Clinical and Translational Oncology (2018) 20:1097–1108
https://doi.org/10.1007/s12094-018-1835-2

REVIEW ARTICLE

Pleiotropic effects of heparins: does anticoagulant treatment increase survival in cancer patients?

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Received: 27 August 2017 / Accepted: 9 January 2018 / Published online: 22 February 2018

Abstract
The association between venous thromboembolism (VTE) and cancer has been recognized for more than 100 years. Numerous studies have been performed to investigate strategies to decrease VTE incidence and to establish whether treating VTE impacts cancer progression and overall survival. Accordingly, it is important to understand the role of the hemostatic system in tumorigenesis and progression, as there is abundant evidence associating it with cell survival and proliferation, tumor angiogenesis, invasion, and dissemination, and metastasis formation. In attempts to further the scientific evidence, several studies examine survival benefits in cancer patients treated with anticoagulant therapy, specifically treatment with vitamin K antagonists, unfractionated heparin, and low-molecular-weight heparin. Several studies and meta-analyses have been conducted with a special focus on brain tumors. However, no definitive conclusions have been obtained, and more well-designed clinical trials are needed.

Keywords Venous thromboembolism · Overall survival · Vitamin K antagonists · Unfractionated heparin · Low-molecular-weight heparin · Brain tumor

Introduction

The association between venous thromboembolism (VTE) and cancer has been recognized for more than 100 years. VTE poses a significant challenge to the treatment of cancer patients, given that they suffer a VTE risk that is fourfold higher than the general population, which increases to 6.5-fold in those receiving chemotherapy [1]. Thrombotic events are the second most common cause of death in this population. The incidence of VTE in patients with cancer ranges between 0.5 and 20%, depending on the type of tumor, and it is more frequent in locally advanced or metastatic pancreatic cancer, brain tumors, and blood neoplasms [2, 3].

The three elements reported in Virchow's triad—hypercoagulability, hemodynamic changes, and endothelial dysfunction—all contribute to the incidence of VTE. Tumor cells produce certain factors involved in thrombosis, such as tissue factor, cancer pro-coagulant factors, human leukocyte antigen, coagulation factor Xa, mucus glycoprotein, and coagulation factor V and its receptor. Furthermore, tumor cells are a cytokine source capable of stimulating the release of pro-coagulant factors by macrophages and the vascular endothelium. For these reasons, tissue factor is the link between VTE and cancer. It is a transmembrane glycoprotein that binds factor VIIa, creating the FT/VIIa complex and leading to thrombin and fibrin generation after activation of factors X and IX [4].

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Expression of adhesion molecules or their receptors on tumor cell surfaces allow these cells to directly interact with host cells. The main event that promotes local thrombus activation is the vessel wall, which initiates thrombus formation because of the capacity of tumor cells to adhere to vascular endothelial cells, which is mediated by adhesion molecules [5].

Numerous studies have been performed to investigate how to decrease VTE incidence and to understand whether treating VTE impacts cancer progression and overall survival. Some suggest that anticoagulant treatment together with antitumor treatment facilitates survival, particularly when low-molecular-weight heparins are administered in early disease stages [6]. Here, we present a review of the literature discussing the biological basis and the current evidence of the antitumor effects of heparins. For this purpose, we searched PubMed from January 1995 to October 2017 using following terms in the title or abstract: venous thromboembolism, overall survival¸ vitamin K antagonists, unfractionated heparin, low-molecular-weight heparin, and brain tumor. The search was restricted to articles published in English, focusing on original articles, narrative reviews, and systematic reviews that were selected by all by-line authors.

Heparins: classification and general characteristics

Unfractionated heparins (UFH) and their derivatives, low-molecular-weight heparins (LMWH), are anticoagulants in the glycosaminoglycan family. LMWH are obtained by fragmenting UFH by chemical or enzymatic depolymerization, which results in shorter compounds with lower molecular weights (between 4500 and 5000 Da). Their anticoagulant action is based on the activation of antithrombin III, an enzyme that inhibits coagulation factors, especially thrombin and Factor Xa [7].

For years, UFH have been the treatment of choice for VTE, but recent randomized studies have shown that LMWH are as safe and efficacious as UFH and are currently considered the standard of care for these patients [8, 9].

Several studies have proven that heparins not only affect the tumor by interacting with the coagulation cascade, they also possess a wide variety of biological activities that might interfere with tumor progression and metastatic ability [10].

The biological activities of heparins may have an important role in patient treatment and survival, which might change medicine, creating great expectations for the future [11].

Molecular mechanisms of heparins: antineoplastic effects and mechanisms from preclinical studies

Although the epidemiologic relationship between cancer and thrombosis is well established, the physiopathological mechanisms connecting the hemostatic system and tumor development are complex, and many aspects are still unclear. The activation of certain oncogenes (K-ras, MET, and EGFR) or inactivation of suppressor genes (p53 and PTEN) induces tissue factor, plasminogen activator inhibitor 1 (PAI-1), and COX-2 overexpression in tumor cells, suggesting that activation of the hemostatic system is part of a genetic program supporting tumor transformation and progression [12, 13]. Tumor cells activate coagulation by creating a pro-coagulant atmosphere around the tumor, increasing thrombotic risk. Furthermore, the activated hemostatic system alters cell survival and proliferation; tumor angiogenesis, invasion, and dissemination; and metastasis formation [14], creating a vicious cycle.

Tumor cells directly activate coagulation by expressing pro-coagulants on the cell surface or secreting them into the extracellular environment as TF [15], cancer pro-coagulant (CP) [16] and, to a lesser degree, tumor mucins [17]; tumor cells indirectly activate coagulation by expressing adhesion molecules that activate platelets and immune system cells (macrophages and neutrophils) or by releasing cytokines (interleukin 1), tumor necrosis factor (TNF), and growth factors (VEGF) [13]. Likewise, tumor cells interact with a number of cells [1], including platelets, immune cells like monocytes and macrophages, and endothelial cells, promoting thrombosis by stimulating coagulation and platelet activation as well as fostering the invasion, extravasation, and dissemination of tumor cells. Cellular interactions occur directly between adhesion proteins such as integrins; P-, L-, and E-selectins [18]; mucin from carcinomas; vascular adhesion molecule 1 (VCAM-1); and endothelial receptors GPIIb and GPIIIa on the surface of tumor cells and healthy cells. Cellular interactions also occur indirectly through the release of cytokines such as VEGF, IL-1, IL-6, and TNF-α.

Considering these interactions, the role of the hemostatic system on tumor genesis and progression is important to understand, given that growing evidence has associated it with cell survival and proliferation; tumor angiogenesis, invasion, and dissemination; and metastasis formation. In the context of this active participation, several factors are particularly relevant, including the TF, thrombin, and protease-activated receptors (PAR) in proliferative, apoptotic, and pro-angiogenic programs; the important function of the fibrin matrix, which is essential during the tumor growth and metastasis process; and selectins required for the development of metastasis [10, 12, 15, 19–22].

The mechanisms that link hemostasis with thrombin production in tumor biology have given rise to the hypothesis that inhibiting coagulation with anticoagulants might have an antitumor effect beyond their known antithrombotic effects. Vitamin K antagonists (VKA) exert an antineoplastic action related to anticoagulant activity, and LMWH also possess antineoplastic properties independent of anti-Factor Xa and IIa anticoagulant action. Numerous studies in animals confirm that heparins prolong survival after tumor cell inoculation. Heparin's antineoplastic effects group several mechanisms of action that have been proposed based on several studies [14, 23], specifically addressing proliferation [24], adhesion and migration [25, 26] processes (required for metastasis) as well as angiogenesis [27–30]. By binding to tumor-derived adhesion factor (TAF), also known as mac 25, high concentrations of heparin can inhibit the formation of endothelial cell tubular structures, suggesting its importance in the initial steps of angiogenesis. On the other hand, LMWH, specifically tinzaparin, reduces endothelial proliferation in vitro with a dose-dependent effect. The inhibition of other pro-angiogenic effects mediated by heparin sulfate proteoglycans, protease-activated receptor 2, or by blocking hepatocyte growth factor or dispersion factor might translate into an opportunity to combine heparin with antiangiogenic drugs. Heparin has also demonstrated an ability to block the cellular uptake of extracellular vesicles, generating another antitumor mechanism by blocking neovascularization. An inhibitory effect has also been shown on extracellular matrix binding proteins, which is critical for GM cells to migrate and survive, although there is controversy among different studies [26–33].

Heparins are also being investigated based on their potential immune system regulation [34–36] and function in cancer growth control, which might have direct implications for cancer treatment, such as sensitizing tumor cells to cytostatic treatments secondary to the inhibition of resistance to the chemotherapy glycoprotein-P [37].

Survival benefit of anticoagulant therapy in cancer patients

Impact of VKA treatment on survival

The earliest evidence associating anticoagulant drugs and cancer development was related to VKA treatment. The publication in 2001 by Schulman and Lindmarker [38] revealed a lower incidence of cancer diagnoses in patients with thrombosis treated with VKA for 6 months compared to those treated for 6 weeks (incidence ratio 3.4, 95% CI 2.2–4.6), calling into question the results of the previous studies failing to show an overall impact of these drugs on mortality. Table 1 describes the characteristics of five randomized or cohort studies evaluating this issue [39–43]. The pooled analysis of these data was presented by Smoremburg in a systematic review published in 2001 [44]. The main finding was that overall 1-year mortality among patients with cancer was not modified by the VKA treatment, with an odds ratio (OR) of 0.89 (95% CI 0.70–1.13). Despite its global results and limitations, this work proposed the hypothesis that a subgroup of patients with small cell pulmonary carcinoma (SCLC) might receive a survival benefit.

Table 1 Characteristics of the studies evaluating the impact of VKA treatment on the survival of cancer patients

	Tumor location/study design	Arms	Results	ETV/bleeding
Maurer et al. [39]	Small cell Limited Randomized	ACE × 5 + RT ± W	8-month analysis 33 vs. 13.7 m, $p = 0.05$	ND
Zacharski et al. [40]	Multi-tumor Randomized	CHT ± W (26.4 m[a])	Differences in the SCLC group ($p = 0.018$) ND rest groups	NR
Levine et al. [41]	Metastatic breast Randomized, double-blind	CHT ± W until 1 week after CHT	No differences in survival	Relative risk reduction of ETV of approximately 85% ($p = 0.031$)
Daly [42]	Colorectal Randomized	Surgery ± CHT ± W	No differences in survival	ND
Chahinian et al. [43]	Small cell Extended Randomized	MACC or MEPH/MACC ± W	FFS (6.6 vs. 5 vs. 5 m; $p = 0.05$) OS (9.3 vs. 7.9 vs. 7.9 m; $p = 0.09$)	ND thrombosis Increased hemorrhagic events MACC + W

ACE doxorubicin, cyclophosphamide, and etoposide; *CHT* chemotherapy; *ETV* thromboembolic disease; *FFS* failure-free survival; *MACC/MEPH* methotrexate, doxorubicin, cyclophosphamide, lomustine/mitomycin, etoposide, cisplatin, and hexamethylmelamine; *ND* no difference; *NR* not reported; *OS* overall survival; *RT* radiotherapy; *W* warfarin

[a]Chemotherapy: median follow up warfarin group

Impact of unfractionated heparin on survival

Interestingly, these results were somewhat consistent with those reported by the same author regarding the potential antitumor effect of UFH. Smorenburg et al. conducted a systematic review [45] including three randomized clinical trials [46–49] and four non-randomized studies [50–53] (Table 2). The authors performed subgroup analysis comparing those receiving prophylactic doses vs. those who receiving therapeutic doses of UFH. In this study, the authors could not demonstrate a net effect of UFH on overall survival. In the subgroup of randomized clinical trials, the authors reported a higher 3-year mortality rate in patients with gastrointestinal cancer who received prophylactic UFH [41, 47, 49]; in contrast, a study evaluating the impact of UHF in patients with microcytic lung cancer [46] showed an improvement in survival, though it was not statistically significant [OR 0.64, 95% (CI) 0.25–1.62].

Impact of low-molecular-weight heparin on survival

In response to two randomized studies comparing LMWH- and UFH-treated patients [54, 55] that showed a difference in unexpected mortality un-attributable to the incidence of hemorrhage and re-thrombosis, Siragusa et al. [56] published the results of a meta-analysis, including randomized studies published between 1980 and 1994, and revealed a 0.51 (95% CI 0.2–0.9, $p = 0.01$) relative risk (RR) for overall mortality favoring the LMWH-treated group. In 1999, Hettiarachchi et al. [57] reported a second analysis of work published up to 1997 that generated similar results. In this study, the OR for 3-month mortality was 0.61 (95% CI 0.40–0.93) favoring the LMWH. Furthermore, this analysis confirmed that this reduction in risk was accounted for via the difference in death due to re-thrombosis and hemorrhage. These outcomes, albeit obtained from retrospective studies, suggested the capacity of LMWH to have antitumor properties and revived the hypothesis that anticoagulants have an antitumor effect.

Later, two additional meta-analyses were published. The first, by Lazo-Langner et al. [58], included four studies; two were randomized, double blinded, and placebo-controlled, whereas the other two were open label. In all of the studies, survival was the primary endpoint. As reflected in Table 3, the four studies were heterogeneous in terms of patient characteristics and treatment [59–62].

Table 2 Characteristics of studies evaluating the impact of low-molecular-weight heparin on the survival of cancer patients

	Tumor location/study design	Arms	Results	ETV and bleeding
Lebeau et al. [46]	SCLC Limited and extended multicenter, randomized	QTP ± 500 UI/kg/24 h × 5 weeks sc	Median survival days (317 vs. 261 days favor experimental arm; $p = 0.01$) Limited forms ($p = 0.03$) extensive diseases ($p = 0.31$)	ND
Nitti et al. [47]	Colorectal limited Multicenter, randomized	5000 UI/24 h × 7 days heparin + 5FU vs. heparin alone vs. control	9-year follow-up 5-year survival: 69 vs. 61% and 71% NS	ND
Papaioannou et al. [48]	Colorectal Limited 2 prospective studies	25,000 UI/24 h × 6 days iv with QTP	No influence of addition of heparin to chemotherapy on survival	ND
Fielding et al. [49]	Colorectal Limited Multicenter randomized	Heparin 10,000 UI/24 h × 7 days ip + 5FU or heparin alone	Stage III, Dukes' C survival advantage 16% ($p < 0.03$)	ND
Kingston et al. [50]	GI Limited Retrospective	5000 UI/8–12 h × 7 days sc/QT vs. control	Risk death reduction of 30% (13–34%) favoring the heparin group	ND
Kakkar et al. [51]	GI Metastatic Retrospective	Postoperative 5000 UI/8 h × 7 days sc vs. placebo	3-year mortality of 7.6 vs. 12.5%, $p = 0.005$	ND
Torngren and Rieger [52]	GI Limited Retrospective	5000 UI/8–12 h × 7 days sc vs. placebo	No differences in the 3-year survival	ND
Kohanna et al. [53]	GI Limited Retrospective	Peri-operative 10,000 UI/12 h sc vs. no heparin	5-year overall mortality in the experimental arm ($p < 0.05$)	ND

ETV thromboembolic disease, *GI* gastrointestinal, *ip* intraportal, *iv* intravenous, *ND* no difference, *QTP* chemotherapy, *sc* subcutaneous, *SCLC* small cell lung cancer

Table 3 Characteristics of studies included in the meta-analysis by Lazo-Langer

	N	Tumor location/stage/study design	Arms	Results	ETV/bleeding
Altinbas et al. [59]	84	Untreated SCLC (LE and EE) Open-label, randomized, controlled	CEV × 6, 21 day) vs. CEV × 6 and dalteparin 5000 (UI)/day × 18 weeks	Median OS 8.0 m CT alone and 13.0 m CT plus LMWH ($p = 0.01$) No differences EE/LE	ND
Klerk et al. [60]	302	Different solid tumors: L or M Randomized, controlled double blind. Placebo	Nadroparin adjusted for weight × 6 weeks vs. placebo	Mean follow-up 1 year. Median survival 8.0 vs. 6.6 months for the nadroparin vs. placebo group	ND
Kakkar et al. [61]	374	Breast; GI GU; Gin (LA or M) Randomized, controlled, double blind. Placebo	Dalteparin 5000 UI/day × 1 year or placebo. No limit previous lines	Dalteparin did not significantly improve the 1-year survival rates. Survival in a subgroup with better prognosis (dalteparin vs. placebo) at 2 and 3 years (78 vs. 55% and 60 vs. 36%, respectively, $p = 0.03$)	Symptomatic ETVs were 2.4 and 3.3% for dalteparin and placebo, respectively. Bleeding rates: 4.7 and 2.7%, respectively
Sideras et al. [62]	141	Failure to 1st line breast, colon, lung, prostate. Initially randomized, double blind vs. placebo/only chemotherapy	Dalteparin 5000 UI 2 years vs. placebo or chemotherapy alone	Median survival times were not significantly different ($p = 0.46$)	ND

CEV cyclophosphamide, epirubicin and vincristine; *ETV* thromboembolic disease; *Gin* gynecologic; *GU* genitor-urinary tumors; *LA/M* locally advance/metastatic; *LE/EE* limited/extensive stage; *ND* no difference

At 1 year, the authors reported an absolute reduction (AR) in risk of death of 0.70 (95% CI 0.49–1.00, $p = 0.05$) and a relative reduction in the 1-year risk of death of 0.87 (95% CI 0.77–0.94, $p = 0.04$); both favored the experimental group. The 2-year results demonstrated an AR of 0.57 (95% CI 0.34–0.96, $p = 0.04$) and relative reduction in the 1-year risk of death of 0.89 (95% CI 0.80–0.99, $p = 0.03$). Although narrowly, these results verified the positive effect of nadroparin and dalteparin on OS. Given that a greater impact on early disease stages has been postulated, a study by Altinbas was performed excluding patients in stages I and II; however, the benefit in terms of AR and RR was maintained. These results, beyond conclusions regarding the impact on survival, corroborated the safety of LMWH in patients with advanced cancer without prior thrombosis.

If we separately examine the results of these four studies, two exhibited significant differences in survival. The greatest benefit was reported by Altinbas et al. [59], who randomized 84 patients with small cell lung cancer to receive the standard treatment (cyclophosphamide, epirubicin, and vincristine in 6- and 21-day cycles) vs. standard treatment and dalteparin [5000 international units (UI)/day for the 18 weeks of treatment]. All of the patients showed that a good EGOG [*sic*] status (PS = 0–2) was mostly male, and presented with both limited (36 patients) and extensive (48 patients) disease. A higher response rate in the experimental arm compared to the control arm (69.2 vs. 42.5% $p = 0.07$) was observed. The median progression-free survival (PFS) was 10.0 vs. 6.0 months ($p = 0.01$), and the median OS was 13.0 vs. 8.0 months ($p = 0.01$). The reduction in the risk of death was 0.56 (95% CI 0.30–0.86, $p = 0.012$). There were no differences with respect to the stage of disease, and toxicity was comparable in both groups. In a second study, Klerk et al. [60] randomized 302 patients with neoplasms with variable locations and histology that were locally advanced or metastatic to receive 6 weeks of the standard treatment or the standard treatment plus nadroparin adjusted for weight. This study was positive, and the RR of death was 0.75 (95% CI 0.59–0.96). The OS at 6 months was 61 vs. 56%; at 12 months, it was 39 vs. 27%; and at 24 months, the OS was 21 vs. 11%. In a preplanned subgroup analysis, a higher RR and better OS were observed in those patients with a life expectancy of more than 6 months compared with those with a lower life expectancy, supporting the hypothesis that patients with a better prognosis benefit the most from the effect of heparin. These patients exhibited an RR of death of 0.64 (95% CI 0.45–0.90) and a 15.4-month median survival vs. an RR of death of 0.88 (95% CI 0.62–1.25) and a 9.4-month median survival was found in the group with a worse prognosis. Again, there were no differences with respect to bleeding events.

The two remaining studies, however, reached contradictory conclusions. The FAMOUS study [61] demonstrated

the superiority of adding dalteparin to the standard treatment compared to the standard treatment alone in patients with carcinomas of the breast, genitourinary tract, digestive tract, and gynecological. Most of these displayed locally advanced or metastatic disease, and no significant differences were observed for hemorrhagic events. The 1-year OS values were 46% (95% CI 39–53) and 41% (95% CI 34–49) in the experimental and control groups, respectively. Survival at 2 years was 27% (95% CI 20–34) vs. 18% (95% CI 11–25), and the results at 3 years were 21% (95% CI 14–28) vs. 12% (95% CI 5–19). Although it was a negative study, we again observed a benefit in survival in preplanned subgroup analysis consisting of patients with survival exceeding 17 months. The survival rates among individuals in the experimental arm of this subgroup were 78 and 60% at 2 and 3 years vs. 55 and 36% in the placebo group ($p = 0.03$). The mean survival times were 43.5 months (95% CI 33–52.3 months) vs. 24.3 months (95% CI 22.4–41.5 months). This subanalysis strengthened the hypothesis that subjects with a better prognosis would receive a greater benefit from heparin addition to the standard treatment. A randomized, double-blind, placebo-controlled study of LMWH by Sideras et al. [62] included 138 patients with cancer of the breast, lung, colon, and prostate as well as locally advanced or metastatic disease, PS 0–2, and treatment after failure of first-line therapy. This study design was changed due to the low accrual rate, the placebo arm was eliminated, and patients received LMWH injections plus standard clinical care or standard clinical care alone; no significant differences in OS, the primary endpoint, were observed between the combined standard care and placebo groups and the combined LMWH arms.

The second meta-analysis [63] was published in 2014 with opposite results from the previous one [58]. The authors included five new studies [64–68] and 5098 patients (Table 4), the majority of which had locally advanced or metastatic disease. These studies were also heterogeneous in terms of oncological disease and intervention. All were randomized studies comparing LMWH with placebo or no anticoagulant therapy with an OR for 1-year mortality of 0.87 (95% CI 0.70–1.08, $p = 0.21$) and an overall RR of 0.94 (95% CI 0.86–1.04, $p = 0.24$). A significant decrease was observed in the risk of thrombotic events with an RR of 0.59 (95% CI 0.42–0.83, $p = 0.002$). The bleeding risk in the group that received heparin was not significantly greater than the control group.

If we examine the five studies added in the second meta-analysis, the greatest contribution of patients comes from two studies by Agnelli, which were both negative. The first one [64], published in 2009, established survival as a secondary endpoint. Its primary endpoint, the number of arterial or venous thrombotic events, was significantly lower in the experimental arm. At 1-year post-randomization, 43.3% of the patients in the arm receiving nadroparin, and 40.7% in the control arm died, although these differences were not statistically significant. The second study [65] also had a primary endpoint of thrombotic event occurrence. Like the previous study, the population contained patients with different solid neoplasms and the absence of thrombosis. In this case, the heparin added to the standard treatment was the ultra-LMWH semuloparin. No statistically significant differences in the occurrence of thrombotic events were detected between groups. The mortality was 43.4% in the experimental group vs. 44.5% in the placebo group (hazards ratio 0.96, 95% CI 0.86–1.06, $p = 0.40$).

The results reported by van Doormaal et al. [66] also failed to demonstrate an impact on survival. This study randomized 503 subjects with locally advanced or metastatic carcinomas of the lung, pancreas, and prostate to receive the standard treatment alone vs. standard treatment plus nadroparin for 6 weeks. The primary endpoint was any mortality, and a secondary endpoint was time-to-progression. No statistically significant differences were noted for either of these two variables, with an overall mortality rate of 56.6 vs. 61.8%. The median survival was 13.1 months in the group administered nadroparin vs. 11.9 months in the control group.

The randomized trial PRODIGE [67] also failed to achieve its primary aim (to lower the number of thrombotic events). The study population consisted of 186 patients with glioma and had to be prematurely ended, because the study drug was withdrawn. This study revealed no positive impact on survival; instead, there were more deaths in the experimental group. This latter fact together with a higher number of bleeding events that were also non-significant intensified hesitation toward the preventative use of heparin in brain tumors.

The randomized trial ABEL [68] showed a positive result, demonstrating increased survival linked to LMWH in cancer patients. It included individuals with limited-stage, small cell pulmonary carcinoma, and its primary outcome was disease-free survival. Its premature closure was due to low recruitment; consequently, only 38 patients were included, which contributed little to the total meta-analysis. The mean PFS was 272 days with the standard treatment and 410 days with the standard treatment plus bemiparin; the HR was 2.58 (95% CI 1.15–7.21, $p = 0.022$); OS was 345 vs. 1133 days; and HR was 2.96 (95% CI 1.22–7.21, $p = 0.0017$). The response rate was similar in both arms, and no significant differences in bleeding were observed. Therefore, the most compelling evidence comes from two meta-analyses with contradictory results. The first meta-analysis had some limitations, such as small sample size, lack of statistical power, and heterogeneity of the results between the different authors. The second meta-analysis, which included a larger number of patients with a specifically greater relative weight than the first three studies [64–66], failed to

Table 4 Characteristics of studies included in the meta-analysis by Sanford

	N	Tumor/stage/design	Arms	Results	ETV/bleeding
Agnelli et al. [64]	1150	Different solid tumors LA or M Randomized, controlled, double blind. Placebo	Nadroparin 3800 IU maximum 4 months vs. placebo	No differences in survival	ETV: 2 vs. 3.9% favoring nadroparin ND bleeding
Agnelli et al. [65]	3212	Different solid tumors LA or M Randomized, controlled, double blind. Placebo	Semuloparin 20 mg sc until a change in line vs. placebo	Rate of death 43.4% in the semuloparin group vs. 44.5% in placebo group (HR 0.96, 95% CI 0.86–1.06, $p = 0.40$)	ETV: 1.2 vs. 3.4% ($p < 0.001$) favoring semuloparin ND in bleeding
van Doormaal et al. [66]	503	Pancreas, prostate, lung LA or M Randomized, controlled. Open-label	Nadroparin therapeutic dose × 2 weeks followed by half of the therapeutic dose × 4 weeks or not	Median survival 13.1 vs. 11.9 months favoring nadroparin arm (HR 0.94, 95% CI 0.75–1.18) No differences in the PFS	ND
Perry et al. [67]	186	Glioma with and without prior surgery Randomized, controlled, double blind. Placebo	Dalteparin 5000 IU × 12 months vs. placebo	12-month mortality rates of 47.8% for LMWH and 45.4% for placebo (HR 1.2, 95% CI 0.73–2.0, $p = 0.48$)	ETV: HR 0.51, 95% CI 0.19–1.4, $p = 0.29$ ND in bleeding
Lecumberri et al. [68]	38	SCLC Limited Open-label randomized, controlled	Bemiparin 3500 IU 26 weeks plus chemotherapy vs. chemotherapy	OS HR 2.96 (95% CI 1.22–7.21), $p = 0.017$, favoring bemiparin	Benefit in ETV ND in mayor bleeding

CI confidence interval, *ETV* thromboembolic disease, *HR* hazard ratio, *LA or M* locally advance or metastatic, *LD* localized disease, *LMWH* low-molecular-weight heparin, *ND* no difference, *OS* overall survival, *PFS* progression-free survival, *sc* subcutaneous, *SCLC* small cell lung cancer

show a significant increase or trend toward greater survival. Strikingly, of the three positive studies included in the two meta-analysis [59, 60, 68], only two included patients with small cell pulmonary carcinoma and used the standard treatment as the conventional arm [59, 68]. These observations inspired the hypothesis that study design is an important factor when accounting for discrepancies on the survival impact of anticoagulants.

More recently, four randomized clinical trials have evaluated the impact of LMWH on survival in patients with various types of cancer [69–72]. The CONKO-004 trial compared the effect of first-line chemotherapy alone or combined with enoxaparin on the frequency of VTE and survival of 312 patients with advanced pancreatic cancer [69]. In this trial, enoxaparin reduced the frequency of VTE, but there were no differences between the two study groups in the progression-free survival (HR 1.06, 95% CI 0.84–1.32, $p = 0.64$) or overall survival (HR 1.01, 95% CI 0.87–1.38, $p = 0.44$). In the FRAGMATIC trial, 2202 patients with newly diagnosed lung cancer at any stage and with any histology were randomized to receive the standard treatment associated or not with a prophylactic dose of LMWH for 24 weeks [70]. Although the trial did not reach the intended number of events for the primary analysis, in the analysis agreed with the independent data monitoring committee, there was no difference between the study groups in the overall survival (1.01, 95% CI 0.93–1.10, $p = 0.814$). In the RANSTEN trial conducted in patients with newly diagnosed small cell lung cancer, the addition of enoxaparin at a supraprophylactic dose to the standard treatment had no impact on the progression-free survival (HR 1.18, 95% CI 0.95–1.46, $p = 0.14$) or overall survival (HR 1.11, 95% CI 0.89–1.38, $p = 0.36$). [71]. Finally, in a randomized trial conducted in 549 patients with non-metastatic resected stage I, II, or IIIA non-small cell lung cancer (the TILT trial), with a median follow-up of 5.7 years, the addition of tinzaparin (100 IU/kg) once a day for 12 weeks to the usual care was not associated with a significant impact on overall survival compared to the usual care alone (HR 1.24, 95% CI 0.92–1.68, $p = 0.17$) [72].

Impact of LMWH on survival from brain tumors and other tumor locations

Brain tumors, given their peculiar characteristics, deserve special consideration in this context. Glioblastoma multiforme (GM) is the most common primary tumor with a poor prognosis. Despite the progress that has been made, there remains a compelling need for treatment development [73].

Despite limited evidence, some studies suggest that heparin might modify the evolution of GM [74–78]. Preclinical trials showed the inhibitory effect of LMWH on the growth of these neoplasms, which might involve angiogenesis, a hallmark of GM. By binding to tumor-derived adhesion factor (TAF), also known as mac 25, high concentrations of heparin can inhibit the formation of endothelial cell tubular structures, suggesting its importance in the initial steps of angiogenesis. On the other hand, LMWH, specifically tinzaparin, reduces endothelial proliferation in vitro with a dose-dependent effect. The inhibition of other pro-angiogenic effects mediated by heparin sulfate proteoglycans, protease-activated receptor 2, or by blocking hepatocyte growth factor or dispersion factor might translate into an opportunity to combine heparin with antiangiogenic drugs. Heparin has also demonstrated an ability to block the cellular uptake of extracellular vesicles, generating another antitumor mechanism by blocking neovascularization. An inhibitory effect has also been shown on extracellular matrix binding proteins, which is critical for GM cells to migrate and survive, although there is controversy among different studies.

Three studies have described the effect of heparin and LMWH on survival in GM patients. Only the PRODIGE study [71], which was a randomized clinical trial reflected in the meta-analysis by Sanford et al. [63], obtained negative results and was terminated early following the introduction of temozolomide in 2004. Robins et al. [79] reported a second study with OS as the primary endpoint in patients treated with radiotherapy and prophylactic doses of dalteparin. Following progression, patients could continue treatment with dalteparin. The control was a historical group treated with radiotherapy. The median survival in the experimental group was 11.9 months (95% CI 10–14), but it was not reported for the control group; although an improvement in OS was observed, it was statistically not significant ($p = 0.47$). Finally, a small, retrospective study [80] included 30 patients with surgically treated GM (radical or biopsy) and subsequent chemoradiotherapy. Of these patients, 13 received enoxaparin (4000 UI/day) for 6 weeks. The 1-year OS was significantly greater ($p = 0.016$) in the group receiving enoxaparin, with an OS of 84.6 vs. 41.2% in the control group. Significance was not achieved in the second year, although the benefit was maintained. Nonetheless, a limitation to this study was that the subjects were not randomized to receive LMWH, because the patients were selected based on their risk for thromboembolism.

These results, although promising, have not led to the generalization of treatment with LMWH even in the group selected for thrombotic risk and in the context of prophylaxis. This lack of a standardized treatment with LMWH is partially due to the risk of intracranial bleeding in patients with GM, although there are no well-designed clinical trials that justify its use.

Pleiotropic effects of heparins in ambulatory patients

Other randomized studies have been published in the last 8 years with a high number of patients that do not demonstrate a survival benefit for ambulatory prophylactic treatment with LMWH. Apart from the PROTECHT40 trial by Agnelli et al. [64], the FRAGMEN-UK41 study [81] included 123 patients with pancreatic cancer. Using a similar design, prophylaxis was compared with dalteparin associated with gemcitabine vs. gemcitabine alone. The study reported a reduction in ETEV incidence in the experimental arm with dalteparin (primary objective of the study, 23 vs. 3.5%, $p = 0.002$), but no differences were found in survival. A second study, the CONKO-004 published in 2015 by Pelzer et al. [70] included a group of patients with high thrombotic risk with pancreatic locally advanced or metastatic cancer, including 312 patients who were randomized to receive chemotherapy (cisplatin, gemcitabine, and 5-fluoruracil) or chemotherapy plus 1 mg/kg enoxaparin each 24 h for 3 months, which was followed by 40 ms every 24 h until disease progression. A significant 3-month reduction in symptomatic ETEV was observed (HR 0.2, 95% CI 0.03–0.52, $p = 0.001$) without differences in survival (HR 1.01, 95% CI 0.87–1.38, $p = 0.44$).

No differences were observed in the survival of patients diagnosed with locally advanced or metastatic breast or lung cancer included in the randomized trials TOPIC-1 [79] and TOPIC-2 [82] that evaluated the role of certoparin (3000 UI/day) during 6 months compared to placebo. In both trials, the mortality was similar in both groups with the same trend as the number of symptomatic or asymptomatic thrombotic events.

Finally, some authors have tried to approximate the survival effects of patients treated with heparin in the context of supportive care. Weber et al. [83] reported the results of a study of 20 ETEV patients in the hospital with a life expectancy of less than 6 months randomized to receive nadroparin 2850/3,800 U (< 70/> 70 kg) sc vs. no treatment. No positive results in terms of overall survival were obtained after 3 months of follow-up, and no significant differences were observed between the two groups.

Ongoing clinical trials

Some trials are currently active, some are in the recruitment phase, and others are under analysis. Among them, we can highlight one promoted by the Ottawa Hospital Research Institute, the PERIOP-01 study (NCTO 1455831), which was designed to analyze extended peri-operative treatment with tinzaparin compared with no anticoagulation treatment in patients with resectable colorectal cancer. The primary endpoint outcome measure was 3-year disease-free survival with an experimental arm consisting of patients who received 4500 UI of tinzaparin daily for 56 days following resection compared to a control arm treated with the standard prophylaxis. In ASCO 2016, the preliminary results of the NVALT-8 trials were presented and demonstrated the antitumor effects of LMWH nadroparin in patients with resected NSCLC when heparin was used as an adjuvant chemotherapy. The experimental arm contained pemetrexed for non-squamous, non-small lung cancer or gemcitabine in squamous carcinoma plus nadroparin for 16 weeks. The primary endpoint was recurrence-free survival (RFS); when stratified for FDG avidity by PET, the RFS was different for LMWH vs. control (HR 0.60, $p = 0.03$).

Summary

Cancer induces a hypercoagulable state, which (in preclinical animal models) contributes to tumor progression. Anticoagulant treatment might limit cancer progression and prolong the life expectancy of cancer patients. The molecular mechanisms that support this hypothesis are becoming increasingly clear. In relation with clinical aspects, although several clinical trials showed increased overall survival for cancer patients treated with LMWH, recent trials do not confirm the survival benefit of LMWH, probably due to methodological issues and/or because it is difficult to assess the actual global effect of heparins on survival in patients who are already receiving powerful cytotoxic and biological treatments. More clinical trials with exhaustive designs will be necessary in the future, including different tumor types and treatment strategies.

In this ongoing process of discerning definitive conclusions, it will also be important to identify the group of patients eligible for anticoagulant therapy and predictive biomarkers that can contribute to patient selection. To address this need, a well-designed clinical trial should be proposed in the future to answer the questions that remain under debate.

Funding This manuscript has not received any financial support.

Compliance with ethical standards

Disclosure of potential conflict of interest Dr. Muñoz Langa has been consultant or member of the advisory boards of LEO Pharma, Pfizer, and Novartis. Dr. Muñoz Martín has been consultant or member of the advisory boards of Sanofi Rovi and LEO Pharma. The remaining authors have no conflict of interest to declare.

Research involving human participants and/or animals The manuscript does not contain clinical studies or patient data. It is not a research involving human subjects and/or animals.

Informed consent Not applicable.

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