTEPH may merit closer clinical attention during follow-up, which most importantly involves clinical monitoring for symptoms (e.g., dyspnea) and functional limitation, but also the targeted use of echocardiography (e.g., to look for elevated RVSP, secondary signs of PH such as RV enlargement and/or RV systolic dysfunction). The panel emphasized that routine follow-up pulmonary vascular imaging (V/Q lung scan or CTPA) is not indicated for screening of CTEPH, even in these higher risk groups. The recommended techniques and diagnostic sequencing of pulmonary vascular imaging when used for CTEPH case finding is summarized in our algorithm (Figure 2).

3. Patients with acute PE who remain symptomatic despite 3 months of effective anticoagulation. Persistent symptoms or low health related quality of life (HRQoL) scores are common in patients with acute PE despite appropriate anticoagulation.^{15,29,30} 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”²⁹ 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, such as to decide on duration of anticoagulation, to assess risk of recurrent PE, or to establish a baseline before ongoing surveillance for recurrent PE.

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 a need for studies to further identify and assess the magnitude of risk factors for CTEPH within the range of populations reflective of clinical practice, including symptomatic and asymptomatic patients as well as those with comorbid conditions. There may also be benefit to the development

Table 5. Risk factors for CTEPH in patients' post-acute pulmonary embolism.

Parameters	References
1. Demographic	
• Older age	Ribeiro et al. 1999; ²² Barros et al. 2013; ³¹ Casazza et al. 2014; ³² Yang et al. 2015; ³³ Klok et al. 2016; ³⁴ and Otero et al. 2013 ³⁶
• Younger age	Pengo et al. 2004 ⁴
• Male gender	Tosun et al. 2016 ³⁵
2. Co-morbid medical conditions	
• Higher BMI >30 kg/ m ²	Barros et al. 2013 ³¹
• Atrial Fibrillation	Otero et al. 2013 ³⁶
• Chronic Heart/Lung Disease	Otero et al. 2013 ³⁶
• Hypothyroidism	Klok et al. 2016 ³⁴
• Varicose veins	Yang et al. 2015; ³³ Otero et al. 2013 ³⁶
3. Clinical / Laboratory features at time of PE diagnosis	
• Previous venous thromboembolism event	Tosun et al. 2016; ³⁵ Guérin et al. 2014; ¹² Abul et al. 2014; ⁶ Korkmaz et al. 2012; ¹⁷ Martí et al. 2010; ¹⁸ Pengo et al. 2004 ⁴
• Unprovoked PE	Pesavento et al. 2017; ³⁷ Klok et al. 2016; ³⁴ Pengo et al. 2004 ⁴
• Symptom onset >14 days before PE diagnosis	Klok et al. 2016 ³⁴
• NYHA functional class III or IV	Berghaus et al. 2011; ⁸ Dentali et al. 2009 ⁹
• Severe PE	Otero et al. 2011 ²⁰ , Pengo et al. 2004 ⁴
• Intermediate risk PE	Yang et al. 2015 ³³
• Thrombolytic use for submassive PE	Sharifi et al. 2013; ³⁸ Sharma et al. 2000 ³⁹
• Shorter duration of anticoagulation	Giuliani et al. 2014 ¹¹
• PaO ₂ < 80 mmHg	Tosun et al. 2016 ³⁵
• Elevated RDW % >15%	Abul et al. 2014; ⁶ Xi et al. 2014 ⁴⁰
4. Pulmonary vascular imaging	
Extent of pulmonary vascular obstruction:	
• Large perfusion defects (62.6 ± 12.9)	Pengo et al. 2004 ⁴
• Vascular obstruction index >50%	Miniati et al. 2006 ¹⁹
• CT obstruction index >30%	Yang et al. 2015 ³³
• CTPER-index value ≥4	Vavera et al. 2015 ²⁶
• Qanadli Score ≥42.5%	Serra et al. 2016 ⁴¹
Proximal PE	Guérin et al. 2014 ¹²
5. Severity of PH / RV failure	
• RV dilation	Gong et al. 2015; ⁴² Park et al. 2017 ⁴³
• SPAP >50 mmHg	Yang et al. 2015; ³³ Guérin et al. 2014; ¹² Korkmaz et al. 2012 ¹⁷
• RV Dysfunction	Klok et al. 2016; ³⁴ Gong et al. 2015 ⁴²
• Septal flattening, RV hypertrophy, or W-pattern in the RV outflow curve	Klok et al. 2015 ¹⁶
• Elevated NT-proBNP	Klok et al. 2015; ¹⁶ Guérin et al. 2014 ¹²

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; BMI, body mass index; PE, pulmonary embolism; NYHA, New York Heart Association; RDW, red blood cell distribution width; CT, computed tomography; CTPER, computed tomography pulmonary embolism residua; PH, pulmonary hypertension; RV, right ventricular; NT-proBNP, N-terminal-pro hormone b-type natriuretic peptide.

of scoring systems which combine multiple risk factors to define a composite or overall CTEPH risk, thereby identifying specific subpopulations of patients post-acute PE who could benefit from structured CTEPH screening.

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

References

- Delcroix M, Lang I, Pepke-Zaba J, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *Circulation* 2016;133(9):859–871.
- Ishida K, Masuda M, Tanabe N, et al. Long-term outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *J Thorac Cardiovasc Surg.* 2012;144(2):321–326.
- Ende-Verhaar YM, Cannegieter SC, Vonk N, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J.* 2017;49(2):1601792.
- Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med.* 2004;350(22):2257–2264.
- Golpe R, Perez-de-Llano LA, Castro AO, et al. Right ventricle dysfunction and pulmonary hypertension in hemodynamically stable pulmonary embolism. *Respir Med.* 2010;104(9):1370–1376.
- Abul Y, Ozsu S, Korkmaz A, et al. Red cell distribution width: A new predictor for chronic thromboembolic pulmonary hypertension after pulmonary embolism. *Chron Respir Dis.* 2014;11(2):73–81.
- Becattini C, Agnelli G, Pesavento R, et al. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. *CHEST* 2006;130(1):172–175.
- Berghaus TM, Barac M, von Scheidt W, et al. Echocardiographic evaluation for pulmonary hypertension after recurrent pulmonary embolism. *Thromb Res.* 2011;128(6):e144–e147.
- Dentali F, Donadini M, Gianni M, et al. Incidence of chronic pulmonary hypertension in patients with previous pulmonary embolism. *Thromb Res.* 2009;124(3):256–258.
- Gary T, Starz I, Belaj K, et al. Hyperlipidemia is associated with a higher pulmonary artery systolic pressure in patients after pulmonary embolism. *Thromb Res.* 2012;129(1):86–88.
- Giuliani L, Piccinino C, D'Armini MA, et al. Prevalence of undiagnosed chronic thromboembolic pulmonary hypertension after pulmonary embolism. *Blood Coagul Fibrinolysis.* 2014;25(7):649–653.
- Guérin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. *Thromb Haemost.* 2014;112(3):598–605.
- Held M, Hesse A, Götte F, et al. A symptom-related monitoring program following pulmonary embolism for the early detection of CTEPH: a prospective observational registry study. *BMC Pulmonary Medicine* 2014;14:141.
- Kayaalp I, Varol Y, Cimen P, et al. The incidence of chronic thromboembolic pulmonary hypertension secondary to acute pulmonary thromboembolism. *Tuberk Toraks* 2014;62(3):199–206.
- Klok FA, van Kralingen KW, van Dijk AP, et al. Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. *Haematologica* 2010;95(6):970–975.
- Klok FA, Tesche C, Rappold L, et al. External validation of a simple non-invasive algorithm to rule out chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *Thromb Res.* 2015;135(5):796–780.
- Korkmaz A, Ozlu T, Ozsu S, et al. Long-term outcomes in acute pulmonary thromboembolism: the incidence of chronic thromboembolic pulmonary hypertension. *Clin Appl Thromb Hemost.* 2012;18(3):281–288.
- Martí D, Gómez V, Escobar C, et al. [Incidence of symptomatic and asymptomatic chronic thromboembolic pulmonary hypertension]. *Arch Bronconeumol.* 2010;46(12):628–633.
- Miniati M, Monti S, Bottai M, et al. Survival and restoration of pulmonary perfusion in a long-term follow-up of patients after acute pulmonary embolism. *Medicine (Baltimore).* 2006;85(5):253–262.
- Otero R, Oribe M, Ballaz A, et al. Echocardiographic assessment of pulmonary arterial pressure in the follow-up of patients with pulmonary embolism. *Thromb Res.* 2011;127(4):303–308.
- Poli D, Grifoni E, Antonucci E, et al. Incidence of recurrent venous thromboembolism and of chronic thromboembolic pulmonary hypertension in patients after a first episode of pulmonary embolism. *J Thromb Thrombolysis.* 2010;30(3):294–299.
- Ribeiro A, Lindmarker P, Johnsson H, et al. Pulmonary embolism: one-year follow-up with echocardiography doppler and five-year survival analysis. *Circulation* 1999;99(10):1325–1330.
- Surie S, Gibson NS, Gerdes VE, et al. Active search for chronic thromboembolic pulmonary hypertension does not appear indicated after acute pulmonary embolism. *Thromb Res.* 2010;125(5):e202–e205.
- Vavera Z, Vojacek J, Pudil R, et al. Chronic thromboembolic pulmonary hypertension after the first episode of pulmonary embolism? How often? *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2016;160(1):125–129.
- den Exter PL, van Es J, Kroft LJ, et al. Thromboembolic resolution assessed by CT pulmonary angiography after treatment for acute pulmonary embolism. *Thromb Haemost.* 2015;114:26–34.
- Vavera Z, Elias P, Ryska P, et al. Computed tomography pulmonary embolism residua index (CTPER-index): a simple tool for pulmonary embolism residua description. *Anatol J Cardiol* 2016;16(4):270–275.
- Andermann A, Blancquaert I, Beauchamp S, et al. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bulletin of the WHO* 2008;86(4):241–320.
- Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO;1968. <http://www.who.int/bulletin/volumes/86/4/07-050112BP.pdf>
- Klok FA, van der Hulle T, den Exter PL, et al. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. *Blood Rev.* 2014;28(6):221–226.
- Kahn SR, Hirsch AM, Akaberi A, et al. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE Prospective Cohort Study. *CHEST* 2017;151(5):1058–1068.
- Barros A, Baptista R, Nogueira A, et al. Predictors of pulmonary hypertension after intermediate-to-high risk pulmonary embolism. *Rev Port Cardiol.* 2013;32(11):857–864.
- Casazza F, Bongarzone A, Forgiione C, et al. Echocardiographic evolution of pulmonary artery pressure after acute pulmonary embolism. Results from IPER registry. *Thromb Res.* 2014;134(6):1224–1228.
- Yang S, Yang Y, Zhai Z, et al. Incidence and risk factors of chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. *J Thorac Dis.* 2015;7(11):1927–1938.
- Klok FA, Dzikowska-Diduch O, Kostrubiec M, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *J Thromb Haemost.* 2016;14(1):121–128.
- Tosun H, Kırkal G, Deveci F, et al. The incidence and related risk factors of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *Turk Toraks Dergisi.* 2016;17(2):53–58.
- Otero R, Elias T, Jara L, et al. Factors associated with elevated pulmonary arterial pressure levels on the echocardiographic assessment in patients with prior pulmonary embolism. *Thromb Res.* 2013;131(5):e191–e195.
- Pesavento R, Filippi L, Palla A, et al. Impact of residual pulmonary obstruction on the long-term outcome of patients with pulmonary embolism. *Eur Respir J.* 2017;49:160–198.
- Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the “MOPETT” Trial). *Am J Cardiol.* 2013;111(2):273–277.
- Sharma GV, Folland ED, McIntyre KM, et al. Long-term benefit of thrombolytic therapy in patients with pulmonary embolism. *Vasc Med.* 2000;5(2):91–95.

40. Xi Q, Zhao Z, Liu Z, et al. The lowest VE/VCO₂ ratio best identifies chronic thromboembolic pulmonary hypertension. *Thromb Res.* 2014;134(6):1208–1213.
41. Serra W, Crisafulli E, Sverzellati N, et al. Transthoracic echocardiography and chest computed tomography arteriography in patients with acute pulmonary embolism: a two-year follow-up study. *Respiration* 2016;92(4):235–240.
42. Gong X, Duan Z, Yuan Y. Long-term prognosis and related factors towards patients with acute pulmonary thromboembolism. *Int J Clin Exp Med* 2015;8(5):7906–7913.
43. Park JS, Ahn J, Choi JH, et al. The predictive value of echocardiography for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism in Korea. *Korean J Intern Med.* 2017;32(1):85–94.

Section 2: Initial testing for CTEPH

PICO 2: How should patients with PH be tested for CTEPH?

Introduction

CTEPH is a common and important cause of PH, with a distinct management strategy. Thus, the possibility of CTEPH should be carefully considered in all patients with PH. History alone is insufficient to confirm or exclude CTEPH, as at least one-quarter of CTEPH patients in registries¹ and likely a greater proportion in clinical practice have not experienced symptomatic or documented acute PE. Moreover, physiologic tests such as cardiopulmonary exercise testing also lack the required high sensitivity to rule out CTEPH.^{2,3}

A diagnosis of CTEPH requires appropriate pulmonary vascular imaging. The three most commonly proposed imaging modalities for initial testing of CTEPH in PH patients are nuclear V/Q lung scanning, CTPA and lung perfusion magnetic resonance imaging (MRI). There have been technical innovations in all of these imaging modalities since our prior guideline recommendations in 2010.

In this section we address how patients with PH should be assessed for CTEPH.

Box 2. Initial testing for CTEPH

PICO 2: How should patients with PH be tested for CTEPH?

Recommendation:

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

Clinical remarks:

Either Planar or SPECT nuclear V/Q are acceptable modalities for initial testing to rule out 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 testing 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 guideline⁴ recommended nuclear V/Q for CTEPH assessment in patients with PH. This recommendation was significantly influenced by one single centre retrospective study⁵ in which 227 patients with PH referred to a tertiary centre were assessed 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 have been a lower proportion of subsegmental PE in the cohort evaluated by He et al.⁶ and/or CTPA improvements related to the use of more advanced CT scanners.

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 an initial test to rule out CTEPH.

A single centre prospective blinded cohort study⁹ compared planar V/Q to SPECT V/Q for a clinical question indirectly related to this PICO question; 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 V/Q 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 V/Q might be more sensitive than planar V/Q in detecting the obstructed pulmonary vessels characteristic of CTEPH.

A subsequent cohort study from the same authors¹⁰ 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 micro-circulation to provide information about pulmonary vessel obstruction and its downstream functional consequences.

A cohort study of 51 patients with established CTEPH¹¹ 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 artifacts.

Another single centre prospective cohort study using DE-CTPA¹² 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 V/Q (the presence of at least once segmental perfusion defect). This study compared planar V/Q 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 artifact. 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 V/Q 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 V/Q (which was used as the reference standard technique in all of the studies) and also demonstrates imaging artifacts 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.

Table 6. Key evidence – initial testing for CTEPH in patients with PH.

Reference	N	Population (% CTEPH)	Reference Standard	Imaging Modality (sensitivity)	Imaging Modality (sensitivity)	Comments
Tunariu et al. 2007 ⁵	227	Mixed PH (34% CTEPH)	Conventional digital subtraction angiography(DSA)	Planar V/Q (97.4%)	4–8 detector CTPA(51%)	
Soler et al. 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 reference standard
Nakazawa et al. 2011 ¹¹	51	CTEPH, treatment not specified (100%)	SPECT V/Q	SPECT V/Q (100%)	DE-CTPA (96%)	8.3 % of dual energy computed tomography (DECT) images couldn't be assessed due to artefact
He et al. 2012 ⁶	114	Mixed PH (45% CTEPH)	Conventional DSA	Planar V/Q (100%)	16-64 detector CTPA(92%)	Both low probability and normal V/Q scans were considered negative
Soler et al. 2012 ¹⁰	9	CTEPH undergoing PEA (100%)	Disease extent including surgical specimen	SPECT V/Q (62%)	4-64 detector CTPA (47.8%)	Same comment as reference #9
Rajaram et al. 2013 ¹⁴	132	PH referred to expert CTEPH centre (59% CTEPH)	Multidisciplinary meeting incl. CTPA, MRI and V/Q	Q (96%)	MRI (97%)	
Dournes et al. 2014 ¹²	40	Mixed PH and chronic thromboembolic disease (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 et al. 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 et al. 2017 ¹⁵	74	Mixed PH and CTED (49% CTEPH)	Multidisciplinary meeting incl. CTPA, MRI and V/Q	SPECT V/Q (97%)	MRI (100%)	One CTEPH patient not identified by SPECT V/Q had “mild inoperable CTEPH” on CTPA and MRI

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; PH, pulmonary hypertension; V/Q, ventilation/perfusion; SPECT V/Q, single photon emission computed tomography ventilation/perfusion; CTPA, computed tomography pulmonary angiogram; DE-CTPA, dual energy computed tomography pulmonary angiogram; DSA, digital subtraction angiography; MRI, magnetic resonance imaging; DECT, Dual energy computed tomography; PAH, pulmonary arterial hypertension; CTED, chronic thromboembolic disease.

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 magnetic resonance (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 MRI¹⁵ enrolled 74 patients undergoing evaluation for CTEPH. Within this cohort, 36 patients were diagnosed with CTEPH, 10 patients with CTED (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 a 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 that 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, is currently limited in most centres worldwide. Lung perfusion MRI has complex image acquisition and post processing needs, which require appropriate expertise.

Other imaging technologies

While Electrocardiogram (ECG)-gated multidetector CT,^{16,17} cone beam CT angiography¹⁷ and 320 detector CTPA¹⁸ have been used in the assessment of CTEPH, these particular studies have focused on establishing the diagnosis and assessing the anatomical extent/location of thromboembolic material (reviewed in PICO 3) rather than as initial testing for CTEPH in populations of patients referred with PH.

Expert panel synthesis of evidence-base and clinical judgement of risk versus benefit

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 initial testing 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 recognized 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 assessment of the possibility of CTEPH in patients with PH. It was the panel's consensus that most patients with PH would be willing to undergo testing with V/Q lung scanning, particularly if this led to a more accurate diagnostic approach with fewer missed cases of CTEPH.

Good practice points

1. In patients with PH who are not anticoagulated, consider testing for acute PE 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. Lack of institution or delayed initiation of anticoagulation might have severe consequences for patients with occult PE.
2. Assessment of the possibility of CTEPH should be the default recommendation in patients found to have PH (following the European Society of Cardiology/European Respiratory Society 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, right atrial (RA) area >18 cm² etc.).^{21,22}
3. The panel recognized that in some selected patients with PH, assessment 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 assessment can be deferred with initial treatment focused on the left heart disease. However, patients with persistent "unexplained" PH following treatment of left heart disease should be considered for subsequent testing 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 assessment can be deferred. However, patients with PH "unexplained" by the existing lung disease should be considered for subsequent testing for the possibility of coexisting CTEPH.

4. A diagnosis of PAH cannot be confirmed until testing has been completed to rule out CTEPH.
5. Patients diagnosed with PAH or CTEPH should be referred to an expert PH centre (Canadian local pulmonary hypertension expert centres listed on www.pha-canada.ca/PHcentres).

Discussions/areas for future research

The panel identified the need for future RCTs of CTEPH assessment in patients with PH. Future trial designs need to consider the varying incidence of CTEPH in different populations of patients²³ 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. For example, future research to define the prevalence of CTEPH in populations of patients followed in emphysema or left heart failure clinics would be of particular relevance to the clinicians working in these areas. Further study is required to fully define the test characteristics of V/Q when used to rule out CTEPH in the setting of an abnormal chest X-ray. Future research 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 study²⁴ has demonstrated the utility of an algorithm starting with a structured symptom questionnaire and followed by diagnostic imaging. The panel suggests ongoing research into multimodality screening algorithms for CTEPH.

Further study is required to assess the outcomes when clinicians use testing algorithms and/or clinical probability scores to assess for 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 V/Q lung scans (especially in the case of SPECT V/Q) remains uncertain. Future studies are needed in order to define significance of low probability V/Q abnormalities, particularly as it relates to their negative predictive value for a diagnosis of CTEPH.

Future studies using newer generations of CT scanners may help further define the role of CTPA in initial testing for CTEPH.

References

1. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation* 2011;124(18):1973–1981.
2. Xi Q, Zhao Z, Liu Z, et al. The lowest VE/VCO₂ ratio best identifies chronic thromboembolic pulmonary hypertension. *Thromb Res.* 2014;134(6):1208–1213.
3. Scheidl SJ, Englisch C, Kovacs G, et al. Diagnosis of CTEPH versus IPAH using capillary to end-tidal carbon dioxide gradients. *Eur Respir J.* 2012;39(1):119–124.
4. Mehta S, Helmersen D, Provencher S, et al. Diagnostic evaluation and management of chronic thromboembolic pulmonary hypertension: a clinical practice guideline. *Can Respir J.* 2010;17(6):301–334.
5. Tunariu N, Gibbs SJ, Win Z, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *J Nucl Med.* 2007;48(5):680–684.
6. He J, Fang W, Lv B, et al. Diagnosis of chronic thromboembolic pulmonary hypertension: comparison of ventilation/perfusion scanning and multidetector compute tomography pulmonary angiography with pulmonary angiography. *Nucl Med Commun.* 2012;33(5):459–463.
7. Reinartz P, Wildberger JE, Schaefer W, et al. Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT. *J Nucl Med.* 2004;45(9):1501–1508.
8. Kan Y, Yuan L, Meeks JK, et al. The accuracy of V/Q SPECT in the diagnosis of pulmonary embolism: a meta-analysis. *Acta Radiol.* 2015;56(5):565–572.
9. Soler X, Hoh CK, Test VJ, et al. Single photon emission computed tomography in chronic thromboembolic pulmonary hypertension. *Respirology* 2011;16(1):131–137.
10. Soler X, Kerr KM, Marsh JJ, et al. Pilot study comparing SPECT perfusion scintigraphy with CT pulmonary angiography in chronic thromboembolic pulmonary hypertension. *Respirology* 2012;17(1):180–184.
11. Nakazawa T, Watanabe Y, Hori Y, et al. Lung perfused blood volume images with dual-energy computed tomography for chronic thromboembolic pulmonary hypertension: correlation to scintigraphy with single-photon emission computed tomography. *J Comput Assist Tomogr.* 2011;35(5):590–595.
12. Dournes G, Verdier D, Montaudon M, et al. Dual-energy CT perfusion and angiography in chronic thromboembolic pulmonary hypertension: diagnostic accuracy and concordance with radionuclide scintigraphy. *Eur Radiol.* 2014;24(1):42–51.
13. Giordano J, Khung S, Duhamel A, et al. Lung perfusion characteristics in pulmonary arterial hypertension (PAH) and peripheral forms of chronic thromboembolic pulmonary hypertension (pCTEPH): Dual-energy CT experience in 31 patients. *Eur Radiol.* 2017;27(4):1631–1639.
14. Rajaram S, Swift AJ, Telfer A, et al. 3D contrast-enhanced lung perfusion MRI is an effective screening tool for chronic thromboembolic pulmonary hypertension: results from the ASPIRE Registry. *Thorax* 2013;68(7):677–678.
15. Johns CS, Swift AJ, Rajaram S, et al. Lung perfusion: MRI vs. SPECT for screening in suspected chronic thromboembolic pulmonary hypertension. *J Magn Reson Imaging.* 2017;46(6):1693–1697.
16. Ley S, Ley-Zaporozhan J, Pitton MB, et al. Diagnostic performance of state-of-the-art imaging techniques for morphological assessment of vascular abnormalities in patients with chronic thromboembolic pulmonary hypertension (CTEPH). *Eur Radiol.* 2012;22(3):607–616.
17. Ogo T, Fukuda T, Tsuji A, et al. Efficacy and safety of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension guided by cone-beam computed tomography and electrocardiogram-gated area detector computed tomography. *Eur J Radiol.* 2017;89:270–276.
18. Sugiura T, Tanabe N, Matsuura Y, et al. Role of 320-slice CT imaging in the diagnostic workup of patients with chronic thromboembolic pulmonary hypertension. *CHEST* 2013;143(4):1070–1077.
19. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 1997;350(9094):1795–1798.
20. Klok FA, Mos ICM, Nijkeuter M, et al. Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. *Arch Intern Med.* 2008;168(19):2131–2136.

21. Donahoe L, Vanderlaan R, Thenganatt J, et al. Symptoms are more useful than echocardiography in patient selection for pulmonary endarterectomy. *Ann Thorac Surg*. 2017;104(4):1179–1185.
22. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2015;46(4):903–975.
23. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J*. 2017;49(2):1601792.
24. Coquoz N, Weilenmann D, Stolz D, et al. Multicentre observational screening survey for the detection of CTEPH following pulmonary embolism. *Eur Respir J* 2018;51(4):1702505.

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

Confirmation of a diagnosis of CTEPH requires establishment 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 PEA or BPA.

Several pulmonary angiographic modalities exist. Traditionally, conventional, invasive 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 centre specific experience in order to obtain the most accurate results.

CTPA can also be used for imaging of the pulmonary arterial tree. 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 centres have used 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.

Findings of chronic thromboembolism on CTPA include intraluminal fibrous bands or webs, stenoses, partial occlusions, total occlusions (pouch defects), and eccentric organized thrombi that form an obtuse angle with the vessel wall.

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 for confirmation of 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 and 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 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 pulmonary arterial disease of 97% and 97% and for segmental disease 86% and 95%. Subsegmental disease was not assessed.

Another 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). Sensitivity and specificity of CTPA for main/lobar disease was 98% and 95% and for segmental disease 94% and 93%.

A 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 analysis 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 V/Q (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 V/Q examination. CTPA and SPECT V/Q were therefore thought to provide complementary information in assessment of operability for PEA.

Three retrospective cohort studies published by the group in Hannover, Germany^{9–11} have evaluated a novel form of invasive pulmonary angiography utilizing cone beam CT images instead of DSA. 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 CTPA¹⁰ or DSA.⁹

Expert panel synthesis of evidence-base and clinical judgment of risk versus benefit

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/subsegmental 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 for confirmation of 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 cohort¹² 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 letter¹³ 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. For the diagnosis of main/lobar pulmonary arterial disease sensitivity and specificity were highest with CTPA (100% and 100%, respectively), followed by MRPA (83%, 99%) and DSA (66%, 100%). For the detection of segmental pulmonary arterial disease, the sensitivities and specificities were: CTPA (100% and 99%), MRPA (88%, 98%) and DSA (75%, 100%).

Expert panel synthesis of evidence-base and clinical judgment of risk versus benefit

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 if required subsequently to a PEA/BPA centre, for additional investigations and treatments.

Good practice points (3a and 3b)

1. 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 cutoff.¹⁵ Maximum intensity projections and oblique reconstructions along the long axis of the left and right pulmonary arteries may also be helpful.
2. 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.
3. Misinterpretation of CTPA images can lead to a missed or delayed diagnosis of CTEPH and/or the use of inappropriate therapies.¹⁶ Referring centres should work with PH expert centres at (or prior to) the stage of CTPA image interpretation, when assessing patients with suspected CTEPH (see diagnostic algorithm, [Figure 2](#)).
4. Pulmonary angiographic and V/Q imaging data may be complementary when used for the planning of CTEPH treatments.
5. Most types of pulmonary vascular imaging can underestimate the true anatomic extent of CTEPH, when compared to intraoperative evaluation at the time of PEA.
6. 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 centres, 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 in confirming a diagnosis of 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, for example a DSA performed in an experienced and high-volume CTEPH expert centre.

There remains only a small body of evidence to support CTPA or other noninvasive 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 clinically 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 quality control practices.

References

1. Auger WR, Kerr KM, Kim NH, et al. Evaluation of patients with chronic thromboembolic pulmonary hypertension for pulmonary endarterectomy. *Pulm Circ.* 2012;2(2):155–162.
2. Castañer E, Gallardo X, Ballesteros E, et al. CT diagnosis of chronic pulmonary thromboembolism. *Radiographics* 2009;29(1):31–50.
3. Kreitner KF, Kunz RP, Ley S, et al. Chronic thromboembolic pulmonary hypertension - assessment by magnetic resonance imaging. *Eur Radiol.* 2007;17(1):11–21.
4. Dong C, Zhou M, Liu D, et al. Diagnostic accuracy of computed tomography for chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis. *PLoS One.* 2015;10(4):e0126985.
5. Sugiura T, Tanabe N, Matsuura Y, et al. Role of 320-slice CT imaging in the diagnostic workup of patients with chronic thromboembolic pulmonary hypertension. *CHEST* 2013;143(4):1070–1077.
6. Reichelt A, Hoepfer MM, Galanski M, et al. Chronic thromboembolic pulmonary hypertension: evaluation with 64-detector row CT versus digital subtraction angiography. *Eur J Radiol.* 2009;71(1):49–54.
7. He J, Fang W, Lv B, et al. Diagnosis of chronic thromboembolic pulmonary hypertension: comparison of ventilation/perfusion scanning and multidetector compute tomography pulmonary angiography with pulmonary angiography. *Nucl Med Commun.* 2012;33(5):459–463.
8. Grgic A, Miodek F, Schafers HJ, et al. Assessment of operability by means of CTPA and perfusion SPECT in patients with chronic thromboembolic pulmonary hypertension. *Acta Radiol.* 2016;57(1):33–40.
9. Hinrichs JB, Marquardt S, von Falck C, et al. Comparison of C-arm computed tomography and digital subtraction angiography in patients with chronic thromboembolic pulmonary hypertension. *Cardiovasc Intervent Radiol.* 2016;39(1):53–63.
10. Hinrichs JB, von Falck C, Hoepfer MM, et al. Pulmonary artery imaging in patients with chronic thromboembolic pulmonary hypertension: comparison of cone-beam CT and 64-row multidetector CT. *J Vasc Interv Radiol.* 2016;27(3):361–368.
11. Hinrichs JB, Werncke T, Kaireit T, et al. C-Arm computed tomography adds diagnostic information in patients with chronic thromboembolic pulmonary hypertension and a positive V/Q SPECT. *Fortschr Röntgenstr.* 2017;189:49–56.
12. Rajaram S, Swift AJ, Capener D, et al. Diagnostic accuracy of contrast-enhanced MR angiography and unenhanced proton MR imaging compared with CT pulmonary angiography in chronic thromboembolic pulmonary hypertension. *Eur Radiol.* 2012;22(2):310–317.
13. Rajaram S, Swift AJ, Telfer A, et al. 3D contrast-enhanced lung perfusion MRI is an effective screening tool for chronic thromboembolic pulmonary hypertension: results from the ASPIRE Registry. *Thorax* 2013;68(7):677–678.
14. Ley S, Ley-Zaporozhan J, Pitton MB, et al. Diagnostic performance of state-of-the-art imaging techniques for morphological assessment of vascular abnormalities in patients with chronic thromboembolic pulmonary hypertension (CTEPH). *Eur Radiol.* 2012;22(3):607–616.
15. Gopalan D, Delcroix M, Held M. Diagnosis of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev* 2017;26(143):160108.
16. Fernandez T, Pretorius V, Kim N, et al. Caution regarding catheter-directed thrombolysis: chronic thromboembolic pulmonary hypertension mistaken for acute submassive pulmonary embolism. *Am J Respir Crit Care Med.* 2017;8:1066–1067.

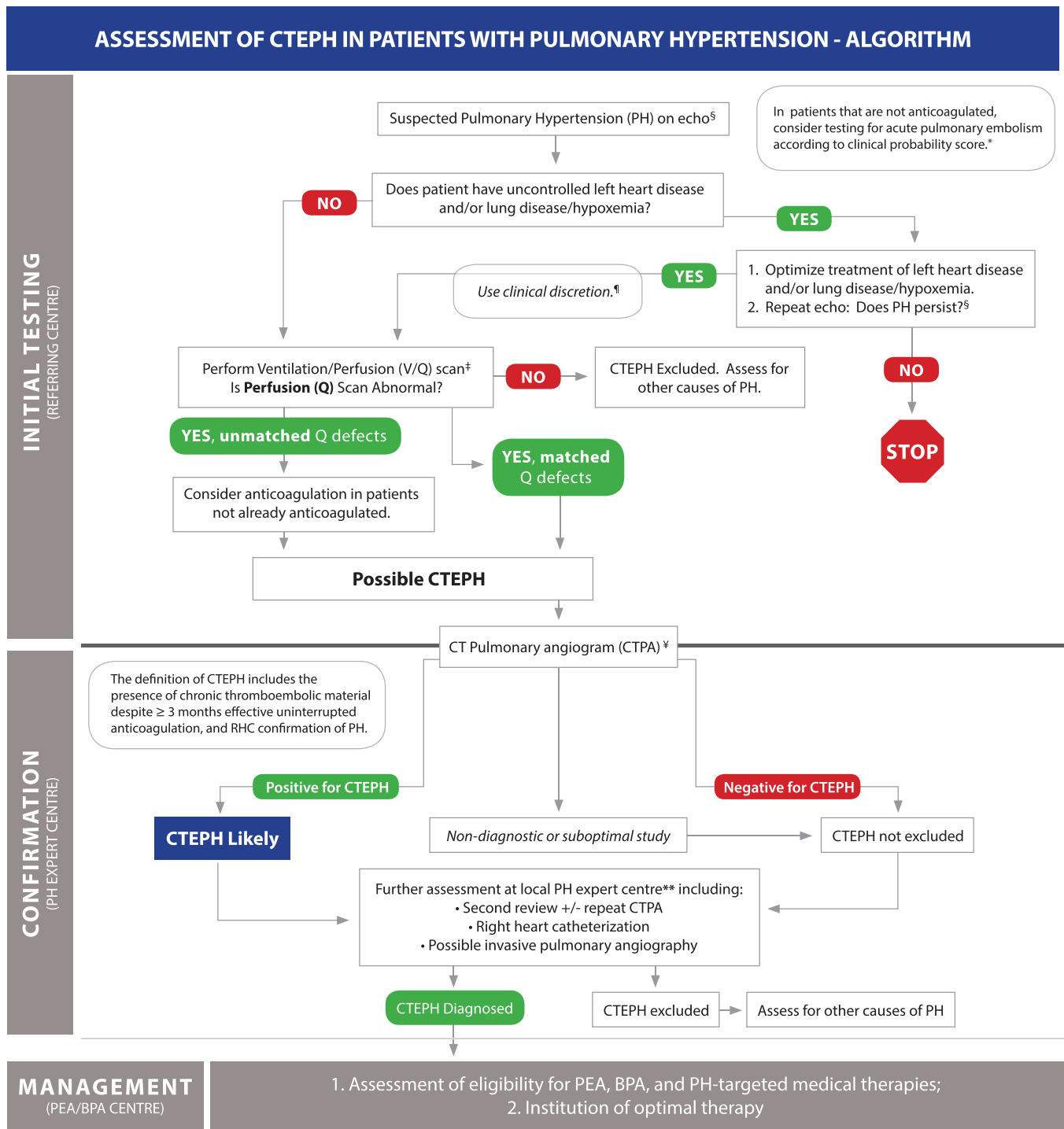


Figure 2. Assessment of chronic thromboembolic pulmonary hypertension (CTEPH) in patients with pulmonary hypertension – algorithm.

[§] Following the ESC/ERS guidelines: we define suspected pulmonary hypertension as tricuspid regurgitant velocity >2.8 m/s or the presence of other secondary echo signs of PH (RV enlargement, flattening of interventricular septum, RA area >18 cm², etc.) (Galie et al., *Eur Respir J.* 2015;46(4):903–975; Donahoe et al., *Ann Thorac Surg.* 2017;104(4):1179–1185).

* Several clinical probability scoring systems for acute pulmonary embolism exist (Wells et al., *Lancet.* 1997 Dec 20–27;350(9094):1795–1798; Klok et al., *Arch Intern Med.* 2008;168(19):2131–2136).

[¶] There is minimal evidence to guide clinicians in selecting patients with left heart disease/lung disease to test for co-existing CTEPH.

Not all patients require testing (refer to PICO 2, Good Practice Point #3 in guideline). In patients with a trajectory of worsening PH 'out of proportion' to the treated left heart/lung disease, the default should be to test for CTEPH.

[‡] Single-photon emission computed tomography (SPECT) or planar ventilation/perfusion (V/Q) acceptable.

[¥] Computed tomographic pulmonary angiography (CTPA) may be done in referring centre but only if utilizing acceptable technique, i.e. short breath hold acquisition (3–5 sec) as well as thin collimation and thin-slice reconstruction (≤ 1 mm) in axial, coronal and sagittal planes. Cases with contrast allergy, renal dysfunction or other barriers to CTPA should be discussed with PH expert centre.

**Canadian local pulmonary hypertension expert centres listed on www.phacanada.ca/PHcentres.

Abbreviations: PEA, pulmonary endarterectomy; BPA, balloon pulmonary angioplasty; RHC, right heart catheterization.

Dissemination and implementation

Our guideline will be disseminated through traditional channels including this publication, through the CTS website and social media channels, and through an accompanying slide deck which will be used to present this content to various groups across the country. Furthermore, an abridged online and electronic “quick reference” guide, including the algorithm addressing assessment of CTEPH in patients with PH (Figure 2), with a reference link to the full document will be produced. These materials will be circulated to all 15 expert adult PH centres in Canada and will be used in educational interventions with non-PH experts.

Our group has also considered the anticipated barriers/enablers to implementation of our recommendations, which types of initiatives might be considered for implementation of recommendations, which metrics should be measured as indices of success, and how these might be measured.

The first recommendation (PICO 1) 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 implemented successfully. Strategies for (de-)implementation of unnecessary testing could include educational and practice improvement programs targeting those users that routinely evaluate patients following acute PE (e.g., thrombosis clinics), and/or those who routinely provide the tests (cardiologists, radiologists). Other behavior change strategies could include audit and feedback, iterative physician learning and practice improvement cycles. Such efforts might be successful in partnership with the Choosing Wisely Canada initiative and Canadian university departments of continuing medical education (CME). Metrics of successful (de)implementation could include a reduction in the proportion of patients at low risk for CTEPH post-acute PE who undergo routine screening echo, V/Q, and/or CTPA scans. Although administrative databases could be used to assess trends in the frequency of these tests among patients with PE, a rigorous measure of successful de-implementation would not be possible through administrative databases, since the indication for each test would need to be considered. Such an analysis would require individual centre and/or individual physician practice audits.

The second recommendation (PICO 2) is a positive recommendation designed to increase the rate of CTEPH diagnosis by placing the most sensitive test (V/Q) as the initial test within the recommended diagnostic algorithm. This recommendation is expected to improve patient outcomes through an earlier diagnosis of CTEPH and through a reduction in the number of misclassified or missed cases of CTEPH. Implementation of this recommendation will similarly require target audience education, and will also require practice improvement programs, in this instance, for users that evaluate patients with PH (ie. respirologists, cardiologists). One barrier to implementation might be the existence of previously established protocols and practice patterns.

Another barrier may be the lack of access to V/Q and/or radiologist expertise in V/Q interpretation in some centres. Metrics of successful implementation would include increased use of V/Q scanning in appropriate patients, increased rates of CTEPH diagnosis and possibly a shortened time from symptom onset to diagnosis, and/or reduced severity of disease at the time of diagnosis as measured by WHO class and right-sided hemodynamics.

The third recommendation (PICO 3) is aimed at helping clinicians to establish an accurate diagnosis of CTEPH and to direct patients to a PH expert centre at the most appropriate stage of the diagnostic evaluation. This is accompanied by the parallel goal to establish the best modality to assess the anatomic extent and location of disease. This recommendation is expected to improve patient outcomes through an increased rate of CTEPH diagnosis, through earlier diagnosis of CTEPH, and by a reduction in the number of misclassified or missed cases of CTEPH. CTEPH can be missed at this stage in the diagnostic process as a result of a false negative CTPA (due to technical inadequacy of the test, inadequate expertise of the interpreting radiologist, or due to distal CTEPH) leading to the patient not being referred to an expert PH centre. This represents a diagnostic care gap which we feel this recommendation will help to address. A key metric of success would be an increased number of appropriate CTEPH referrals to the PH centres.

Considering the various possible targets of our dissemination and implementation strategy, for messages targeting expert centres, it may be of benefit to define (and audit practices of) PH centres of excellence. Audits could include peer assessments of the technical adequacy and performance of readers for key imaging technologies pertinent to CTEPH including V/Q, CTPA and conventional pulmonary angiography. Such initiatives might be possible in collaboration with PHA Canada, similar to a PH centre accreditation process instituted by PHA in the United States.

For messages targeting non-experts, there is currently significant uncertainty surrounding the types and magnitude of existing knowledge gaps. In order to tailor educational material, some of these knowledge gaps are currently being assessed. Specifically, a pre and post guidelines survey is underway to assess knowledge gaps in urban and rural respirologists as well as urban internists and hematologists. Further research to assess knowledge gaps specifically affecting clinicians in rural and remote settings would be of benefit. An anticipated barrier to implementation of the CPG recommendations in these contexts is the possible lack of access to key diagnostic technologies (i.e., echocardiography and/or V/Q scan) and/or expert interpretation of these tests. Clinicians working in rural or remote areas are therefore likely to have unique implementation needs. Interventions targeting non-experts might also include CTEPH training modules and local quality improvement programs for clinicians, radiologists and health system managers.

Summary

Table 7. Diagnosis of CTEPH: Summary of recommendations.

Clinical (PICO) Questions	Recommendations	GRADE
Screening for CTEPH		
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
Initial testing for CTEPH		
How should patients with PH be tested for CTEPH?	2. In patients with PH, we recommend that clinicians perform nuclear V/Q lung scanning as initial testing to rule out CTEPH. Clinical remarks: <i>Either Planar or SPECT nuclear V/Q are acceptable modalities for initial testing to rule out CTEPH.</i> <i>A normal perfusion (Q) scan effectively rules out the possibility of CTEPH.</i> <i>A negative CTPA does NOT effectively rule out CTEPH.</i>	1C
Diagnosis of CTEPH		
In patients with suspected CTEPH: a) Should CTPA be used to establish the diagnosis and assess anatomic extent and location of chronic thromboembolic material?	3a) 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: <i>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.</i> <i>Findings of chronic thromboembolism on CTPA include intraluminal fibrous bands or webs, stenoses, partial occlusions, total occlusions (pouch defects), and eccentric organized thrombi that form an obtuse angle with the vessel wall.</i> <i>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.</i>	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?	3b) 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: <i>There are few centres with MRPA experience in CTEPH.</i> <i>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.</i>	1C

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; V/Q, ventilation/perfusion; CTPA, computed tomography pulmonary angiogram.

Acknowledgments

The authors would like to thank Samir Gupta and Christopher Licskai from the CTS Canadian Respiratory Guideline Executive Committee for their input and guidance throughout the process. We would like to acknowledge the Canadian Society of Thoracic Radiology Executive Committee members for their input and endorsement of the manuscript. We would also like to acknowledge with deep appreciation our Expert Peer Reviewers who made valuable contributions to the manuscript: Fraser Rubens, Centre for the Advancement of Patient Care in Cardiac Surgery, University of Ottawa Heart Institute, Ottawa, Canada; Olaf Mercier, Department of Thoracic and Vascular Surgery and Heart–Lung Transplantation, Hôpital Marie-Lannelongue, Le Plessis-Robinson, France; David Jenkins, Cardiothoracic Surgery, Royal Papworth Hospital, Cambridge, United Kingdom; and John Granton, Division of Respiriology and Pulmonary Hypertension Program, Toronto, Canada. We would like to thank Ms. Jamie Myrah, Executive Director of the Pulmonary Hypertension Association of Canada (PHA Canada) and Nicole Dempsey, patient and PHA Canada Board member for their time and input.

Editorial independence

The CTS Pulmonary Vascular Disease (PVD) Assembly is accountable to the CTS CRGC and the CTS Board of Directors. The CTS PVD 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/>.

Abbreviations

BMI	Body mass index
BPA	Balloon pulmonary angioplasty
CPG	Clinical practice guideline
CRGC	Canadian Respiratory Guidelines Committee
CT	Computed tomography
CTED	Chronic thromboembolic disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomography pulmonary angiogram
CTPER	Computed tomography pulmonary embolism residua
CTS	Canadian Thoracic Society
DCE	Dynamic contrast enhanced
DECT	Dual energy computed tomography
DE-CTPA	Dual energy computed tomography pulmonary angiogram
DSA	Digital subtraction angiography
DVT	Deep vein thrombosis
ECG	Echocardiogram
ERS	European Respiratory Society
ESC	European Society of Cardiology
HRQoL	Health-related quality of life
LVEF	Left ventricular ejection fraction
mPAP	mean Pulmonary Arterial Pressure
MRI	Magnetic Resonance Imaging
NT-proBNP	N-terminal-pro hormone b-type natriuretic peptide
NYHA	New York Heart Association
OR	Odds Ratio
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PAWP	Pulmonary artery wedge pressure
PCH	Pulmonary capillary haemangiomatosis
PE	Pulmonary embolism or emboli
PEA	Pulmonary endarterectomy
PH	Pulmonary hypertension
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
RA	Right atrial
RCTs	Randomized controlled trials
RDW	Red blood cell distribution width
RHC	Right heart catheterization
RV	Right ventricular
RVSP	Right ventricular systolic pressure
SPECT	Single photon emission computed tomography
V/Q	Ventilation/perfusion
WHO	World Health Organization

Appendix 1. Summary of Patient/problem, Intervention, Comparison, Outcome (PICO) questions and search strategy.

Study design	Any. To be as inclusive as possible, priority was given to RCTs if enough RCTs were 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 gray 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 were cross-checked with our citation database and any that were new were 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 were 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 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 were reviewed and considered for inclusion.
General/main terminology or key words	<ol style="list-style-type: none"> 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 (V/Q 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, V/Q lung scan, CT Pulmonary angiography, CTPA, Echocardiogram, Transthoracic echo, Diagnosis
Q2: How should patients with PH be tested for CTEPH?	P: All patients with PH I: Specific assessment for CTEPH: Clinical, imaging (V/Q 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

Abbreviations: RCT, randomized controlled trials; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PH, pulmonary hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; PE, pulmonary embolism; CPG, clinical practice guideline; PEA, pulmonary endarterectomy; CTPH, chronic thrombotic pulmonary hypertension; VTE, venous thromboembolism; RV, right ventricular; WHO, World Health Organisation; NYHA, New York Health Association; V/Q, ventilation/perfusion; CTPA, computed tomographic pulmonary angiography; MRA, magnetic resonance angiogram; BPA, balloon pulmonary angioplasty; MRPA, magnetic resonance pulmonary angiography.