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Risk of Recurrent Venous Thromboembolism and Major Haemorrhage in Cancer-Associated Incidental Pulmonary Embolism amongst Treated and Untreated Patients

- a pooled analysis of 926 patients -

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Abstract

Introductions: Incidental pulmonary embolism (IPE) is defined as pulmonary embolism (PE) diagnosed on CT-scan not performed for suspected PE. IPE has been estimated to occur in 3.1% of all cancer patients and is a growing challenge for clinicians and patients. Nevertheless, knowledge about the treatment and prognosis of cancer-associated IPE is scarce. We aimed to provide the best available evidence on IPE management.

Methods: Incidence rates of symptomatic recurrent venous thromboembolism (VTE), major haemorrhage and mortality during 6-month follow-up were pooled using individual patient data from studies identified by a systematic literature search. Subgroup analyses based on cancer stage, thrombus localization and management were performed.

Results: In 926 cancer patients with IPE from 11 cohorts, weighted pooled 6-month risks of recurrent VTE, major haemorrhage and mortality were 5.8% (95%CI 3.7-8.3), 4.7% (95%CI 3.0-6.8) and 37% (95%CI 28-47). VTE recurrence risk was comparable under low molecular weight heparins (LMWH) and vitamin-K antagonists (VKA) (6.2% vs. 6.4%; hazard ratio (HR) 0.9; 95%CI 0.3-3.1), while 12% in untreated patients (HR 2.6; 95%CI 0.91-7.3). Risk of major haemorrhage was higher under VKA than LMWH (13% vs 3.9%; HR 3.9; 95%CI 1.6-10). VTE recurrence risk was comparable in patients with an subsegmental IPE and those with a more proximally localized IPE (HR 1.1; 95%CI 0.50-2.4).

Conclusion: These results support the current recommendation to anticoagulate cancer-associated IPE with LMWH and argue against different management of subsegmental IPE.

Keywords: pulmonary embolism; incidental finding; venous thromboembolism; prognosis; hemorrhage

Introduction

Incidental pulmonary embolism (IPE) is defined as pulmonary embolism diagnosed on a computed tomography (CT) scan performed for reasons other than a clinical suspicion of pulmonary embolism (PE). In cancer patients IPE has been estimated to occur in 2.2 to 4.1% [1]. Knowledge of the clinical implications of cancer-associated IPE is scarce and almost entirely based on small observational studies. Key finding of these studies was the similar prognosis with regard to recurrence risk, major haemorrhage and mortality in cancer patients with IPE compared to those with proven symptomatic PE (SPE) [2-4]. Based on these observations, international guidelines recommend an identical anticoagulant treatment regimen for cancer-associated IPE and SPE, and consequently almost all patients with IPE receive anticoagulant treatment (ACCP level of Evidence 2B) [5,6].

However, it should be noted that the supporting evidence for this recommendation is limited by the small size of the studies. In addition, essential clinical questions on the subject of IPE management remain unanswered, namely i) the risks of recurrent venous thrombolembolism (VTE) if left untreated, ii) the risks of haemorrhage and its dependence on the type of anticoagulation, and iii) the relevance of subsegmental IPE versus more centrally located IPE. In order to provide the best available evidence on the management of IPE, we pooled individual patient data from 11 observational studies and ongoing registries, that were identified by a systematic literature search.

Methods

Data sources, searches and study selection

We searched PubMed, MEDLINE, EMBASE, Web of Science, Academic Search Premier, Science Direct and the Cochrane Database of systematic reviews for publications concerning cancer patients with IPE from inception to November 2013. The search strategy is avaialable in **Supplement 1**. The electronic

search was complemented by a manual review of reference lists of relevant articles and we contacted experts to ask about the existence of unpublished cohorts.

References were screened for relevance by two independent reviewers based on the title and abstract (TvdH and PdE). Discrepancies were resolved by consensus after contacting a third reviewer (FK). Abstracts or full-text articles identified by either reviewer as potentially relevant were retrieved for further evaluation. Predefined inclusion criteria for eligible cohorts were: 1) ≥20 consecutive patients with IPE; 2) patients with a concomitant active cancer (both solid and hematologic cancer), defined as cancer diagnosed within six months before IPE, recurrence or progressive cancer or any cancer that necessitated curative or palliative treatment within the previous six months; 3) at least six months follow-up; 4) information about the management of the IPE; and 5) reporting at least one of the predefined primary and/or secondary study endpoints. Completed studies as well as ongoing patient registries were eligible. An invitation and study proposal were sent to the authors of the selected references as well as at least one reminder.

Patients and clinical data collection

IPE was defined as PE detected on a CT scan ordered for reasons other than a clinical suspicion of PE [7]. Patients were managed according to local practices. International guidelines available during the study periods recommended anticoagulant treatment for a period of at least six months with prolongation for as long as the cancer was active [5,8,9]. Low molecular weight heparin (LMWH) was the treatment of choice for cancer-associated -incidental- VTE from 2004 onwards.

Individual patient level data were collected, consisting of general baseline characteristics, the location of IPE and the applied anticoagulant treatment regimen. The primary endpoint was the occurrence of symptomatic recurrent VTE, defined as a positive finding of the diagnostic work-up of suspected acute PE or DVT of the lower or upper extremities [10]. Incidental VTE events were not

adjudicated as recurrent events. Secondary endpoints included major haemorrhage, fatal haemorrhage and mortality. The duration of follow-up was six months. DVT of the lower extremities was diagnosed in case of non-compressibility by compression ultrasonography (CUS) at the trifurcation of the popliteal vein or above, or in case of an intraluminal filling defect above the trifurcation of the popliteal vein by CT-scan or venography [5,10]. Recurrent PE was diagnosed in case of a new intraluminal filling defect in a subsegmental or greater sized pulmonary artery, or in case of a ventilation/perfusion scanning with a high probability of PE in a new lung segment unaffected by the index IPE, or in case of a new intraluminal filling defect by pulmonary angiography [6]. Major haemorrhage was defined as overt and associated with a decrease in the hemoglobin level of ≥2 g dL^{-1}, requiring transfusion of at least two units of blood, occurring in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular intramuscular with compartment syndrome, retroperitoneal), or contributing to death [11].

Statistical analysis

The endpoints were defined and all statistical analyses were performed according to a predefined statistical protocol, agreed upon by all authors. Baseline characteristics were reported for the combined cohorts and for subgroups based on the management of the IPE. All outcomes were pooled using the DerSimonian-Laird weights in a random effects model. Additionally, baseline characteristics and outcomes were reported for the individual cohorts **(Supplement 3)**.

For the subgroup analyses, outcomes were pooled using the DerSimonian-Laird weights in a random effects model. In order to calculate hazard ratios, all cohorts and registries were combined and considered as one cohort. Subgroups analyses were performed for: 1) patients treated with LMWH, patients treated with vitamin-K antagonists (VKA) after an initial course of LMWH and those who were left untreated; 2) patients with metastatic cancer and non-metastatic cancer; 3) patients

with centrally located thrombi (defined as a central or lobar thrombus location) and more peripherally located thrombi (defined as a segmental or subsegmental thrombus location). Additionally, outcomes for patients with isolated subsegmental IPE were reported separately. Hazard ratios were calculated using Cox regression analysis. Regarding the subgroup analysis based on management, an intention to treat analysis was used for which patients were classified according to the initial management even when anticoagulant treatment was prematurely discontinued. Additionally, per-treatment analysis was performed for which outcomes were related to the management at the time the outcome occurred. A competing risk model was used for the survival tables for recurrent VTE and major bleeding with death as competing risk. SPSS, version 20 (SPSS Inc, Chicago, IL) and StatsDirect software (StatsDirect Ltd, Cheshire, UK) were used for all analyses.

Results

Identification of cohorts and registries

The initial search identified 106 records in PubMed, 61 unique references in MEDLINE, 153 unique references in EMBASE, 28 unique references in Web of Science, 12 unique references in the Cochrane Database of systematic reviews and two unique references in Academic Search Premier, resulting in a total of 362 references. Based on screening titles and abstracts, 44 references were extensively studied and when available read in full text. Of these 44 references, 11 references were excluded because no or only limited follow-up was reported, 12 because they concerned fewer than 20 patients, one because IPE were diagnosed on additionally performed CTPA after the initial CT-scan, and one because it did not meet the definition of IPE (See **Supplement 2** for excluded references). Finally, 19 references from the literature search and one unpublished registry that met our inclusion criteria were included. Patients of the unpublished registry were collected in the Ramón y Cajal Hospital in Madrid, Spain. Of these 20 cohorts, the authors of four references refrained from

participating [12-15] and the authors of five references [16-20] did not respond to repeated invitations, resulting in the inclusion of 11 cohorts and registries [2,4,21-28] **(Figure 1)**.

Baseline characteristics

The number of patients of the 11 included individual cohorts and registries varied from 21 to 204 patients **(Supplement 3, Table i)**. All cohorts and registries were collected from 2001 and 2013. Nine of the 11 cohorts and registres were retrospectively collected and two were prospectively collected. In total, individual patient data of 945 patients were available of which 6-month follow-up data were complete for 926 patients (98%) and these comprised the study patients of which baseline characteristics are shown in **Table 1**. A total of 732 patients (79%) were treated with prolonged therapeutic LMWH, 100 patients (11%) were treated with VKA, 41 patients (4.4%) received another treatment, i.e. inferior vena cava filter or unfractionated heparin, and 53 patients (5.7%) did not receive any treatment.

Symptomatic recurrent venous thromboembolism

Data regarding the occurrence of recurrent VTE were available from 10 of the 11 cohorts including 857 patients, of whom 19 patients developed an objectively proven DVT and 22 recurrent PE (±DVT) and of three patients the type of the recurrent VTE was unspecified. Overall weighed pooled incidence rates are provided in **Table 2**. Nine (20%) of these 44 recurrent VTE occurred while anticoagulant treatment was discontinued: four events during temporarily discontinuation of LMWH, and five after treatment with LMWH was permanently stopped.

The risk of recurrent VTE was non-significantly higher in patients with metastatic cancer at time of diagnosing IPE compared to those with non-metastatic cancer with a hazard ratio (HR) of 1.4

(95%CI 0.59-3.2) adjusted for age, sex, type of cancer and management **(Supplement 3, Table iv)**. Regarding the location of the IPE, the weighted pooled 6-month risk of recurrent VTE was comparable in patients with a centrally located IPE compared to those with peripherally located IPE, 5.6% (95%CI 3.1-8.7) and 6.6% (95%CI 3.5-11) respectively with a HR of 0.65 (95%CI 0.22-1.9) adjusted for age, sex, type of cancer, cancer stage and management **(Supplement 3, Table v)**. When patients with a subsegmental IPE were compared to those with a more centrally located IPE, incidence rates were 7.8% (95%CI 2.8-14.9) and 5.5% (95%CI 2.9-8.8) respectively, with a HR of 1.3 (95%CI 0.57-3.0) adjusted for age, sex, type of cancer, cancer stage and management.

Based on the intention to treat analysis, the weighted pooled 6-month risk of recurrent VTE was 6.2% (95%CI 3.5-12) in patients treated with LMWH and 6.4% (95%CI 2.2-12) in those who received VKA **(Table 2A, Figure 2)**, with a hazard ratio adjusted for sex, age, type of cancer and cancer stage of 0.92 (95%CI 0.3-3.1). In the 10 cohorts that reported data on recurrent VTE, a total of 42 (4.9%) patients did not receive any anticoagulant treatment of whom four developed symptomatic VTE, resulting in a weighted pooled 6-month risk of 12% (95%CI 4.7-23). Of these 42 patients, seven had a centrally located IPE, 18 had a segmental IPE, four had a subsegmental IPE and in 13 patients the thrombus location was unspecified. Of the 4 patients who did not receive anticoagulant treatment and developed a recurrent VTE, two had a subsegmentally located IPE and the other two had a segmentally located IPE. Compared to patients who were treated with either LMWH or VKA, the HR of symptomatic recurrent VTE in patients who did not receive anticoagulant treatment was 2.0 (95%CI 0.65-5.9) adjusted for age, sex, type of cancer and cancer stage.

Based on the per-treatment analysis, the incidence rates of recurrent VTE were 12 per 100 patient years (PY) (31 events during 252 years of treatment; 95%CI 8.3-17) and 9.8 per 100 PY (3 events during 31 years of treatment; 95%CI 2.0-29) while on LMWH and while on VKA, respectively. For patients who did not receive anticoagulant treatment, either from the initial diagnosis or after

LMWH or VKA was stopped within 6 months for reasons other than death, the incidence rate was 20 per 100 PY (9 events during 45 years of treatment; 95%CI 9.2-38) **(Table 2B)**.

Major haemorrhage

Information regarding major haemorrhage was available for 10 cohorts concerning a total of 857 patients of whom 38 patients experienced a major haemorrhage. Overall weighed pooled incidence rates are provided in **Table 2**. The risk of major haemorrhage was comparable in patients with metastatic and non-metastatic cancer and in patients with a centrally located IPE compared to those with a peripherally located IPE, with a HR of 1.8 (95%CI 0.68-4.8) adjusted for age, sex, type of cancer and management and 1.0 (95%CI 0.31-3.0), adjusted for age, sex, type of cancer, cancer stage and management **(Supplement 3, Tables iv and v)**.

Based on the intention to treat analysis, the weighted pooled 6-month risk of major haemorrhage was significantly higher in patients treated with VKA compared to those treated with LMWH, 13% (95%CI 6.4-20) versus 3.9% (95%CI 2.3-5.9) with a HR of 4.0 (95%CI 1.5-10) adjusted for age, sex, type of cancer and cancer stage. The weighted 6-month pooled risk of major haemorrhage in patients who were left untreated was 6.4% (95%CI 1.3-15) (**Table 2A**, **Figure 3**). Based on the per-treatment analysis, the incidence rate of major haemorrhage while on VKA treatment was 26 per 100 PY (8 events during 30 years of treatment; 95%CI 11-52), and while on LMWH treatment the incidence rate was 10 per 100 PY (26 events during 257 years of treatment; 95%CI 6.6-15) **(Table 2B)**.

Mortality

Of the 926 patients, 331 died during follow-up resulting in a weighted pooled 6-month mortality of 37% (95%CI 28-47; **Table 2A**). Mortality varied between cancer type and cancer stage **(Supplement 3,**

Tables iii and iv). The weighted pooled 6-month mortality was higher in patients with a centrally located IPE compared to those with a peripherally located IPE: 42% (95%CI 33-52) versus 30% (95%CI 25-36) with a HR of 1.5 (95%CI 1.1-2.0) adjusted for age, sex, type of cancer, cancer stage and management. Patients with a centrally located IPE more frequently had metastatic cancer (79%) compared to those with a more peripherally located IPE (67%) (Chi-Square test: $p<0.01$).

The weighted pooled 6-month mortality was 37% (95%CI 29-44) in patients treated with LMWH and 28% (95%CI 18-40) in those treated with VKA (HR 1.1; 95%CI 0.70-1.6 adjusted for age, sex, cancer type and cancer stage). In patients who did not receive any treatment, the weighted pooled 6-month mortality was 47% (95%CI 28-66).

Discussion

This study of individual patient data of 926 patients from 11 registries is the largest study on cancer-associated IPE thus far and provides several important new findings.

First, this study demonstrates a 6-month VTE recurrence risk of 12% (95%CI 4.7-23) in patients who were left untreated. Although it is possible that these patients were left untreated for a specific reason, i.e. a high risk of haemorrhage, a poor overall prognosis or a supposed low risk of recurrent VTE, the patient's characteristics did not differ greatly from treated patients. Importantly, the higher mortality in the untreated patients may even have resulted in an underestimation of the pooled 6-month VTE recurrence risk due to significant competing risk of death. In the per-treatment analysis, the incidence rate of recurrent VTE in patients who did not receive anticoagulant treatment was even 30 per 100 PY (95%CI 8.2-77). Thus, this observation emphasizes the high risk of symptomatic recurrent VTE in cancer patients with IPE and recalls the effect size of anticoagulants used in symptomatic PE, thereby supporting the initiation of anticoagulation in cancer-associated IPE [5,6].

Second, we observed a comparable efficacy of VKA and LMWH with a significantly higher risk of major haemorrhage in patients who were treated with VKA. Although these findings should be interpreted with caution due to the observational study design and the lack of information about the quality of anticoagulant treatment, it seems unlikely that patients with a high risk of major haemorrhage were predominantly assigned to VKA. This is reflected by the comparable baseline characteristics of both groups and by the non-significantly lower mortality in patients treated with VKA. Notably, a comparable risk of major haemorrhage between oral and parenteral anticoagulants has been demonstrated in cancer patients with proven clinically suspected PE, while the recurrence risk was lower in those treated with LMWH [29]. This notable difference between the efficacy and safety of oral versus parenteral anticoagulants in IPE and SPE may be caused by the observational design of our study in which all cancer patients with IPE were included, whereas patients with a high risk of major haemorrhage were excluded from the trials in cancer patients with SPE. A second explanation could be poor quality of anticoagulant treatment, on which information was unfortunately unavailable for our study subjects. However, the comparable risk of recurrent VTE in patients treated with VKA and LMWH argues against a poor quality of anticoagulant management. Regardless, the observations from the current study supports LMWH as treatment of choice for cancer-associated VTE [5,6].

Given the debate regarding the clinical relevance of isolated subsegmental SPE, the clinical significance and management of subsegmental IPE may be even less clear [30,31]. Therefore, the comparable risk of recurrent VTE in cancer patients with a subsegmental IPE versus more centrally located IPE, and the observation of recurrent events in untreated patients with subsegmental IPE are further key findings of this study. Both observations argue against subsegmental IPE as a distinct disease entity and support an identical management. Since the presence of (asymptomatic) DVT in patients with a subsegmental IPE was not investigated in the cohorts, conclusions regarding the clinical relevance of isolated subsegmental IPE can not be drawn. The finding that subsegmental PE is

not associated with a more favorable prognosis with regard to VTE recurrences was recently described in non-cancer patients with SPE as well [32]. Notably, in line with the observation of O'Connell and colleagues, the current analysis centrally located IPE was associated with a higher mortality than distally located PE [24]. Two likely explanations for this phenomenon could be a higher mortality directly related to VTE, as observed for SPE, or a higher cancer-related mortality [33].

Strengths of this study are the systematic literature search for potential studies and ongoing registries, the high number of included patients, far exceeding previously published cohorts, the strict and identical diagnostic criteria for IPE among the included studies and registries, the reporting of objectively established outcomes, and the use of patient-level data.

The most relevant limitation of this study is related to the observational and predominantly retrospective designs of the individual registries and the unavailability of results from nine identified cohorts that may have introduced selection bias. Since four cohorts were only described in a meeting abstract and the risk of recurrent VTE is only described for one of five cohorts published in a peer-reviewed journal, our study seems to be a good representation of existing literature. It should be mentioned that patients were not randomly assigned to treatment and no uniform management protocol was applied and it is unknown whether the presence of asymptomatic DVT had been investigated and influenced management decisions. Also, initial CT-scans results and outcomes were not adjudicated by an independent committee. The impact of ongoing oncological management (e.g. systemic chemotherapy) and its potential contribution to the risk of recurrent VTE and/or cancer related prognosis is another confounding factor which cannot fully be accounted for in this study. Due to the study design, we were unable to provide a reliable estimation of the burden of recurrent VTE on mortality. Ideally, a RCT should be performed to provide more definite answers. However, given all available evidence to date, we consider conducting a RCT allocating patients with cancer-associated IPE to placebo or anticoagulant treatment as ethically very challenging. This is supported by the results

of the enquiry among physicians in which 89% to 100% judged treatment of cancer associated IPE necessary [34].

In conclusion, this study demonstrates a substantial risk of symptomatic recurrent VTE in cancer patients with IPE, and suggests an even higher recurrence risk when anticoagulant treatment is withheld. An LMWH-based treatment regime was associated with a lower risk of major haemorrhage than treatment with VKA. These observations support the current guideline recommendations to initiate anticoagulant treatment with LMWH for cancer-associated VTE. Finally, our data argue against different management of subsegmental cancer-associated IPE.

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Conflicts of interest

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Tables and Figures

Table 1: Baseline characteristics of total cohort and stratified by management

Treatment	Total cohort n=926 (100%)	LMWH n=732 (79%)	VKA n=100 (11%)	Other n=41 (4.4%)	None n=53 (5.7%)
Mean age (SD; range)	65 (12; 19-94)	64 (12; 19-94)	68 (12; 20-91)	68 (13; 28-90)	65 (14; 27-91)
Male sex, n (%)	491 (53)	378 (52)	60 (60)	22 (54)	31 (58)
Heart failure, n (%)	27/470 (5.7)	19/382 (5.0)	4/56 (7.1)	1/10 (10)	3/22 (14)
COPD, n (%)	35/471 (7.4)	25/383 (6.5)	7/56 (13)	0/10 (0)	3/22 (14)
Previous VTE, n (%)	47/566 (8.3)	32/435 (7.4)	10/86 (12)	1/13 (7.7)	4/32 (13)
Stage of malignancy, n (%)					
Metastatic cancer	501 (54)	400 (55)	56 (56)	12 (29)	33 (62)
Non-metastatic cancer	192 (21)	143 (20)	34 (34)	3 (7.3)	12 (23)
Unspecified	233 (25)	189 (26)	10 (10)	26 (63)	8 (15)
Type of malignancy, n (%)					
Lung	176 (19)	135 (18)	16 (16)	7 (17)	18 (34)
Colorectal	185 (20)	150 (20)	20 (20)	6 (15)	9 (17)
Other gastrointestinal	187 (20)	147 (20)	15 (15)	12 (29)	13 (25)
Breast	65 (7.0)	52 (7.1)	10 (10)	2 (4.9)	1 (1.9)
Gynaecological	64 (6.9)	56 (7.7)	5 (5.0)	3 (7.3)	0 (0)
Other or unknown	206 (22)	155 (21)	31 (31)	10 (24)	10 (19)
Haematological	43 (4.6)	37 (5.1)	3 (3.0)	1 (2.4)	2 (3.8)
Largest artery involved, n (%)					
Central	292 (32)	230 (31)	30 (30)	21 (51)	11 (21)
Segmental	301 (33)	238 (33)	35 (35)	7 (17)	21 (40)
Subsegmental	193 (21)	156 (21)	27 (27)	2 (4.9)	8 (15)
Unspecified	140 (15)	108 (15)	8 (8.0)	11 (27)	13 (25)

Note: COPD: chronic obstructive pulmonary disease; VTE: venous thromboembolism; LMWH: low molecular weight heparins; VKA: vitamin K antagonists

Table 2: Primary and secondary outcomes for total cohort and stratified by management

A: Pooled outcomes after 6 months of follow-up and stratified by initial management

Outcome	**Weight pooled risk in % (95%CI)**				
	Total cohort	**LMWH**	**VKA**	**Other**	**None**
Recurrent VTE	5.8 (3.7-8.3)	6.2 (3.5-9.6)	6.4 (2.2-12)	4.3 (3.3-12)	12 (4.7-23)
Major haemorrhage	4.7 (3.0-6.8)	3.9 (2.3-5.9)	13 (6.4-20)	6.4 (0.2-20)	6.4 (1.3-15)
Mortality	37 (28-47)	37 (29-44)	28 (18-40)	58 (38-77)	47 (28-66)

B: Incidence rates per 100 patient-years and stratified by management based on a per-protocol analysis

Outcome	**Incidence rate per 100 patient-years (95%CI)**			
	LMWH	**VKA**	**Other**	**None**
Recurrent VTE	12 (8.3-17)	9.8 (2.0-29)	9.5 (0.24-53)	30 (8.2-77)
Major haemorrhage	10 (6.6-15)	26 (11-52)	18 (2.2-66)	4.6 (0.55-17)

Note: VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; CI: confidence interval

Figure 1: Flow chart selection of cohorts

Figure 2: Cumulative risk of recurrent venous thromboembolism related to management

Note: VKA: vitamin K antagonists; LMWH: low molecular weight heparins. Based on a competing risk analysis.

Figure 3: Cumulative risk of major haemorrhage complications according to anticoagulant treatment

Note: VKA: vitamin K antagonists; LMWH: low molecular weight heparins. Based on a competing risk analysis.