Anticoagulation therapy for venous thromboembolism in adult patients with malignancy

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- Individuals with cancer are at risk for thrombotic complications due to a hypercoagulable state.
- Thrombotic events are the second leading cause of death in cancer patients after death from cancer itself .
- Thrombosis may precede the diagnosis of malignancy by months, or it may only occur during treatment or hospitalization.

Overall risk of VTE in individuals with cancer

- VTE occurs in as many as 10 percent of patients with cancer .
- Autopsy series have described even higher rates of thrombosis for certain tumor types.

- The tumor type, location, stage, and time since diagnosis influence VTE risk, along with patient comorbidities and certain cancer therapies.

Tumor-specific factors

- Tumor cells can express procoagulant activity that induces thrombin generation
- the patient's noncancerous tissues may express procoagulant activity in response to the tumor.
- Blood-borne tissue factor in microparticles may play a role in the pathogenesis of the hypercoagulable state accompanying cancer .

Anatomic factors

- Some tumors increase VTE risk by externally compressing or directly invading large vessels.
- renal cell carcinoma infiltrates the inferior vena cava in 5 to 9 percent of patients ; hepatocellular carcinoma can compress or invade the hepatic vein; and large mediastinal tumors or bulky axillary lymphadenopathy can compress upper extremity veins, leading to thrombosis.
- Large abdominal/pelvic tumors can compress major veins leading to deep venous thrombosis in the legs.

- **Patient-specific factors** – VTE risk is increased in patients with prior VTE, advanced age, obesity, and inherited thrombophilia . In contrast, smoking does not appear to significantly increase risk.

- **Therapy-associated factors** – Some chemotherapy agents and high risk surgeries (eg, large intraabdominal or pelvic procedures) increase VTE risk .

- The overall risk of VTE per patient is greater in inpatients, but the vast majority of VTE events occur in outpatients (around 80 percent) because most patients with cancer are treated in the outpatient setting.

- In a Danish cohort of 57,591 individuals hospitalized with cancer, the incidence rates of VTE were highest in individuals with cancer of the pancreas, brain, liver, multiple myeloma, and any form of advanced-stage cancer (incidence rates: 41, 18, 20, 23, and 28, respectively)

Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997–2006

DP Cronin-Fenton[*,1], F Søndergaard[1], LA Pedersen[1], JP Fryzek[2], K Cetin[2], J Acquavella[2], JA Baron[3] and HT Sørensen[1]

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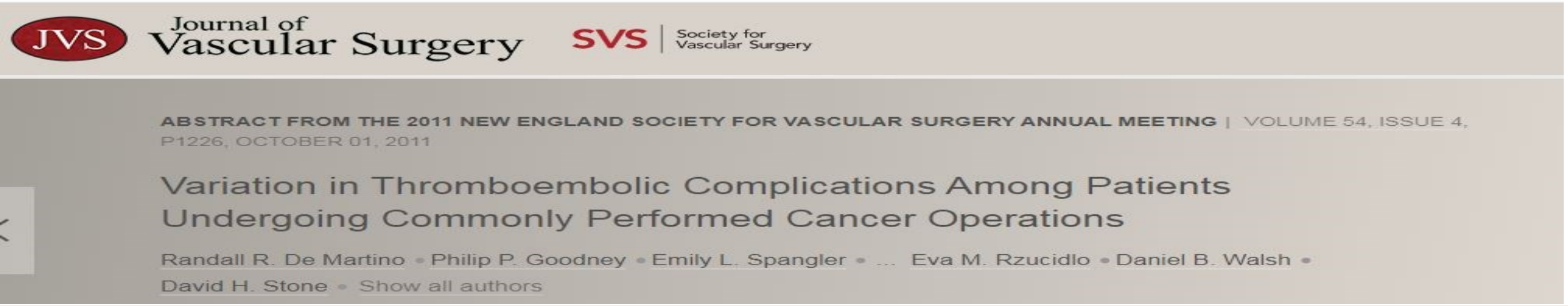


- Some cancer surgeries, especially large intraabdominal or pelvic procedures, are associated with a higher risk of VTE than other types of surgery (eg, mastectomy). This was demonstrated in a review of 43,808 cancer surgeries from a surgical database, which found that the risk of VTE was highest in patients undergoing esophagectomy, followed by cystectomy, pancreatectomy, gastrectomy, colectomy, lung cancer surgery, and hysterectomy.

predictors for the development of VTE

Increased age

Recent steroid use

Body mass index (BMI) ≥35 kg/m

Postoperative complications (wound infection, reintubation, cardiac arrest,sepsis)

Longer hospitalization (>1 week)

increased risk of postoperative VTE

- Age ≥65
- Metastatic disease

- Ascites
- Congestive failure

- BMI ≥25 kg/m_2
- Platelet count >400,000/microL

- Serum albumin <3 g/dL
- Duration of surgery >2 hours

Outpatients (VTE prophylaxis)

- **VTE risk assessment/Khorana score**

- calculated by assigning points for clinical parameters available for most patients (ie, site of primary tumor, hematologic parameters, and body mass index)

- The majority of patients had a Khorana score of 1 or 2 (64 percent).

- Six-month VTE risk correlated with the score: those with a score of 0 had a risk of 5 percent; those with a score of 1 or 2 had a risk of 6.6 percent; and those with a score of 3 or greater had a risk of 11 percent.

Cancer type	Stomach +2	
	Pancreas +2	
	Lung +1	
	Lymphoma +1	
	Gynecologic +1	
	Bladder +1	
	Testicular +1	
	Other 0	
Pre-chemotherapy platelet count ≥350x10⁹/L	**No 0**	Yes +1
Hemoglobin level <10 g/dL or using RBC growth factors	**No 0**	Yes +1
Pre-chemotherapy leukocyte count >11x10⁹/L	**No 0**	Yes +1
BMI ≥35 kg/m²	**No 0**	Yes +1

Whom to anticoagulated

- guidelines published by the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), did not recommend routine VTE prophylaxis in ambulatory patients with cancer, except for those at very high risk of VTE (eg, multiple myeloma receiving **thalidomide** or **lenalidomide** plus chemotherapy or dexamethasone).

- Based on the results of the AVERT and CASSINI trials , updated guidelines from 2019 state that anticoagulation (**apixaban**, **rivaroxaban**, or **low molecular weight heparin**) may be offered to outpatients with a Khorana score of 2 or higher who are starting a new chemotherapy regimen, as long as there are no significant risk factors for bleeding or drug interactions.

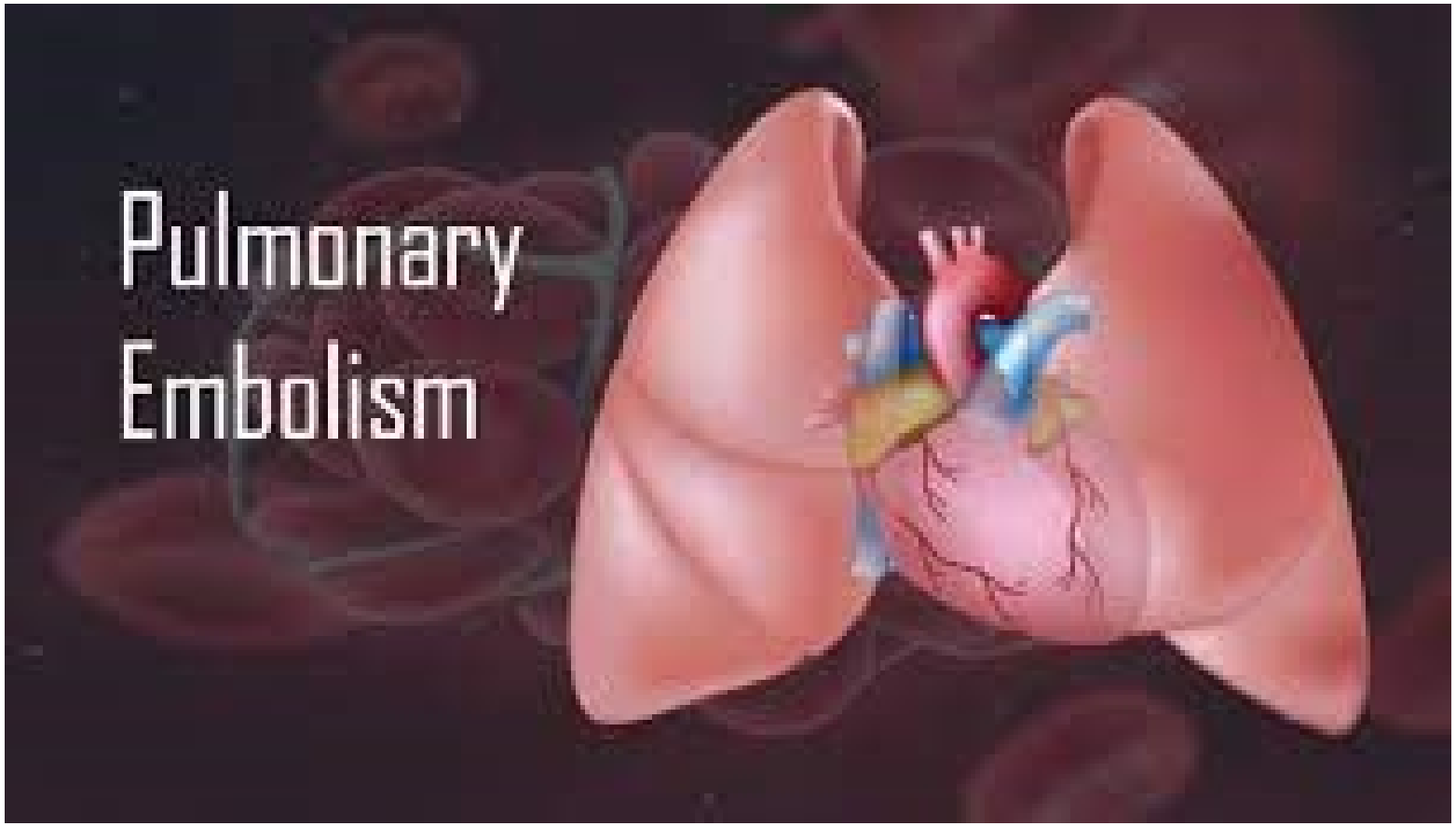
- For most individuals at relatively low risk of VTE (eg, Khorana score <2), we suggest not using anticoagulation for primary VTE prophylaxis.
- secondary prophylaxis may be considered for selected patients such as those with a prior history of a major venous thromboembolic event if they are not chronically maintained on anticoagulation.
- to suggest anticoagulation for primary VTE prophylaxis in individuals at especially high VTE risk, as they are likely to have a greater absolute risk reduction.

- Individuals with multiple myeloma or non-Hodgkin lymphoma treated with an immunomodulatory drug (**thalidomide** or **lenalidomide**)

- Selected ambulatory patients with a Khorana score ≥3, or individuals with a Khorana score of 2 who place a higher value on avoiding VTE than on avoiding bleeding.

- Some individuals with a prior history of unprovoked VTE unrelated to their tumor who are not already on chronic anticoagulation. Prior VTE is not included in the Khorana score. Decisions for these patients should be individualized to reflect the relative risks and benefits of anticoagulation.

- individuals with a higher baseline risk (eg, Khorana score ≥3, or Khorana score ≥2 with a high value placed on avoiding VTE) may reasonably choose anticoagulation, using either a direct factor Xa inhibitor such as apixaban or rivaroxaban or a LMW heparin, at prophylactic doses.


Pulmonary
Embolism

Agent selection

— In general, for inpatients and outpatients with VTE and malignancy, either low molecular weight (LMW) heparin or a direct oral anticoagulant (DOAC) can be used provided there are no contraindications to the chosen agent.

While there is extensive experience using LMW heparin as monotherapy for cancer-associated thrombosis, a well-conducted randomized controlled trial showed that the DOAC, **apixaban** (ie, without a previous five day course of heparin), is an effective and safe alternative; use of **rivaroxaban** in this setting is limited to a pilot study.

- For patients with renal insufficiency (creatinine clearance <30 mL/min), in whom LMW heparin is contraindicated and DOACs have not been investigated, intravenous unfractionated heparin (UFH) is preferred, although some experts administer renally-dosed enoxaparin with monitoring of antifactor Xa levels.

- For patients in whom a need to discontinue or reverse anticoagulation is anticipated for the near future, UFH is also preferred.

LMW heparin and UFH

- Best studied are the LMW heparin formulations, **enoxaparin**, **dalteparin,** and **tinzaparin .**

- Compared with UFH for the initial treatment of VTE, LMW heparin was associated with a possible reduction in mortality at three months .

DOACs

- For the initial treatment of VTE in cancer patients, a randomized trial of **apixaban** (CARAVAGGIO) has evaluated its efficacy as **monotherapy** (ie, no LMW heparin given in advance) in comparison to LMW heparin .

- In this trial, 576 patients with active cancer and VTE, two-thirds of whom had locally-advanced or metastatic disease, were administered apixaban at a dose of 10 mg twice daily for seven days followed by 5 mg twice daily for six months ; 579 patients were treated with subcutaneous **dalteparin** (200 IU/kg for one month followed by 150 IU/kg once daily).

- Similar rates of VTE were seen in both groups without any impact on major bleeding events.

Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT−D)

Annie M Young [1], Andrea Marshall [1], Jenny Thirlwall [1], Oliver Chapman [1], Anand Lokare [1], Catherine Hill [1], Danielle Hale [1], Janet A Dunn [1], Gary H Lyman [1], Charles Hutchinson [1], Peter MacCallum [1], Ajay Kakkar [1], F D Richard Hobbs [1], Stavros Petrou [1], Jeremy Dale [1], Christopher J Poole [1], Anthony Maraveyas [1], Mark Levine [1]

- A pilot study (SELECT-D) of 406 patients reported that six months of **rivaroxaban** (15 mg twice daily for three weeks, then 20 mg once daily) given as monotherapy resulted in a reduction in VTE recurrence (4 versus 11 percent) compared with LMW heparin (**dalteparin**; 200 international units [IU]/kg daily during month 1, then 150 IU/kg daily for months 2 to 6). At six months, while the rate of major bleeding was similar (6 versus 4 percent), there was an excess number of clinically relevant non-major bleeds with rivaroxaban (13 versus 4 percent), especially from cancers of the upper GI tract .

Outpatient therapy

- Deep venous thrombosis (DVT)
- treat uncomplicated DVT (eg, without concomitant pulmonary embolism) with LMW heparin as outpatients using similar principles to those in the non-cancer population.

• Pulmonary embolism (PE)

- The treatment for uncomplicated PE is similar to that for DVT. In those **without** malignancy, only patients with PE who are considered at low risk of recurrence are treated as outpatients.

- Risk is assessed by the simplified pulmonary embolism index (sPESI). Since patients with malignancy are automatically assigned a sPESI score of 1 , this renders them “high risk,” warranting inpatient treatment or an extended observation period before discharge.

- small or asymptomatic PE patients who are clinically stable may be considered for outpatient treatment on an individualized basis

Pulmonary embolism severity index scores: Full and simplified

Pulmonary embolism severity index (PESI) - Full		
Clinical feature		**Points**
Age		x (eg, 65)
Male gender		10
History of cancer		30
Heart failure		10
Chronic lung disease		10
Pulse ≥110/min		20
Systolic blood pressure <100 mmHg		30
Respiratory rate ≥30/min		20
Temperature <36° Celcius		20
Altered mental status		60
Arterial oxygen saturation <90 percent		20
Class I	Low risk	<66
Class II		66 to 85
Class III	High risk	86 to 105
Class IV		106 to 125
Class V		>125
Simplified pulmonary embolism severity index (sPESI)		
Clinical feature		**Points**
Age >80 years		1
History of cancer		1
Chronic cardiopulmonary disease		1
Pulse ≥110/min		1
Systolic blood pressure <100 mmHg		1
Arterial oxygen saturation <90 percent		1
Low risk		0
High risk		≥1

CONTINUED ANTICOAGULATION

- **Agent selection**

LMW heparin, the direct oral anticoagulants (DOACs), apixaban, edoxaban, and rivaroxaban, the synthetic pentasaccharide, fondaparinux, and the oral vitamin K antagonist, warfarin.

Choosing among these agents should take into consideration efficacy/safety, the presence of renal/hepatic insufficiency, risk of bleeding, tumor type, patient preferences, and cost.

- In most patients with VTE and malignancy who do not have severe renal insufficiency (creatinine clearance <30 mL/minute), we suggest the continued use of the DOAC, or edoxaban (which should follow a five day course of LMW heparin) or LMW heparin.

- Only apixaban showed a risk of major bleeding similar to LMW heparin, while a higher risk was found for edoxaban and rivaroxaban, most of which occurred in patients with upper GI cancers.

- Randomized trials and meta-analyses have demonstrated superior efficacy of LMW heparin as compared with warfarin in patients with VTE in association with active cancer . Several trials have shown comparable efficacy between LMW heparin and DOACs .

- LMW heparin and, indirectly, DOACs are preferred to vitamin K-antagonists for continued anticoagulation in VTE .

- In patients with renal insufficiency (creatinine clearance <30 mL/minute), LMW heparin, fondaparinux, and DOACs are generally avoided, and warfarin is the preferred agent for long-term anticoagulation.

- For those unable to ingest or absorb medications, renally-dosed LMW heparin or subcutaneous unfractionated heparin are alternatives.

DURATION OF ANTICOAGULATION

- For a first episode of acute VTE in patients with active cancer, anticoagulant therapy should be administered for at least three to six months, provided the bleeding risk is low and no clinically relevant complications from anticoagulation have occurred (bleeding, thrombocytopenia).

- extending therapy beyond the conventional period in the following:

  - Patients with **active** cancer

  - Patients who recur while on or off anticoagulation.

- Active cancer is defined by the International Society on Thrombosis and Hemostasis :

- cancer diagnosed within the previous six months
- recurrent
- regionally advanced or metastatic cancer
- cancer for which treatment has been administered within six months
- hematologic cancer that is not in complete remission

- select patients assessed as high risk for recurrence by their physician may also be considered for extended treatment (eg, persistent clot despite therapy, additional risk factors, high clot burden, or hypotension at initial presentation).

ANTICOAGULATION IN SPECIAL POPULATIONS

- Patients with cancer frequently have thrombocytopenia placing them at increased risk of bleeding on anticoagulants. Thrombocytopenia is not a contraindication to anticoagulation for individuals with platelet counts >50,000/microL. However, anticoagulation is typically contraindicated in those with platelet counts <20,000/microL

- For many individuals with cancer and acute VTE who have platelet counts between 20,000 and 50,000/microL, the decision to anticoagulate should be individualized and based upon the risk of serious complications from VTE and the risk of bleeding associated with anticoagulation, especially when anticoagulant dose modifications or platelet transfusions are used .

Incidental and small subsegmental pulmonary embolism

- Despite the lack of data, we generally consider incidental (ie, asymptomatic) PE (generally diagnosed on CT scans done for cancer restaging) and small subsegmental PE (SSPE) in patients with cancer as an indication for therapeutic anticoagulation for a minimum of three months.

RECURRENCE

- VTE recurrence rates up to 21 percent (ie, three to four times that of the general population) have been reported in cancer patients despite anticoagulation and may be associated with increased morbidity and mortality.

- Compared with patients without malignancy, patients with malignancy have a higher incidence of major bleeding ranging from 6.5 to 18 percent. Careful observation is warranted so that the therapeutic strategy can be altered when bleeding is detected .