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Pulmonary Thromboembolic Disease. Clinical Management of Acute and Chronic Disease

Adam Torbicki

National Institute for Tuberculosis and Lung Diseases, Warsaw, Poland

Pulmonary thromboembolism falls between the areas of pulmonology and cardiology, internal medicine and intensive care, radiology and nuclear medicine, and hematology and cardiothoracic surgery. Depending on their clinical background, physicians faced with a patient with a pulmonary thromboembolism may speak different languages and adopt different treatment approaches. Now, however, there is an opportunity to end the Tower of Babel surrounding pulmonary thromboembolism. There is a growing acknowledgement that the key clinical problems in both acute pulmonary embolism and chronic thromboembolic pulmonary hypertension are linked to right ventricular pressure overload and right ventricular failure. As a result, cardiologists and cardiac intensive care specialists are taking an increasing interest in understanding and combating these conditions. The European Society of Cardiology was the first to elaborate comprehensive clinical practice guidelines for pulmonary thromboembolism and chronic thromboembolic pulmonary hypertension. The task forces involved in producing these guidelines included radiologists, pulmonologists, hematologists, intensive care physicians and surgeons, which ensured that the final document was universally acceptable. The aim of this article was to provide an overview of the epidemiology, risk factors, diagnosis, treatment, prognosis and prevention of acute pulmonary thromboembolism and chronic thromboembolic pulmonary hypertension, while taking into account European Society of Cardiology guidelines and incorporating new evidence where necessary.

Key words: *Pulmonary thromboembolism. Pulmonary hypertension. Right ventricle. Venous thromboembolism.*

Enfermedad tromboembólica pulmonar. Manejo clínico de la enfermedad aguda y crónica

La tromboembolia pulmonar cae entre las especialidades de neumología y cardiología, entre la medicina interna y la de cuidados intensivos, entre la radiología y la medicina nuclear, entre la hematología y la cirugía cardiotorácica. Según su ámbito clínico de procedencia, los médicos que se enfrentan a un paciente con tromboembolia pulmonar pueden utilizar lenguajes diferentes y estrategias terapéuticas distintas. Sin embargo, hay posibilidad de acabar con esta torre de Babel que es la tromboembolia pulmonar. Existe una apreciación creciente de que los problemas clave tanto en la embolia pulmonar aguda como en la hipertensión pulmonar tromboembólica crónica están relacionados con la insuficiencia del ventrículo derecho y la sobrecarga de presión. Como resultado, los cardiólogos y los especialistas en cuidados intensivos cardiacos se interesan cada vez más en conocer y combatir esta enfermedad. La Sociedad Europea de Cardiología fue la primera en elaborar una guía de práctica clínica detallada sobre la tromboembolia pulmonar y la hipertensión pulmonar tromboembólica crónica. Los grupos de trabajo que participaron en la elaboración de estas guías incluían a radiólogos, neumólogos, hematólogos, intensivistas y cirujanos, lo que aseguró que el documento fuera universalmente aceptable. El objetivo de este artículo es proporcionar una visión general de la epidemiología, los factores de riesgo, el diagnóstico, el tratamiento, el pronóstico y la prevención de la tromboembolia pulmonar aguda y la hipertensión pulmonar tromboembólica crónica, al tiempo que toma en consideración la guía de la Sociedad Europea de Cardiología e incorpora nueva evidencia cuando es necesario.

Palabras clave: *Tromboembolia pulmonar. Hipertensión pulmonar. Ventrículo derecho. Tromboembolia venosa.*

INTRODUCTION

Pulmonary thromboembolism (PE) has remained a "no-man's-land" for decades. It was positioned somewhere between pulmonology and cardiology, internal medicine and intensive care, radiology and nuclear medicine, hematology and cardio-thoracic surgery. Moreover, the strongest risk factors for PE cluster in patients followed in orthopedic, neurological, oncological, and obstetric departments. Physicians faced with PE are speaking different languages and using different

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Correspondence: Prof. A. Torbicki.
Department of Chest Medicine. Institute of Tuberculosis and Lung Diseases.
ul Płocka 26, 01-138 Warsaw. Poland.
E-mail: a.torbicki@igichp.edu.pl

ABBREVIATIONS

CTEPH: chronic thromboembolic pulmonary hypertension
DVT: deep vein thrombosis
LMWH: low-molecular-weight heparin
MDCT: multidetector computed tomography
PE: pulmonary thromboembolism
RV: right ventricle
UFH: unfractionated heparin

management strategies depending on their clinical background. There seems to be a chance to put an end to PE Babel Tower. This is due to the growing understanding that the key clinical problems—both in acute PE and chronic thromboembolic pulmonary hypertension (CTEPH)—are related to right ventricular (RV) pressure overload and failure. Cardiologists, including intensive cardiac care specialists, are therefore becoming more interested in understanding and combating the disease. European Society of Cardiology was the first to elaborate comprehensive clinical practice guidelines in PE and CTEPH.[1,2] Importantly, Task Forces preparing and updating the documents included radiologists, pulmonologists, hematologists, intensivists and surgeons, offering a universally acceptable common platform for communication. The current text will respect the recent European Society of Cardiology guidelines, adding new evidence wherever necessary.

ACUTE THROMBOEMBOLIC DISEASE

Epidemiology and Predisposing Factors

The epidemiology of PE is difficult to estimate because of non-specific presentation and common errors in diagnosis. The annual incidence rate of venous thromboembolism (VTE) is probably between 20 and 70 cases per 100 000 population.[3,4] Approximately one third of those patients will have acute PE while the remaining will have isolated deep vein thrombosis (DVT).[5] Clinical and post-mortem data collected in Malmo area in Sweden, where most deaths were followed by autopsy, suggested the incidence of PE of approximately 20/10 000 inhabitants/year.[6] Approximately 10% of all patients with acute PE die during the first 1-3 months.[7,8] One of each 10 patients dying in the hospital will die because of PE and one out of each 100 patients admitted to the hospital will die because of it.[9-11]

Venous thromboembolism is a result of the interaction between patient-related and setting-related risk factors. Patient-related predisposing factors are usually permanent while setting-related predisposing factors are temporary[12] (Table 1). PE which occurs in the absence of any obvious setting related factor is often called "unprovoked."

Patient-related predisposing factors include age, history of previous VTE, active cancer, neurologic disease with extremity paresis, medical disorders causing prolonged bed rest, such as heart or respiratory failure, and congenital or acquired thrombophilia, hormone replacement therapy, oral contraceptive therapy.[12] The 2 last factors can be also considered as setting related, particularly, if an embolic episode occurs relatively early after the beginning of hormonal administration. Identification of the presence and estimation of relative significance of predisposing factors may be helpful both in assessment of clinical probability for diagnostic purposes as well as for decisions regarding primary prevention. Unfortunately, PE can occur in patients without any identifiable predisposing factors. The proportion of patients with idiopathic or unprovoked

TABLE 1. **Predisposing Factors for Venous Thromboembolic Disease**

Predisposing Factor	Patient-Related	Setting-Related
Strong predisposing factors		
Hip or leg fracture		X
Hip or knee replacement		X
Major general surgery		X
Major trauma		X
Spinal cord injury		X
Moderate predisposing factors		
Arthroscopic knee surgery		X
Central venous lines		X
Chemotherapy		X
Chronic heart or respiratory failure	X	
Hormone replacement therapy	X	X
Malignancy	X	
Oral contraceptive therapy	X	X
Paralytic stroke	X	
Pregnancy/postpartum		X
Previous venous thromboembolism	X	
Thrombophilia	X	
Weak predisposing factors		
Bed rest		X
Prolonged travel		X
Increasing age	X	
Laparoscopic surgery		X
Obesity	X	
Pregnancy/antepartum	X	
Varicose veins	X	

PE was about 20% in the International Cooperative Pulmonary Embolism Registry (ICOPER).[13]

In several areas of particular interest or controversy, new relevant evidence related to predisposing factors emerged recently:

– A meta-analysis of 14 studies assessed travel as a VTE predisposing factor. Based on 4055 documented VTE cases, its relative risk in travelers was increased by 2.8 (CI, 2.2-3.7). Risk increased by 18% and 26% for each 2-hour increase in duration of travel by any mode and by airplane, respectively.[14]

– In a Danish national cohort study with 10.4 million woman years recorded, including 3.3 million woman years in receipt of oral contraceptives, 4,213 venous thrombotic events, including PE, were observed. The overall absolute risk of VTE per 10 000 woman years was 3.01 in non-users and 6.29 in current users of oral contraceptives. The risk decreased with duration of use and decreasing oestrogen dose. Oral contraceptives with desogestrel, gestodene, or drospirenone were associated with a 1.5 to 2.0 higher risk than with levonorgestrel. Progestogen only pills and hormone releasing intrauterine devices were not associatd with increased risk of venous thrombosis.[15]

– To clarify which obesity marker best describes increased VTE risk 27 178 men and 29 876 women 50 to 64 years of age were followed in prospective study for 10 years. Six hundred forty one VTE incidents were verified by review of medical records. Hip circumference was positively associated with VTE in women but not in men, whereas waist circumference was positively associated with VTE in men but not in women. Positive associations were found between VTE and body weight, body mass index and total body fat mass.[16]

The mystery of idiopathic PE remains unexplored. Recently, markers of inflammation, such as high sensitivity-C Reactive Protein (hs-CRP), fibrinogen, and factor VIII, were found to be increased in patients with idiopathic compared to "secondary" VTE,[17] supporting the hypothesis that the former may share some predisposing factors with arterial thromboembolism.[18]

The genetic background of VTE was highlited by a recent finding that thrombosis at a young age in patients was the strongest predictor of venous thromboembolism in relatives, (OR, 3.27; 95% CI, 1.68-6.38) for patients <45 years of age at the time of VTE compared with those >71 years of age. Interestingly, the presence of factor V Leiden or the G20210A thromboplastin gene was a weaker independent predictor of venous thromboembolism in relatives (adjusted OR, 1.48; 95% CI, 0.94-2.33).[19] Genetic contribution to the aetiology of venous thromboembolism has been recently assessed in more detail in a meta-analyses which included 126 525 cases and 184 068 controls derived from 173 case-control studies.[20] It looked at 21 genes and 28 polymorphisms. In Caucasian population Factor V G1691A and A4070G, prothrombin G20210A and G11991A, PAI-1 4G/5G, alpha-fibrinogen Thr312Ala were found to be significantly associated with VTE. Interestingly, Factor XIII Val34Leu and beta-fibrinogen 455 G/A both showed significantly protective effects.

While all these data improve our understanding of the VTE pathophysiology and particularly support the concept of an important genetic component in the aetiology of idiopathic VTE disease, they do not offer at present much help in everyday clinical management.

Diagnostic Management According to Initial Prognostic Staging

Current approach to a patient with suspected PE is based on initial prognostic stratification into patients at high (>15%) and non-high risk of early PE-related death.[1] This stratification is based entirely on clinical evaluation, namely a search for the presence of shock or systemic hypotension. Hypotension is defined as systolic blood pressure <90 or its fall by ≥40 mmHg compared to usual level for at least 15 min and without an apparent alternative cause.[21]

High-Risk Patients

Most of the diagnostic recommendations regarding patients in shock or hypotension do not have support in evidence from appropriately designed trails and are based on expert opinions.

In high-risk patients the priority is put on emergency confirmation or exclusion of hemodynamically significant pulmonary arterial thrombi, which are usually multiple, large and proximal. However, first line diagnostic test should also allow differential diagnosis with other immediately life threatening conditions. Acute coronary syndromes, aortic dissection with cardiac tamponade, acute left ventricular or valvular dysfunction but also tension pneumothorax or even major internal bleeding may all present with symptoms and signs to similar those occurring in acute PE, including acute dyspnea, chest pain, syncope, hemodynamic instability.

Computed tomography (CT) angiography is the recommended first-choice diagnostic test in high risk patients suspected of PE (Figure 1). However, bedside emergency echocardiography is an acceptable alternative in case clinical condition of

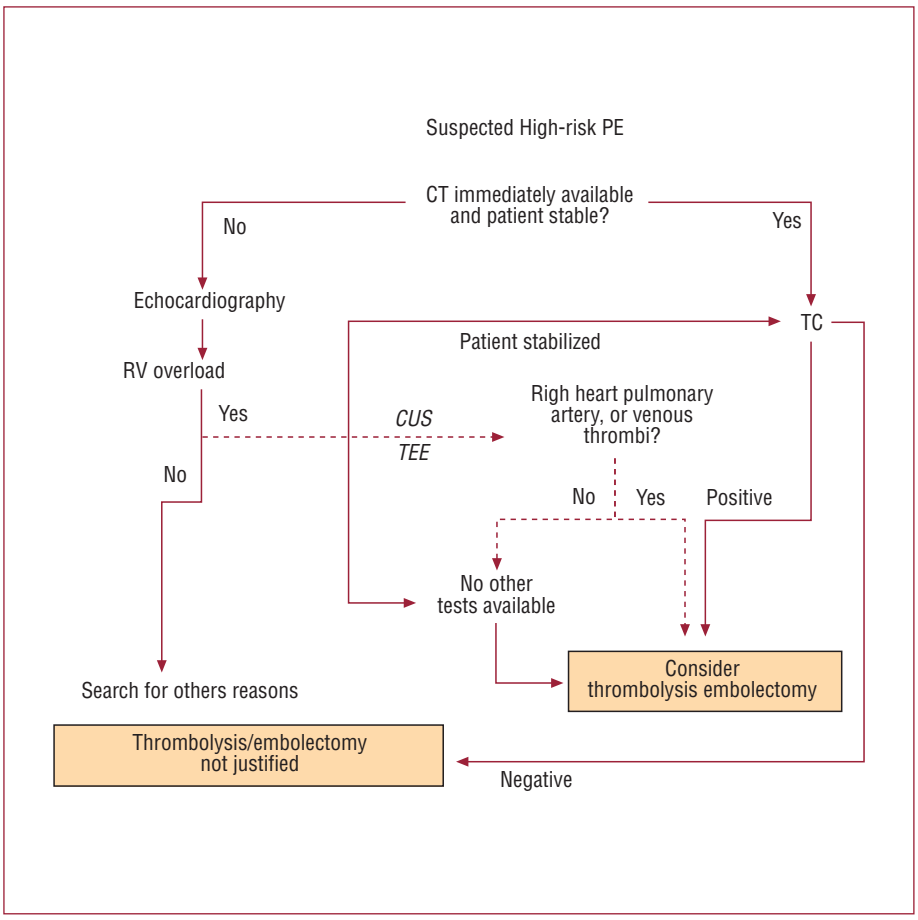

Figure 1. Suggested diagnostic algorithm in patients with suspected acute pulmonary thromboembolism presenting with shock or hypotension. CT indicates computed tomography angiography; CUS, venous compression ultrasound; TEE, transesophageal echocardiography; RV, right ventricle; PE, pulmonary thromboembolism. Italics and dotted lines represent additional suggestions, not included in the original European Society of Cardiology guidelines algorithm.

the patient is critical.[1] Normal RV echocardiogram excludes life-threatening PE. Unequivocal signs of acute RV pressure overload are highly suggestive (though not diagnostic) of PE in such clinical setting. Intravenous unfractionated heparin (UFH) should be started and thrombolytic therapy should be strongly considered.[1] Right heart thrombi found at echocardiography justify aggressive treatment including thrombolysis or embolectomy, without the need of further diagnostic evaluation.[22]

While preparing for thrombolytic therapy, confirmation with CT (in case the patient could be stabilized) or bedside venous compression ultrasound (CUS) or transesophageal echocardiography (TEE) should be considered.[23] Direct confirmation of thrombi is particularly important in patients with relative contraindications to thrombolysis. Non-invasive assessment is preferable, in view of lower rate of local bleeding complications.[24,25] However, classical angiography can also be useful, particularly in a patient referred to hemodynamic laboratory because of suspected acute coronary syndrome. If echocardiography reveals right, rather than left heart dysfunction, immediate pulmonary angiography may be more appropriate than transferring an unstable patient to CT laboratory.

Non-High Risk Patients

In non-high risk patients the diagnostic strategy is focused not only on confirmation of PE (or DVT as both conditions result in the same therapeutic decisions in hemodynamically stable patients). Even more importantly, diagnostic evaluation should identify patients who, despite clinical suspicion of PE can be left without anticoagulation with an acceptably low risk of suffering any VTE episode in the near future. This risk is defined in terms of the frequency of any clinically evident VTE episode in the subsequent 3 months, which should not exceed 1%-2% (with upper limit of 95% CI of 3%) i.e. the expected VTE rate after a negative pulmonary angiography.[26]

Such "probabilistic" approach is necessary to deal with large numbers of patients who present with dyspnea, chest pain and/or other non-specific symptoms and signs. Indeed only 25%-30% of such patients will have PE confirmed by complete

diagnostic evaluation. Therefore, the diagnostic evaluation should start with identification of patients with low to moderate pre-test clinical probability of PE according to Wells or Geneva prediction rules or according to subjective assessment.[27,28] Such patients may be released without anticoagulation based on negative plasma D-dimer result alone. Moderate sensitivity D-dimer tests are sufficient to make such a decision in patients with low clinical probability, while high sensitivity tests allow it also in patients with intermediate clinical probability.[29,30] Because D-dimer levels increase with age, co-morbidities or pregnancy,[30-33] the test is more useful for evaluation of previously healthy acutely ill patients of the emergency department.[31,33-35] Patients with elevated D-dimer as well as those with high clinical probability require imaging tests, preferably multidetector CT angiography.[36] Two landmark accuracy trails assessed diagnostic value of key non-invasive imaging methods in the context of clinical probability of acute PE. PIOPED focused on lung scintigraphy[37] and PIOPED II on multidetector CT (MDCT).[38] Both trials revealed important influence of the pre-test probability on the diagnostic performance of an individual test. Therefore, discrepancies between clinical and laboratory assessment needs further diagnostic considerations. A negative MDCT result in a patient with high clinical probability of PE, as well as a positive MDCT (limited to subsegmental arteries) in a patient with low pre-test probability should be verified by additional tests.[39] Further increasing the number of CT detectors may result in excessive reporting of distal, subsegmental pulmonary emboli, with unclear clinical significance.[40]

A concise list of diagnostic tests, and their validated combinations accounting for clinical probability of PE, is given in Table 2.[1] It may offer advice regarding construction of alternative diagnostic algorithms which must be sometimes tailored to the limited local availability or laboratory tests.

Diagnostic approach compatible with current guidelines is related to better outcome[41] and should be actively implemented. Modern hardware and software may help in standardization of management of patients with suspected and confirmed acute PE.[42]

Except for patients with low clinical probability of PE, and those with hemoptysis or other

TABLE 2. **Validity of Diagnostic Tests According to Clinical Probability of Pulmonary Thromboembolism**

Diagnostic Criteria Useful for:	Clinical Probability of PE		
	Low	Intermediate	High
Exclusion of pulmonary embolism			
Normal pulmonary angiogram	+	+	+
D-dimer			
Negative result, highly sensitive assay	+	+	–
Negative result, moderately sensitive assay	+	–	–
V/Q scan			
Normal lung scan	+	+	+
Nondiagnostic lung scana	+	–	–
Nondiagnostic lung scana and negative proximal CUS	+	+	±
Chest CT angiography			
Normal single-detector CT and negative proximal CUS	+	+	±
Normal multidetector CT alone	+	+	±
Confirmation of pulmonary embolism			
Pulmonary angiogram showing PE	+	+	+
High probability V/Q scan	±	+	+
CUS showing a proximal DVT	+	+	+
Chest CT angiography			
CT scan showing PE (at least segmental)	±	+	+
CT scan showing subsegmental PE	±	±	±

+: valid criterion (no further testing required); –: invalid criterion (further testing mandatory); ±: controversial criterion (further testing to be considered).
[a]Non diagnostic lung scan: low or intermediate probability lung scan according to the PIOPED classification.[37]
CT indicates computed tomography; CUS, proximal lower limb venous ultrasonography; DVT, deep venous thrombosis; PE, pulmonary embolism; V/Q scan, ventilation-perfusion scintigraphy.
Modified from Torbicki A et al.[1]

significant contraindications, anticoagulation with low molecular weight heparin (LMWH) should be started upon clinical suspicion in order to reduce the risk of early PE recurrence during the time needed to complete the diagnostic assessment.[1]

Recent attempts to simplify two previously validated prediction rules should be noted.[43-46] In the Wells score a binominal scale ("unlikely-likely") has been suggested, instead of three levels of pre-test clinical probability ("low-intermediate-high"). In addition, equal rank was recently assigned to all prediction score elements, apparently without significantly affecting its performance.[43-45] Similar changes are being made in the Geneva score.[46] Though currently some confusion has been introduced, ultimately these efforts may result in easier and wider use of prediction rules.

New diagnostic methods and ideas are constantly being suggested. Bedside assessment of end-tidal CO2 has been proposed as a potential alternative to D-dimer testing as an adjunct to Wells prediction rule.[47] PIOPED II assessed the value of extending CT angiography also to CT venography. However, the additional diagnostic yield was negligible and did not justify increased exposure to radiation.[38] Lung scintigraphy has been suggested as more appropriate than CT in pregnancy, because of similar risk for the foetus but lower risk of inducing maternal breast cancer.[48,49] Potential role of new radiation-free tests such as thoracic[50-52] and endobronchial ultrasound (EBUS)[53] still need prospective validation trials to assess their value in suspected PE.

The role of magnetic resonance imaging (MRI) as a diagnostic test in PE has been suggested by smaller trials[54-57] and has been recently defined in a large prospective PIOPED III trial. The main limitation of MRI was related to high rate of technically inadequate images, which ranged from 11% to 52% (mean, 25%) in the 7 participating centers. Consequently, magnetic resonance angiography identified only 57% (59 of 104) of patients with objectively confirmed PE. Technically adequate magnetic resonance angiography had a sensitivity of 78% and a specificity of 99% and when combined with magnetic resonance venography, 92% and 96%, respectively. Unfortunately only half of the patients (194 of 370) had technically adequate results of both tests.[58]

Initial Treatment and Comprehensive Prognostic Assessment

Main recommendations for initial management of acute PE are summarized in Table 3.

High Risk Pulmonary Thromboembolism

As already mentioned patients with acute PE at high-risk of early death are identified by the presence of shock or systemic hypotension. The treatment goal in those patients consists not only of preventing early life-threatening recurrence of emboli (initially with IV heparin) but aims at prompt unloading of the RV. The latter can be attempted and in most cases achieved by intravenous thrombolysis.[59]

Unfractionated heparin started immediately as a weight adjusted IV bolus (80 U/kg) followed by 18 U/kg/h and further activated prothrombin time (APTT)-adjusted infusion[60] is preferred to LMWH in high-risk patients with PE. There is no consensus whether heparin should be discontinued during the administration of thrombolytic agent, and if so, when it should be restarted.

Out of three thrombolytic regimens formally approved for PE only alteplase (recombinant tissue plasminogen activator), 100 mg infusion over 2 hours, with the first 10 mg usually given as bolus injection, is currently used. Alternatively, fast infusion of alteplase at the dosage of 0.6 mg/kg (maximum 50 mg) within 15 minutes can be used in emergency situations, eg, during cardiopulmonary resuscitation.[61] Bolus followed by prolonged streptokinase or urokinase i.v. regimens have been replaced in clinical practice by more rapid, 1-2-hour high dose infusions. Those regimens were similar to those used in acute myocardial infarction, as they achieve more rapid clot lysis at lower bleeding risk.[62]

Satisfactory haemodynamic results also have been obtained in acute PE with double-bolus reteplase, 2 injections (10 U) 30 minutes apart[63] or bolus tenecteplase.[64] However, neither reteplase nor tenecteplase are formally approved for treatment of PE at present.

In patients with contraindications to thrombolysis and in approximately 10 % who fail to improve despite such therapy, surgical embolectomy should be considered.[65] It is worth reminding, that a patient with life-threatening PE is stabilized immediately after introducing cardio-pulmonary bypass. More recent series provide reassuring data on the results of surgical embolectomy.[66] Alternatively, catheter embolectomy, thrombus fragmentation, or both, may be considered, if adequate experience and equipment is available.[67,68] If neither surgical nor catheter intervention are immediately available in a patient critically ill due to objectively confirmed PE hardly any contraindications preclude the use of thrombolysis.[1] With the exception of recent

TABLE 3. **Main Recommendations for Initial Treatment in Pulmonary Embolism[1]**

High-risk PE (ie, patients with shock or hypotension):	
Admission to ICCU	Are recommended
Bolus/ weight adjusted IV UFH infusion	
Vasopressive drugs - if hypotension	
Oxygen - if hypoxemia	
Thrombolytic treatment	
Surgical embolectomy	Is recommended[a]
Catheter embolectomy/fragmentation	May be considered[a]
Intermediate-risk PE (ie, normotensive but with RV dysfunction and/or myocardial injury)	
Weight adjusted SC LMWH or fondaparinux	Are recommended
IV UFH infusion - if high bleeding risk/low GFR	Is recommended
Admission to ICCU and thrombolytic treatment	May be considered
Low risk PE (ie, normotensive with nither RV dysfunction nor myocardial injury)	
Weight adjusted s.c. LMWH or fondaparinux	Are recommended
IV UFH infusion - if high bleeding risk/low GFR	Is recommended
Home treatment after excluding co-morbidities	May be considered
Confirmed PE and hemorrhagic complications or PE recurrence despite therapy	
Permanent or retrievable vena cava filter	Should be considered

ICCU indicates intensive cardiac care unit; GFR, glomerular filtration rate; IV, intravenous; LMWH, low molecular weight heparin; UFH, unfractionated heparin; RV, right ventricle; SC, subcutaneous.
[a]If thrombolysis fails or is contraindicated.

cerebral or severe uncontrolled internal bleeding, thrombolysis should be considered, eg, in patients with recent surgery. Severe hemorrhagic complications should be expected and promptly handled. Intrapulmonary administration of thrombolytic agents is neither safer nor more effective than its systemic administration.[68,69]

Non-High Risk Pulmonary Thromboembolism

The main treatment goal in normotensive patients with PE is an immediate and effective prevention of recurrences of emboli and of local extension of intrapulmonary thrombi. This should be attempted and is usually achieved by anticoagulation, which allows intrinsic thrombolysis and thrombus retraction to prevail. Clearing of the pulmonary bed and restoring normal hemodynamics may take weeks to months, and may not be complete.[70]

Weight-adjusted LMWH are the first choice therapy for the majority of patients with documented acute PE,[71-73] including those presenting with hemoptysis due to pulmonary infarction. Fondaparinux in three fixed doses depending on the body weight (5 mg for patients with <50 kg, 7.5 mg for patients with 50-100 kg and 10 mg for patients with >100 kg of body weight) is a valid alternative,[74] particularly in patients with renal insufficiency as it allows non-modified administration down to glomerular filtration rate (GFR) of 20 mL/kg/min, compared to 30 mL/kg/min for the LMWH. Fondaparinux is probably not inducing PF4 antiplatelet antibodies and "heparin induced" thrombocytopenia. In contrast to LMWH it should not be used in pregnancy due to lack of evidence. LMWH treatment does not require laboratory monitoring, except in extremes of body weight, significantly reduced renal clearance and pre-delivery period in pregnancy. In such situations anti Xa activity-guided treatment may be considered.[71] Tinzaparine, enoxaparine and—for cancer patients—dalteparine have formal labeling for PE. However, it is common practice to extrapolate existing evidence to other LMWHs, which have documented efficacy in treatment of DVT.

Unfractionated i.v. heparin is preferred to LMWH in several clinical situations, including: unstable and "high-risk" PE, significant bleeding risk, severe renal failure. Adequately high dose of UFH is crucial for successful prevention of recurrent PE episodes. Daily IV dose ≥40 000 U should be effective even in cases without adequate APTT prolongation (defined as >1.5 to 2.5 control value), though monitoring of anti-Xa would be even more reassuring.[75]

Anticoagulation initiated with heparins or Fondaparinux should be continued with a vitamin K antagonist (VKA). Oral VKA may be started already on the first day of therapy and continued in parallel with a parenteral anticoagulant in therapeutic doses for at least 4 days. The latter can be stopped only after bringing the international nomalizing ratio (INR) to the target range, ie, 2.0–3.0 for ≥ 2 consecutive days.[71] In selected patients in whom optimal INR monitoring seems difficult, LMWH may be used for secondary prevention at doses recommended by the manufacturer for such purpose, usually representing 50%-75% of the full therapeutic dose.[1] Pregnancy represent specific situation in which most experts suggest LMWH dose at 75%-100% of therapeutic dose until delivery, because of its increased clearance.[76]

Thrombofilia does not require modification of initial therapy, with the exception of significant antithrombin deficiency. It may result in resistance to unfractionated heparin manifesting as lack of APTT prolongation and can be corrected by increasing the dose of UFH or by substitution of antithrombin. The effect of antithrombin deficiency on LMWH efficacy is less clear.

Intermediate Risk Pulmonary Thromboembolism

Thrombolysis may be also considered in selected patients, who do not meet the criteria for high risk of early PE-related death.[1] Comprehensive prognostic evaluation by searching for RV pressure overload/dysfunction and/or myocardial injury may identify normotensive patients who are at relatively higher risk

Echocardiography was considered a key test predicting in-hospital outcome in acute PE.[25,77-80] This has been questioned by a recent meta-analysis including 475 normotensive patients with PE which reported only moderate negative (60%) and positive (58%) value of echocardiography for predicting early death.[81] Standardization of the echocardiographic criteria which could be universally applied for prognostic staging in acute PE remains an unresolved issue.[82]

MDCT, currently the preferred method for diagnosing PE, may simultaneously detect RV enlargement due to PE and such finding has prognostic implications.[83] A meta-analysis of 2 studies including 191 normotensive patients with PE reported a 58% overall negative and a 57% positive value of RV dilatation on CT for predicting early death.[81]

Natriuretic peptides offer a non-imaging insight into ventricular dysfunction, including that caused by acute PE.[84-87] A meta-analysis including 1,132 patients found increased plasma BNP/NT-proBNP levels to be related to significant risk of early death (OR, 7.6; 95% CI, 3.4-17).[88] The prognostic value of natriuretic peptides may be improved when considered together with echocardiography[89] and/or clinical data.[90]

While all the above markers of RV dysfunction seem useful for prognostic stratification in normotensive, i.e. otherwise "non-high risk" patients with PE, no universal cut-off values were defined and no therapeutic recommendations can be formulated at present. Particularly RV overload/dysfunction alone does not appear to justify rutine use of more invasive treatment regimens such as thrombolysis or embolectomy.[24]

Just as in acute coronary syndromes cardiac troponins can be detected in up to 50% of patients with acute PE.[91] A metaanalysis enrolling 1,985 patients from 20 studies reported increased risk of death (OR, 5.24; 95% CI, 3.28-8.38) in patients with elevated troponin levels.[92] When a similar assessment was restricted to 1,366 normotensive patients patients enrolled in 9 studies troponin elevation alone was not found to contribute satisfactorily to prognostic staging.[93] The value of high sensitivity troponin tests in PE remains to be evaluated. Other potentially prognostically useful markers of myocardial injury or ischemia in PE include heart-type fatty acid-binding proteins (H-FABP)[94-97] and growth-differentiation factor-15 (GDF-15).[98]

Unfortunately, the positive predictive value for mortality is low and the optimal cut-off point is not universally established for any of the individual biomarkers indicating myocardial injury. Even a single risk marker found "positive" according to local criteria is sufficient to consider a patient as one at "intermediate-risk" of early death (3%-15% in hospital or 30 days mortality). Possible additive value of signs of myocardial injury and dysfunction is likely. Since approximately 25% of intermediate-risk patients will have a complicated clinical course,[24] they should be considered for close monitoring either by telemetry or at the intensive care unit , to allow early "rescue" therapy (so called "watchful waiting" strategy). Results of a long awaited randomized controlled study assessing potential benefit of thrombolysis over heparin alone in patients with acute PE presenting with echocardiographic signs of RV overload an increased plasma troponin (PEITHO) should be available in 2012.

Low-Risk Pulmonary Thromboembolism

Low risk PE can be diagnosed in patients in whom markers of RV dysfunction and myocardial

damage were tested but found to be negative. However, outcome may additionally be influenced by comorbidities and general condition of the patient. Recently, a Pulmonary Embolism Severity Index (PESI) was validated in large populations of patients with PE[99,100] and found capable of identifying patients with very low rates of adverse events.[101] The index considers such factors like age, sex, comorbidities, presence of tachycardia, tachypnea, hypotension, hypothermia, hypoxemia and confusion. Low PESI index may help in decisions regarding early discharge and home treatment of low-risk patients with acute PE.

Long-Term Secondary Prevention

Prevention of recurrence is a priority after a documented PE episode. Without it up to 50% of patients may suffer a recurrent episode within the first 3 months.[102] While provoked PE requires only 3 months of anticoagulation with negligible risk of late recurrence, unprovoked PE is considered a lifelong disease. The frequency of recurrence appears to be independent of the initial clinical manifestation of VTE, but recurrent VTE is three times more likely to present as PE if the initial clinical event was PE, than if it was DVT.[103] However, the majority of available data refer to DVT rather than PE alone and indicate at least 30% recurrence rate after 8-10 years.[104-106] Treatment with VKA is highly effective in reducing the risk for recurrent thromboembolism by up to 90%.[107] However, the risk of recurrence returns after their discontinuation, regardless of the duration of therapy.[108,109] After unprovoked PE indications for longer or indefinite oral anticoagulation should be assessed on an individual basis after at least 3 months of initial secondary prevention. This population of patients is in clear need of additional markers for further risk stratification for VTE recurrence. Some help is offered by D-dimer testing one month after discontinuation of vitamin K antagonists. Patients with abnormal D-dimer plasma levels should resume anticoagulation, because of relatively high risk of recurrent events.[110] Persistent thrombotic deposits detected by CUS in deep venous system represent another marker of increased recurrence risk in idiopathic PE. [111]

While effective, routine prescription of indefinite anticoagulant prevention is questionable in view of the resulting increased risk of major bleeding.[1,71,107,112] In fact, chronic anticoagulation prevents recurrent VTE at a cost of major bleeding rate of 3-4% within clinical trials, and up to 5%-9% in everyday clinical practice.[113] Bleeding complications during the first 3 months of therapy are strong determinants of mortality. Out of 407 patients followed in RIETE registry who had major bleeding during the study period 133 (33%) died in the next 30 days –half of them because of bleeding-.[114] Periodical reassessment of indications and contraindications to continued VTE prevention, accounting also for patient's preferences, is therefore important.[71] Double antiplatelet therapies following many cardiovascular interventions represent a new challenge for prophylactic long term anticoagulation. Venous filters seem to reduce mortality when inserted because of bleeding complications in patients receiving anticoagulants up to 3 months after a VTE episode. In the RIETE registry insertion of a vena cava filter was the only variable independently associated with a lower incidence of fatal bleeding (OR, 0.10; 95% CI, 0.01-0.79) and all-cause mortality (OR, 0.21; 95% CI, 0.07-0.63). Stopping anticoagulation was related to increased risk of death (OR, 2.31; 95% CI, 1.37-3.94).[114]

Indefinite anticoagulation is recommended after a second unprovoked episode of VTE. Patients with thrombophilia or active cancer are also candidates for indefinite anticoagulation with VKA. Patients with cancer require secondary prevention with LMWH instead of VKA, as it seems to improve their outcome at least when given during the first 6 months after an acute VTE event.[115,116]

New generation oral anticoagulants, mostly anti Xa, and direct antithrombin agents are currently under investigation for prophylaxis and treatment of VTE and may help in improving the balance between efficacy of prevention and the risk of bleeding.[117]

CHRONIC THROMBOEMBOLIC DISEASE

Chronic thromboembolic pulmonary hypertension (CTEPH) can be diagnosed if organized thrombi in main, lobar, segmental or subsegmental pulmonary arteries can be visualized in a patient with precapillary pulmonary hypertension ie, with mean pulmonary artery pressure (PAP) ≥25 mmHg, pulmonary vascular resistance (PVR) >2 IU and pulmonary artery occlusion pressure ≤15 mmHg.

Epidemiology and Predisposing Factors

CTEPH is a rare consequence of acute PE. Until recently it was believed, that only 0.1%-0.5% of patients with acute PE develop CETPH,[118] while vast majority clear their pulmonary bed from thromboemboli mostly by means of endogeneous thrombolytic activity.[119] More recent reports suggest higher prevalence of CTEPH reaching

3.1% and 3.8%, at one and 2 years after an embolic episode, respectively.[120] A multicentre prospective observation of 259 patients after a first episode of PE revealed overall 0.8% incidence of CTEPH during 46 months of observation, with twice as high (1.5%) incidence among patients with idiopathic PE.[121]

CTEPH is considered to be primarily due to aborted endogenous thrombolysis after a thromboembolic episode.[122] Few pro-thrombotic risk factors have been identified in subjects with the disease and only 50% of patients with documented CTEPH have traceable history of acute PE.[123] Other medical conditions associated with CTEPH include splenectomy, ventricular valve for treatment of hydrocephalus, chronic osteomyelitis and inflammatory bowel disease.[124]

Diagnostic Approach

Any new limitation in exercise capacity due to dyspnea, requires consideration of CTEPH among its potential causes. This is true particularly—but not only—in patients with a history of venous thromboembolic disease. CTEPH should be also considered in all patients with echocardiographic signs suggesting RV pressure overload, in whom common causes of PH have been excluded.

Prospective echocardiographic screening of asymptomatic survivors of acute PE for CTEPH is questionable. A recent Dutch prospective screening study enrolling 866 patients with history of acute PE revealed 0.57% (95% CI, 0.02-1.2) prevalence of CTEPH , again higher (1.5%; 95% CI, 0.08-3.1) in idiopathic cases. However, most of the patients with CTEPH were already identified because of clinical symptoms and signs. This happened before they were invited for formal echocardiographic screening, which had very low additional diagnostic yield for CTEPH, and was not found practically useful by the authors.[125] An algorithm which may be useful for planning diagnostic strategy in suspected CTEPH is shown in figure 2

Contrary to acute PE, lung perfusion scintigraphy maintained an important position in the differential diagnosis of chronic pulmonary hypertension. It is an excellent screening tool for CTEPH.[126] Normal perfusion scan excludes CTEPH while multiple defects prompt further diagnostic imaging. CT angiography is a recommended next step. If mural thrombi, intraluminal bands or webs can be visualized CTEPH is highly probable. Mozaic perfusion pattern on high resolution CT is a common finding supporting the diagnosis. Depending on the extension and character of intrapulmonary lesions, and local experience classical pulmonary angiography may or may not be needed for surgical qualification. If performed, it helps to identify not only mural organized post-thrombotic deposits but also residual webs and bands which represent fibrotic remnants of thrombi and may contribute to increased PVR. Intravascular changes are therefore different in CTEPH than those encountered in acute PE.[126] Of note, organized thrombi in proximal pulmonary arteries may be found in pulmonary arterial hypertension, particularly in patients with Eisenmenger syndrome. Such deposits result from local stasis in markedly dilated arteries, and do not have direct hemodynamic consequences, except for potential artery-to-artery embolization. Anomalies of pulmonary arteries, vascular tumors (such as angiosarcoma, leyomyoma), Takayasu arteritis and mediastinal fibrosis may sometimes cause major diagnostic problems, mimicking CTEPH when assessed with imaging methods.[127-129] Interpretation of images as well as diagnostic and therapeutic decisions in suspected CTEPH requires particular experience, multidisciplinary approach and therefore should be restricted to specialized referral centers.

Treatment

Advanced CTEPH, if left untreated carries a very poor prognosis. This is due not only to persistent post-embolic deposits but remodeling of pulmonary arterioles similar to those found in pulmonary arterial hypertension, progressively increasing RV afterload.[130] Historical data referring to patients with CTEPH remaining on supportive therapy alone suggest 30% to 80% mortality depending on their mean PAP at presentation (>30 mmHg and >50 mmHg, respectively).[131] Patients with CTEPH but a mean PAP <30 mmHg had 12% mortality during 18.7 months of follow-up which contrasted with 50% mortality in those with mean PAP >30 mmHg.[132]

Surgical Therapy

Surgical pulmonary endarteriectomy (PEA) is the preferred mode of treatment of patients with CTEPH.[123,126]

The successful intervention was reported in 1973 by Kenneth Moser and Nina Braunwald from UC San Diego.[133] Since that time PEA is performed with the help of cardio-pulmonary by-pass and requires remittent periods of deep hypothermia. This prevents from back-bleeding from bronchial circulation and allows removal

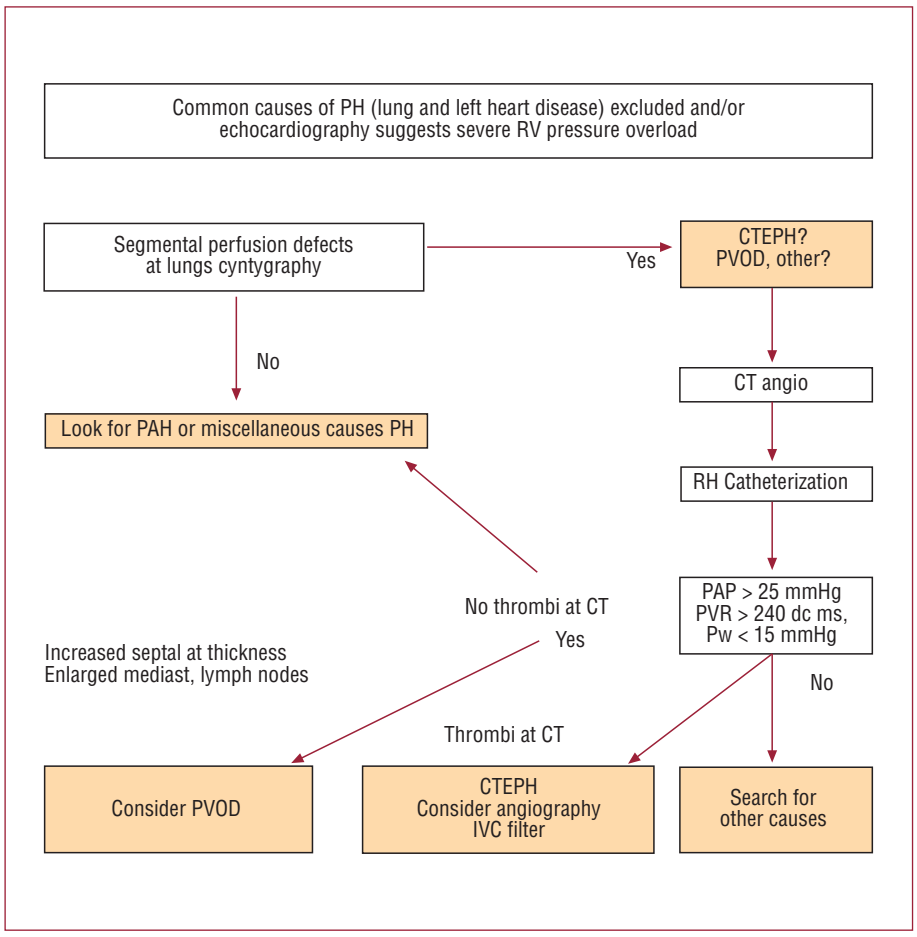

Figure 2. Suggested diagnostic approach to patients with echocardiographic signs of unexplained right ventricular pressure overload. CT indicates computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; IVC, inferior vena cava; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RH, right heart; RV, right ventricle; Pw, wedge pressure; PAH, pulmonary arterial hypertension.

of pulmonary artery intima down to segmental and sometimes sub-segmental branches, together with attached intraluminal organized post-thrombotic deposits. If complete bilateral endarterectomy is technically successful and potential perioperative complications, such as reperfusion lung oedema or bleeding, are controlled clinical, hemodynamic and long-term prognostic improvement can be dramatic.[134] Most centers routinely implant vena cava filters before PEA to prevent peri-operative or late recurrence of PE. The latter sometimes occur in patients with excellent result of PEA, who may neglect chronic anticoagulation, considering themselves cured of the disease. Recently, some surgeons performing PEA advice against implantation of vena cava filters, as they may interfere with implementation of extracorporeal life support systems (ECLS). Such interventions may be life-saving in patients with severe respiratory and RV failure developing in the early post-surgical period.[135] Retrievable venous filters might be a solution but in this clinical setting the experience is still lacking.

Not in all patients endarterectomy can be effective. This depends mostly on the relative contribution of proximal postthrombotic and distal proliferative element to the elevation of PVR and to increase in RV afterload. Jamieson and Kapelaski described four types of intrapulmonary findings revealed during PEA interventions, and correlating with their outcome.[136] In the majority of potential surgical candidates with CTEPH the decision regarding their operability is relatively clear. In others more sophisticated methods based on the Doppler-assessed site of reflected PAP wave, assessing partitioning of PVR or pulmonary vasoreactivity tests may offer some help.[137-140] However, there is still a significant group of patients in whom there is no method which would allow unequivocal preoperative prediction of the final hemodynamic result of surgery.

Universally accepted indications for PEA include:

– III or IV WHO functional class.
– PVR >300 dyn•s•cm^{-5}.
– Proximal changes localized in main, lobar, segmental pulmonary arteries.

– Absence of severe comorbidities.

Main indicators for successful outcome of PEA include[141]:

– Surgeon and team experience.
– Concordance between PVR and % occlusion of pulmonary artery bed.
– Preoperative PVR <1000-1200 dyn•s•cm^{-5}.
– Absence of specific comorbidities (splenectomy, ventriculo-atrial shunt).
– Early postoperative PVR < 500 dyn•s•cm^{-5}.

In some patients complete unilateral occlusion result in exercise limitation despite relatively mild hemodynamic disturbances at rest. This is due mostly to increased dead space in the non-perfused lung and may also represent an indication for PEA.[142] However, for not completely clear reasons unilateral pulmonary artery occlusions are related to high risk of recurrences after PEA,[143] and this should be considered when qualifying a patient for surgery.

Experience and multidisciplinary approach is essential in achieving success in CTEPH surgery. Data from the center in San Diego, where over 2000 PEA was performed the mortality from initial 20% was reduced to 4.5% for the interventions performed after 2004.[144,145]

Medical Therapy

All CTEPH patients should receive life-long anticoagulation, usually with a VKA, to prevent both the recurrence of PE and local extension of thrombi in pulmonary arteries, arterioles and pulmonary microcirculation.[124] It is true both before and after PEA (including patients with implanted vena cava filters) as well as in patients who remain on medical treatment alone

In symptomatic patients supportive measures similar to those recommended in PAH should be considered.[2] These include diuretics in patients with RV failure and oxygen supplementation in hypoxemic patients. Vaccinations against influenza, avoiding pregnancy and excessive physical activity should be also suggested.

Despite improvement in surgical technique and experience still almost 50% of patients with symptomatic CTEPH remain on medical treatment alone. This is mostly because of inoperable distal changes or comorbidities.[123,141,145] In addition in about 10% of patients pulmonary hypertension persists after PEA, because of the remaining distal deposits or the contribution of arteriolar remodeling.[123,141,145] With increasingly encouraging evidence on vasodilative and anti-remodeling therapy in pulmonary arterial hypertension[146] potential indications for targeted medical treatment in CTEPH emerged and stimulated clinical trials.

Potential indications for medical therapy in CTEPH include:

– Distal disease considered inoperable.
– Comorbidities prohibitively increasing risk for surgery.
– Bridge to PEA or transplantation for high-risk patients.
– Persistent pulmonary hypertension despite PEA.

Several small pilot series and case control trials supported the concept of targeted medical therapy in CTEPH. However, reliable evidence from prospective randomized controlled trials including a placebo group is still inconclusive. The main results from three trials which have been undertaken in CTEPH[147-149] are listed in Table 4. Two of those trials were small. The only one powered to detect a statistical difference between the active treatment and control was the BENEFIT trial. It included patients with either inoperable CTEPH or pulmonary hypertension persisting >6 months after PEA. Independent co-primary end points were change in PVR as a percentage of baseline and change from baseline in 6-min walk distance after 16 weeks of treatment with bosentan 125 bid or placebo. Secondary end points included change from baseline in the World Heart Organization functional class and other hemodynamic parameters. The trial showed a statistically significant treatment effect of bosentan over placebo on PVR with its 24.1% reduction from baseline (95% CI, -31.5 to -16.0; P<.0001) after 16 weeks.[147] The other co-primary endpoint, distance walked during 6 minute walk test was not met, with mean improvement in active versus placebo group of only +2.2 m (95% CI, –22.5 to 26.8 m; P=.5449). Several clinically relevant parameters significantly improved in patients randomised to bosentan when compared to those on placebo, including total pulmonary resistance and cardiac index as well as NT-proBNP plasma levels. Bosentan treatment was well tolerated. How to explain discrepancy between hemodynamic and functional results remains unclear. Physical deconditioning delaying functional recovery in the CTEPH patients, due to comorbidities and older age, as compared to PAH, has been suggested.

In a recent retrospective observational study 355 patients treated with PEA at San Diego between 2005-2007 apparently did not benefit

TABLE 4. **Main Data from the Randomized Controlled Trials of Targeted Medical Therapy Enrolling Chronic Thromboembolic Pulmonary Hypertension Patients**[147-149]

Trial	Active Drug	Patinets	Time, wks	Δ 6MWT, m	Δ PVR, J.Wooda	NTproBNP, pg/mL
Olschewski et al (2002)[148]	Iloprost	33	12	(NS)	–	–
	Placebo	24				
Jais et al (2009)[147]	Bosentan	77	16	2,2	–24%	–622
	Placebo	80		(NS)	*P*<.0001	*P*<.0003
Suntharalingam et al (2008)[149]	Sildenafil	9	12	17,5	–5,30%	–278
	Placebo	10		(NS)	*P*=.04	(NS)

6MWT indicates 6 minutes walk test; PVR, pulmonary vascular resistance.

from preoperative treatment with bosentan, sildenafil or epoprostenol (as a monotherapy or in combinations) when compared to 244 patients who received supportive treatment alone. Targeted therapy resulted in delayed surgical referrals, but did not influence the postoperative course.[150] Despite those inconclusive data a significant proportion of CTEPH patients receive targeted pharmacotherapy worldwide. Recently completed large European CTEPH Registry should provide further information on the current diagnostic and therapeutic strategies and outcome of patients with CTEPH in Europe. Even more importantly most of the new drugs tested for treatment of pulmonary arterial hypertension are also in parallel tested in inoperable and "persistent" CTEPH patients. This should help in objective assessment of the value and place of specific medical therapy for these indications.

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