Low-Molecular-Weight Heparin and Cancer Survival: Review of the Literature and Pooled Analysis of 1,726 Patients Treated for at Least Three Months

Serenella Conti Francesco Guercini Alfonso Iorio

Sezione di Medicina Interna e Cardiovascolare, Università di Perugia, Perugia, Italy

Key Words

Heparin, low molecular weight · Unfractionated heparin · Cancer survival · Venous thromboembolism

Abstract

Background: Heparin has been the main subject of intensive investigation and clinical use because of its therapeutic anticoagulant properties. It also exhibits many other biological activities, and it was claimed that it shows a beneficial effect on cancer spreading. Searching for papers investigating the effect of low-molecular-weight heparin (LMWH) on cancer mortality we found clinical trials and meta-analyses which showed a reduction in the mortality rate in cancer patients. However, the biological rationale of this effect for a short treatment with LMWH remains unclear. We wanted to check if similar results were achieved in cancer patients treated with LMWH for a longer period of time. **Aim:** To evaluate the effect on cancer mortality of a 3-month treatment with LMWH by performing a meta-analysis of published studies comparing LMWH and oral anticoagulants (OA) in the prevention of recurrent venous thromboembolism (VTE). **Materials and Methods:** Computerized searches of Medline and Embase were performed; clinical trials were also located through colleagues and hand scanning of meeting proceedings. Eligibility of the studies and extraction of data were performed by two authors using a standard

form. The meta-analysis was performed assuming a fixed-effect model. **Results:** Eight studies were identified that fulfilled our predefined criteria for a total of 1,726 patients. After a mean of 8.6 months of follow-up, 327 patients had died of cancer, 160 in the LMWH group and 167 in the OA control group (OR 0.95, 95% CI 0.73–1.23; $z = 0.42$; $p = 0.67$). Considering cancer mortality in 948 cancer patients the figures were 160/472 in the LMWH group and 167/476 in the OA control group (OR 0.96, 95% CI 0.73–1.25; $z = 0.33$; $p = 0.74$). **Conclusions:** In 1,726 patients randomized to receive a long-term course of at least 3 months of LMWH or OA for the treatment of VTE, no effect on cancer mortality was found.

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Introduction

One of the most interesting effects of unfractionated heparin (UFH) is on the spread of cancer [1] mainly due to its central role in the regulation of angiogenesis [2]. In 1983 Folkman et al. [3] reported that angiogenesis was inhibited and tumor regressed in mice treated with heparin (or heparin fragments) and cortisone. In the last decade a number of prospective randomized clinical trials compared low-molecular-weight heparin (LMWH) with UFH for the prevention and initial treatment of venous thromboembolism (VTE), showing for LMWH the same

Table 1. Summary of results from meta-analyses of short-term treatment

Author, year	Number of studies	Treatment	Patients	Deaths	OR (95% CI)	Cancer patients	Deaths	OR (95% CI)
Gould et al. [6], 1999	11	UFH	1,792	122	0.73 (0.50; 1.00)	147	38	0.57 (0.32; 1.03)
		LMWH	1,744	88		132	22	
Hettiarachchi et al. [7], 1999	9	UFH	1,794	112	0.75 (0.56; 1.00)	323	71	0.63 (0.42; 0.95)
		LMWH	1,787	85		306	46	

Deaths refer to deaths as a result of cancer. The results of the first and last published meta-analysis performed with different methodologies are given.

efficacy and a better safety profile than UFH, mainly due to the higher predictability of the anticoagulant effect of LMWH. More recently both clinical trials and meta-analyses [4–7] pointed out a mortality reduction in patients treated with a short course of LMWH versus those treated with UFH, and the difference was correlated to cancer mortality. The two most recent meta-analyses [6, 7] achieved the same conclusions although with slightly different methodologies (table 1). However, it is difficult to understand how a short treatment with LMWH (5–10 days) can influence such a complex event like cancer mortality, and the possibility remains that the results are simply a chance finding.

The objective of this review was to assess, through the analysis of the evidence available in the literature whether an advantage in cancer survival was achieved in cancer patients with VTE treated with LMWH for at least 3 months.

Materials and Methods

Criteria for the Selection of the Studies

Studies were considered in which patients with symptomatic VTE were randomly allocated to long-term treatment (at least 3 months) with oral anticoagulants (OA) or LMWH, and accepted objective tests were used to confirm the diagnosis of deep venous thrombosis (venography, ultrasound or any sequence of tests that results in a high positive predictive value for the diagnosis of symptomatic deep venous thrombosis) or the diagnosis of pulmonary embolism (high-probability ventilation-perfusion lung scan or pulmonary angiography).

Primary outcomes were the mortality for cancer and the rate of major bleeding.

Search Strategy

Relevant studies were looked for through computerized queries of Medline and Embase and by hand searching relevant journals, meeting proceedings and reference lists of relevant studies. In ad-

dition, randomized clinical trials were located through personal communication with colleagues.

The search strategy employed for identifying possible trials that compare LMWH and OA for the long-term treatment of symptomatic VTE was [(‘deep vein thrombosis’ or ‘deep venous thrombosis’ or ‘DVT’ or ‘pulmonary embolism’ or ‘PE’ or ‘venous thromboembolism’) and (‘recurrent’ or ‘secondary’ or ‘prevention’)] and [(‘oral anticoag*’ or ‘warfarin’ or ‘acenocoumarol’ or ‘coumarin*’) and (‘heparin’ or ‘low-molecular-weight heparin’)] and (‘cancer’ or ‘neoplasia’ or ‘malignancy’).

All headings were searched with the/all subheadings’ option active.

Methods of Meta-Analysis

Evaluation of potentially eligible studies was independently performed by two reviewers (SC and FG). Disagreements were solved by discussion and by consulting a third reviewer (AI). Eligible articles were reviewed and summary information extracted. The data were extracted independently by two reviewers (SC and FG) using a standard form. When raw data needed for the analysis were not found in the published paper the authors were asked to provide them. The analysis was performed with a fixed-effect model [8] using RevMan ver. 4.2.6 (The Cochrane Collaboration, Wintertree Software).

Statistical Analysis

The rate of mortality for cancer and major bleeding for the different treatment arms was used to calculate an odds ratio separately for each trial. These odds ratios were combined across studies, giving weight to the number of events in each of the two treatment groups in each separate study using the Mantel-Haenszel procedure, which assumes a fixed treatment effect [9]. Primary analysis concerned all patients in the studies, during the period of randomized treatment and follow-up. Moreover, the subset of cancer patients was analyzed separately. The statistical appropriateness of combining the trials was addressed with a statistical test of homogeneity, which considers whether differences in treatment effect in individual trials are consistent with natural variation around a constant effect [8].

Table 2.Meta-analysis of long-term treatment studies

	Pini et al. [10]	Das et al. [11]	Lopaciuk et al. [13]	González- Fajardo et al. [12]	Veiga et al. [14]	Lopez- Beret et al. [15]	Meyer et al. [16]	Lee et al. [17]
<i>General characteristics</i>								
Design of the study	Open	Open	Open	Open	Open	Open	Open	Open
Patients	187	105	202	185	100	158	146	674
Length, months								
Treatment	3–12	3	3–12	3	3–6	3–6	3	6
Observation	12	3	12	12	12	12	6	6
<i>LMWH</i>								
Type	Enoxaparin	Dalteparin	Nadroparin	Enoxaparin	Enoxaparin	Nadroparin	Enoxaparin	Dalteparin
Dosage	4,000 IU o.d.	5,000 IU o.d.	85 IU/kg o.d.	4,000 IU o.d.	4,000 IU o.d.	85 IU/kg t.d.	1.5 mg/kg o.d.	200/150 IU/kg o.d.
<i>Analysis</i>								
Patients excluded from the analysis	0	6 (LMWH) 13 (OA)	3 (LMWH) 6 (OA)	8 (LMWH) 12 (OA)	0	0	8 (LMWH) 8 (OA)	0

Results

Eight studies were identified that fulfilled our inclusion criteria: Pini et al. [10] 1994, Das et al. [11] 1996, Gonzalez-Fajardo et al. [12] 1999, Lopaciuk et al. [13] 1999, Veiga et al. [14] 2000, Lopez-Beret et al. [15] 2001, Meyer et al. [16] 2002 and Lee et al. [17] 2003 involving a total of 1,726 patients, of whom 948 with cancer.

One study [18] was not included in the analysis since the authors did not agree to provide us with raw data about the cancer mortality in their cancer patients. Two additional studies were excluded for the following reasons: poor methodological quality [19] and data [20] later published in full by Das et al. [11]. The main characteristics of the studies included in the analysis are reported in table 2.

The studies were open trials comparing safety and efficacy of a long-term treatment with LMWH or OA in the prevention of recurrences after an episode of VTE. The mean duration of the treatment period was 4.9 months (range 3–12 months), while the mean observation period was 8.6 months (range 3–12 months).

According to the initial treatment, six studies used the same initial treatment in both arms: three used UFH intravenously or subcutaneously in adjusted doses [10, 11, 14], while four used LMWH: nadroparin at the dosage of 85 IU/kg of body weight subcutaneously twice daily was given in two studies [13, 15], dalteparin at the dosage of 200 IU/kg s.c. daily was given in one study [17] and

enoxaparin 1.5 mg/kg s.c. daily was given in one study [16]. In contrast the initial treatment was different in the two treatment arms in the study of Gonzalez-Fajardo et al. [12]: enoxaparin 40 mg s.c. twice daily for 10 days was given in the LMWH arm, while adjusted-dose intravenous UFH was used for patients randomized to the OA arm.

According to the long term of treatment each study adopted a different type and dosage of LMWH. In four studies it was adopted as a prophylactic dosage of heparin [10–12, 14], in one study [13] as half a therapeutic dosage and in three studies as a full therapeutic dosage [15–17].

The results of cancer mortality are summarized in table 3. Three-hundred and twenty-seven patients died of cancer within 6 months of VTE diagnosis. The individual studies did not find a statistically significant difference between the two treatment groups. In the combined analysis of these studies, 167 of the 862 patients (19.2%) died in the control group versus 160 of the 864 patients (18.4%) in the LMWH group (OR 0.95, 95% CI 0.73–1.23; $z = 0.42$; $p = 0.67$; table 3, top). Since only two studies [16, 17] included only patients with cancer, we also considered cancer mortality in the subgroup of cancer patients, to exclude an unequal distribution of cancer patients in the treatment arms of the remaining six studies. The pooled figures for the death rate were 167 out of 476 patients (35.1%) in the OA group and 160 out of 472 (33.9%) in the LMWH group (OR 0.96, 95% CI 0.73–1.25; $z =$

Table 3. Cancer mortality in long-term treatment patients

Study	LMWH n/N	OA n/N	OR (fixed) 95% CI	OR (fixed) 95% CI
<i>Cancer mortality in all the patients</i>				
Pini et al. [10]	8/93	7/94		1.17 (0.41, 3.37)
Das et al. [11]	1/50	3/55		0.35 (0.04, 3.52)
Gonzalez-Fajardo et al. [12]	3/85	2/80		1.43 (0.23, 8.77)
Lopaciuk et al. [13]	4/98	3/95		1.30 (0.28, 5.99)
Veiga et al. [14]	4/50	3/50		1.36 (0.29, 6.43)
Lopez-Beret et al. [15]	7/81	6/77		1.12 (0.36, 3.49)
Meyer et al. [16]	15/71	20/75		0.74 (0.34, 1.58)
Lee et al. [17]	118/336	123/336		0.94 (0.68, 1.28)
Total (95% CI)	160/864	167/862		0.95 (0.73, 1.23)
Test for heterogeneity: $\chi^2 = 1.94$, $df = 7$ ($p = 0.96$), $I^2 = 0\%$				
Test for overall effect: $z = 0.42$ ($p = 0.67$)				
			0.01 0.1 1 10 100 Favours LMWH Favours OA	
<i>Cancer mortality in cancer patients</i>				
Pini et al. [10]	8/22	7/23		1.31 (0.38, 4.52)
Das et al. [11]	1/1	3/3		Not estimable
Gonzalez-Fajardo et al. [12]	3/10	2/8		1.29 (0.16, 10.45)
Lopaciuk et al. [13]	4/6	3/6		2.00 (0.19, 20.61)
Veiga et al. [14]	4/9	3/7		1.07 (0.15, 7.82)
Lopez-Beret et al. [15]	7/17	6/18		1.40 (0.35, 5.54)
Meyer et al. [16]	15/71	20/75		0.74 (0.34, 1.58)
Lee et al. [17]	118/336	123/336		0.94 (0.68, 1.28)
Total (95% CI)	160/472	167/476		0.96 (0.73, 1.25)
Test for heterogeneity: $\chi^2 = 1.49$, $df = 6$ ($p = 0.96$), $I^2 = 0\%$				
Test for overall effect: $z = 0.33$ ($p = 0.74$)				
			0.001 0.01 0.1 1 10 100 1000 Favours LMWH Favours OA	

Upper panel shows the effect of treatment on cancer mortality in the overall population. Lower panel shows the effect of treatment on cancer mortality in the population of patients with known cancer at VTE diagnosis. n = Number of events; N = number of patients.

0.33; $p = 0.74$; table 3, bottom). The test for heterogeneity was negative in both analyses.

The individual studies did not show a significant difference in major bleeding rates between the treatment groups. The pooled studies showed major bleeding complications in 36 of 861 patients (4.2%) in the OA group versus 29 of the 866 (3.3%) in the LMWH group (OR 0.80, 95% CI 0.49–1.32; $z = 0.86$; $p = 0.39$).

Conclusion and Discussion

According to the results of this meta-analysis no anti-cancer effect of a 3-month course of LMWH was found in 327 patients who died of cancer within 6 months of VTE diagnosis both out of 1,726 VTE patients and out

of 948 patients with cancer at the time of diagnosis. This result is in contrast with the previous evidence, but different considerations are needed. Together with the potential common limitations of the meta-analysis, this review included small open studies which did not have cancer mortality as primary end point with the partial exception of Meyer et al. [16] and Lee et al. [17] that were primarily designed to specifically evaluate cancer patients. Finally, even though no formal heterogeneity was found, the studies used different initial and long-term regimens, so that the results should be evaluated cautiously.

On the other hand, a randomized controlled trial designed to evaluate the effect of 1 year's treatment with LMWH on cancer patients has recently been published [21]. The study was not included in our meta-analysis

since heparin was not given for VTE treatment, but the results at 1 year did not show any difference between LMWH (105 deaths in 190 patients) and placebo (112 deaths in 184 patients; OR 0.79, 95% CI 0.53–1.20).

Thus, unless different results will emerge from another ongoing study (MALT trial) whose primary objective it is to investigate the effect of LMWH on cancer survival in an adequate sample of cancer patients, our meta-

analysis and one single randomized controlled trial of long-term LMWH treatment do not seem to support the anticancer effect of LMWH.

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