

## APŽVALGINIS STRAIPSNIS

### Venous thromboembolism and prophylaxis in cancer patients

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**Key words:** venous thromboembolism; cancer; prophylaxis.

**Summary.** Venous thromboembolism is a serious complication in patients with cancer. The seriousness of venous thromboembolism as a complication in cancer patients is becoming recognized as an important medical issue. Venous thromboembolism is a multifactorial disease associated with vascular endothelial damage, stasis of blood flow, and hypercoagulation. Preexisting morbidity, mutations of factor V Leiden or prothrombin 20210A, type of cancer, presence of metastases, use of central venous access, surgery, anesthesia, etc., increase the risk of venous thromboembolism. The patients with malignancies have a 7-fold increase in the risk of venous thromboembolism compared with individuals without cancer. Venous thromboembolism is the second most common cause of mortality in cancer patients. Venous thromboembolism is the most common cause of death at 30 days after surgery in patients undergoing surgery for cancer. Venous thromboembolism caused death in 46.3% of the cases after surgery for cancer. The Geneva prognostic index identified predictive factors for an adverse outcome, and the American College of Chest Physicians (ACCP) has suggested the guidelines for the prevention of venous thromboembolism in cancer patients. Cancer patients should receive appropriate venous thromboembolism prophylaxis. The methods used for venous thromboembolism prophylaxis are mechanical, pharmacological, or a combination of both. Well-timed thromboprophylaxis may protect patients from venous thromboembolism, early lethal outcome and even influence survival.

#### Cancer and venous thromboembolism

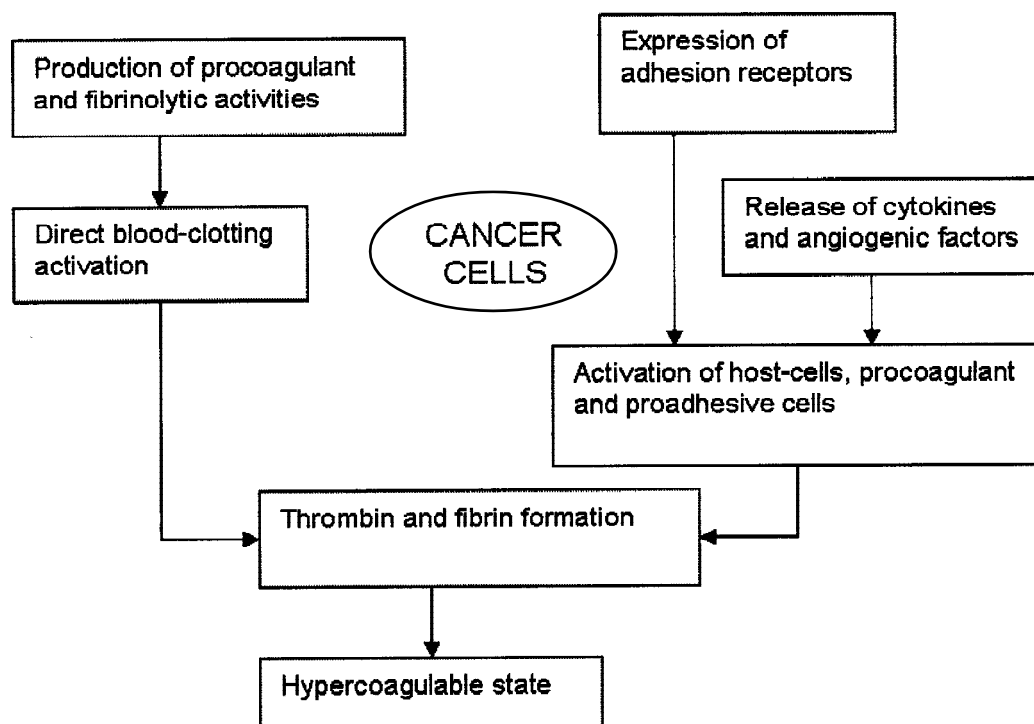
The very strong association between cancer and venous thromboembolism (VTE) was first suggested by Dr. Armand Trousseau in 1865. VTE, including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a frequent complication in patients with active cancer and is a potentially fatal disorder. VTE is a multifactorial disease associated with patient characteristics (age, previous VTE, inherited thrombophilia, immobility), cancer characteristics (cancer type, stage, interaction with host tissues and coagulation system), and treatment options (surgery, radiotherapy, chemotherapy, hormone therapy). Cancer increases the risk of DVT and PE in the general medical population (1) and is an independent risk factor for perioperative arterial and venous thromboembolism (2). Patients with cancer have a 4- to 7-fold higher risk of VTE compared with patients without cancer (3, 4). VTE is the second most common cause of mortality in cancer patients and points towards unfavorable prognosis (5). The development of VTE is a

significant predictor of death within 1 year (6).

#### Pathogenesis of thrombosis in cancer

In 1884, Rudolph Virchow proposed that thrombosis is the result of at least one of three underlying etiologic factors: vascular endothelial damage, stasis of blood flow, and hypercoagulation. All three mechanisms contribute to development of VTE in cancer patients:

- Abnormalities of the vessel wall develop as a consequence of direct neoplastic damage (vascular invasion, extrinsic invasion), angiogenesis, chemotherapy/hormone therapy, etc.;
- Stasis of blood flow in malignancy is associated with patient immobilization, vascular compression from bulky tumor or masses, hyperviscosity (dysproteinemias);
- Cancer growth is associated with the development of hypercoagulation and involves many complex and interdependent mechanisms (7–10) (Fig.). Malignant cells can activate blood coagulation in



**Fig. Prothrombotic properties of cancer cells [modified from Prandoni *et al.*, 2005 (10)]**

several ways: producing procoagulant, fibrinolytic, and proaggregating activities, releasing proinflammatory and proangiogenic cytokines, and interacting directly with host vascular and blood cells such as endothelial cells, leukocytes, and platelets by means of adhesion molecules (10).

#### **Incidence of thrombosis and risk factors in cancer patients**

Autopsy studies suggest that pulmonary embolism (PE) might be associated with a mortality rate of 20% to 30% in cancer patients (11, 12). A clinical outcome-based prospective study on VTE after surgery for cancer reported that VTE caused death in 46.3% of the cases (13).

The Multiple Environmental and Genetic Assessment (MEGA) population study of risk factors for venous thrombosis has identified a 7-fold increase in the risk of VTE in patients with malignancies compared with individuals without cancer (14).

Several factors influence the risk of VTE. These include mutations of factor V Leiden or prothrombin 20210A, immobility of the patient, type of cancer, presence of metastases, preexisting morbidity, use of central venous access, hormonal therapy, chemotherapy, surgery, cigarette smoking, varicose veins, heart or respiratory failure, atrial fibrillation, nephrotic syn-

drome, *etc.* Risk factors are generally cumulative. The presence of more than one risk factor may lead to the development of DVT or PE. The risk of venous thrombosis is highest in the first few months after the diagnosis of malignancy, and it decreases rapidly thereafter (14, 15). Similarly, the risk of thrombosis is higher in patients with metastatic cancer disease (11) and in those undergoing active therapy (14).

The risk of VTE among cancer patients has been observed to vary by tumor type (Table 1). Patients with cancer of the ovary, brain, pancreas, stomach, colon, kidney, and lung are considered to be at the highest risk of VTE (14, 17) and death (6). The risk further increases in patients with metastatic disease.

Several VTE risk factors may occur simultaneously in patients with cancers, thus compounding the risk (2). Several comorbidities and the indicators of severity of PE were associated with adverse outcome. The Geneva prognostic index identified six factors predictive of adverse outcome: cancer (point score +2), heart failure (point score +1), previous DVT (point score +1), hypotension – systolic blood pressure of <100 mmHg (point score +2), hypoxemia –  $pO_2 < 8$  kPa (point score +1), and DVT on ultrasonography (point score +1). Patients with a total score of 3 or more points are assigned to the high-risk category (18).

**Table 1. Incidence and relative risk of venous thromboembolism by tumor type [modified from Helt, 2005 (16)]**

Cancer type	Incidence*	Relative risk
Ovary	120	2.16
Brain	117	2.37
Pancreas	110	2.05
Lymphoma	98	1.80
Stomach	85	1.49
Renal	84	1.41
Leukemia	81	2.18
Colon	76	1.36
Liver	69	0.92
Rectal	62	1.11
Lung	61	1.13
Prostate	55	0.98
Cervix	49	0.90
Uterus	44	3.40
Esophagus	43	0.76
Breast	22	0.44
Bladder	22	0.42

\*Incidence per 10 000 persons a year.

### **Surgery and central venous catheters (CVCs) as risk factors to develop VTE**

VTE is the most common cause of death at 30 days after surgery in patients undergoing surgery for cancer (13). Cancer patients who require surgery seem to have at least twice the risk of postoperative DVT and more than 3 times the risk of fatal PE when compared with those after similar surgical procedures not related to cancer (19).

The following risk factors for VTE in postoperative cancer patients were identified: age more than 60 years, previous VTE, advanced cancer, anesthesia lasting more than 2 hours, and bed rest longer than 3 days (13, 19).

Chemotherapy or surgical procedures are often associated with the long-term use of the CVCs. The presence of a central venous access device alters the blood flow in the upper venous system and is an independent risk factor for venous thrombosis in the upper extremities. Symptomatic thrombosis was shown to develop in 3.4–4.3% of cancer patients with CVCs (20, 21), whereas radiologically detectable thrombosis was diagnosed in 62% of patients (22).

### **Thromboprophylaxis in cancer patients**

The American College of Chest Physicians (ACCP) has utilized systematic review of the literature

related to the risks of venous thromboembolism to set forth guidelines for the prevention of VTE in cancer setting (Table 2).

ACCP guidelines described the four risk categories for VTE in cancer patients:

- *Low-risk patient* (minor surgery in a patient younger than aged 40 years without additional risk factors);
- *Moderate-risk patient* (minor surgery in patients with additional risk factors. Surgery in patients aged 40 to 60 years without additional risk factors);
- *High-risk patient* (surgery in patients older than aged 60 years. Patient aged 40 to 60 years with additional risk factors);
- *Highest-risk patient* (surgery in any patient with multiple risk factors).

The methods used for VTE prophylaxis are mechanical, pharmacological, or a combination of both.

1. Mechanical methods of prophylaxis include graduated compression stockings, intermittent pneumatic compression, electrical stimulation of the calf muscles, rotating tables, and the venous foot pump. Mechanical methods of prophylaxis must be used primarily in patients who are at high risk of bleeding (Grade 1C+) or as an adjunct to anticoagulant-based prophylaxis (Grade 2A) at least initially until the risk of bleeding decreases (Grade 1A) (19). On the other hand, the concurrent use of intermittent compression devices has a synergistic effect on reduction in the risk of VTE (23).

2. Pharmacological methods. Thromboprophylaxis with low-molecular-weight heparins (LMWHs) has been shown to minimize the incidence of VTE, and it is a well-established therapy worldwide. The first evidence regarding the efficacy of LMWH therapy as surgical prophylaxis in cancer patients emerged in trials with dalteparin sodium (Fragmin®) (24).

A detailed review of specific types, doses, and durations of prophylactic treatments recommended for each population is provided in the most recent guidelines of ACCP. According to the guidelines, cancer patients are assigned to the high and the highest risk groups for VTE and require thromboprophylaxis (19).

The guidelines have provided Grade 1A evidence-based recommendations for therapy with LMWH or unfractionated heparin (UFH) in only high-risk patients, with cancer patients undergoing surgery considered most significant. Hospitalized cancer patients have also been considered to be at high risk of DVT, and Grade 1A recommendations include prophylaxis with LMWH (dalteparin or enoxaparin) or low-dose UFH 3 times daily (Table 3). Although VTE prophylaxis has generally been recommended for 7 to 10 days

**Table 2. Levels of evidence and grade of recommendations for venous thromboembolism prophylaxis by American College of Chest Physicians (19)**

Grade	Evidence	Methodology	Recommendations
1A	Clear evidence of benefit	Randomized clinical trial with no critical limitations	Strong recommendations applicable to most patients in most circumstances
1B	Clear evidence of benefit	Randomized clinical trial with inconsistent results or methodological flaws	Strong recommendations likely to apply to most patients
1C+	Clear evidence of benefit	Observational trial with overwhelming evidence in most circumstances	Strong recommendations applicable to most patients
1C	Clear evidence of benefit	Observational trial	Intermediate recommendations that may change when stronger evidence becomes available
2A	Evidence unclear	Randomized clinical trial with no critical limitations	Intermediate recommendations; best action may differ depending on circumstances or patient's societal values
2B	Evidence unclear	Randomized clinical trial with methodological flaws	Weak recommendations; alternative actions likely to be better for some patients under some circumstances
2C+	Evidence unclear	Observational trial with overwhelming evidence depending on circumstances or patients societal values	Weak recommendations; best action likely to differ
2C	Evidence unclear	Observational trial	Very weak recommendations; alternative actions may be equally reasonable

**Table 3. Pharmacological thromboprophylaxis in cancer patients**

Indication	Drugs	Dose	Duration	Evidence
Major surgery planned Immobilized Comorbidities	UFH or LMWH: Enoxaparin Dalteparin Fondaparinux	5000 IU 3×pro d. s.c.  40 mg 1×pro d. s.c. 5000 IU 1×pro d. s.c. 2.5 mg 1×pro d. s.c.	7–10 d. (19)	Grade 1A
Central venous catheter	No LMWH	–	–	Grade 2B
Radiotherapy Chemotherapy Hormone therapy	No evidence			

UFH – unfractionated heparin; LMWH – low-molecular-weight heparin; d. – day; s.c. – subcutaneous.

(19), recent studies showed that extending preventive treatment for 4 weeks after discharge from hospital is beneficial in patients undergoing surgery for cancer (2, 25). Prophylaxis with LMWH is generally started 10 to 12 hours before surgery (19, 25, 26). LMWH is administered subcutaneously, and this procedure does not require either hospitalization or routine laboratory

monitoring. Among LMWH products, the current literature does not indicate that any single LMWH is superior to any other in the primary prevention setting.

The optimal management to prevent catheter-related thrombosis remains undetermined. Some studies have clearly demonstrated that low-dose warfarin (27, 28) as well as LMWH (20) prophylaxis is ineffective

preventing CVC-associated VTE. Therefore, ACCP guidelines have not recommended thromboprophylaxis for patients with CVCs, including cancer patients (19).

Interestingly, extended secondary prophylaxis with LMWH is more effective when compared with warfarin for cancer-related VTE and is accordingly more expensive (29). Marchetti *et al.* have demonstrated that the cost-effectiveness of enoxaparin decreased when the treatment duration was extended from 3 to 6 months (30).

#### Does LMWH improve survival in cancer patients?

Recent clinical trials have shown that use of

LMWH was associated with improved response to chemotherapy and prolonged survival in cancer patients (Table 4.)

The results of the aforementioned trials are difficult to compare as cancer stage, duration of treatment, and other conditions were different. Further well-designed studies are needed to confirm these initial observations.

#### Conclusion

Cancer is a prethrombotic state. Venous thromboembolism is a common and potentially lethal complication among cancer patients. Well-timed thromboprophylaxis may protect the patients from venous thromboembolism, early lethal outcome and even influence survival.

**Table 4. Effect of low-molecular-weight heparin on survival in cancer patients (summary of randomized trials)**

Tumor type	Randomization	Patients No.	Duration of treatment	Results	References
Breast, lung, GI, liver, pancreas, <i>etc.</i> (locally advanced or metastatic)	Dalteparin vs. placebo	190 vs. 184	1 year	No difference in survival	Kakkar <i>et al.</i> , 2004 (31)
Small cell lung cancer	Chemotherapy vs. chemotherapy + dalteparin	40 vs. 39	18 weeks	Increased survival with dalteparin (all patients)	Altinbas <i>et al.</i> , 2004 (32)
Breast, brain, GU, colorectal, lung, <i>etc.</i> (~75% metastatic)	Coumarin vs. dalteparin	306 vs. 296	6 months	Increased survival with dalteparin (only patients without mts)	Lee <i>et al.</i> , 2005 (33)
Breast, colorectal, lung, GI, <i>etc.</i> (locally advanced or metastatic)	Nadroparin vs. placebo	148 vs. 154	6 weeks	Increased survival with nadroparin (all patients)	Klerk <i>et al.</i> , 2005 (34)

GI – gastrointestinal; GU – genitourinary; mts – metastases.

## Veninė tromboembolija ir jos profilaktika vėžiu sergantiems pacientams

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**Raktažodžiai:** veninė tromboembolija, vėžys, profilaktika.

**Santrauka.** Veninė tromboembolija yra svarbi medicininė problema. Tai yra viena grėsmingiausių komplikacijų pacientams, sergantiems vėžiu. Veninės tromboembolijos atsiradimui įtakos turi daug veiksnių: kraujagyslių endotelio pažeidimas, kraujo sąstovis kraujagyslėse, padidėjęs kraujo krešėjimas. Gretutinės ligos, Leideno faktoriaus ar protrombino 20210A mutacijos, vėžio tipas, metastazės, centrinis veninis kateteris, operacija, anestezija ir kiti veiksniai didina veninės tromboembolijos riziką. Pacientams, sergantiems vėžiu,

veninės tromboembolijos rizika septynis kartus didesnė palyginus su pacientais, kurie neserga vėžiu. Veninė tromboembolija yra antroji pagal dažnį mirties priežastis ligoniams, sergantiems vėžiu, ir dažniausia mirties priežastis per pirmąsias 30 dienų po vėžio operacijos. 46,3 proc. mirčių po vėžio operacijos nulemia veninė tromboembolija. Ženevos prognostinis indeksas rodo veiksnius, nulemiančius veninę tromboemboliją ir blogą baigtį pacientams sergantiems vėžiu. Vėžiu sergantiems pacientams laiku turi būti skiriama veninės tromboembolijos profilaktika. Amerikos krūtinės ląstos gydytojų kolegija (angl. *American College of Chest Physicians – ACCP*) parengė veninės tromboembolijos profilaktikos rekomendacijas vėžiu sergantiems pacientams. Veninės tromboembolijos profilaktikai vartojamos mechaninės ir (arba) farmakologinės priemonės, kurios gali apsaugoti pacientą nuo šios komplikacijos, letalios baigties ir turėti įtakos išgyvenimui.

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