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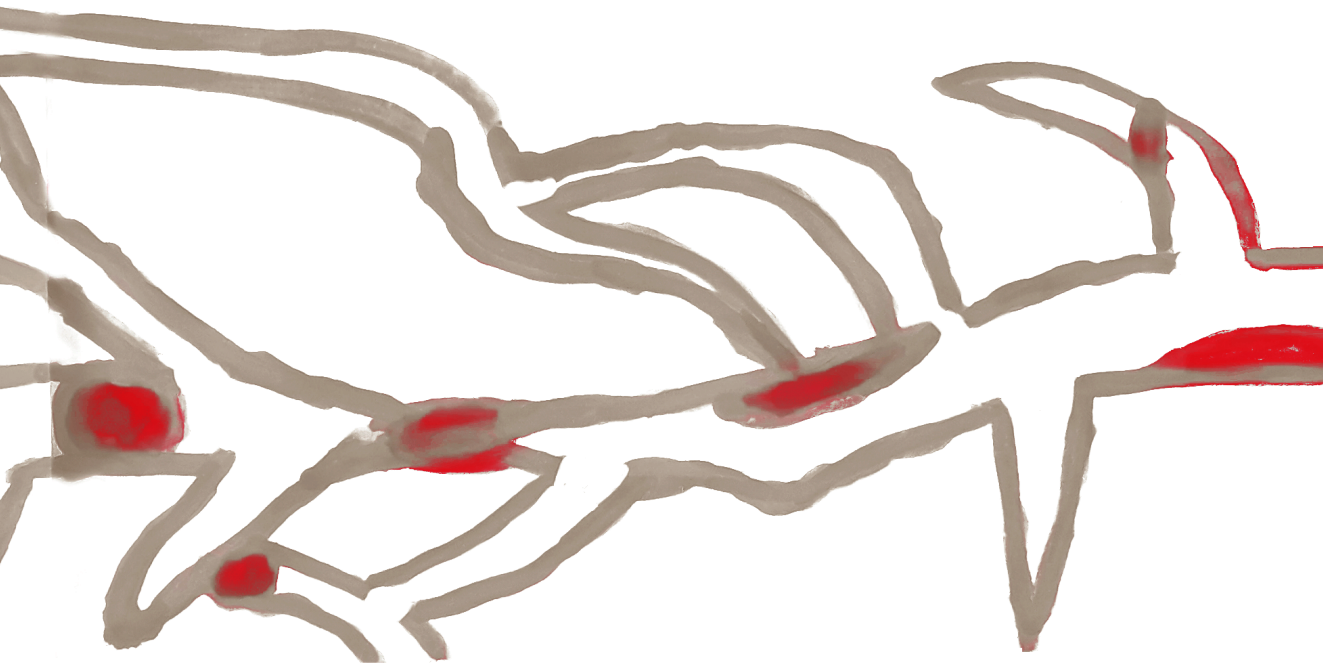
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Chapter 3

Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism, a contemporary view on the published literature

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ABSTRACT

Introduction: The incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary embolism (PE) is relevant for management decisions but is currently unknown.

Methods: We performed a meta-analysis of studies including consecutive PE patients followed for CTEPH. Study cohorts were predefined as '*all comers*', '*survivors*' or '*survivors without major comorbidities*'. CTEPH incidences were calculated using random effects models.

Results: We selected 16 studies totalling 4047 PE patients who were mostly followed up for >2-year. In 1186 '*all comers*' (2 studies), the pooled CTEPH incidence was 0.56% (95%CI 0.1-1.0). In 999 '*survivors*' (4 studies), CTEPH incidence was 3.2% (95%CI 2.0-4.4). In 1775 '*survivors without major comorbidities*' (9 studies), CTEPH incidence was 2.8% (95%CI 1.5-4.1). Both recurrent venous thromboembolism and unprovoked PE were significantly associated with a higher risk of CTEPH, with Odds Ratios of 3.2 (95%CI 1.7-5.9) and 4.1 (95%CI 2.1-8.2) respectively. Pooled CTEPH incidence in 12 studies that did not use right heart catheterisation as diagnostic standard was 6.3% (95%CI 4.1-8.4).

Conclusion: The 0.56% incidence in the all-comer group probably provides the best reflection of the incidence of CTEPH after PE on population level. The ~3% incidences in the survivor categories may be more relevant for daily clinical practice. Studies that assessed CTEPH diagnosis by tests other than right heart catheterisation provide over-estimated CTEPH incidences.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct form of pulmonary hypertension (PH). CTEPH is believed to arise from one or multiple endothelialized pulmonary thrombi that do not resolve but lead to chronic obstruction of the pulmonary artery tree, small-vessel arteriopathy, high pulmonary vascular resistance, PH and progressive right heart failure [1]. Patient prognosis is very poor when CTEPH is left untreated [2]. The only curative treatment option is surgical removal of these chronic thrombi with pulmonary endarterectomy (PEA) [1, 3]. If PEA is not feasible or fails to significantly reduce the pulmonary artery pressure, the patient's prognosis is poor. Operability of a patient depends among others factors on the presence of more advanced distal pulmonary artery remodelling, a feature that is less expected if CTEPH is diagnosed early. Also, the duration between last pulmonary embolism (PE) and PEA was found to be a risk factor for in-hospital mortality [4]. Hence, early diagnosis is crucial for optimal treatment and a favourable outcome.

Early CTEPH diagnosis, however, has proven to be a major clinical challenge. This is demonstrated by a staggering median diagnostic delay of 14 months demonstrated in the European CTEPH registry [5]. One explanation for this delay could be that symptoms of CTEPH are largely non-specific. Patients can even remain asymptomatic or do not mention their symptoms for months despite the presence of relevant PH [1, 5]. Also, validated cost-effective CTEPH screening tools remain unavailable to date. The incidence of CTEPH after symptomatic acute PE is not exactly known and is reported to range from 0.1% to 11.8% [6-9]. More precise knowledge of the incidence of CTEPH after acute PE is clearly relevant for defining the appropriate long-term management of acute PE. An incidence of 10% or higher would certainly warrant a standardized screening protocol for CTEPH, whereas an incidence of 0.1% or lower would not.

The notable wide range in reported incidences could be caused by major differences in the selection of the studied patient populations. For instance, most studies focussed on smaller subgroups of PE patients selected by the presence or absence of thrombotic risk factors, previous venous thromboembolism (VTE) and/or absence of cardiopulmonary comorbidities. In addition and importantly, in several reports the CTEPH diagnosis was not based on the diagnostic gold standard, i.e. right heart catheterisation (RHC) [3].

We aimed to gain an accurate overview in the variety of reported incidences of CTEPH after acute PE in different patient subgroups. To do so, we conducted a systematic review and meta-analysis of the literature focussing on those studies that applied validated diagnostic criteria of CTEPH according to current guideline recommendations [3].

METHODS

Data sources and literature search

We conducted a search for all relevant publications in PubMed, MEDLINE, Embase, Web of Science, Cochrane, CINAHL, Academic Search Premier and Science Direct. We performed our search in August 2015 with a search string focusing on 'chronic thromboembolic pulmonary hypertension,' 'pulmonary embolism,' 'thromboembolism,' 'incidence' and 'risk' (**Supplementary material**). These key words were database-specifically translated. We additionally performed a manual search of references of the identified relevant original and review articles.

Study selection, data extraction and quality assessment

Search results were combined and duplicates were removed. Studies were screened for relevance by two independent reviewers (Y. E-V and F.K), on the basis of title and abstract. Discrepancies were resolved by consensus or by contacting a third reviewer (S.C). Full-text articles or conference abstracts in the English or Dutch language identified by either reviewer as potentially relevant were retrieved for further evaluation. We did not apply any time limitations. Final selection of studies for the meta-analysis was restricted to cohort studies of patients with an objectified index diagnosis of the first or recurrent acute PE episode, who were followed for the development of CTEPH for a period of six months or longer and that explicitly reported the incidence of CTEPH.

The PRISMA statement [10] was used as a basis for reporting our systematic review. Data extraction was performed by two reviewers (Y. E-V and F.K). For each included study, we extracted the first author's name and year of publication, study design (prospective or retrospective), setting of the study (single- or multicentre), number of patients in the index cohort, number of patients who were followed for the occurrence of CTEPH, number of patients with a recurrent venous thromboembolic event, number of patients with unprovoked PE, the method of selection of patients for assessment of CTEPH (all patients or only those with specific signs and symptoms), the primary test for assessment of CTEPH, the applied gold standard for CTEPH diagnosis, the total duration of follow up, and finally the incidence of CTEPH as reported by the authors.

For included studies, the risk of bias was evaluated in accordance with the Cochrane Collaboration's tool for assessing risk of bias and the PRISMA statement [10, 11]. We focussed on the following criteria: 1) pre-specified study protocol, 2) clear description of inclusion and exclusion criteria, 3) inclusion of consecutive patients, 4) objectified diagnosis of PE and CTEPH based on the results of a RHC according to current guidelines [3, 12], 5) adequate anticoagulant treatment according to international standards, 6) loss to follow up, and 7) assessment of the primary endpoint in all patients. Only studies with a low risk of bias were included in the meta-analysis.

Study outcomes and definitions

Our primary aim was to determine the incidence of CTEPH after acute PE in three pre-defined cohort subtypes: 1) 'all comers' (i.e. all consecutive patients with symptomatic PE, no exclusion criteria), 2) 'survivors' (i.e. all consecutive patients with symptomatic PE who were alive after an initial treatment period of 6 months), and 3) 'survivors without major comorbidity' (i.e. all consecutive patients with symptomatic PE who were alive after an initial treatment period of 6 months and did not have predefined significant cardiopulmonary, oncologic or rheumatologic comorbidities).

Our secondary aim was to determine the association of unprovoked PE and recurrent VTE with the incidence of CTEPH. Unprovoked PE was defined as VTE occurring without any of the following risk factors: major surgery or immobilization for at least 3 days within 4 weeks preceding the PE diagnosis, active malignancy (a diagnosis of cancer within 6 months prior to enrolment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer), a recent long flight (more than 6 hours) in the past 3 weeks, being pregnant or in the peripartum period, and use of oral contraceptives or hormone replacement therapy. Recurrent VTE was defined when a documented prior episode of objectified deep vein thrombosis or PE was available [12]. We additionally aimed to evaluate the method of CTEPH screening (application of a CTEPH specific diagnostic test in all patients or only in those who displayed or reported signs and symptoms suggestive of CTEPH) on the incidence of CTEPH. To compare the reported incidences in studies that diagnosed CTEPH based on the results of a RHC we aimed to establish the reported incidence of CTEPH after acute PE in studies in which the diagnosis of CTEPH was based on other diagnostic criteria.

Statistical analysis

The incidence was calculated by dividing the number of confirmed cases of CTEPH during follow-up by the number of patients in the cohort initially selected for screening. For the calculation of the pooled incidences of CTEPH in the three cohort subtypes, we applied a random effects model according to DerSimonian and Laird [13]. To assess the association for unprovoked PE and recurrent VTE with CTEPH, we calculated the pooled odds ratios (OR) and 95% confidence intervals (95%CI) for both settings, applying the same random effects model to all studies that reported the study outcomes for these subgroups separately, irrespective of the cohort subtype. We assessed heterogeneity across the various cohort studies by calculating the I^2 statistic. Heterogeneity was defined as low in when $I^2 < 25\%$, as intermediate when $I^2 = 25-75\%$ and as high when $I^2 > 75\%$ [14]. The presence of publication bias was evaluated using funnel plot analysis. All analyses were performed in Stata 14.0 (Stata Corp., college Station, TX USA).

RESULTS

Study selection

The initial search identified 477 records in PubMed, 381 records in Medline, 555 records in EMBASE, 302 records in Web of Science, 19 records in the Cochrane Library, 36 records in CINAHL, 85 records in Academic Search Premier and 108 records in Science Direct, resulting in a total of 1062 unique references, including 170 meeting abstracts. After the first screening of title and abstract, 991 records were excluded leaving 71 for more detailed evaluation. An additional 31 studies were excluded after full review: 18 concerned a cohort that (partly) overlapped with other cohorts identified in our search strategy, 7 studies did not provide the study endpoint, 3 were review articles, 2 studies included fewer than 20 patients, and in one study the CTEPH diagnosis was based on International Classification of Diseases insurance codes. We identified one additional relevant study by reviewing the references of the included studies. Therefore, 41 studies were fully assessed for study quality (**Figure 1**) [7, 9, 15-53]. Of those, 13 had intermediate to high risk of bias and were thus not included in the meta-analysis. The evaluation of quality of bias is shown in **Table 1**.

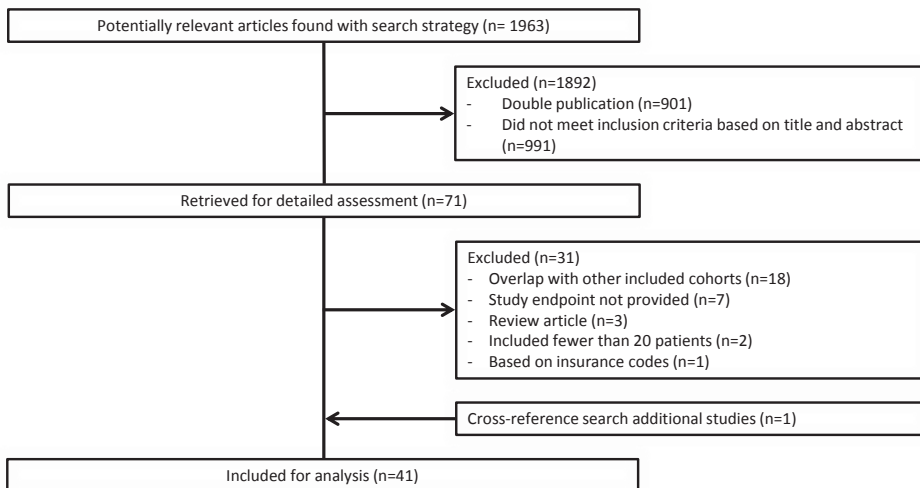


Figure 1. Flow diagram of study selection.

Included studies

All studies were cohort studies including consecutive patients with an episode of acute PE. Sixteen studies confirmed the presence of CTEPH with RHC [7, 17, 18, 22, 27, 28, 30, 31, 33-35, 38, 40, 44, 46, 50] and 12 applied other tests as diagnostic standard (**Table 1**) [9, 15, 19, 21, 23, 26, 37, 41, 43, 45, 48, 49].

The 16 articles using RHC were published between 2004 [7] and 2015 [35], and included 4047 patients selected for screening (range 87-866 per study) [18, 34]. The follow-up duration varied between ≥ 3 months [22] to 8 years [31], with most studies reporting a follow-up period of 2 years (**Table 2**). The diagnostic process of selecting patients for RHC differed among the selected studies. In nine studies all included patients were screened by echocardiography [18, 27, 28, 33-35, 38, 44, 50] and in one study all patients underwent a lung scintigraphy investigation as initial step [40]. In five other studies, echocardiography was only performed if dyspnoea was reported by the individual patients [7, 17, 30, 31, 46]. One study applied the need for further investigation based on a not further defined clinical assessment prior to RHC [22]. Three studies targeted patients with a first PE (595 patients in total) [17, 44, 50] and one study included 87 patients with recurrent VTE only [18]. The other studies focussed on a combination of first and recurrent PE. The general characteristics of the studies are shown in **Table 2**.

Primary analysis: meta-analysis of incidence of CTEPH

The overall weighted pooled incidence of CTEPH across all 16 studies was 2.3% (95%CI 1.5-3.1; $I^2=70.3$; **Figures 2 and 3**). Two studies reported the CTEPH incidences in 1186 'all comers' who had been followed for 2-3 years [34, 40]. The weighted pooled incidence of CTEPH in the 'all comers' was 0.56% (95%CI 0.13-0.98; $I^2=98.3\%$). Four studies focussed on unselected consecutive patients who were alive after an initial treatment period of at least 3 months [22, 30, 31, 35]. The weighted pooled incidence of CTEPH in these 999 'survivors' followed for a period varying from 3 months to 8 years was 3.2% (95%CI 2.0-4.4; $I^2=7.0\%$). One additional study in 'survivors' included 87 patients with recurrent PE only, of whom 5.7% (95%CI 2.5-12.8) were diagnosed with CTEPH after a 22-month follow-up period [18]. Lastly, nine studies focussed on 'survivors without major comorbidity' [7, 17, 27, 28, 33, 38, 44, 46, 50]. In these studies, 1775 patients were followed for 24 months or longer. Their weighted pooled incidence of CTEPH was 2.8% (95%CI 1.5-4.1; $I^2=74.0\%$) (**Figures 2 and 3**). Overall, there was no difference in the incidence of CTEPH between the studies that screened all included patients versus studies that only screened patients who developed symptoms during the follow-up period. Also, a sensitivity analysis confined to studies with ~ 2 years of follow-up did not yield different incidences. Funnel plot analysis illustrated asymmetry which based on the distribution of the studies, is most likely due to between-study heterogeneity (**Figure 4**).

Secondary analysis: effect of unprovoked and recurrent PE

In six of the 16 included articles, the incidences of CTEPH were provided for patients with unprovoked and provoked PE separately [7, 17, 34, 35, 38, 44]. In all these studies, the incidence of CTEPH was higher after unprovoked PE versus provoked PE, for a pooled weighted OR of 4.1 (95%CI 2.1-8.2; $I^2=0.0\%$). A total of seven articles allowed for the

Table 1. Evaluation of presence of bias for all 41 identified relevant studies.

Article	Assessment of bias									Study included	Study included
	Assessment of relevance				Assessment of bias						
	Cohort of consecutive patients	Confirmed PE	Follow-up for CTEPH	CTEPH incidence reported	Incomplete outcome data	Selective outcome reporting	Representative study sample	Quality of CTEPH diagnosis	Overall judgement	CTEPH diagnosed according to current guidelines	CTEPH not diagnosed according to current guidelines
Abul <i>et al</i> 2014 [15]	○	○	○	○	○	○	○	●	●	●	○‡
Barros <i>et al</i> 2013 [16]	○	○	○	○	○	●	○	●	●	●	●
Becattini <i>et al</i> 2006 [17]	○	○	○	○	○	●	○	○	○	○	●
Berghaus <i>et al</i> 2011 [18]	○	○	○	○	○	●	○	○	○	○	●
Beyer-Westendorf <i>et al</i> 2013 [19]	○	○	○	○	○	●	○	○	●	●	○
Casazza <i>et al</i> 2014 [20]	○	○	○	○	●	●	●	○	○	○	●
Choi <i>et al</i> 2014 [21] *	○	○	○	○	○	○	○	○	●	●	○‡
De Foneska <i>et al</i> 2014 [22] *	○	●†	○	○	○	○	○	○	○	○	●
Dentali <i>et al</i> 2009 [23]	○	○	○	○	○	○	○	○	●	●	○‡
Dutt <i>et al</i> 2013 [24]	○	○	○	○	○	●	●	●	●	●	●
Fagerbrink <i>et al</i> 2011 [25]*	○	●†	○	○	●	●	○	●	○	●	●
Gary <i>et al</i> 2012 [26]	●	○	○	○	○	○	○	○	●	●	○
Giuliani <i>et al</i> 2014 [27]	○	○	○	○	○	○	○	○	○	○	●
Golpe <i>et al</i> 2010 [9]	○	○	○	○	○	○	○	○	●	●	○
Guerin <i>et al</i> 2014 [28]	○	○	○	○	○	●	○	○	○	○	●
Hall <i>et al</i> 1977 [29]	○	○	○	○	○	●	●	●	○	●	●
Held <i>et al</i> 2014[30]£	○	○	○	○	○	●	○	○	○	○	●
Hogele <i>et al</i> 2014 [31]*	○	●†	○	○	○	○	○	●	○	○	●
Jie <i>et al</i> 2011 [32]*	●	○	○	○	○	●	●	●	●	●	●
Kayaalp <i>et al</i> 2014 [33]	○	●†	○	○	●	●	○	○	○	○	●
Klok <i>et al</i> 2010 [34]	○	○	○	○	○	○	○	○	○	○	●
Klok <i>et al</i> 2015 [35]	○	○	○	○	○	●	○	○	○	○	●
KolatKirkpantur <i>et al</i> 2004 [36]	●	●†	○	○	○	●	●	●	●	●	●

Table 1. Evaluation of presence of bias for all 41 identified relevant studies. (continued)

Article	Assessment of bias										Study included	Study included	
	Assessment of relevance				Assessment of bias								
	Incomplete outcome data	Selective outcome reporting	Representative study sample	Quality of CTEPH diagnosis	Overall judgement	CTEPH diagnosed according to current guidelines	CTEPH not diagnosed according to current guidelines						
	Cohort of consecutive patients	Confirmed PE	Follow-up for CTEPH	CTEPH incidence reported	Described follow-up of all patients	Missing outcome data <5%	Reporting study protocol and all pre-specified outcomes	Described inclusion and exclusion criteria	CTEPH diagnosed according to current guidelines	Bias in a certain direction?			
Korkmaz <i>et al</i> 2012 [37]	○	○	○	○	○	○	○	○	●	●	●	⊕	
Marti <i>et al</i> 2010 [38]	○	○	○	○	○	●	○	○	○	○	○	●	
Mi <i>et al</i> 2012 [39]*¥	●	○	○	○	●	●	○	●	○	●	●	●	
Miniati <i>et al</i> 2006 [40]	○	○	○	○	●	○	○	○	○	○	○	●	
Otero <i>et al</i> 2011 [41]	○	○	○	○	○	●	○	○	●	●	●	○	
Palwatwinchai <i>et al</i> 2000 [42] *	●	⊕	○	○	●	●	○	●	○	●	●	●	
Pengo <i>et al</i> 2004 [7]	○	○	○	○	○	○	○	○	○	○	○	●	
Pesavento <i>et al</i> 2015 [43] *	○	○	○	○	●	●	○	○	●	●	●	⊕	
Poli <i>et al</i> 2010 [44]	○	○	○	○	○	●	○	○	○	○	○	●	
Ribeiro <i>et al</i> 1999 [45]	●	○	○	○	○	●	○	○	●	●	●	○	
Surie <i>et al</i> 2010 [46]	○	○	○	○	○	●	○	○	○	○	○	●	
Thomas <i>et al</i> 2012 [47]*	○	⊕	○	○	●	●	●	●	●	●	●	●	
Tosun <i>et al</i> 2014 [48]*	●	○	○	○	○	○	○	○	●	●	●	○	
Vanni <i>et al</i> 2010 [49]*	○	⊕	○	○	○	○	○	○	●	●	●	○	
Vavera <i>et al</i> 2014 [50]	○	○	○	○	○	●	○	○	○	○	○	●	
Wilczynska <i>et al</i> 2011 [51]*	●	⊕	○	○	●	●	●	●	○	●	●	●	
Xi <i>et al</i> 2014 [52]	○	○	○	○	●	●	●	○	○	●	●	●	
Yang <i>et al</i> 2014 [53]*	○	⊕	○	○	●	●	●	●	○	●	●	●	

Note: Data are presented as the risk of bias. white: low risk of bias; black: risk of bias; grey: uncertain risk of bias.

PE: pulmonary embolism; CTEPH: chronic thromboembolic pulmonary hypertension. * Only the abstract was available; £ Study is still recruiting patients, data collection not finalized yet; ¥ Article in Chinese; † diagnostic criteria for PE not specified; ‡ Number of patients with abnormal echocardiography not reported.



comparison of first PE versus recurrent VTE [7, 28, 34, 35, 38, 40, 46]. As with unprovoked PE, recurrent VTE was associated with a higher CTEPH incidence than after a first PE for a weighted pooled OR of 3.2 (95%CI 1.7-5.9; $I^2=0.0\%$; **Figure 3**).

Reported incidence of CTEPH not based on RHC

Twelve additional studies that reported the incidence of CTEPH after PE, but failed to confirm this diagnosis by RHC, were selected (**Table 1**). The overall pooled CTEPH incidence in these studies was 6.3% (95%CI 4.1-8.4; $I^2=91.0\%$). In six of these 12 studies CTEPH was diagnosed by echocardiography only, for a pooled CTEPH incidence of 9.1% (95%CI 4.1-14.0; $I^2=94.4\%$) (**Supplementary figure S1**) [9, 19, 26, 41, 45, 48].

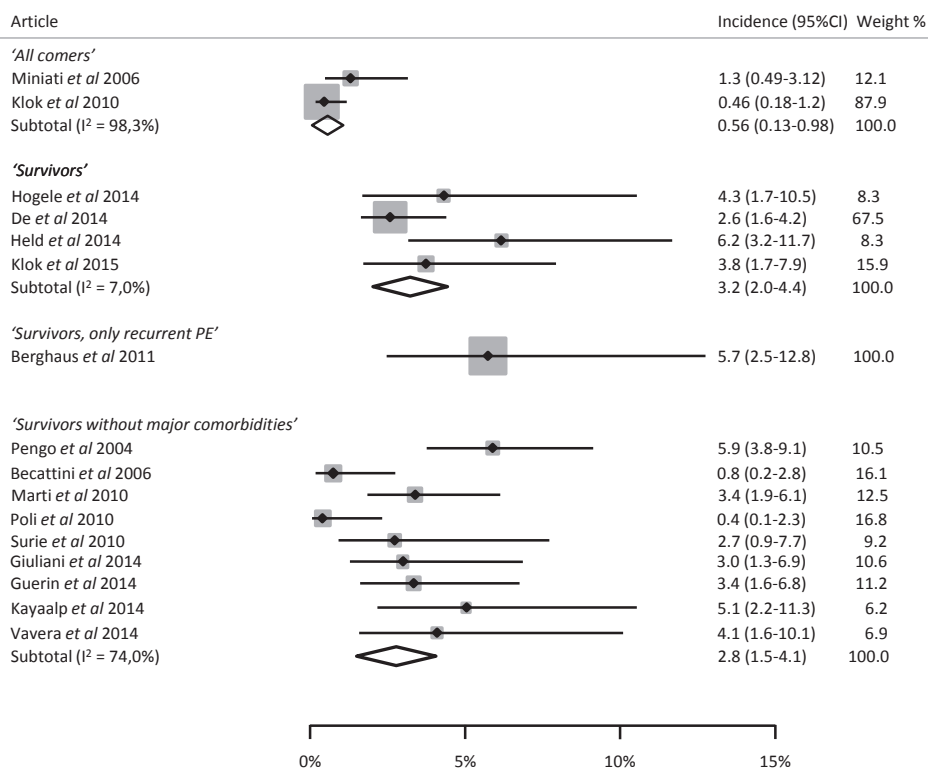


Figure 2. Meta-analysis of the incidences of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism diagnosed with right heart catheterisation.

DISCUSSION

This systematic review and meta-analysis summarizes the existing literature on the incidence of CTEPH after acute PE. Our main findings are incidences of 0.56%, 3.2% and

Table 2. Characteristics of the included articles for the meta-analysis of the primary endpoint.

	Analysis in pro-/ retrospective	Single / multicentre	Number of patients selected for screening	Follow up duration months	Study design	Echo criteria	Number of patients with CTEPH
'All comers'							
Miniati <i>et al</i> 2006 [40]	prospective	single	320	0-4.8	A	<i>not specified</i>	4
Klok <i>et al</i> 2010 [34]	prospective	multi	866	34 †	A	C	4
'Survivors'							
Hogele <i>et al</i> 2014 [31]	<i>not specified</i>	single	93	96	B	D	4
De Foneska <i>et al</i> 2014 [22]	retrospective	single	616	3 £	B	<i>not specified</i>	16
Held <i>et al</i> 2014 [30]	prospective	single	130	3-6	B	E	8
Klok <i>et al</i> 2015 [35]	prospective	single	160	7	A	F	6
'Survivors, only recurrent PE'							
Berghaus <i>et al</i> 2011 [18]	retrospective	single	87	22.5 ¥	A	G	5
'Survivors without major comorbidities'							
Pengo <i>et al</i> 2004 [7]	prospective	single	314	94 ¥	B	<i>not specified</i>	18
Becattini <i>et al</i> 2006 [17]	prospective	multi	259	46 †	B	H	2
Marti <i>et al</i> 2010 [38]	prospective	single	294	24	A	I	10
Poli <i>et al</i> 2010 [44]	prospective	single	239	36 ¥	A	J	1
Surie <i>et al</i> 2010 [46]	retrospective	single	110	24-48	B	D	3
Giuliani <i>et al</i> 2014 [27]	retrospective	single	164	24 †	A	I	5
Guerin <i>et al</i> 2014 [28]	prospective	multi	208	26 ¥	B	K	7
Kayaalp <i>et al</i> 2014 [33]	prospective	single	99	12-24	A	<i>not specified</i>	5
Vavera <i>et al</i> 2014 [50]	prospective	single	97	24	A	<i>not specified</i>	2

Note: CTEPH: chronic thromboembolic pulmonary hypertension; PE: pulmonary embolism; SPAP: systolic pulmonary artery pressure; MPAP: mean pulmonary artery pressure; RVSP: right ventricular systolic pressure; ePASP: estimated pulmonary arterial systolic pressure PAP: pulmonary artery pressure; rV-rA: right ventricle – right atrial; VTR: velocity of the tricuspid regurgitation; VPR: velocity of pulmonary regurgitation. * range in years; † Average; £ Approximately; ¥ Median; A: all consecutive patients with PE were screened for CTEPH; B: Only patients with symptoms were screened for CTEPH; C: SPAP \geq 35 or MPAP \geq 25 or 4 other criteria, needed was 1; D SPAP >40; E: RVSP \geq 35; F: SPAP >36 or 2 other criteria; G: ePASP >50 mmHg; H: PASP >40mmHg, PAP >30; I: PASP \geq 40mmHg; J: rV-rA gradient >35; K: VTR \geq 2,8m/sec or proto-diastolic VPR \geq 2,0 /s and end-diastolic VPR \geq 1,2m/s.

2.8% in the three predefined subpopulations that we focussed on: 'all comers', 'survivors' and 'survivors without major comorbidities'. In accordance with current knowledge [54], we identified unprovoked PE and recurrent VTE as strong risk factors for the development of CTEPH. Lastly, we showed that studies assessing the CTEPH diagnosis with other tests than RHC provide an overestimation of CTEPH incidence (pooled incidence 6.3%), especially those using echocardiographic assessment only (pooled incidence 9.1%).

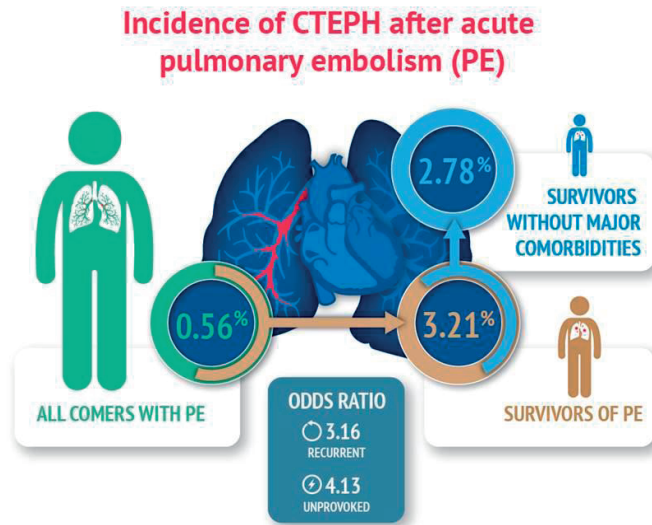


Figure 3. Infographic of primary and secondary study outcomes.
Note: PE: pulmonary embolism.

The pooled incidence of the ‘*all comers*’ after a follow up period of 2-3 years was found to be 0.56%. This number represents the development of CTEPH in unselected patients after a PE diagnosis within this period and best reflects the incidence of CTEPH on population level, mostly because no selection criteria were applied in the relevant studies. Nonetheless, several factors could have influenced this number. The incidence of 0.56% could be an underestimation caused by patients that died or were lost to follow-up without being subjected to objective tests for CTEPH. On the other hand, this number could be an overestimation caused by the possibility that patients diagnosed with an acute PE had been misdiagnosed and already had CTEPH at baseline. This may be even more relevant to studies applying ventilation perfusion (VQ)-scintigraphy as primary diagnostic test for PE, because computed tomography (CT) can show signs of PH that will remain hidden on VQ-scintigraphy. Increasing evidence supports the hypothesis that CTEPH is often misclassified as acute PE [3, 28, 55, 56]. One of the included survivor studies addressed this issue with an echocardiography shortly after the PE diagnosis and a retrospective evaluation of the initial CT for signs of CTEPH at the time of the index PE. It appeared that 5 out of 7 patients diagnosed with CTEPH already had signs of the disease at the initial presentation [28].

Epidemiological studies in CTEPH patients further support the validity of the incidence of CTEPH in the ‘*all comers*’ we describe. Reported annual incidence rates of confirmed CTEPH are 0.9, 4.0 and 5 per million adults in the western world [57-59]. Approximately 25% of these CTEPH patients lack a history of acute PE [5]. Considering the latter and a 1-per-1000 annual rate of PE, the estimated incidence of confirmed CTEPH after acute

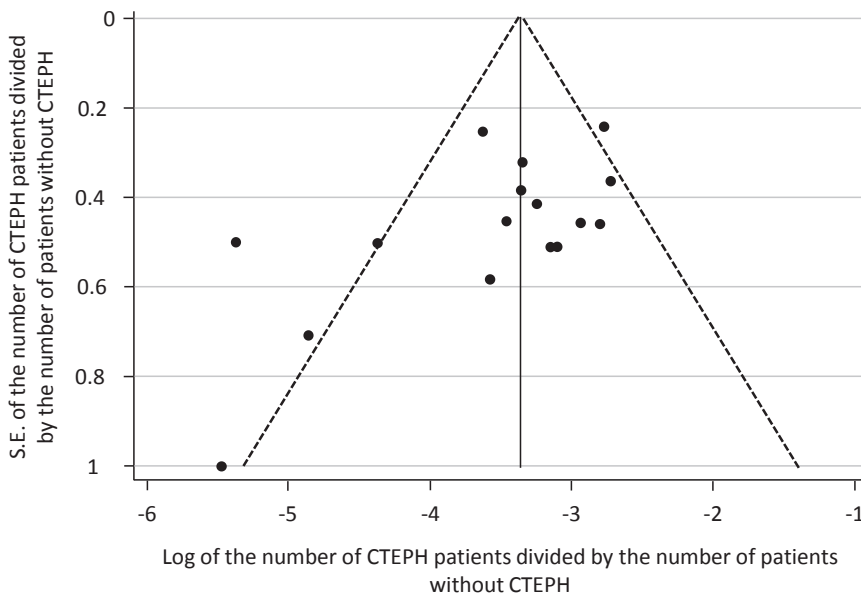


Figure 4. Funnel plot analysis with the log of the number of patients with CTEPH divided by the number of patients without CTEPH.

Note: CTEPH: chronic thromboembolic pulmonary hypertension; SE: Standard Error.

PE ranges between 0.1 and 0.4%. Of note, it is generally accepted that CTEPH is underdiagnosed in current clinical practice [60]. Taking the latter into account, the upper limit of this range is likely more accurate.

The incidence of 3.2% in the 'survivor' cohort and 2.8% in the 'survivor without major comorbidities' cohort may be more relevant for clinical practice because these are the patients who visit the outpatient clinic of our daily practices. With a 0.56% incidence in 'all comers' and considering the number of patients who died or were lost to follow-up without being subjected to objective tests for CTEPH, we expected to find an incidence of CTEPH between 1.2 and 1.8%. However, we observed a five-fold higher incidence in the survivor cohorts instead. The main reason for an overestimation of the CTEPH incidence in the 'survivor' cohorts is that patients with unprovoked PE were overrepresented in the 'survivor' cohort (48% versus 36% in the 'all comers' cohort), indicating patient selection towards a higher CTEPH risk profile. Other, less clear patient selection differences between all-comer patient cohorts and survivor patient cohorts could have further contributed to an overestimation of the CTEPH incidence in the latter, such as the exclusion of patients with high risk PE who were not excluded from the 'all-comer' study cohorts but were mostly excluded from the studies evaluating the 'survivors'. Also, misclassification of acute PE at baseline as described above may be more relevant for the 'survivor' cohorts since VQ-scintigraphy was not applied as diagnostic test for PE in

the '*all comer*' cohorts, in contrast to the '*survivor cohorts*'. Of note, the differentiation of acute PE, CTEPH or subacute PE in pre-existing CTEPH is very difficult to make in clinical practice because PH is a common finding in acute PE and information on the preceding pulmonary hemodynamic status is lacking for most patients. Although no systematic search has ever been performed, perhaps extensive evaluation of the CT scans including actively looking for webs, bands, vascular strictures, recanalised thrombi and right ventricular hypertrophy, which are all findings of CTEPH and not acute PE, as well as monitoring of the hemodynamic recovery by sequential echocardiography in the weeks after treatment initiation may help the clinician to make the distinction. This would have to be the topic of further study.

We expected to find a higher incidence of CTEPH in the '*survivors without major comorbidities*' compared to the '*survivors*' because the presence of cardiopulmonary diseases may impede optimal diagnosis of CTEPH. Nevertheless, we did not find a difference in the pooled incidence of CTEPH between survivors with or without major comorbidities (3.2% versus 2.8%). In a recent study of the European CTEPH registry including 679 patients diagnosed with CTEPH, many indeed had a concomitant diagnosis of cancer (12.7%), of coronary disease and/or myocardial infarction (11.8%) and chronic obstructive pulmonary disease (9.5%) [5]. From this we conclude that CTEPH should be considered in all patients with CTEPH-associated symptoms despite any known other cardiopulmonary disease.

Interestingly, the reported incidences of CTEPH after acute PE in the studies that applied screening tests to all patients were not higher than in those that only screened patients who reported CTEPH-associated signs or symptoms throughout the study period. This could indicate that, although CTEPH can remain asymptomatic for months, all or almost all patients will become symptomatic at some point in the course of the disease. Notably, the studies that screened all patients and described whether the patients diagnosed with CTEPH had symptoms or not, reported that all CTEPH patients had mild to severe symptoms at the moment of diagnosis, and all were diagnosed within a period of 2 years from the PE diagnosis [18, 34, 38, 44]. Based on this observation one might argue that specific diagnostic tests for CTEPH need only be initiated when symptoms occur, as recommended by the European Society of Cardiology guideline [3]. On the other hand, the mean time to diagnosis may have been considerably shorter in the studies that screened all patients. This would support a strategy of screening patients independent of symptoms. Unfortunately, these relevant data could not be extracted from the included studies. Based on current analysis, no firm conclusions can be made on if, in whom, when and how screening for CTEPH should optimally be performed. An algorithm that was specifically designed for this purpose consisting of sequential application of a recently published clinical decision rule and the simple '*CTEPH rule-out*' criteria, is being evaluated in an international multicentre prospective outcome study

(Clinical Trials.gov identifier NCT02555137) [35, 61, 62]. The results of this study will allow for more accurate recommendations with regard to optimal follow-up of patients with PE on the development of CTEPH.

Strengths of our analysis include the strict selection criteria applied, allowing for the pooling of high quality studies with adequate diagnosis of CTEPH. We also harmonized the calculation of the CTEPH incidences using identical criteria for each study. Further, we predefined three relevant subcategories and compared studies that did or did not use RHC to diagnose CTEPH. Lastly, our finding that unprovoked PE and recurrent VTE are risk factors for CTEPH are in accordance with the literature which underlines the validity of our work [54].

This meta-analysis has limitations as well. First as mentioned before CTEPH can be misclassified as acute PE [3, 28, 55, 56] although unfortunately we are not able to make this distinction in the information that was available from the studies. Of note, because CTEPH could have been present at baseline in some patients, the incidences found in our meta-analyses could actually reflect a combination of the incidence and prevalence of CTEPH. Second the duration of follow-up varied between the included studies. Because we did not have access to patient level data and the reporting of the follow-up time differed (means versus medians versus ranges), it was technically impossible to take individual follow-up time into account. Nonetheless, 12 of the 16 studies reported on a follow-up duration ≥ 2 years. As argued above, this period is likely to capture all cases of CTEPH. Third, the echocardiographic criteria for referral for RHC were slightly different across the studies, which could have induced misclassification and further patient selection. Fourth, we were not able to select the number of patients adequately treated with anticoagulants, because this was not reported in any of the studies. Inadequate anticoagulation may contribute to the development of CTEPH [63]. Fifth, despite categorizing the included studies in 3 subgroups, we only achieved relevant inter-study homogeneity for the cohort that included 'survivors' ($I^2 = 7.0$) [14]. The main reason this was not achieved in the 'all-comer' cohort was the low number of two studies in this category. For the 'survivors without major comorbidities', this lack of homogeneity was probably caused by important differences in the definition of major comorbidities among the studies. Finally, by design, we were unable studying interesting patient groups such as those with cancer or systemic inflammatory disease [64].

In conclusion, the overall pooled incidence of CTEPH in the included studies was 2.3%. The incidence of CTEPH in 'all comer' cohort was low (0.56%). This number provides the best estimation of the incidence of CTEPH on population level while the ~3% incidences in the survivor categories may be more relevant for daily clinical practice. Studies that assessed the CTEPH diagnosis by tests other than RHC provide overestimated CTEPH incidences.

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APPENDIX A: SEARCH STRATEGY

PubMed

('CTEPH'[tw] OR 'chronic thromboembolic pulmonary hypertension'[tw] OR chronic thromboembolic pulmonary hypertens*[tw] OR 'chronic thromboembolic pulmonary arterial hypertension'[tw] OR 'chronic thrombo-embolic pulmonary hypertension'[tw] OR chronic thrombo-embolic pulmonary hypertens*[tw] OR chronic major vessel thromboembolic pulmonary hypertens*[tw] OR 'chronic thromboembolic PH'[tw] OR 'chronic thrombo-embolic PH'[tw] OR 'chronic thromboembolic hypertension'[tw] OR 'chronic thrombo-embolic hypertension'[tw] OR ('chronic'[tw] AND (thromboembolic pulmonary hypertens*[tw] OR thrombo-embolic pulmonary hypertens*[tw])) OR (('chronic'[ti] AND (thromboembol*[ti] OR thrombo-embol*[ti]) AND pulmonary hypertens*[ti])) OR (('Chronic Disease'[mesh] AND 'Hypertension, Pulmonary'[mesh] AND 'Pulmonary Embolism'[mesh])) OR (('chronic'[tw] AND (thromboembol*[tw] OR thrombo-embol*[tw]) AND pulmonary hypertens*[tw])) OR ('Hypertension, Pulmonary'[mesh] AND 'Pulmonary Embolism'[mesh] AND 'Thromboembolism'[mesh]) OR (('Hypertension, Pulmonary'[majr] AND 'Pulmonary Embolism'[mesh]) OR ('Hypertension, Pulmonary'[mesh] AND 'Pulmonary Embolism'[majr])) AND ('Incidence'[Mesh] OR 'incidence'[tw] OR incidence*[tw] OR 'Epidemiology'[Mesh] OR 'epidemiology'[Subheading] OR 'Risk Factors'[Mesh] OR 'Risk'[mesh] OR 'clinical profile'[tw] OR 'clinical profiles'[tw])

MEDLINE

('CTEPH'.mp OR 'chronic thromboembolic pulmonary hypertension'.mp OR chronic thromboembolic pulmonary hypertens*.mp OR 'chronic thromboembolic pulmonary arterial hypertension'.mp OR 'chronic thrombo-embolic pulmonary hypertension'.mp OR chronic thrombo-embolic pulmonary hypertens*.mp OR chronic major vessel thromboembolic pulmonary hypertens*.mp OR 'chronic thromboembolic PH'.mp OR 'chronic thrombo-embolic PH'.mp OR 'chronic thromboembolic hypertension'.mp OR 'chronic thrombo-embolic hypertension'.mp OR ('chronic'.mp AND (thromboembolic pulmonary hypertens*.mp OR thrombo-embolic pulmonary hypertens*.mp)) OR (('chronic'.ti AND (thromboembol*.ti OR thrombo-embol*.ti) AND pulmonary hypertens*.ti)) OR ((exp 'Chronic Disease'/ AND exp 'Hypertension, Pulmonary'/ AND exp 'Pulmonary Embolism'/) OR (('chronic'.mp AND (thromboembol*.mp OR thrombo-embol*.mp) AND pulmonary hypertens*.mp)) OR (exp 'Hypertension, Pulmonary'/ AND exp 'Pulmonary Embolism'/ AND exp 'Thromboembolism'/) OR ((exp *'Hypertension, Pulmonary'/ AND exp 'Pulmonary Embolism'/) OR (exp 'Hypertension, Pulmonary'/ AND exp *'Pulmonary Embolism'/))) AND (exp 'Incidence'/ OR 'incidence'.mp OR incidence*.mp OR exp 'Epidemiology'/ OR 'ep'.fs OR exp 'Risk Factors'/ OR exp 'Risk'/ OR 'clinical profile'.mp OR 'clinical profiles'.mp)

Embase

(chronic thromboembolic pulmonary hypertension'/ep) OR (('chronic thromboembolic pulmonary hypertension'/ OR 'CTEPH'.mp OR 'chronic thromboembolic pulmonary hypertension'.mp OR chronic thromboembolic pulmonary hypertens*.mp OR 'chronic thromboembolic pulmonary arterial hypertension'.mp OR 'chronic thrombo-embolic pulmonary hypertension'.mp OR chronic thrombo-embolic pulmonary hypertens*.mp OR chronic major vessel thromboembolic pulmonary hypertens*.mp OR 'chronic thromboembolic PH'.mp OR 'chronic thrombo-embolic PH'.mp OR 'chronic thromboembolic hypertension'.mp OR 'chronic thrombo-embolic hypertension'.mp OR ('chronic'.ti AND (thromboembolic pulmonary hypertens*.ti OR thrombo-embolic pulmonary hypertens*.ti)) OR (('chronic'.ti AND (thromboembol*.ti OR thrombo-embol*.ti) AND pulmonary hypertens*.ti) OR ((exp '*Chronic Disease'/ AND exp '*Pulmonary Hypertension'/ AND exp '*Lung Embolism'/)) OR (('chronic'.ti AND (thromboembol*.ti OR thrombo-embol*.ti) AND pulmonary hypertens*.ti) OR (exp '*Pulmonary Hypertension'/ AND exp '*Lung Embolism'/ AND exp '*Thromboembolism'/) OR ((exp '*Pulmonary Hypertension'/ AND exp '*Lung Embolism'/) OR (exp '*Pulmonary Hypertension'/ AND exp '*Lung Embolism'/)) AND (exp 'Incidence'/ OR 'incidence'.mp OR incidence*.mp OR 'Epidemiology'/ OR exp 'Risk Factor'/ OR exp 'Risk'/ OR 'clinical profile'.mp OR 'clinical profiles'.mp))

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(TS=('chronic thromboembolic pulmonary hypertension' OR 'CTEPH' OR 'chronic thromboembolic pulmonary hypertension' OR chronic thromboembolic pulmonary hypertens* OR 'chronic thromboembolic pulmonary arterial hypertension' OR 'chronic thrombo-embolic pulmonary hypertension' OR chronic thrombo-embolic pulmonary hypertens* OR chronic major vessel thromboembolic pulmonary hypertens* OR 'chronic thromboembolic PH' OR 'chronic thrombo-embolic PH' OR 'chronic thromboembolic hypertension' OR 'chronic thrombo-embolic hypertension') OR TI=('chronic' AND (thromboembolic pulmonary hypertens* OR thrombo-embolic pulmonary hypertens*)) OR TI=((('chronic' AND (thromboembol* OR thrombo-embol*) AND pulmonary hypertens*)) OR TI=((('Chronic Disease' AND 'Pulmonary Hypertension' AND 'Lung Embolism')) OR TI=((('chronic' AND (thromboembol* OR thrombo-embol*) AND pulmonary hypertens*)) OR TI=('Pulmonary Hypertension' AND 'Lung Embolism' AND 'Thromboembolism') OR TI=('Pulmonary Hypertension' AND 'Lung Embolism')) AND TS=('Incidence' OR 'incidence' OR incidence* OR 'Epidemiology' OR 'Risk Factor' OR 'Risk' OR 'clinical profile' OR 'clinical profiles')

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((('chronic thromboembolic pulmonary hypertension' OR 'CTEPH' OR 'chronic thromboembolic pulmonary hypertension' OR chronic thromboembolic pulmonary hypertens* OR 'chronic thromboembolic pulmonary arterial hypertension' OR 'chronic thrombo-embolic pulmonary hypertension' OR chronic thrombo-embolic pulmonary hypertens* OR chronic major vessel thromboembolic pulmonary hypertens* OR 'chronic

thromboembolic PH' OR 'chronic thrombo-embolic PH' OR 'chronic thromboembolic hypertension' OR 'chronic thrombo-embolic hypertension') OR ('chronic' AND (thromboembolic pulmonary hypertens* OR thrombo-embolic pulmonary hypertens*)) OR (('chronic' AND (thromboembol* OR thrombo-embol*) AND pulmonary hypertens*)) OR (('Chronic Disease' AND 'Pulmonary Hypertension' AND 'Lung Embolism')) OR (('chronic' AND (thromboembol* OR thrombo-embol*) AND pulmonary hypertens*)) OR ('Pulmonary Hypertension' AND 'Lung Embolism' AND 'Thromboembolism') OR ('Pulmonary Hypertension' AND 'Lung Embolism')) AND ('Incidence' OR 'incidence' OR incidence* OR 'Epidemiology' OR 'Risk Factor' OR 'Risk' OR 'clinical profile' OR 'clinical profiles')

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(('chronic thromboembolic pulmonary hypertension' OR 'CTEPH' OR 'chronic thromboembolic pulmonary hypertension' OR chronic thromboembolic pulmonary hypertens* OR 'chronic thromboembolic pulmonary arterial hypertension' OR 'chronic thrombo-embolic pulmonary hypertension' OR chronic thrombo-embolic pulmonary hypertens* OR chronic major vessel thromboembolic pulmonary hypertens* OR 'chronic thromboembolic PH' OR 'chronic thrombo-embolic PH' OR 'chronic thromboembolic hypertension' OR 'chronic thrombo-embolic hypertension') OR ('chronic' AND (thromboembolic pulmonary hypertens* OR thrombo-embolic pulmonary hypertens*)) OR (('chronic' AND (thromboembol* OR thrombo-embol*) AND pulmonary hypertens*)) OR (('Chronic Disease' AND 'Pulmonary Hypertension' AND 'Lung Embolism')) OR (('chronic' AND (thromboembol* OR thrombo-embol*) AND pulmonary hypertens*)) OR ('Pulmonary Hypertension' AND 'Lung Embolism' AND 'Thromboembolism') OR ('Pulmonary Hypertension' AND 'Lung Embolism')) AND ('Incidence' OR 'incidence' OR incidence* OR 'Epidemiology' OR 'Risk Factor' OR 'Risk' OR 'clinical profile' OR 'clinical profiles')

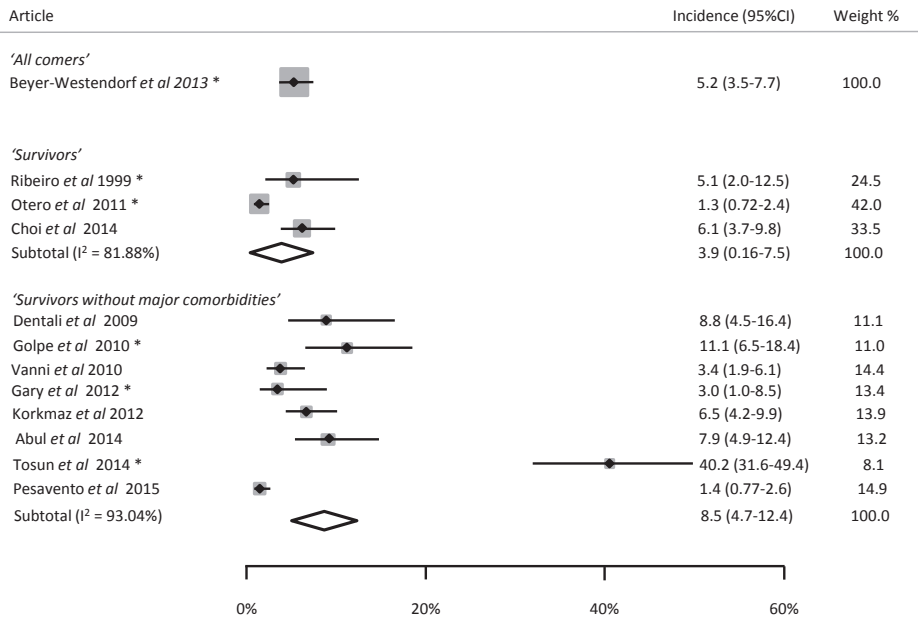
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pulmonary hypertens* OR chronic major vessel thromboembolic pulmonary hypertens* OR 'chronic thromboembolic PH' OR 'chronic thrombo-embolic PH' OR 'chronic thrombo-embolic hypertension' OR 'chronic thrombo-embolic hypertension') AND ('Incidence' OR 'incidence' OR incidence* OR 'Risk Factor' OR 'risk factors' OR 'clinical profile' OR 'clinical profiles'))



Appendix B. Meta-analysis of the incidences of CTEPH diagnosed with other diagnostic tests than RHC. Note: * CTEPH diagnosed by echocardiogram only; CTEPH: chronic thromboembolic pulmonary hypertension; RHC: right heart catheterization.

