

# Anticoagulant treatment of cancer patients with pulmonary embolism in the real world

## Actual use of low-molecular-weight heparin in cancer

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### ABSTRACT

**Background:** Since 2004, guidelines recommend long-term treatment with low-molecular-weight heparin (LMWH) in patients with cancer and pulmonary embolism (PE). We assessed the proportion of cancer patients with PE actually treated with LMWH and the duration of anticoagulant treatment in the Netherlands.

**Methods:** A retrospective cohort study in patients that were hospitalised for PE between 1998-2008. Patients with PE were selected from national hospital discharge records, after linkage to a national pharmacy database. Cancer patients with PE were matched for age, sex and year of diagnosis of PE to subjects with PE without cancer.

**Results:** 600 cancer patients with PE were matched to 1200 patients with PE without cancer. Long-term LMWH was prescribed in 82 (13.7%) of the cancer patients and in eight (0.7%) of the cancer-free patients ( $p < 0.001$ ); all the other patients received vitamin K antagonists (VKA). From 1998-2008, there was an increase in the use of LMWH in cancer patients: in 2007-2008, LMWH was prescribed in 42 (32%) cases, compared with one (1.7%) of the cancer patients with PE in 1998-1999. Median duration of treatment was 5.8 months (interquartile range 3.1-8.8) in cancer patients, compared with 7.0 months (4.9-11) in patients without cancer ( $p < 0.001$ ), a difference that persisted after adjustment for mortality.

**Conclusions:** Although the use of LMWH in patients with cancer and PE is increasing, in 2008, patients in the Netherlands are still mostly treated with VKA, and not with LMWH as recommended by guidelines. Cancer patients with PE on average receive shorter treatment than matched patients without cancer.

### KEYWORDS

Pulmonary embolism, cancer, anticoagulant treatment

### INTRODUCTION

Almost two centuries ago, Bouillaud associated the presence of cancer to the development of venous thromboembolism (VTE).<sup>1</sup> Since then, many studies have confirmed that malignancy increases the risk of VTE, and to a lesser extent also of arterial thrombosis.<sup>2-5</sup> The consequences of VTE in cancer patients cannot be underestimated, since it causes morbidity and pulmonary embolism (PE) related mortality.<sup>6,7</sup> While patients with VTE are usually treated with vitamin K antagonists (VKA) for 3-12 months, since 2004, international guidelines provide specific recommendations for patients with cancer and VTE, namely long-term treatment with low-molecular-weight heparin (LMWH).<sup>8-10</sup> These recommendations are based primarily on the results of the pivotal CLOT study, which showed a 50% reduction in the risk for recurrent VTE in the LMWH group, when compared with the VKA group.<sup>11</sup> Other smaller studies and two meta-analyses confirmed these findings.<sup>12-15</sup> Next to the superior efficacy, there are other advantages of LMWH use in cancer patients, including the more stable anticoagulant effect and the lack of need for monitoring, when compared with VKA. However, it is unclear whether the bleeding risk is lower with LMWH compared with VKA, as most studies are relatively underpowered to adequately assess this clinically important question. In general, VKA-associated bleeding risk is twofold increased in cancer patients as compared with patients without cancer.<sup>16-18</sup>

Although the recommendations regarding LMWH date from ten years ago, more recent studies indicate that the use of LMWH monotherapy in cancer patients is far from optimal. Using the medical records of four hospitals in the United States, Delate and colleagues showed that the use of LMWH – although increasing over the years – was still as low as 31% for cancer patients diagnosed with VTE in 2008.<sup>19</sup> Recent data from a cohort of 144 cancer patients with PE suggested that the use of LMWH is not much higher in Europe.<sup>20</sup>

An important area of uncertainty in the management of PE in cancer patients is the duration of the anticoagulant treatment. Guidelines – based on expert opinion – advise to continue treatment as long as the cancer is active.<sup>19,21</sup> However, no study has specifically evaluated the use of anticoagulants in cancer patients beyond six months. In the absence of supporting evidence, the choice on the duration and type of anticoagulants is left to the treating physicians who are often posed with the dilemma of a patient in the terminal phase, with a high risk for both bleeding and recurrent VTE.

The aim of this study was to evaluate the type and duration of anticoagulant treatment used in the real world in cancer patients with PE relative to PE patients without cancer.

## MATERIALS AND METHODS

### Study design and population

Data for this retrospective cohort study were derived from the Pharmo Record Linkage System (Pharmo Institute, Utrecht, the Netherlands; available at [www.pharmo.nl](http://www.pharmo.nl)). The registry includes demographic details and complete medical histories of more than two million Dutch patients based on data from community pharmacies (in-hospital pharmacies not included). These medication histories were linked to hospital admission and discharge records from the Dutch National Medical Register (LMR). Drugs were coded according to the Anatomic Therapeutic Chemical (ATC) classification. The hospital admission and discharge codes were coded according to the International Classification of Diseases Ninth Revision Clinical Modification (ICD9 CM). Data on all-cause mortality were retrieved from the Dutch Registry for Mortality, coordinated by the Central Bureau for Statistics ([www.cbs.nl](http://www.cbs.nl)).

All subjects with a first hospitalisation for PE (ICD 415.1) between 1998-2008 were identified. In a previous study which used the same patient dataset, 10% of all PEs had been randomly verified, by checking whether the diagnosis had been objectively confirmed, which was the case in more than 95% of the events.<sup>22</sup> We excluded patients without a prescription for anticoagulants after the PE diagnosis.

Among patients with PE, cancer patients were identified based on at least one hospitalisation for cancer in the time period of two years prior to the PE and one year after the PE. Hospitalisation for cancer was retrieved with ICD9 codes: 140-199 (excluding code 176 and 181) and 200-208, including all admissions for solid and haematological cancer and melanoma and excluding all other skin cancers. Data were manually checked for all patients with a diagnosis of cancer outside the defined time range, to see if they received chemotherapeutic agents around the time of PE (two years before to one year after PE). If so, these patients were also considered to be cancer patients. Information on chemotherapy agents was available if prescribed via the local pharmacy. This included drugs under the classification 'hormones and hormone antagonists' (ATC L02...) and the antineoplastic agents (ATC L01...).

For every patient with PE and cancer, two PE patients without cancer were matched for age ( $\pm 1$  year), sex and year of diagnosis of PE. The last moment of follow-up was defined as either the last date of hospitalisation in the database, or two months after the last prescription (for any indication), or the date of death, whichever date came last.

### Study objectives

The primary objective was to assess the type and duration of outpatient anticoagulant treatment for PE. Anticoagulants were divided into LMWH (enoxaparin, tinzaparin, dalteparin and nadroparin) and VKA (acenocoumarol and phenprocoumon), based on ATC codes B01AA07, B01AA04, B01AB05, B01AB04, B01AB10 and B01AB06. Warfarin is not approved for use in the Netherlands and the new anticoagulants were not yet approved at the time of the study. For LMWH prescriptions, we checked each dose to see whether it was indeed therapeutic, i.e. more than 5500 anti-Xa units per day.

Normally, the duration of a medication prescription is approximately 2-3 months; therefore, conservatively, a patient was considered treated until two months after the last prescription. Subsequently, the duration of treatment was calculated by subtracting the date of PE from this date. The secondary objective of the study was to evaluate the incidence of hospitalisations for bleeding during the entire follow-up. Bleeding was defined with ICD codes 430-432, 578, 362.81, 379.23, 599.7, 786.3, 784.7, 459, 569.3, 929.92, 998.11, 719.1 and 287.9. Unadjusted rates of bleeding were calculated, and then expressed as incidence rate per 1000 patient-years of follow-up. Furthermore, rates were assessed for untreated, LMWH-treated and VKA-treated patient-years.

### Data analysis

The analyses were performed with PASW statistics version 19 (Ill) statistical software. Groups were described

using means and standard deviations for normally distributed continuous type of variables, and medians and interquartile ranges (IQR) for the non-normally distributed data. Differences between groups were tested using the t-test for data with a normal distribution or the Mann-Whitney test for non-normally distributed data. Chi-square tests were applied for comparing dichotomous and nominal data. A p-value of less than 0.05 was considered to be statistically significant.

## RESULTS

Between January 1998 and August 2008, 6988 patients were diagnosed with PE, of which 947 with cancer at the time of PE. After excluding patients for whom no prescription for anticoagulants was present in the database, 600 cancer patients with PE were eligible for the analyses: 306 women and 294 men (figure 1 and table 1). These patients suffered from the following types of cancer: genital/urinary tract cancer (n = 114; 19%), gastrointestinal cancer (n = 106; 18%), lung/bronchus cancer (n = 106; 18%), breast cancer (n = 99; 17%), haematological cancer (n = 51; 8.5%), brain cancer (n = 21; 3.5%), cancer of the gallbladder/pancreas/liver (n = 17; 2.8%) malignant melanoma (n = 10; 1.7%), and cancer of the bone and soft tissue (n = 6; 1.0%). Lastly, in 11 patients (1.8%) the cancer type was unspecified, or rare (lip, adrenal, conjunctivae),

**Table 1.** Characteristics of cancer patients with pulmonary embolism and control subjects with pulmonary embolism and without cancer

	Cancer (n = 600)	No cancer (n = 1200)
Mean age (SD)*	66.4 (12.1)	66.4 (12.1)
Female sex (n, %)	306 (51%)	612 (51%)
Year of diagnosis of PE (n, %)		
1998	27 (4.5%)	49 (4.1%)
1999	31 (5.2%)	71 (5.9%)
2000	39 (6.5%)	76 (6.3%)
2001	39 (6.5%)	76 (6.3%)
2002	48 (8.0%)	100 (8.3%)
2003	62 (10%)	118 (9.8%)
2004	78 (13%)	158 (13%)
2005	67 (11%)	134 (11%)
2006	76 (13%)	150 (13%)
2007	75 (13%)	150 (13%)
2008	58 (9.7%)	118 (9.8%)

\*Age in years; PE = pulmonary embolism; SD = standard deviation.

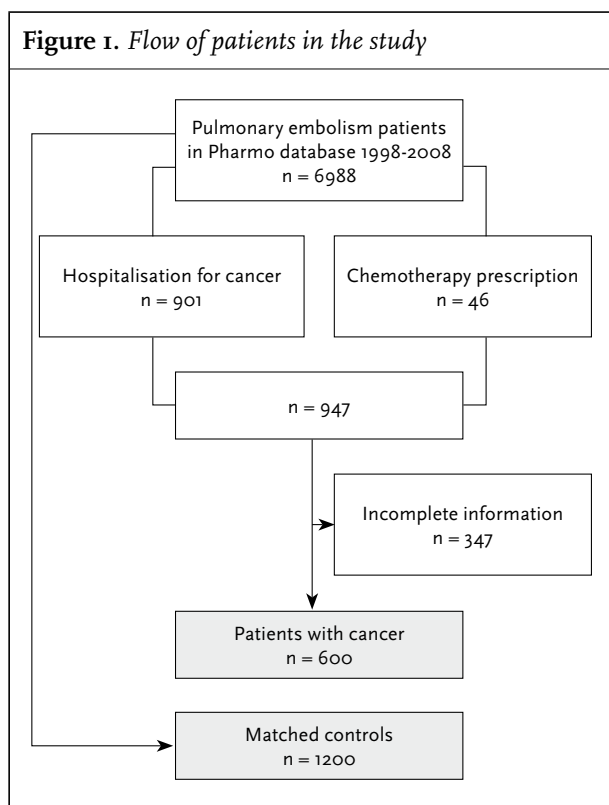
and 59 patients (9.8%) suffered from metastases of a non-specified or unknown primary tumour.

For comparison, 1200 PE patients without cancer, 612 women and 588 men, were enrolled. The median duration between the index PE event and the end of the follow-up was 14 months (IQR 6.1-36) for the cancer patients and 40 months (IQR 19-69) for those without cancer ( $p < 0.001$ ).

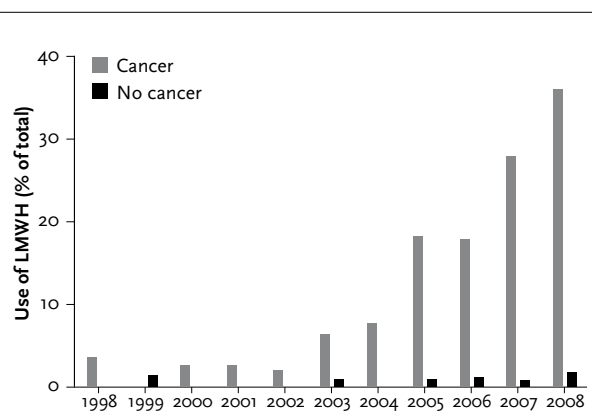
### Type of treatment prescribed for the first episode of PE

Long-term treatment of PE in cancer patients consisted of therapeutic doses of LMWH in 13.7% (82/600) of the cases, whereas this was 0.7% (8/1200) of the non-cancer patients ( $p < 0.001$ ). All other PE patients were treated with VKA. When the year of diagnosis of PE was taken into account, there was a clear increase in the use of LMWH in cancer patients in the more recent years (figure 2;  $p < 0.001$ ), but not for the patients without cancer ( $p = 0.76$ ). In 2007-2008, 42/133 (32%) of the patients with cancer and PE were treated with LMWH monotherapy, compared with 1/58 (1.7%) of the cancer patients with PE in 1998-1999. Of all 82 cancer patients on long-term LMWH, 14 (17%) switched to VKA after a median time of 3.7 months (0.0-6.1), after which they were treated with VKA for a median of 2.2 months (1.9-2.4). Of the 518 cancer patients treated with VKA, 40 (7.7%) switched to LMWH after a median of 3.9 months (3.1-5.9); subsequently they were treated with LMWH for 3.2 months (2.2-6.0).

**Figure 1.** Flow of patients in the study



**Figure 2.** Treatment with LMWH per year of diagnosis



The Y-axis indicates the percentage of patients with PE who are treated with therapeutic doses of LMWH, at the first prescription after discharge from the hospital.

### Duration

The median duration of treatment for PE was 5.8 months (3.1-8.8) in the patients with cancer, compared with 7.0 months (4.9-11) in the patients without cancer ( $p < 0.001$ ). A total of 116 (19%) cancer patients died after a median time of 4.9 months (IQR: 2.2-12), compared with 81 (7%) patients in the control population after a median time of 26 months (9-40;  $p < 0.001$ ). Of all cancer patients who died, 69 (59%) died while using anticoagulant treatment. When patients who died during anticoagulant treatment were excluded from the analysis, the median duration of treatment did not significantly change (6.1 months for cancer patients vs. 7.0 months for patients without cancer, respectively).

Cancer patients on long-term LMWH were treated for a median duration of 5.1 (3.4-9.7) months, compared with 5.9 months (3.0-8.7) in the cancer patients treated with long-term VKA ( $p = 0.36$ ). The year of PE diagnosis did not affect the treatment duration, neither in the cancer patients, nor in the control patients ( $p = 0.98$ ).

### Major bleeding

Patients with cancer were hospitalised for 29 major bleeding episodes during a median follow-up of 14 months (IQR: 6.1-36), i.e., 22 hospitalisations for bleeding per 1000 patient-years of follow-up, compared with 43 bleeding episodes in the control population during a median follow-up of 40 months (IQR: 19-69), i.e. 11 hospitalisations for bleeding per 1000 patient-years of follow-up (table 2), corresponding with a twofold increased risk of major bleeding in patients with cancer (OR 1.9, 95% CI 1.2-3.1). The major bleeding events occurred after a median of 5.3 months (IQR 1.3-19) in cancer patients, compared with a median of 11 months (4.4-47) in the

**Table 2.** Rates of hospitalisations for bleeding in patients with and without cancer

	Cancer	No cancer	p-value
Per 1000 patient-years, overall	22	11	0.0049
Per 1000 untreated-patient years	6.9	4.1	0.17
Per 1000 VKA treated patient-years	36	18	0.011
Per 1000 LMWH treated patient-years	68	0	0.018

VKA = vitamin K antagonists; LMWH = low-molecular-weight heparin.

controls ( $p = 0.026$ ). Of the 29 major bleeding episodes in cancer patients, 18 occurred during treatment with VKA, and subsequently these patients were switched to LMWH in five cases (28%), anticoagulants were stopped in seven patients (39%) and in the remaining six patients (33%) VKA treatment was continued. Another six bleeding episodes occurred during LMWH treatment; two of these patients were switched to VKA, in one patient anticoagulants were stopped and three patients continued LMWH therapy. The remaining five hospitalisations for bleeding occurred without the use of anticoagulant treatment.

When excluding those patients who had a major bleeding episode during anticoagulant treatment, the treatment duration remained unaffected, i.e. 5.7 months in the cancer patients vs. 7.0 months in the controls.

### DISCUSSION

In this study, we evaluated the clinical practice of anticoagulant treatment in a large cohort of Dutch cancer patients with PE between 1998-2008, and found that the long-term use of LMWH in cancer patients was only 14%. We observed a steady increase to 32% in 2008. Our findings are consistent with those of Delate and colleagues in a cohort of American patients. They found that in 2008, 31% of the cancer patients, received LMWH.<sup>19</sup> Also, our results are in line with a cohort of 141 European cancer patients with PE of which 40% received LMWH.<sup>20</sup> The question arises why LMWH is underused in cancer patients despite clear recommendations in guidelines that date from nine years ago. Barriers for LMWH long-term use were studied in a small cohort of North American patients which found that in 49% of the cases the problem was represented by the insurance coverage.<sup>23</sup> Financial reimbursement is very unlikely to be the reason for LMWH prescription in our cohort as there is universal coverage of LMWH by insurance companies in the Netherlands.

Another explanation could be that not all treating physicians are aware of the specific treatment guidelines for cancer patients with VTE. However, in a recent survey study among different specialists, LMWH was indicated as the first choice for the long-term treatment by 82% of the respondents.<sup>24</sup> Alternatively, patients might have a preference for oral VKA instead of subcutaneous LMWH administration, which is not supported by evidence from qualitative studies in patients with terminal cancer.<sup>25,26</sup> The present data indicate that, unexpectedly, the duration of anticoagulant treatment in cancer patients is not longer, but on average one month shorter than matched non-cancer patients with PE, which cannot be explained by a higher mortality of cancer patients during anticoagulant treatment. Unfortunately, information on the stage of cancer and chemotherapeutic treatment was not available from the dataset, which precluded assessing whether anticoagulant treatment was stopped while patients were still receiving active oncological treatment or still had active cancer.<sup>10</sup> Therefore, in view of the retrospective nature of the study, this finding needs to be confirmed in a prospective series of patients. Our findings, however, appear to be in line with those from previous studies reporting a median duration of treatment of 200 days,<sup>19</sup> with up to 77% of cancer patients with PE being treated for six months or shorter.<sup>20</sup> In this last cohort of hospitalised patients, the reason for stopping in 41% of the patients was death, which is much higher than in our cohort of ambulant patients. Physicians might not be aware of the specific advice with regard to the duration of treatment in cancer patients, or possibly, they might feel that the beneficial effects of anticoagulants do not outweigh the bleeding risk after six months. Finally, we confirmed the increased risk for major bleeding in cancer patients compared with age- and sex-matched patients without cancer, in agreement with earlier reports.<sup>16,18</sup> Several aspects of the present study design and results require comment. First, we included patients with pulmonary embolism in the present analysis, and no patients with deep vein thrombosis (DVT). Patients with DVT nowadays are often treated at home, while in the Netherlands most patients with PE before 2009 were treated in the hospital, according to the Dutch guideline on thrombosis treatment.<sup>27,28</sup> Delate and colleagues found no differences between the treatment of patients with cancer with either DVT or PE.<sup>19</sup> Second, to identify cancer patients, we used the definition of a hospitalisation for cancer, and manually checked to see whether they had also received chemotherapy or had been hospitalised for chemotherapy. We may have missed outpatients with cancer, with a potential selection of the more severe cases. Thirdly, this retrospective database study relied on the correct selection of patients with certain diagnoses.

However, a random sample of the pulmonary embolism cases in the database was checked and correctness was confirmed in nearly all cases. Finally, we had no information about the stage of cancer and we were not able to relate the use of LMWH to the stage of disease.

In conclusion, although the use of LMWH in patients with cancer and PE is increasing, patients in 2008 are still mostly treated with VKA rather than with LMWH as recommended by major guidelines. Furthermore, most cancer patients receive anticoagulants for less than six months.

## DISCLOSURES

The authors declare no conflicts of interest. No grant support was received.

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