REVIEW ARTICLE

Heparins in cancer-associated venous thrombosis

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KEY WORDS

cancer, heparin, low-molecular-weight heparins, prophylaxis, venous thromboembolism

ABSTRACT

A close causal relationship between cancer and venous thrombosis gives rise to questions about the effect of treatment modalities, in particular of the administered drugs, in patients with cancer-related venous thrombosis. An increased risk of chemotherapy-associated venous thromboembolism (VTE) has been well documented, while the effect of heparins used in VTE treatment on the disease course and prognosis in cancer patients has not been fully elucidated. This paper discusses the outcomes of the studies conducted so far investigating the role of heparins, in particular, low-molecular-weight heparins (LMWHs), in the prevention of thrombosis in cancer patients. It also focuses on such aspects of the treatment for cancer-associated VTE as treatment duration and drugs used. The paper summarizes the often discrepant results of long-term therapies with various LMWH products, emphasising that in this specific case the class effect is rather unlikely. It also presents the possible effects of heparins administered as part of cancer treatment, and points to the effects of LMWHs on cancer that are not related to an antithrombotic effect. On the 100th anniversary of heparin discovery, it can be said that heparin is irreversibly connected with thrombosis in the course of cancer.

Introduction The history of heparin (unfractionated heparin [UFH]) began exactly 100 years ago, when in 1916 it was discovered by Jay McLean and William H. Howell. However, the first intravenous product was approved in Sweden 20 years later, and the Food and Drug Administration approved it only in 1940.[1] Brinkhous et al[2] showed that heparin requires plasmatic cofactor, today called antithrombin. Only 40 years later, in 1976, Johnson et al[3] and Andersson et al[4] published data which indicated that low-molecular-weight heparin (LMWH) fractions prepared using standard heparin had a lower inhibitory effect on factor IIa, which reflected the lack of changes in activated partial thromboplastin time, with a simultaneous inhibitory effect on active factor X (Xa).

More than 50 years before the discovery of heparins, in 1865, Trousseau[5] described the relationship between the development of venous thromboembolism (VTE) and cancer, which is now referred to as cancer-associated thrombosis (CAT).

The pathomechanism of CAT is well known. Its development in patients with malignancies involves all the components of the classic Virchow triad, namely, changes in blood vessels, blood flow, and blood composition.[6] Cancer cells may produce a number of substances that modify the coagulation and fibrinolysis processes, including tissue factor, cancer procoagulant, histocompatibility complex antigen, platelet aggregating activity/procoagulant activity (blood platelet and factor X activator), mucus glycoprotein, and non-procoagulant factors such as factor V and factor V receptor.[7-10] Cancer cell-produced procoagulants, tissue factor and cancer procoagulant, activate factor X to its active form, Xa. Tissue factor expressed in macrophages and endothelial cells may be released under the influence of cytokines present in tumor cells, which enhances tissue factor-dependent activation of factor X.[11] The relationship between cancer and hypercoagulable states is illustrated in FIGURE 1. However,

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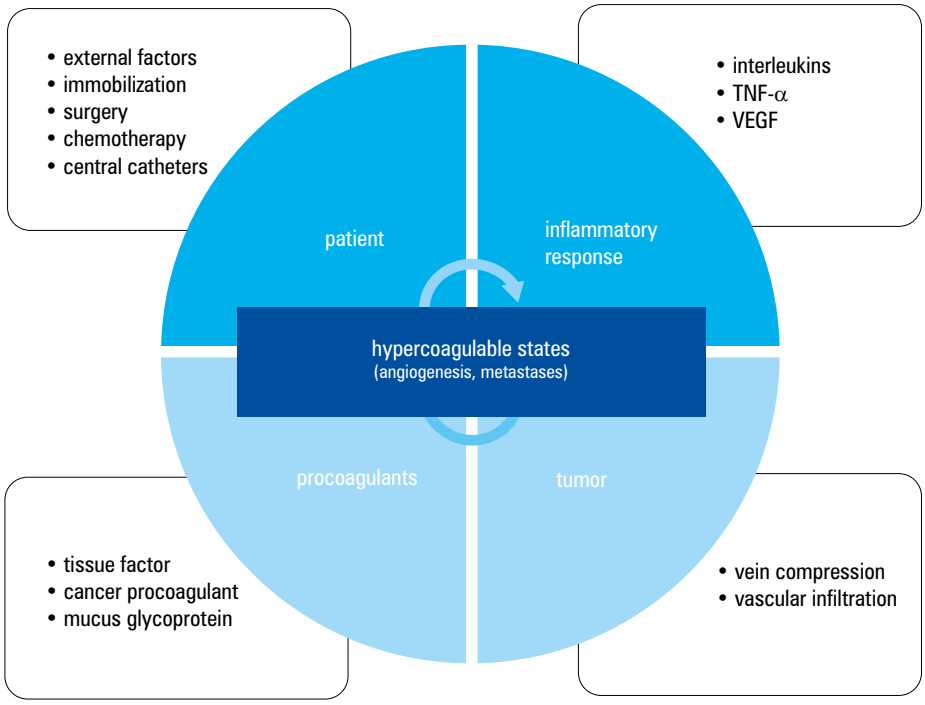
Received: May 19, 2016.
Revision accepted: May 20, 2016.
Published online: June 23, 2016.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2016; 126 (6): 419-429
doi:10.20452/pamw.3449

FIGURE 1
Relationship between cancer and hypercoagulable states
Abbreviations: TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor



from the clinical point of view, the most important fact seems to be that thrombosis may either precede cancer or develop as a result of cancer, and the development of CAT is closely related to worse prognosis and survival.[12,13] As compared with UFHs, LMWHs are characterized by a longer plasma half-life as well as the greater predictability and lower intersubject variability of the antithrombotic effect when used in fixed doses.[14]

The above facts justify new investigation into the role of heparins, in particular LMWHs, in terms of CAT prophylaxis and treatment, the use of heparins in the treatment of cancer, and certainly possible options for their use in cancer patients.

Prevention of thromboembolic complications in cancer patients

Surgical patients Surgical procedures play a multifactorial role in the risk of developing venous thrombosis. In cancer patients, the risk of postoperative thrombosis is 3- to 5-fold higher than in patients without cancer.[15] The complication is significantly more common in individuals diagnosed with cancer than in the general population, and was confirmed by phlebography in up to 40% of cancer patients.[16-18]

The effect of surgery on the risk of developing postoperative thrombosis has been allowed for in a number of decision algorithms. In the commonly used Caprini risk score model, a surgical procedure in a patient with active cancer is assigned 5 points. This means that surgery in this patient population is associated with the highest risk. In the Olmstead County study,[19] the risk was assessed as 22-fold higher in patients hospitalized due to surgery as compared with nonhospitalized or nonsurgical patients. Of patients undergoing similarly extensive surgeries, cancer patients have a 2-fold higher risk of VTE and a 3-fold higher risk of death from pulmonary embolism than noncancer patients.[20] The risk of thrombosis depends on the type of procedure as well as the duration and type of anesthesia and the patient's general health status.[21,22]

Pharmacological prophylaxis of VTE in cancer patients may include LMWHs, UFH, and fondaparinux. The effectiveness of UFH has been well established for a long time, and comparative studies of UFHs and LMWHs in perioperative VTE prophylaxis in cancer patients have been subject to multiple analyses.[23-29] In a meta-analysis published in 2014 (and involving 12 890 participants), LMWH was not found superior to UFH in the study population. Administration of LMWHs, as compared with UFHs, was associated with similar fatality (relative risk [RR], 0.89; 95% confidence interval [CI], 0.74–1.08), pulmonary embolism (RR, 0.73; 95% CI, 0.34–1.54), symptomatic deep vein thrombosis (DVT) (RR, 0.50; 95% CI, 0.20–1.28), and "major" bleeding complications (RR, 0.85; 95% CI, 0.52–1.37).[30] In 2 randomized controlled trials (RCTs), UFH and LMWHs were found equivalent in the prevention of postoperative DVT, with the rates of bleeding complications being lower with LMWHs.[31,32] It should be noted that the studies included in the analysis did not involve cancer patients only, and to a great extent were based on older data, in which the diagnosis of DVT was confirmed by phlebography. In 2010, the results of the CANBESURE study[25] were published, which involved 625 subjects undergoing procedures for cancer and receiving bemiparin or placebo as part of perioperative prophylaxis. The incidence of VTE was significantly lower in patients receiving LMWH as compared with placebo (0.8% vs 4.6%; $P = 0.01$).[25]

Currently, LMWH is the most commonly used agent in antithrombotic prophylaxis in cancer

patients referred for surgical procedures. Its unquestionable advantage lies not only in a simple dosage regimen but also in predictable pharmacokinetics, high bioavailability, and lower risk of heparin-induced thrombocytopenia as compared with UFH. Pharmacological prophylaxis with heparins is characterized by a considerably higher effectiveness also in comparison with mechanical thromboprophylaxis used in surgical oncology. Sakon et al[26] assessed the prophylactic use of enoxaparin or intermittent pneumatic compression in 164 cancer patients undergoing laparotomy, and found symptomatic VTE in 1.2% and 19.4% of the patients, respectively.[26] When using heparins for the prophylaxis of postoperative thromboembolic complications in cancer patients, in addition to the very decision on their use, there are 3 troublesome aspects that need to be addressed: the moment when prophylaxis with heparins is initiated, its duration, and heparin dose. As for LMWH products, which are available in various prophylactic doses for surgical patients with moderate and high risk, a number of study reports have suggested that higher prophylactic doses should be used. In a study involving 1375 subjects, 70% of which were cancer patients, the prophylactic dose of dalteparin, 5000 U, proved significantly more effective in preventing postoperative VTE than a dose of 2500 U, and postoperative thrombosis occurred in 8.5% and 14.9% of the patients, respectively ($P < 0.001$).[29]

Currently, few RCTs are available that compared various LMWH products. The SAVE-ABDO study[33] involved 4414 subjects, 80% of whom underwent major abdominal surgery for a tumor. Particpants were randomized to prophylaxis with either enoxaparin or semuloparin (ultra-LMWH). Study endpoints included VTE or patient's death. The endpoints were reported for 5.5% of the patients receiving enoxaparin and 6.3% of those receiving semuloparin, with a lower rate of bleeding complications in the latter group.[33] In a study comparing the efficacy of prophylactic doses of nadroparin (2850 U of anti-Xa activity) and enoxaparin (4000 U = 40 mg) in patients with colorectal cancer, by postoperative day 12, DVT or pulmonary embolism was diagnosed in 15.9% and 12.6% of the patients, respectively (RR, 1.27; 95% CI, 0.93–1.74; P = nonsignificant), with a lower incidence of major bleeding complications in the nadroparin group (7.3% vs 11.5%).[34] The comparison of dalteparin (5000 U) and fondaparinux (2.5 mg) administered once daily for 5 to 9 days showed that the benefit/risk rates were comparable for both products when used in prophylaxis in general surgery. An analysis of a relatively small subpopulation of cancer patients participating in the above study revealed a significant reduction in the number of VTE episodes in the pentasaccharide group (4.7% vs 7.7%; $P = 0.02$), but this was also associated with a higher incidence of bleeding complications.[35]

In the above studies of subjects undergoing major abdominal and pelvic surgeries, prophylaxis was typically used for up to 7 to 11 days after surgery, which may prove insufficient in light of the current state of knowledge.[36] The results of 4 RCTs investigating the extension of primary prevention of VTE after surgical procedures to 4 weeks are inconsistent.[37-40] The ENOXACAN II study[37,38] (dedicated to cancer patients) as well as the FAME study[38] (dedicated to the population of patients undergoing extensive general surgery of the abdominal cavity and pelvis) revealed potential benefits of the above management of patients with a high risk of thromboembolic complications. In both studies, 4-week antithrombotic prophylaxis (ENOXACAN II, enoxaparin 40 mg once daily; FAME, dalteparin 5000 U once daily) proved effective in reducing the incidence of VTE after extensive surgical procedures as compared with standard-length prophylaxis (7–11 days), with no significant increase in the incidence of bleeding complications. In another 2 RCTs dedicated to extended antithrombotic prophylaxis in surgical cancer patients (bemiparin) or general surgical patients (tinzaparin), no benefits of extended perioperative prophylaxis were observed.[25,39]

Three meta-analyses of 2008, 2009, and 2016 seem to dispel all doubts. In patients undergoing major abdominal surgery, extended prophylaxis with LMWH (3–4 weeks after a surgical procedure) was associated with a significant reduction in the incidence of all thromboembolic complications when compared with prophylaxis limited to hospital stay.[40-42] Fagarasanu et al[42] analyzed 7 prospective randomized studies involving 4807 adult cancer patients undergoing abdominal and pelvic surgeries. Extended prophylaxis was associated with a significant reduction in the incidence of all VTE episodes (2.6% vs 5.6%; RR, 0.44; 95% CI, 0.28–0.70; number needed to treat [NNT], 39) and proximal DVT (1.4% vs 2.8%; RR, 0.46, 95% CI, 0.23–0.91; NNT, 71). The authors of the meta-analysis did not show a significant difference in the incidence of symptomatic pulmonary embolism (0.8% vs 1.3%; RR, 0.56; 95% CI, 0.23–1.40), major bleeding (1.8% vs 1.0%; RR, 1.19; 95% CI, 0.47–2.97), or fatality (4.2% vs 3.6%; RR, 0.79; 95% CI, 0.47–1.33). In their conclusions, the authors emphasized that extended prophylaxis with LMWH after surgery for abdominal or pelvic tumor should be a routine practice in the management of this patient population.[41,42] Extending prophylaxis with LMWHs up to 4 weeks appears justified in patients undergoing extensive surgery for tumor within the abdominal cavity or lesser pelvis (or both), without a high risk of major bleeding complications but with risk factors for thrombosis, such as prolonged immobilization, obesity, a past history of VTE, and others.[37,38,41,42] In other cases, the decision on extending prophylaxis should be made on an individual basis.

Medical patients So far, no results of prospective clinical studies investigating VTE prophylaxis in hospitalized nonsurgical cancer patients have been published. However, we know the results

of studies investigating the efficacy of pharmacological antithrombotic prophylaxis in hospitalized patients with acute medical illness ("medical patients"), and cancer patients accounted for 5% to 15% of the study population.[43,44] In medical patients, a major risk factor for thrombosis, that is, surgical intervention, is not involved. Other factors, such as tumor location, type, and advancement as well as anticancer therapy, particularly chemotherapy, play a vital role. Most patients require antithrombotic prophylaxis.[43] The above studies showed the superiority of active pharmacological prophylaxis with heparins over placebo. Also UFHs and LMWHs were assessed when used in subjects hospitalized due to acute medical illness—the efficacy and safety of both types of heparins were comparable.[45-50] A meta-analysis conducted by Carrier et al[51] did not show a significant reduction in the incidence of VTE after therapy with LMWH or fondaparinux in this population of patients (RR: 0.91; 95% CI, 0.21–4.0).[51] Nevertheless, it would be hard to disagree with the authors of the Canadian guidelines, according to which LMWHs are the treatment of choice for the prevention of thrombosis in cancer patients.[52]

Ambulatory patients Ambulatory patients, especially patients undergoing chemotherapy, have been the subject of numerous studies and analyses. One analysis, which involved 2857 patients with solid tumors who received heparins (UFH in 1 study and LMWH in 8 studies) as part of thrombosis prophylaxis, showed a significant reduction in the incidence of symptomatic VTE (RR, 0.55; 95% CI, 0.37–0.82).[53] Another meta-analysis of patients undergoing chemotherapy in the outpatient setting confirmed that the use of LMWH was associated with a significant reduction in the incidence of symptomatic VTE (RR, 0.62; 95% CI, 0.41–0.93; NNT = 60), with an insignificant increase in the risk of bleeding.[54] The 2 largest studies included in this meta-analysis (PROTECHT, nadroparin, and SAVE-ONCO, semuloparin) showed that the highest-risk patients (Khoran score $\geq$3) obtained the greatest benefits in terms of the bleeding risk.[55,56] In the PROTECHT study, 3.9% of participants in the control arm developed thrombosis as compared to 2.0% of participants receiving nadroparin (P = 0.02); no differences in bleeding were observed.[55] Likewise, in the SAVE-ONCO study, the incidence of VTE was lower in the semuloparin group (1.2%) than in the placebo group (3.4%; hazard ratio, 0.36; 95% CI, 0.21–0.60; P <0.001).[56]

A post hoc analysis of 2 double-blind RCTs involving subjects with metastatic breast cancer (TOPIC-1) and subjects with advanced, stage III/IV non-small-cell lung cancer (TOPIC-2), in which prophylactic certoparin (3000 IU/d subcutaneously) versus placebo was administered once daily for 6 months, showed a significant reduction in the incidence of VTE in lung cancer patients receiving LMWH (3.5% vs 10.2%; P = 0.032).[57] Two studies (FRAGEM, dalteparin,[58] and PROSPECT-CONKO 004, enoxaparin)[59] investigated the effect of primary prophylaxis with LMWH on the reduction in thromboembolic complications in patients with advanced pancreatic cancer undergoing chemotherapy with gemcitabine. It was shown that a 3-month therapy with heparin was associated with a significant reduction in the incidence of thrombosis.

The above meta-analysis, conducted by Akl et al,[53] pointed to another important aspect of primary prophylaxis of thrombosis with LMWH, which still raises controversies and is yet to be recognized by guideline authors. It is the effect of heparin prophylaxis on fatality. In this meta-analysis, survival of patients receiving such prophylaxis was not significantly longer after a 12-month follow-up (RR, 0.93; 95% CI, 0.85–1.02), but after a 24-month follow-up, the fatality rate was significantly lower in the heparin group (RR, 0.92; 95% CI, 0.88–0.97). Furthermore, after a subgroup of patients with small-cell lung cancer was set apart from other tumor types, a significant effect on fatality was observed as soon as after 12 months (P = 0.03) (RR, 0.86; 95% CI, 0.75–0.98 for small-cell lung cancer vs RR, 0.96; 95% CI, 0.86–1.07 for other tumor types), which was no longer seen after 24 months.[53]

Treatment of cancer-associated thrombosis An analysis of the effect of heparins on VTE treatment in cancer patients may be carried out in the pre- and post-CLOT context as the study set the standard of care for patients with CAT.[60] The previous traditional algorithm allowed for a separate pathway in the management of CAT. The initial treatment included UFH, LMWH, and fondaparinux administered for 5 to 10 days. A meta-analysis performed in 2014 was devoted to parenteral initial therapy with these agents.[61] It included 16 RCTs, including 13 studies comparing LMWH and UFH, 2 studies comparing fondaparinux and heparin, and 1 study comparing dalteparin and tinzaparin. An analysis of 11 studies revealed a significant reduction in 3-month fatality rates in favor of LMWH, as compared with UFH (RR, 0.71; 95% CI, 0.52–0.98). No difference in thrombosis recurrence rates was seen between LMWH and UFH used in an initial treatment (RR, 0.78; 95% CI, 0.29–2.08). The authors concluded that the initial treatment with LMWH, due to lower incidence of bleeding complications and lower fatality rates, may be superior to UFH when used in patients with CAT.[61]

In the CLOT study (677 randomized subjects), the group receiving a therapeutic dalteparin dose of 200 IU/kg body weight for 1 month and subsequently 75% to 83% of the full dose (mean 150 IU/kg body weight) for 5 months was compared with the group receiving the dalteparin dose of 200 IU/kg in combination with an oral anticoagulant for 5 to 7 days and subsequently receiving warfarin. During the 6 months of treatment, thrombosis recurred in 8% of the patients in the

heparin group as compared with 15.8% of the patients in the vitamin K antagonist group (P = 0.002). There was no significant difference between the daltaperin group and the oral anticoagulant group in terms of major bleeding (6% and 4%, respectively) or any bleeding (14% and 19%, respectively). The 6-month fatality rates were 39% in the dalteparin group and 41% in the oral anticoagulant group.[60]

Other studies with similar aims and study groups were ONCENOX[62] and CATCH.[63] The first one involved a relatively small number of cancer patients (122) treated with enoxaparin (1 mg/kg every 12 hours for 5 days, and subsequently 1 mg/kg/d or 1.5 mg/kg/d) versus initial enoxaparin (1 mg/kg every 12 hours for at least 5 days) followed by warfarin. In 180 days, there were no significant differences in the incidence of recurrent VTE or bleeding between the study groups.[62] In 2013, Lee et al[63] published the results of the CATCH study whose primary objective was to assess the efficacy of tinzaparin in preventing recurrent VTE in patients with active cancer and acute symptomatic proximal deep vein thrombosis or pulmonary embolism (or both). The follow-up lasted 6 months. In the study, 900 patients were randomized to the group receiving tinzaparin, 175 IU/kg, once daily for 6 months or the group initially receiving tinzaparin, 175 IU/kg, once daily for 5 to 10 days and subsequently warfarin for 6 months. The VTE recurrence rate was insignificantly lower in subjects undergoing long-term treatment with tinzaparin (7% vs 11%). Likewise, no differences in fatality rates or the incidence of major bleeding were observed.[63] A meta-analysis of studies comparing long-term treatment with LMWH in combination with oral anticoagulant showed that heparins did not affect fatality rates (HR, 0.96; 95% CI, 0.81–1.14), but significantly reduced thrombosis recurrence rates in patients treated parenterally (HR, 0.47; 95% CI, 0.32–0.71).[64]

In cancer patients who developed VTE, both initial and long-term use of LMWHs seems to be more effective than starting an oral anticoagulant in the second phase of therapy aimed at preventing CAT recurrence.[65] However, it should be noted that no conducted studies (CLOT,[60] ONCENOX ,[62] CATCH,[63] Agneli,[65] Lopez-Beret,[66] LITE,[67] CANTHANOX,[68] Romera,[69] DALTECAN[71]) showed a class effect of LMWHs used for the prevention of recurrent thrombosis in cancer patients.[60,62,63,65-71] Lopez-Beret et al,[66] in a study assessing the use of nadroparin administered twice daily at a body weight-adjusted dose, demonstrated the efficacy and safety of such an approach as well as reduced the incidence of deep vein valvular incompetence after oral anticoagulants, with no impact on VTE recurrence.[66] In the Main-LITE study[67] which enrolled 200 patients with CAT, 100 subjects were treated with tinzaparin at 175 anti-Xa U/kg body weight/d for 3 months, and the other half received classic therapy with UFH in combination with oral anticoagulants for the same period of time. Patients were assessed after 3 and 12 months. The first assessment revealed no differences in endpoints between the study groups. After 12 months, the DVT recurrence rate (16%) was significantly higher in the oral anticoagulant group than in the LMWH group (7%) (P = 0.044).[67]

In the CANTHANOX study,[68] which included 146 patients, warfarin was compared with enoxaparin (1.5 mg/kg once daily for 4 days, and subsequently warfarin or enoxaparin for 3 months, no change of dosing) when used in patients with CAT. During a 3-month follow-up, 15 subjects (21.1%) receiving warfarin developed major bleeding or recurrent thromboembolism (95% CI, 12.3–32.4%) as compared with 7 subjects (10.5%) receiving enoxaparin (95% CI, 4.3–20.3%). The study did not show any differences in the incidence of recurrent VTE between cancer patients treated with enoxaparin and those treated with warfarin (P = 0.09).[68]

The CATCH study[69] investigated the efficacy of tinzaparin in preventing recurrent VTE in patients with active cancer and symptomatic proximal DVT or pulmonary embolism. The follow-up lasted 6 months, and 900 subjects were randomized to the group receiving tinzaparin (175 IU/kg/d) or the group receiving tinzaparin (175 IU/kg/d) for 5 to 10 days and subsequently receiving warfarin (international normalized ratio, 2.0–3.0) for 6 months. The VTE recurrence rate was insignificantly lower in subjects undergoing long-term treatment with tinzaparin (7% vs 11%). Likewise, no differences in fatality rates or the incidence of major bleeding were observed.[63] The results of the CATCH study[69] were consistent with the earlier published results of the study conducted by Romer et al.[69]

In 2012, a meta-analysis of 5 RCTs assessing the use of tinzaparin in patients with CAT was published, revealing a nonsignificant 38% reduction in the risk of recurrence as compared with oral anticoagulants.[70] The results of the DALTECAN study[71] (334 subjects) with the longest follow-up period in this patient population (12 months) were published in 2015. It should be noted that the therapeutic regimen of dalteparin monotherapy was identical to that in the heparin group in the CLOT study.[60] Thanks to this, the group of subjects using identical therapeutic regimen and followed up for 6 months was considerably larger.[72] In the CLOT study,[60] the LMWH group comprised 336 subjects and the treatment was discontinued within 6 months in 40%, while in the DALTECAN study,[71] the numbers were 334 and 45.3%, respectively. The study population, as regards age, Eastern Cooperative Oncology Group performance status, and sex, was similar to that of the CLOT study.[72] Interestingly, in the DALTECAN study,[71] the VTE recurrence and bleeding rates between months 7 and 12 were similar as between months 2 and 6. During follow-up, VTE recurred in 11.1% of the patients (37 of 334), and the incidence rate was 5.7% in month 1, 3.4% between months 2 and 6, and 4.1% between months

7 and month 12.[71] The incidence of major bleeding during the first 6 months was 7.8% (1.7% per month) and was similar as in the CLOT study[60] (6%), with most episodes of major bleeding occurring during the first month of the study (3.6%).[71] These results are considered of immense clinical significance as they mean that the initial stage of CAT treatment with LMWHs is the most dangerous in terms of the risk of both recurrence and bleeding, of which both physicians and patients should be aware.[72] This may imply that the longer the period of the LMWH use, the more effective and safe the treatment.

Most of the studies discussed here were similar in methodology, especially in terms of the endpoints. What is particularly important is the fact that various doses were used in secondary prophylaxis (long-term/chronic treatment) with LMWHs. In the first reports, the fixed-dose of enoxaparin was 4000 IU once daily, and of dalteparin—5000 IU once daily.[73,74] In other studies, subjects were treated with enoxaparin, 1.5 mg/kg once daily, or tinzaparin, 175 U/kg/d, that is, a full therapeutic dose.[63,68] In CLOT[60] and DALTECAN studies,[71] a full therapeutic dose was administered for 1 month, and subsequently 75% of the dose was administered for 6 to 12 months. In a Polish multicenter study in which cancer patients constituted an insignificant percentage of participants, only half of the therapeutic dose was used in long-term treatment with nadroparin.[75] A meta-analysis involving 1322 subjects who received various doses of LMWH, as compared with vitamin K antagonist, as part of long-term treatment, showed a significant reduction in VTE recurrence rates in the groups receiving full LMWH doses (RR, 0.37; 95% CI, 0.19–0.74; n = 304) and intermediate LMWH doses (RR, 0.52; 95% CI, 0.35–0.79; n = 880). No significant difference in VTE recurrence rates was seen between vitamin K antagonists and prophylactic dose of LMWH (n = 138).[76]

Patients with renal failure A number of clinical studies as well as the prospective RIETE registry[77] have shown that during VTE treatment patients with renal failure (RF), the elderly, and individuals with low body weight have an increased risk of bleeding.[77,78] No data on LMWH safety in patients with CAT and coexistent RF are available. RF was a frequent cause of exclusion among cancer patients with coexistent thrombosis. Renal function deteriorates with age, which means that many patients with CAT will suffer from RF.[79] In a large observational study conducted in France, which involved nearly 5000 participants with solid tumors, creatinine clearance (CrCl) calculated using the Cockcroft–Gault formula was lower than 60 ml/min in 16.6%, and lower than 90 ml/min in 60.3% of the patients.[80]

Chemotherapy plays a significant role in the development of RF. In a paper by Bauersachs,[81] before chemotherapy, 40.4% of the subjects had normal RF, that is, a glomerular filtration rate of over 90 ml/min, and after chemotherapy, only 25.8% of the subjects had normal RF. LMWHs are excreted through the kidneys, which means that patients with RF are at risk of bioaccumulation, the extent of which depends on the type of LMWH.[82,83] The phenomenon may result in excessive anticoagulant effect, which in turn leads to an increased risk of bleeding with standard LMWH doses.[84] A meta-analysis of 18 RCTs showed that 5% of subjects with severe RF (CrCl <30 ml/min) undergoing treatment for VTE suffered from major bleeding as compared with 2.4% of subjects with CrCl of 30 ml/min or higher.[85] Renal clearance relative to total drug clearance is lower for LMWHs with higher mean molecular weight, which naturally promotes the use of heparins with higher molecular weight, such as dalteparin and tinzaparin, as compared with those with lower molecular weight, such as enoxaparin and nadroparin.[86] In patients with significant RF (CrCl ≤30 ml/min), monitoring anti-Xa levels may be recommended to exclude LMWH accumulation. The therapeutic range for anti-Xa levels during VTE treatment with twice-daily dosing should be between 0.5 and 1.1 IU/ml, and with once-daily dosing, it is much wider: between 1.0 and 2.0 IU/ml.[87,88] Of the individuals enrolled to the DALTECAN study,[71] 6.0% were initially diagnosed with moderate renal failure (CrCl, 30–50 ml/min) and 1.3%—with severe renal failure (CrCl < 30 ml/min). VTE recurred in 11.8% of the subjects with moderate or severe RF, and 2.9% of subjects suffered from major bleeding. In 19 subjects with severe RF in whom anti-Xa levels were determined, the mean level (0.3 IU/ml) was safe.[12] In DALTECAN,[71] anti-Xa levels were higher than 1.0 U/ml only in 3 subjects.The results show that individuals with severe RF represent a small group of patients with CAT and the risk of dalteparin bioaccumulation is low.

Obese patients The available data suggest that the risk of bleeding or other undesirable effects is not increased when higher doses of LMWH are used in obese patients. The results of cohort studies of enoxaparin, dalteparin, and tinzaparin show that the dose of LMWH is safe when based on the actual body weight of the patient.[89-91]

Anticancer activity of heparins The suggested pathomechanisms of tumor growth may be related to the activity of heparin-like glycosaminoglycans, neoangiogenesis, proteases activity, as well as the function of the immune system and gene expression.[92] These factors play a significant role also in neoplastic dissemination. Heparins, in addition to an antithrombotic activity, exhibit anticancer activity (LMWHs in particular). In animal models of cancer, heparins containing less than 10 saccharide residues inhibited the biological activity of fibroblast growth factor, and fragments of heparins containing less than 18 saccharide residues inhibited vascular endothelial growth factor binding to its receptors on endothelial cells.[92-94]

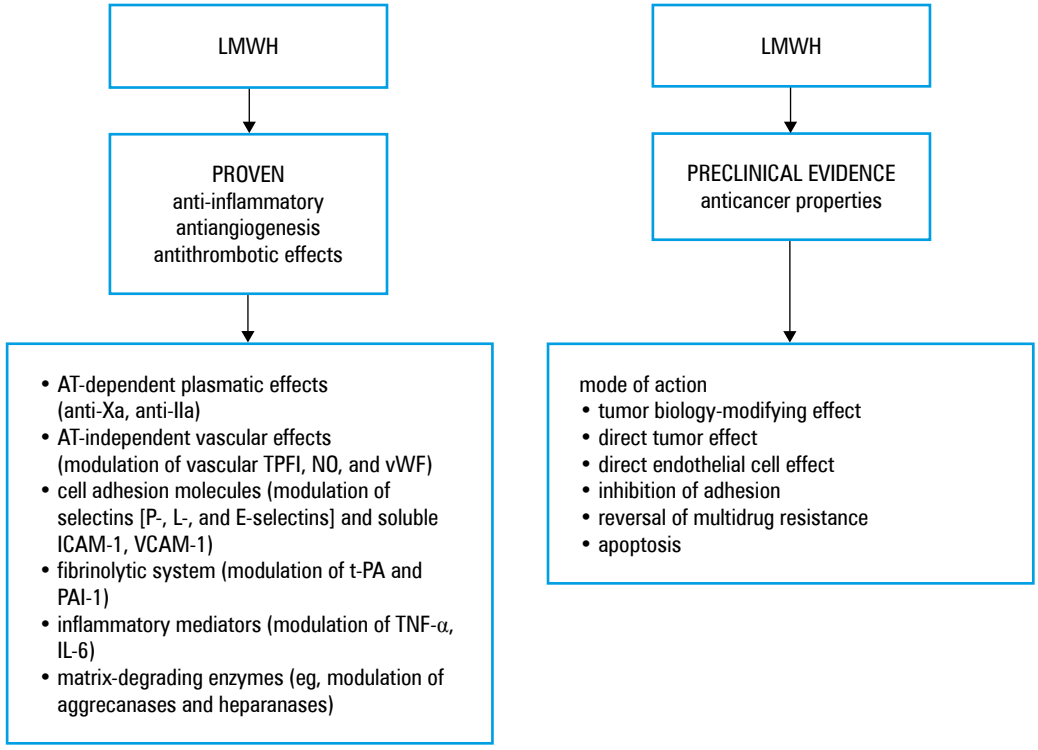


FIGURE 2 Mechanisms of anticancer activity of heparins[92-94] Abbreviations: AT, antithrombin; ICAM-I, intercellular adhesion molecule 1; IL-6, interleukin 6; LMWH, low-molecular-weight heparins; NO, nitric oxide; TNF-α, tumor necrosis factor α; TFPI, tissue factor pathway inhibitor; vWF, von Willebrand factor; VCAM-1, vascular cell adhesion protein 1

Furthermore, heparins may influence the growth of tumor cells via various other mechanisms such as inhibition of heparinases, which mediate tumor cell invasion and inhibition of selectins that are involved in tumor metastasis and cancer-related thrombophilia.[92] The mechanism underlying the effect of LMWHs on tumor biology is presented in FIGURE 2.

Summary The role of LMWHs in CAT treatment is well documented, as evidenced by the fact that the largest scientific associations for the prevention and treatment of VTE in cancer patients, such as the American College of Chest Physicians (ACCP), American Society of Clinical Oncology, and International Society on Thrombosis and Haemostasis (ISTH), recommend LMWHs as the standard of care in the prophylaxis and treatment of CAT.[36,95,96] In the updated ACCP guidelines (the 9th edition published in 2016), LMWHs are recommended as the preferred treatment for this group of patients.[97] In light of the above studies which assessed the use of LMWHs in the prevention and treatment of CAT, many questions are still unanswered. One of them is the question about the possible benefits from various treatment modalities in which heparins may be used. It is significant that more thought is given to a personalized approach to cancer patients (with/without metastasis), tumor location and type, as well as drugs used. Listed in the ISTH guidelines, pancreatic and lung cancers (locally advanced or metastatic) treated with chemotherapy are good examples, as primary prophylaxis with LMWH is recommended in patients with either pancreatic or lung cancer. VTE prevention using prophylactic doses of LMWHs is recommended also in patients treated with immunomodulators combined with steroids and/or chemotherapy (doxorubicin).[96]

Another tumor that may be added to this group is small-cell lung cancer. In this case, the beneficial effects of LMWHs may be considered from two aspects. It has been proved that prophylaxis with LMWH is associated with reduced incidence of VTE treated in the outpatient setting and enhanced tumor response to treatment.[57,98] This means that the use of LMWHs in patients with small-cell lung cancer may be associated with better prognosis in this patient population. In the age of rapid advancement in cancer pharmacotherapy, the impact on tumor response and increased bioavailability of the drugs used still appears to be the reason to use heparins.

Various studies are being conducted to investigate extended primary and secondary prophylaxis.[71,99,100] Collation of the findings of 2 studies assessing the use of dalteparin in primary prophylaxis (FAMOUS)[99] and secondary prophylaxis (CLOT)[60] yields interesting data on the use of LMWHs in patients with less advanced tumors (without metastasis). In the former study, a post hoc analysis of survival in subjects with better initial prognosis and subjects alive 17 months after randomization was conducted. Subjects who received dalteparin lived longer, as compared with subjects receiving placebo. Mortality rates in the LMWH group and the placebo group were 78% and 55%, respectively, after 2 years, and 60% and 36%, respectively, after 3 years ($P = 0.03$).[99] In both studies, the survival curve trend for patients with less advanced tumor was similar (FIGURE 3).

Recently, another prophylaxis protocol has been proposed by Polish investigators.[100] For the first time, LMWHs were initiated at the time of diagnosis and referral for a procedure. Prophylaxis was extended to over 45 days. As a result, during a 3-month follow-up, a significant reduction in the incidence of postoperative thromboembolic

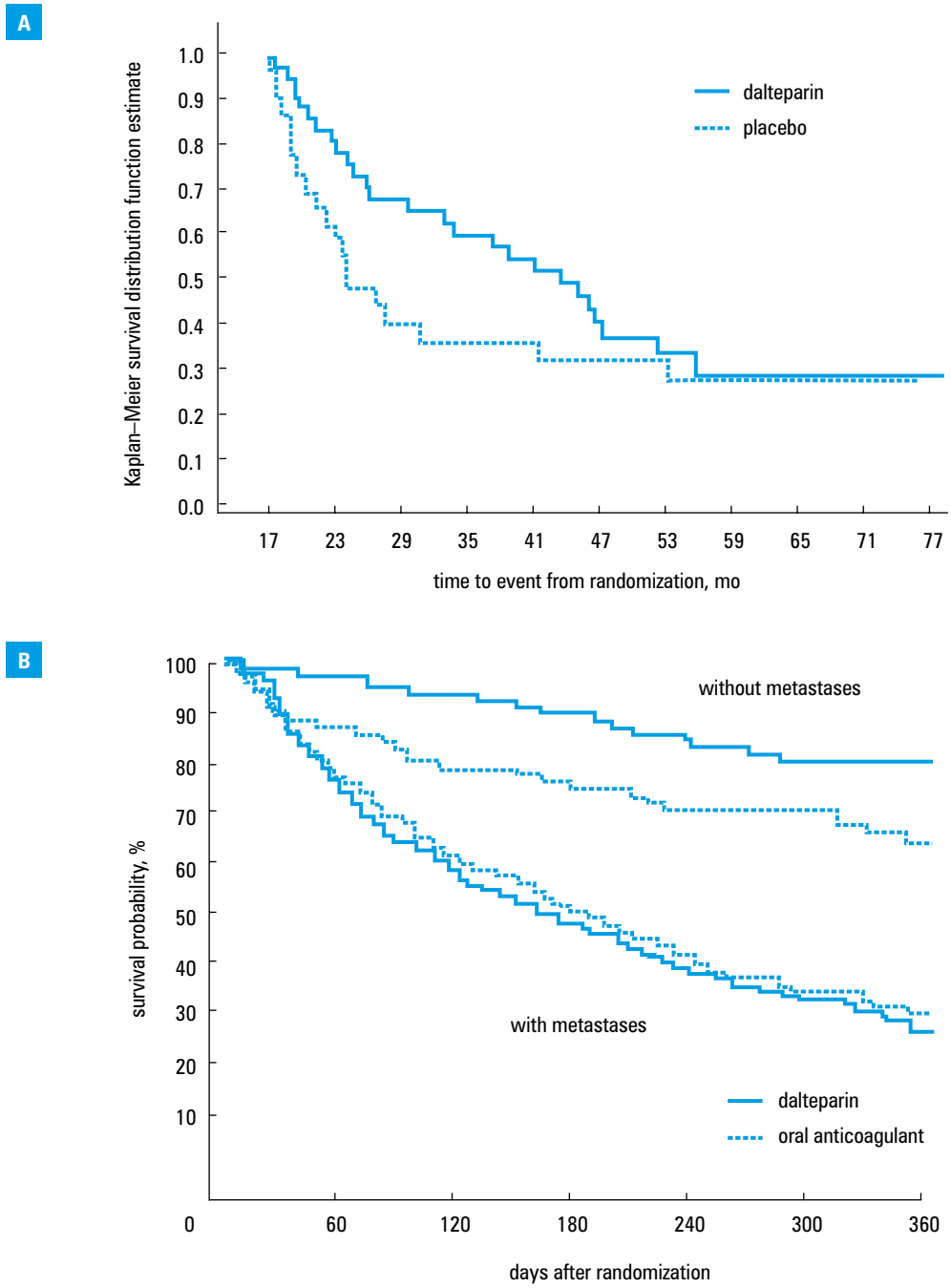


FIGURE 3 The Kaplan–Meier estimate of the probability of death: **A** – FAMOUS[99] (for the subgroup of patients with a better prognosis who survived beyond 17 months after randomization); **B** – CLOT[60] (for patients without metastatic and metastatic disease, for the overall comparison between the treatment groups warfarin vs dalteparin)

complications was observed as compared with standard perioperative prophylaxis: 2.7% vs 16.4%, respectively (P = 0.042).[100]

In summary, it may be said that in the 21st century the third component has been permanently added to the association discovered in the 19th century by Trouseau,[5] who identified the law of cause and effect: tumor–thrombosis. It is LMWHs that may be located in 2 constellations, namely, tumor–LMWH–thrombosis for CAT prevention, and tumor–thrombosis–LMWH for CAT treatment. The LMWH–tumor relationship is still unclear, particularly, the class effect of LMWHs on cancer treatment, and the determination of patient populations, tumor types, and therapies in which LMWHs would have most favorable effects.

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ARTYKUŁ POGLĄDOWY

Rola heparyny w zakrzepicy związanej z nowotworami

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heparyna, heparyny drobnocząsteczkowe, profilaktyka, rak, żylna choroba zatorowo-zakrzepowa

STRESZCZENIE

Ścisły związek przyczynowy między nowotworami złośliwymi a żylną chorobą zatorowo-zakrzepową powoduje konieczność odpowiedzi na pytania dotyczące wpływu stosowanego leczenia, a zwłaszcza podawanych leków u chorych z zakrzepicą z powodu raka. Zwiększone ryzyko zakrzepicy żylnej związanej z chemioterapią zostało dobrze udokumentowane, podczas gdy wpływ heparyn używanych w leczeniu zakrzepicy na przebieg i rokowanie w tej grupie chorych nie jest do końca znany. W artykule omówiono wyniki dotychczas przeprowadzonych badań dotyczących roli heparyn, w szczególności heparyn drobnocząsteczkowych, w profilaktyce zakrzepicy u pacjentów onkologicznych. Zwrócono również uwagę na takie zagadnienia związane z leczeniem zakrzepicy w przebiegu choroby nowotworowej, jak czas trwania terapii oraz stosowane leki. W artykule podsumowano często różniące się wyniki badań dotyczących przewlekłej terapii zakrzepicy z użyciem różnych heparyn drobnocząsteczkowych, podkreślając, że w tym konkretnym przypadku efekt klasy jest raczej mało prawdopodobny. Przedstawiono także możliwy wpływ heparyn stosowanych jako uzupełnienie terapii nowotworowej, ze szczególnym uwzględnieniem heparyn drobnocząsteczkowych i ich działania, na nowotór złośliwy niezwiązany z efektem przeciwzakrzepowym. W 100 rocznicę odkrycia heparyny, można powiedzieć, że heparyna jest nieodwracalnie związana z zakrzepicą w przebiegu raka.

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Praca wpłynęła: 19.05.2016.
Przyjęta do druku: 20.05.2016.
Publikacja *online*: 23.06.2016.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2016; 126 (6): 419-429
doi:10.20452/pamw.3449