Treatment and Prophylaxis for VTE in the Patients with Cancer

Division of Pulmonology, Allergy and Critical Care Medicine
Department of Internal Medicine, College of Medicine
The Catholic University of Korea

Chan Kwon Park

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   : Patients, Cancer, Treatment
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Overview

VTE is a common and **life-threatening** condition in cancer patients

Table 1 Causes of death in 4466 cancer patients receiving outpatient chemotherapy*

Cause of death	*n* (%)
All	141 (100)
Progression of cancer	100 (70.9)
Thromboembolism	13 (9.2)
Arterial	8 (5.6)
Venous	5 (3.5)
Infection	13 (9.2)
Respiratory failure	5 (3.5)
Bleeding	2 (1.4)
Aspiration pneumonitis	2 (1.4)
Other	9 (6.4)
Unknown	5 (3.5)

*Causes of death exceed total number of deaths because six patients had more than one cause of death identified.

(Khorana, Francis et al. 2007)

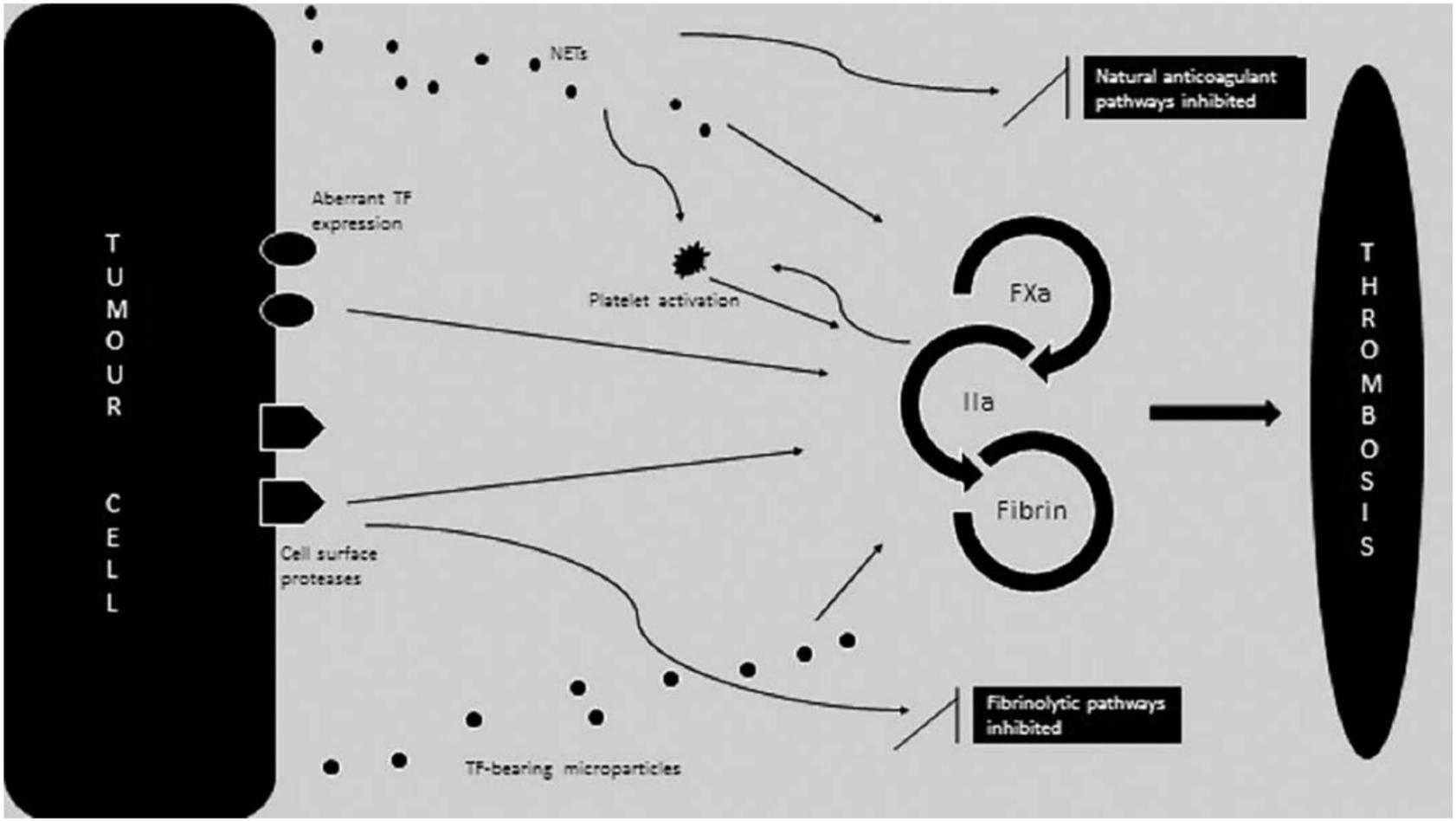
Overview

- Retrospective study
  : **hospitalized adult cancer Pts with neutropenia** (n=66,106) showed that approximately **3% to 12%** of these patients, depending on the type of malignancy, **experienced VTE** during their **first hospitalization**

Overview

- Health claims database analysis
  : patients undergoing CTx for solid tumors in the **ambulatory setting** (n=17,284), VTE occurred in 12.6% of patients during the 12-month period from initiation of chemotherapy.
  : The incidence ranged from 8% to 19% depending on the tumor type.
  cf) VTE incidence was **1.4%** among age- and gender-matched control cohort **without cancer**

Mechanisms underlying the cancer-associated procoagulant state



(Donnellan and Khorana 2017)

Mechanisms underlying the cancer-associated procoagulant state

Table 1
Virchow's triad in patients with cancer.

1. Venous stasis
• Prolonged bed rest/immobility (after surgery)
• Compression of blood vessels by tumor
2. Hypercoagulability
• Procoagulant effects
• Tumor cytokines
• Recent major surgery
• Active chemotherapy, hormonal therapy
• Current erythropoiesis-stimulating agents
• Current or recent antiangiogenic therapy
3. Endothelial injury
• Direct invasion by tumor
• Damaged or dysfunctional endothelium
• Tumor cytokine
• Presence of central venous catheters
• Chemotherapy drugs
• Radiation therapy (late phase complication)

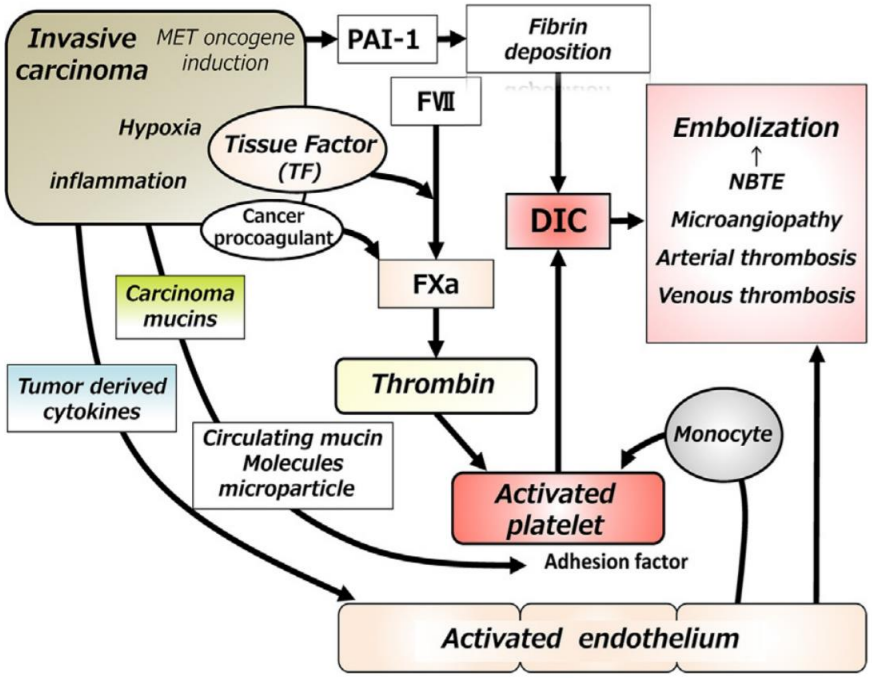


Fig. 2. Multiple mechanisms in cancer-associated thrombosis. There are multiple, overlapping, and interacting mechanisms that can explain the increased incidence of thrombosis in patients with malignancies. In cancer-associated thrombosis, hypercoagulability is probably the result of products arising from the tumor itself. CP, cancer procoagulant; DIC, disseminated intravascular coagulation; NBTE, non-bacterial thrombotic endocarditis; PAI-1, plasminogen activator inhibitor-1.

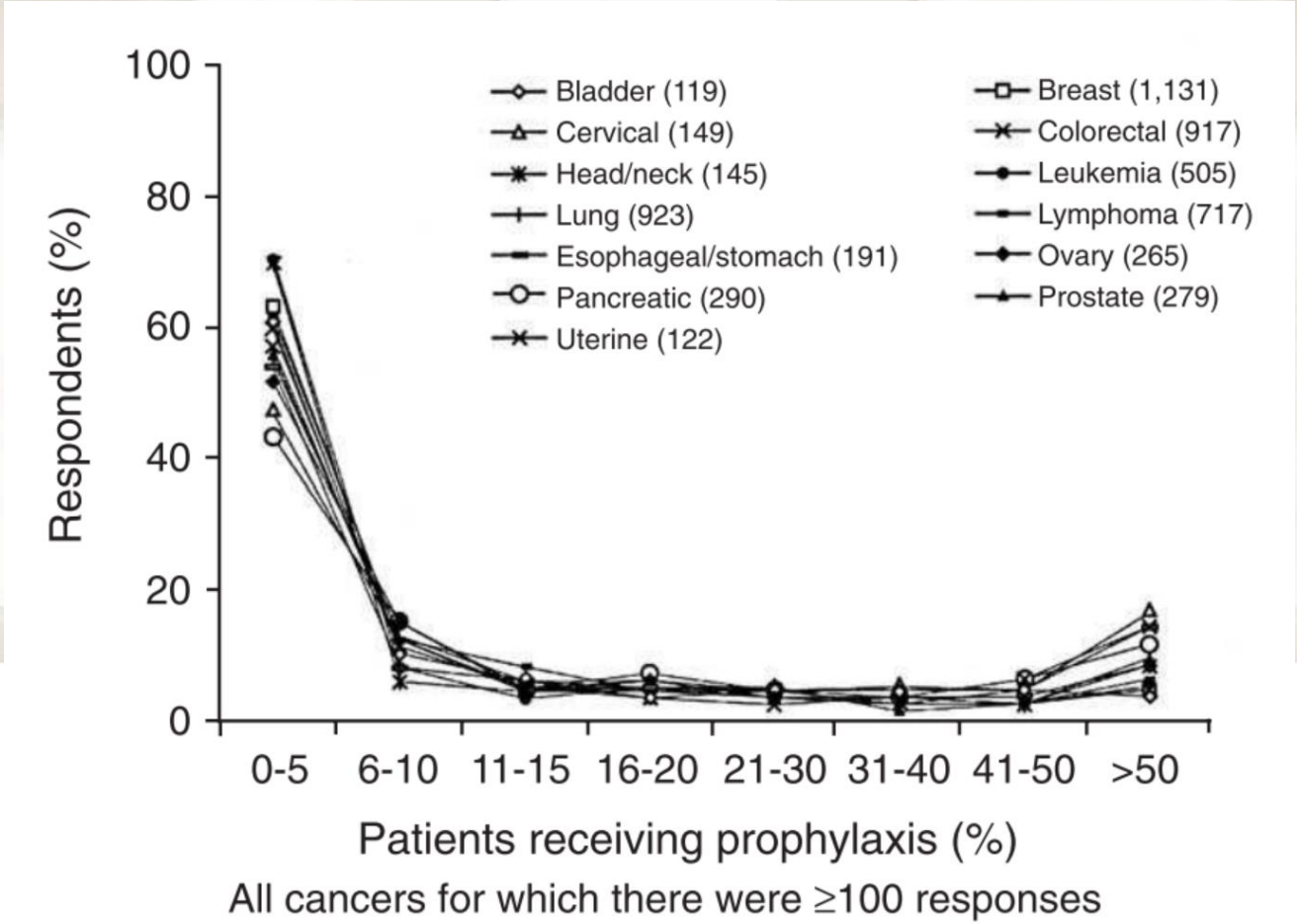
(Mukai and Oka 2018)

Overview

- The occurrence of VTE has been reported to increase the likelihood of death for cancer patients by **2- to 6-fold**.
  Ex) **gynecologic cancer** patients **with PE**
  cf) 6-fold increased risk for death at 2 years
  compared with similar patients without PE.

- Furthermore, VTE has been reported to be the most common cause of death at 30-day follow-up among cancer patients undergoing surgery.

The Fundamental Research in Oncology and Thrombosis **(FRONTLINE)** survey
: only 50% of surgical oncologists and 5% of medical oncologists routinely used VTE prophylaxis in their cancer Pts.



(Tapson, Decousus et al. 2007)

The multinational **IMPROVE** and **ENDORSE** registries
: hospitalized medically ill patients in which only 45% of cancer patients received any form of VTE prophylaxis.

Table 2—*Use of VTE Prophylaxis in the Hospital

Variables	United States	Other Participating Countries
Patients, Total No.	3,410	11,746
Patients receiving one or more types of VTE prophylaxis†	1,852/3,410 (54)	5,788/11,746 (49)
LMWH (all doses)‡	476/3,410 (14)	4,657/11,746 (40)
Once daily	380/457 (83)	4,231/4,589 (92)
q12h	73/457 (16)	347/4,589 (8)
Other	4/457 (0.9)	11/4,589 (0.2)

	Medical patients (N=15 487)	Surgical patients (N=19 842)	Overall (N=35 329)
Any anticoagulant	6596 (43%)	10 901 (55%)	17 497 (50%)
Intermittent pneumatic compression without anticoagulant	318 (2%)	880 (4%)	1198 (3%)

(Cohen, Tapson et al. 2008)
(Kakkar, Levine et al. 2003)

Postmortem reports
: approximately **80% of cases of fatal PE** occur in nonsurgical patients

Table 2 Fatal pulmonary embolism and reason for hospitalisation (1991–2000) 214/265(80.8%)

Year	Surgical n (%)	Non-surgical n (%)	Total (n)
1991	7 (1.5)	17 (3.7)	24
1992	4 (0.8)	21 (4.2)	25
1993	3 (0.6)	29 (5.6)	32
1994	8 (1.6)	19 (3.7)	27
1995	10 (1.6)	21 (3.3)	31
1996	5 (0.8)	25 (3.9)	30
1997	5 (0.9)	22 (4.1)	27
1998	1 (0.2)	15 (3.2)	16
1999	4 (0.8)	24 (5.0)	28
2000	4 (1.0)	21 (5.5)	25
Total	51 (1.0)	214 (4.2)	265 (5.2)

n, cases of fatal pulmonary embolism; %, percentage of necropsies undertaken.

(Alikhan, Peters et al. 2004)

A history of prior VTE
: **independent risk factor** for developing a subsequent VTE

Table 1. Risk factors documented at enrollment

60 patients (12%) suffered from new venous thromboembolic events (VTE) from 507

Variables present at enrollment	Total *N*	No VTE after enrollment	New VTE after enrollment	*P*-value
Age (mean ± SD)	507	55.9 ± 11.9	54.1 ± 13.2	
Gender (male/female; *n*, %)	507	242 (54%)/205 (46%)	28 (46%)/32 (54%)	0.34
Body Mass Index >30 (mean ± SD)	497	25.0 ± 4.2	25.2 ± 5.6	
CEAP (clinical condition, etiology, anatomic location, pathophysiology) score >2 (*n*, %)	462	56 (14%)	12 (22%)	0.15
Deep vein thrombosis (DVT) in medical history (*n*, %)	507	93 (21%)	20 (33%)	0.03
Deep vein thrombosis (DVT) in family (*n*, %)	507	89 (20%)	17 (28%)	0.13
Tumor diagnosed less than 1 year before (*n*, %)	507	147 (33%)	30 (50%)	0.01
Metastasis according to TNM (M = 1, Mx; *n*, %)	208	69 (37%)	7 (33%)	0.59
Outdoor patients (*n*, %)	507	253 (57%)	17 (28%)	<0.0001

SD, standard deviation; VTE, venous thromboembolic event.

(Kröger, Weiland et al. 2006)

Hospitalization is an important risk factor for VTE
: emphasizes the need for greater awareness of VTE risks
: appropriate implementation of preventive measures

TABLE. Estimated average annual rate (per 100,000 population) of hospitalizations with a diagnosis of deep vein thrombosis (DVT), pulmonary embolism (PE), or venous thromboembolism (VTE), by patient sex and age group — National Hospital Discharge Survey, United States, 2007–2009*

	DVT			PE			VTE		
Age group (yrs)	Total (95% CI)	Men (95% CI)	Women (95% CI)	Total (95% CI)	Men (95% CI)	Women (95% CI)	Total (95% CI)	Men (95% CI)	Women (95% CI)
Overall	**152 (127–177)**	**146 (122–171)**	**158 (131–185)**	**121 (98–144)**	**115 (91–138)**	**127 (102–153)**	**239 (199–279)**	**226 (187–265)**	**252 (208–296)**
18–39	34 (26–42)	32 (23–40)	36 (27–45)	33 (25–40)	28 (19–36)	38 (28–48)	60 (47–72)	53 (40–65)	67 (52–81)
40–49	81 (63–98)	97 (72–123)	64 (47–81)	82 (63–100)	85 (61–109)	78 (58–99)	143 (114–172)	154 (117–190)	132 (103–161)
50–59	120 (98–143)	144 (113–175)	97 (75–119)	111 (86–135)	124 (91–156)	99 (73–124)	200 (164–237)	226 (180–272)	176 (138–213)
60–69	247 (194–299)	254 (197–311)	241 (181–301)	203 (160–246)	208 (159–257)	199 (150–247)	391 (315–468)	405 (321–490)	379 (293–465)
70–79	487 (389–584)	469 (362–576)	501 (388–614)	349 (264–434)	337 (229–445)	359 (276–442)	727 (582–872)	720 (556–884)	732 (578–885)
≥80	791 (649–934)	821 (635–1,007)	775 (629–921)	500 (392–609)	537 (390–684)	480 (368–592)	1,134 (927–1,340)	1,153 (904–1,402)	1,123 (911–1,336)

Abbreviation: CI = confidence interval.
* Diagnoses of DVT and PE are not mutually exclusive; an estimated 78,511 patients received diagnoses of both DVT and PE. VTE estimates include patients with diagnoses of either DVT or PE.

(CDC 2012)

Recent cancer diagnosis and the occurrence of **advanced malignancies** and **distant metastases** also increase VTE risk

Table 1. Effect of Malignancy on the Risk of Venous Thrombosis Depending on the Duration Between Diagnosis of Cancer and Venous Thrombosis

Duration Between Malignancy and Venous Thrombosis	No. of Individuals (%)		Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
	Patients (n = 3220)	Control Participants (n = 2131)		
No malignancy	2831 (87.9)	2062 (96.8)	1.00	1.00
All malignancies	389 (12.1)	69 (3.2)	4.1 (3.2-5.3)	4.3 (3.3-5.6)
Time after index date (diagnosis)†				
0 to ≤3 mo	80 (20.6)	1 (1.5)	58.2 (8.1-419.1)	53.5 (8.6-334.3)
>3 mo to ≤1 y	92 (23.7)	5 (7.6)	13.4 (5.4-33.0)	14.3 (5.8-35.2)
>1 to ≤3 y	67 (17.2)	14 (21.2)	3.5 (2.0-6.2)	3.6 (2.0-6.5)
>3 to ≤5 y	43 (11.1)	11 (16.7)	2.8 (1.5-5.5)	3.0 (1.5-5.7)
>5 to ≤10 y	47 (12.1)	14 (21.2)	2.4 (1.3-4.5)	2.6 (1.4-4.7)
>10 to ≤15 y	19 (4.8)	6 (9.0)	2.3 (0.9-5.8)	2.3 (0.9-5.8)

Table 3. Effect of Distant Metastases on the Risk of Venous Thrombosis in Patients With Solid Tumors and Diagnosis of Malignancy Within 5 Years Before the Diagnosis of Venous Thrombosis

Malignancy	Distant Metastases	No. of Patients (n = 3050)*	No. of Control Participants (n = 2088)*	OR (95% CI)	Adjusted OR (95% CI)†	Adjusted OR (95% CI)‡
No	No	2831	2062	1.00	1.00	
Yes	No	126	25	3.7 (2.4-5.7)	3.9 (2.5-6.0)	1.00
	Yes	93	1	67.7 (9.4-486.6)	58.0 (9.7-346.7)	19.8 (2.6-149.1)

Abbreviations: CI, confidence interval; OR, odds ratio.
*A total of 37 cases and 1 control participant had a hematological malignancy; 26 cases and 4 control participants did not provide information about stage of disease.
†Adjusted for age and sex; reference group is patients with no malignancy.
‡Adjusted for age and sex; reference group is patients with malignancy but without distant metastases.

(Blom, Doggen et al. 2005)

Association between different **types of cancer and the risk for a VTE** : **pancreatic cancer** and brain tumors were associated with a high risk(1)

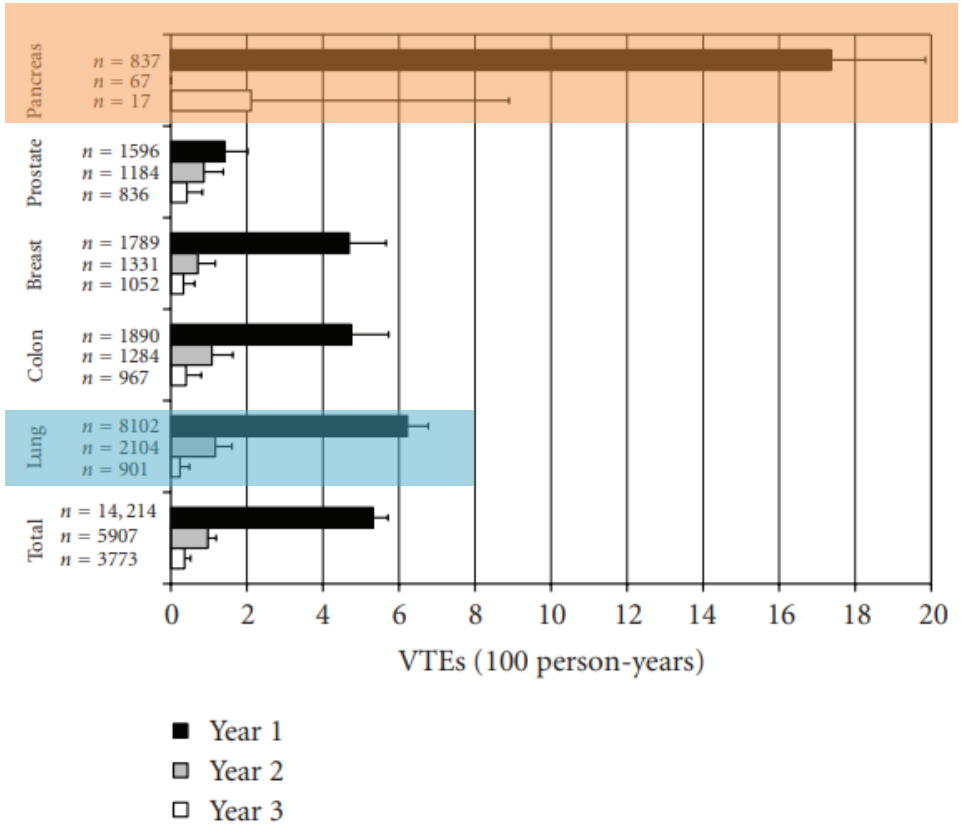


FIGURE 2: Incidence of VTE according to cancer type and time. Incidence of VTE within each year after cancer diagnosis is shown with error bars depicting standard deviations.

(Hall, Andersen et al. 2009)

Association between different **types of cancer and the risk for a VTE** : pancreatic cancer and **brain tumors** were associated with a high risk (2)

TABLE 3
Venous Thromboembolism in Patients with Malignant Glioma: Extended Follow-Up

Reference	Design	Follow-up duration	VTE diagnosis	Routine screening	Perioperative DVT prophylaxis	n	DVT (%)	DVT/ patient-month[a]	PE (%)	PE mortality (%)
Ruff and Posner (1983)[8]	Retrospective	≤96 weeks	Venogram	No	Intraoperative elastic bandages	188	16	0.023	NS	NS
					Intraoperative elastic bandages + IPC 8–12 hrs postoperative	108	7	0.013	NS	NS
Cheruku et al. (1991)[11]	Retrospective	Until death	DUS or V/Q	No	NS	77	13[b]	NS	10[b]	1[b]
Dhami et al. (1993)[10]	Retrospective	> 6 months	IPG, DUS, venogram or V/Q	No	GCS in 3 patients	58	9	NS	NS	NS
Brandes et al. (1997)[6]	Prospective	Until death	DUS or V/Q	No	Heparin 5000 U t.i.d. × 20 days perioperative	75	24	0.015	5	4

VTE: venous thromboembolism; DVT: deep venous thrombosis; PE: pulmonary embolus; IPC: intermittent pneumatic compression; NS: not significant; DUS: duplex ultrasound; V/Q: ventilation/perfusion lung scanning; IPG: impedance plethysmography; GCS: graduated compression stockings; t.i.d.: three times a day.

[a] Deep venous thrombosis per patient-month of follow-up.

[b] Beyond third postoperative week.

(Marras, Geerts et al. 2000)

Adenocarcinomas appear to be associated with a **higher risk** than squamous cell cancers

Table 3: PE risk in relation to primary cancer; in univariate analysis and when adjusting for age, gender, presence of metastatic cancer disease and for adenocarcinoma (AC) type of cancer disease.

Primary cancer			Odds for PE (95% CI)					
Type	Site		Univariate OR	p-value	Adjusted OR *)	p-value	Adjusted OR #)	p-value
AC	Pancreatic	*Yes vs. no*	2.55 (2.10 – 3.09)	<0.001	2.29 (1.88 – 2.79)	<0.001	2.10 (1.72 – 2.58)	<0.001
AC	Gall bladder	*Yes vs. no*	1.76 (1.34 – 2.32)	<0.001	1.53 (1.16 – 2.03)	0.002	1.39 (1.05 – 1.84)	0.023
AC	Gastric	*Yes vs. no*	1.61 (1.36 – 1.90)	<0.001	1.44 (1.21 – 1.71)	<0.001	1.30 (1.09 – 1.55)	0.004
AC	Pulmonary	*Yes vs. no*	1.57 (1.24 – 1.99)	0.003	1.38 (1.09 – 1.76)	0.008	1.24 (0.97 – 1.58)	0.087
AC	Colorectal	*Yes vs. no*	1.26 (1.11 – 1.44)	<0.001	1.14 (1.00 – 1.30)	0.053	0.98 (0.85 – 1.13)	0.78
Carcinoma	Renal	*Yes vs. no*	1.14 (0.92 – 1.41)	0.16	1.06 (0.86 – 1.31)	0.58	..	..
Carcinoid	Small bowel	*Yes vs. no*	0.98 (0.69 – 1.37)	0.99	0.93 (0.66 – 1.30)	0.66	..	..
SqCC	Pulmonary	*Yes vs. no*	1.00 (0.80 – 1.25)	0.23	0.88 (0.70 – 1.11)	0.28	..	..
Carcinoma	Hepatic	*Yes vs. no*	0.58 (0.43 – 0.78)	<0.001	0.52 (0.39 – 0.71)	<0.001	..	..
SqCC	Oesophageal	*Yes vs. no*	0.59 (0.36 – 0.96)	0.008	0.53 (0.32 – 0.86)	0.010	..	..
SCLC	Pulmonary	*Yes vs. no*	0.60 (0.45 – 0.79)	<0.001	0.50 (0.38 – 0.67)	<0.001	..	..
Any of studied cancers		*Yes vs. no*	*1.27 (1.18 – 1.36)*	*<0.001*	*1.21 (1.10 – 1.33)*	*<0.001*	..	..

AC: adenocarcinoma, SqCC: squamous cell carcinoma, SCLC: small cell lung cancer, *) logistic regression model including age, gender and presence of metastatic cancer disease as covariates, #)logistic regression model including age, gender, presence of adenocarcinoma and presence of metastatic cancer disease as covariates.

Between 1970 and 1982, **23,796 standardised autopsies** were performed, representing **84% of all in-hospital deaths** in an urban Swedish population

(Ogren, Bergqvist et al. 2006)

Breast cancer was associated with a relatively **low VTE risk** in some studies

TABLE 3. Characteristics of Patients With VTE Within 60 Days After Breast Cancer Surgery

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age at surgery (yr)	48	41	66	45	72	58	66
Breast cancer stage	T1 N0 M0	T2 N0 M0	T2 N1 M0	Tis N0 M0	T1 N0 M0	T4 N1 M0	T4 N1 M0
Procedure	MRM	Mastectomy ALND TRAM	B/L mastectomies Left ALND	B/L mastectomies B/L Lat dorsi flaps Tissue expanders	B/L mastectomies Left SLNB Left ALND	Mastectomy	Segmental mastectomy ALND
VTE diagnosis							
Days after surgery	2	11	13	14	25	29	60
Symptoms and signs	Dyspnea	Dyspnea Chest pain Hypoxia	Calf pain/swelling	Thigh pain/swelling	Dyspnea Chest pain Upper extremity swelling	Dyspnea Chest pain	Thigh and calf pain/swelling
DVT	No	No	Yes	Yes	No	Yes	Yes
PE	Yes	Yes	No	No	Yes	Yes	No
Method of VTE diagnosis							
Ventilation-perfusion scan		Positive				Positive	
CT pulmonary angiography	Positive				Positive	Positive	
Duplex Doppler sonography	Negative	Negative	Positive	Negative	Negative	Positive	Positive
CT of abdomen and pelvis				Positive			
Anticoagulation therapy							
Type	IV heparin Enoxaparin Warfarin	Enoxaparin Warfarin Dalteparin	IV heparin Warfarin	Enoxaparin Warfarin	Enoxaparin IV heparin Warfarin	Enoxaparin Warfarin	Enoxaparin Warfarin
Duration (mo)	12	4	11	6	6	18	11.5
Comment		Recurrent cancer				Neoadjuvant chemotherapy	Neoadjuvant chemotherapy

ALND indicates axillary lymph node dissection; B/L, bilateral; CT, computed tomography; DVT, deep venous thrombosis; IV, intravenous; Lat, latissimus; MRM, modified radical mastectomy; PE, pulmonary embolism; SLNB, sentinel lymph node biopsy; TRAM, transverse rectus abdominis myocutaneous flap; VTE, venous thromboembolism.

3898 Pts underwent 4416 surgical procedures
Seven patients with postoperative VTE within 60 days were identified, for a rate of 0.16% per procedure

(Andtbacka, Babiera et al. 2006)

The risk for VTE was shown to increase by **6-fold** when Pts with **metastatic breast cancer** were compared with patients with localized disease

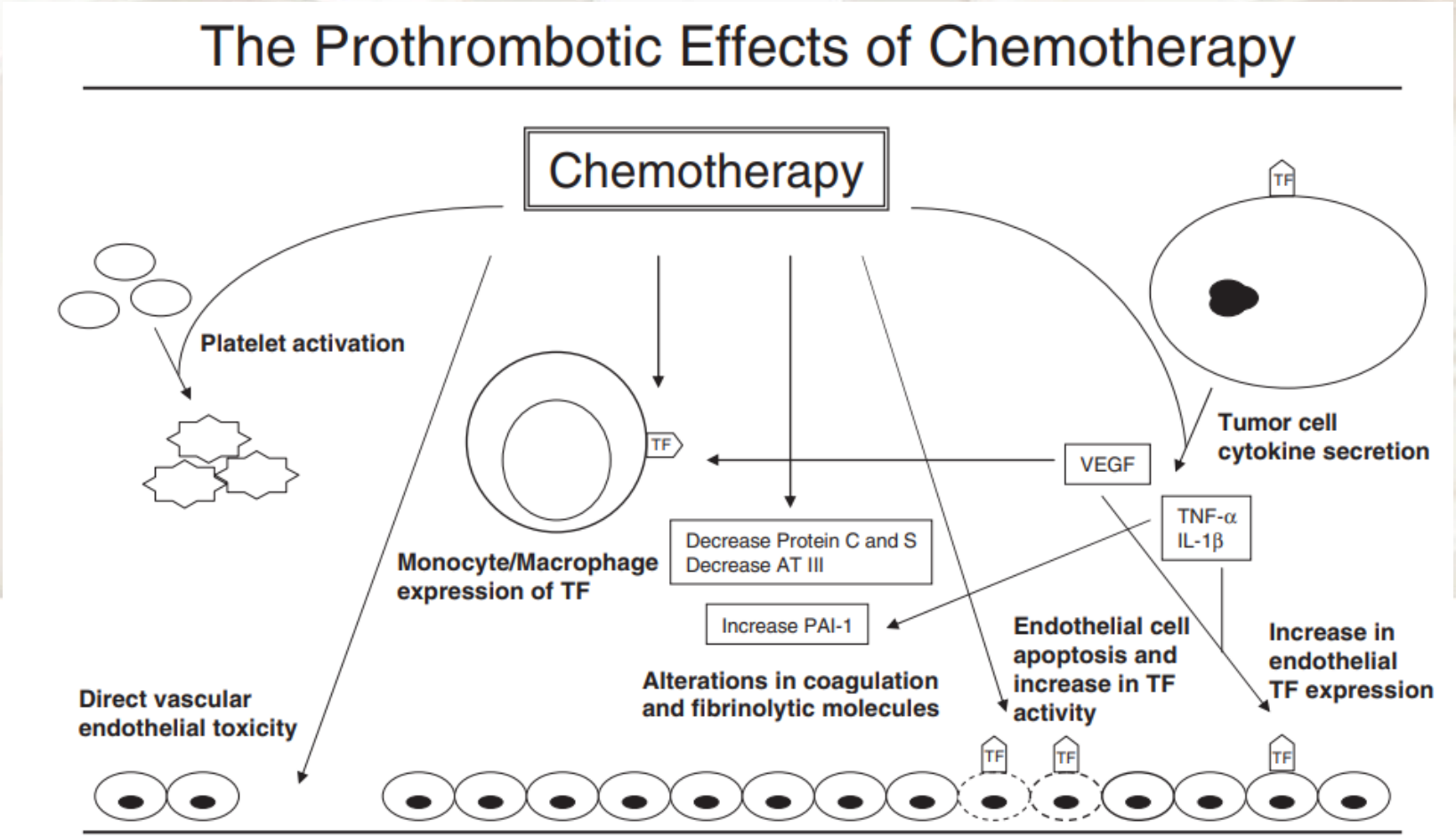
Table 1. Incidence of VTE Based on Demographic and Clinical Characteristics

Variable	Patients		Rate of VTE per 100 Patient-Years				2-Year Cumulative Incidence of VTE		Alive at 2 Years	
	No.	%	0-6 Months	95% CI	7-12 Months	95% CI	%	95% CI	%	95% CI
Total patients	108,255		1.2	1.1 to 1.3	0.6	0.6 to 0.7	1.2	1.1 to 1.3	89.8	89.6 to 90.0
Age, years										
< 45	14,767	14	0.7	0.5 to 0.9	0.3	0.2 to 0.5	0.7	0.6 to 0.9	92.8	92.4 to 93.2
45-64	45,276	42	1.1	1.0 to 1.3	0.5	0.4 to 0.6	1.0	0.9 to 1.1	93.4	93.2 to 93.6
65-74	24,886	23	1.3	1.1 to 1.5	0.9	0.7 to 1.0	1.5	1.3 to 1.6	91.2	90.9 to 91.6
≥ 75	23,326	21	1.6	1.4 to 1.9	0.9	0.7 to 1.1	1.6	1.4 to 1.7	79.4	78.9 to 79.9
Race/ethnicity*										
White	81,721	75	1.3	1.2 to 1.4	0.7	0.6 to 0.8	1.3	1.2 to 1.3	89.7	89.5 to 89.9
Hispanic	12,157	11	1.1	0.9 to 1.4	0.6	0.4 to 0.8	1.1	1.0 to 1.3	90.8	90.3 to 91.3
Asian American	7,490	7	0.4	0.2 to 0.6	0.2	0.1 to 0.3	0.3	0.2 to 0.4	93.8	93.3 to 94.4
African American	6,107	6	1.5	1.1 to 2.0	1.0	0.7 to 1.4	1.8	1.5 to 2.1	83.7	82.7 to 84.6
Stage										
Localized	66,475	61	0.8	0.7 to 0.9	0.4	0.4 to 0.5	0.8	0.8 to 0.9	95.6	95.5 to 95.8
Regional	32,990	30	1.5	1.3 to 1.7	0.9	0.8 to 1.0	1.6	1.4 to 1.7	88.9	88.6 to 89.3
Metastatic	4,499	4	6.8	5.7 to 8.1	2.4	1.7 to 3.3	4.2	3.6 to 4.8	40.5	39.0 to 41.9
Unknown	4,291	4	1.3	0.8 to 1.9	0.7	0.3 to 1.2	1.0	0.7 to 1.3	57.9	56.4 to 59.4

Approximately **1% of breast cancer** patients developed VTE within 2 years, with the **highest incidence in the first 6 months** after diagnosis. **Metastatic disease and comorbidities were the strongest predictors**. The diagnosis of VTE was associated with a higher risk of death within 2 years

(Chew, Wun et al. 2007)

The association of **cytotoxic chemotherapy** with the development of VTE in cancer patients has been shown in several studies



(Haddad and Greeno 2006)

Khorana Predictive Model for **CTx-Associated VTE**

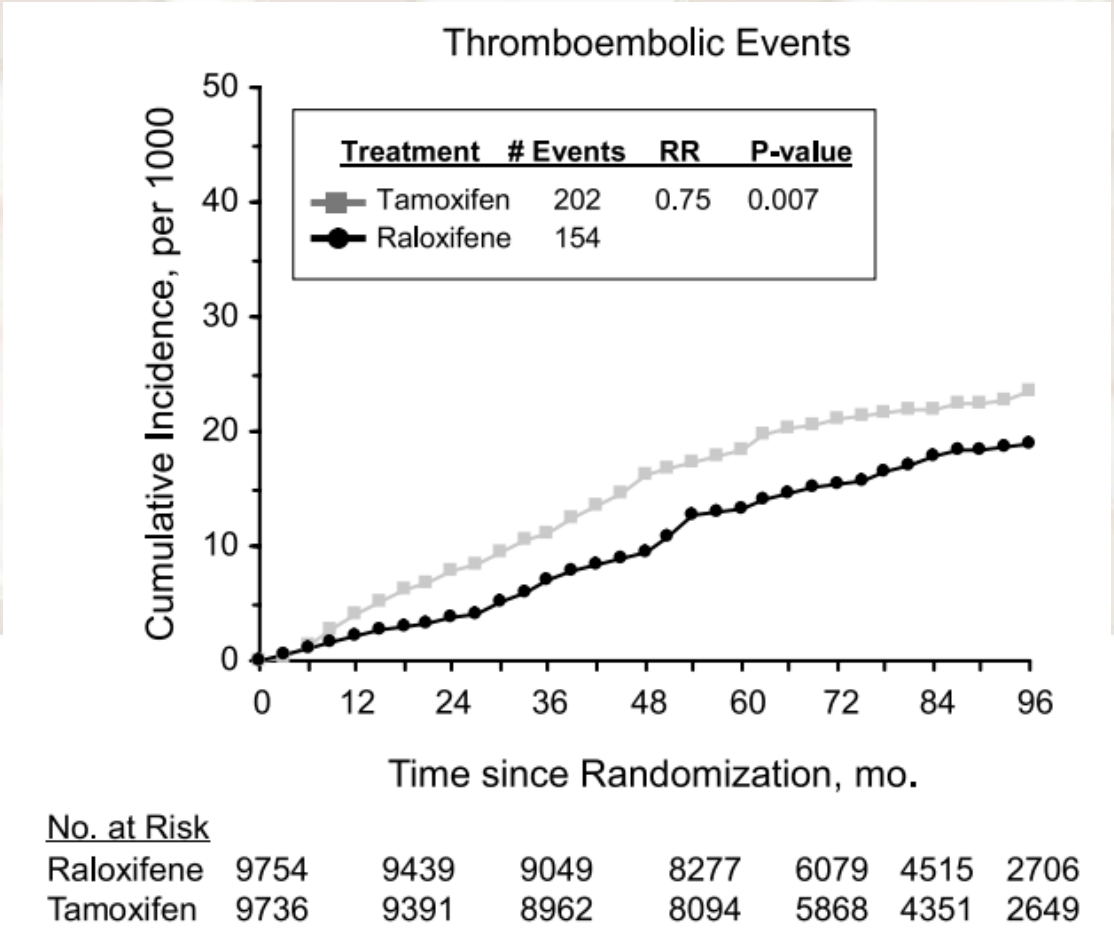
Patient Characteristic	Risk Score
• Site of primary cancer	
▸ Very high risk (stomach, pancreas)	2
▸ High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
• Prechemotherapy platelet count 350 x 10^9/L or higher	1
• Hemoglobin level less than 10 g/dL or use of red cell growth factors	1
• Prechemotherapy leukocyte count higher than 11 x 10^9/L	1
• BMI 35 kg/m^2 or higher	1

Total Score	Risk Category	Risk of Symptomatic VTE
0	Low	0.3–1.5%
1, 2	Intermediate	1.8–4.8%
3 or higher	High	6.7–12.9%

NCCN 2021

Increased VTE risk was shown to be associated with the use of exogenous hormonal compounds, such as **selective estrogen receptor modulators** (eg, tamoxifen, raloxifene)

the Study of Tamoxifen and Raloxifene (STAR)



(Vogel, Costantino et al. 2010)

VTE Risk Factors in Patients With Cancer

- ***General patient risk factors***
  - **Active cancer**
  - **Advanced stage of cancer**
  - Cancer types at higher risk
    : **Brain, Pancreas, Stomach**, Bladder, Gynecologic, Lung o Lymphoma
    Myeloproliferative neoplasms (MPN), Kidney, Metastatic cancers
  - Regional bulky lymphadenopathy with extrinsic vascular compression
  - Familial and/or acquired hypercoagulability (including pregnancy)
  - Medical comorbidities
    : Infection, renal disease, pulmonary disease, congestive heart failure (CHF), arterial thromboembolism
  - Poor performance status
  - Older age

VTE Risk Factors in Patients With Cancer

- ***Modifiable risk factors***
  - Smoking, tobacco
  - Obesity
  - Activity level/exercise

- ***High-risk outpatients on chemotherapy, based on combinations of the following risk factors***
  - Active cancers associated with high incidence of VTE:
    stomach, pancreas, lung, lymphoma, gynecologic, bladder, testicular
  - Prechemotherapy ***platelet count >350,000/µL***
  - Prechemotherapy white blood cell ***(WBC) count >11,000/µL***
  - ***Hemoglobin <10 g/dL***
  - Use of erythropoiesis-stimulating agents **(ESAs)**
  - Body mass index (BMI) ≥35 kg/m2
  - ***Prior VTE***

VTE Risk Factors in Patients With Cancer

- ***Treatment-related risk factors***
  - **Major surgery**
  - **Central venous catheter/IV catheter**
  - Chemotherapy such as:
    - IMiDs plus high-dose dexamethasone
    - Proteasome inhibitors
  - Exogenous hormonal therapies such as:
    - Hormone replacement therapy (HRT)
    - Contraceptives
    - Tamoxifen/raloxifene
    - Diethylstilbestrol

CVAD as a risk factor for development of an upper-extremity DVT (UEDVT) between 0.3% and 28.3%

Table 3. Incidence of Venographic CVC-Related DVT in Cancer Patients

Author	Year	Study Design	Population	No. of CVCs	CVC-Related DVT (%)
Stoney[70]	1976	Prospective	Adults	203	31.0
Ladefoged[71]	1978	Retrospective	Adults	48	27.1
Burt[72]	1981	Prospective	Adults	21	33.3
Valerio[73]	1981	Prospective	Adults	22	27.3
Brismar[74]	1982	Prospective	Adults	53	35.8
Bozetti[75]	1983	Prospective	Adults	52	28.8
Lokich[23]	1983	Prospective and retrospective	Adults	53	41.5
Pottecher[76]	1984	Prospective	Adults	52	38.5
Bern[77]	1990*	Retrospective, controlled	Adults	42	37.5
Balestrieri[78]	1995	Prospective	Adults	57	56.0
Monreal[79]	1996*	Retrospective, controlled	Adults	29	62.0
De Cicco[80]	1997	Prospective	Adults	127	66.0
Martin[10]	1999	Prospective	Adults‡	60	58.3
Glaser[81]	2001	Prospective	Children	24	50.0
Frank[82]	2000†	Retrospective	Adults	319	35.1

NOTE. Most thrombi in these studies were asymptomatic.
Abbreviations: CVC, central venous catheter; DVT, deep venous thrombosis.
*In the control group.
†Radionuclide venography.
‡Intensive care unit patients.

(Verso and Agnelli 2003)

CAVT
: **Diagnosis and Evaluation**
in Cancer Patients

Large prospective study of patients with **suspected DVT that had been excluded on radiologic testing** showed that high D-dimer levels were present in a large percentage of patients with cancer

Table 1 Patient demographics

Characteristic	
Number of patient episodes	2263
Women/men	1518/754
Median age at presentation (range), years	69 (18–105)
Age >60 years (%)	1472 (65.4)
Median D-dimer, ng FEU/ml	1000 (300–35 500)
D-dimer>1000 ng FEU/ml (%)	1165 (51.7)
D-dimer>4000 ng FEU/ml (%)	111 (4.9)
D-dimer>8000 ng FEU/ml (%)	40 (1.8)
Presence of malignancy (%)	247 (10.9)
Median follow-up (range), months	22.2 (0–65)

Table 2 Multivariate cox regression analysis for prognostic factors on overall survival

Variable	p Value
D-dimer >1000 ng FEU/ml	0.08
D-dimer >4000 ng FEU/ml	0.782
D-dimer >8000 ng FEU/ml	<0.001
Age >60 years	<0.001

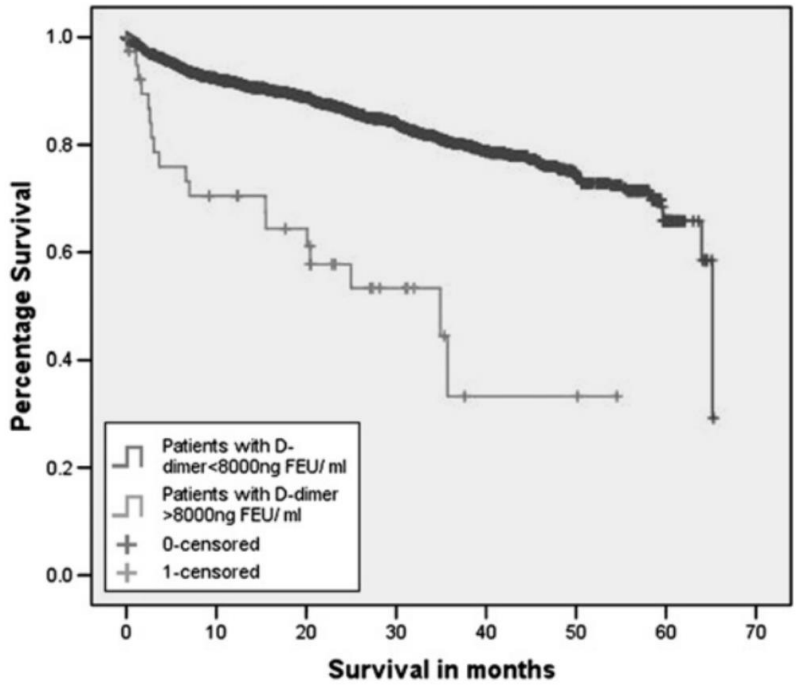


Figure 3 Kaplan–Meier survival curve showing the impact of D-dimer >8000 ng FEU/ml on survival.

(Knowlson, Bacchu et al. 2010)

The most common presenting symptoms of DVT

- **extremity edema (80%)**
- Pain (75%)
- erythema (26%)

Dx.: Duplex venous ultrasonography is recommended as the preferred venous imaging method for initial diagnosis of DVT

- Other imaging modalities (listed in order of preference) are recommended

1) Contrast-enhanced CT, also known as indirect CT venography

: reportedly as accurate as ultrasonography in diagnosing femoro-popliteal DVT and provides accurate imaging of the large pelvic and iliac veins, the IVC, subclavian veins, and the SVC

cf) requires relatively high concentrations of contrast agent

2) MRI

: a sensitive and specific evaluation of the pelvic and iliac veins and vena cava *without the need for nephrotoxic contrast agents*

cf) include higher cost, longer imaging times, and limited availability in some practice settings

3) Standard invasive venography(once considered the gold standard)

=> *replaced by less invasive methods*

Anticoagulation in Cancer Patients : **Contraindications and Risks**

Contraindications to Anticoagulation

1) chronic, clinically significant bleeding (for >48hrs)
2) recent major surgery associated with a high risk of bleeding
3) high risk for falls and/or head trauma
4) **thrombocytopenia (platelets <50,000/mcL)**
5) **severe platelet dysfunction**
   (eg, due to uremia, medications, dysplastic hematopoiesis)
6) underlying hemorrhagic coagulopathy
7) neuraxial anesthesia or lumbar puncture.

Risks Associated with Anticoagulation Therapy

- Prospective follow-up study of anticoagulation therapy for VTE,
  12-month cumulative incidence
  : major bleeding was **12.4%** and **4.9%** in patients **with** and
  without cancer, respectively (HR, 2.2; 95% CI, 1.2–4.1)

- **Cancer patients** remain at increased risk of bleeding during vitamin K antagonist therapy regardless of INR level.
  => **thrombocytopenia** and **organ or vascular invasion by tumors**

- Other risks associated with chronic use of anticoagulants
  : osteoporosis and heparin-induced thrombocytopenia (HIT)
  => oral anticoagulant or enoxaparin, **decreases in bone mineral density** of 4.8% at 2-year follow-up

Risks Associated with Anticoagulation Therapy

- **Warfarin**, its activity is known to be affected by many other drugs

  1) antibiotics and antifungal therapies

  - trimethoprim sulfamethoxazole, ciprofloxacin, metronidazole, fluconazole=> **potentiate** the effect of warfarin
  - cf) rifampin and dicloxacillin => **antagonize** the effect of warfarin

  2) chemotherapeutic agents

  - fluoropyrimidines (5-fluorouracil and capecitabine) => increase the INR
  - interactions between warfarin and certain selective estrogen receptor modulators (tamoxifen and raloxifene)
  - Dietary intake of vitamin K and certain dietary supplements can also influence the effects of warfarin.

Therapies for **Prophylaxis and Treatment** of VTE in Cancer Patients

Heparin followed by warfarin reduced VTE recurrence and associated mortality in Pts with symptoms of acute PE

TABLE III—RESULTS IN COMPLETE SERIES OF 73 CASES

Group	Total	Deaths from pulmonary embolism	Non-fatal recurrences	Other deaths
Untreated ..	19	5	5	0
Treated ..	54	0	1	2

⇒ **hospitalized patients with cancer receive anticoagulation therapy** in the absence of contraindications

(Barritt and Jordan **1960**)

Advanced cancer undergoing treatment with chemotherapy
(**PROTECHT trial**: randomised, placebo-controlled, double-blind study)
: statistically significant decrease in thromboembolic events in the group receiving prophylactic LMWH (ie, nadroparin)

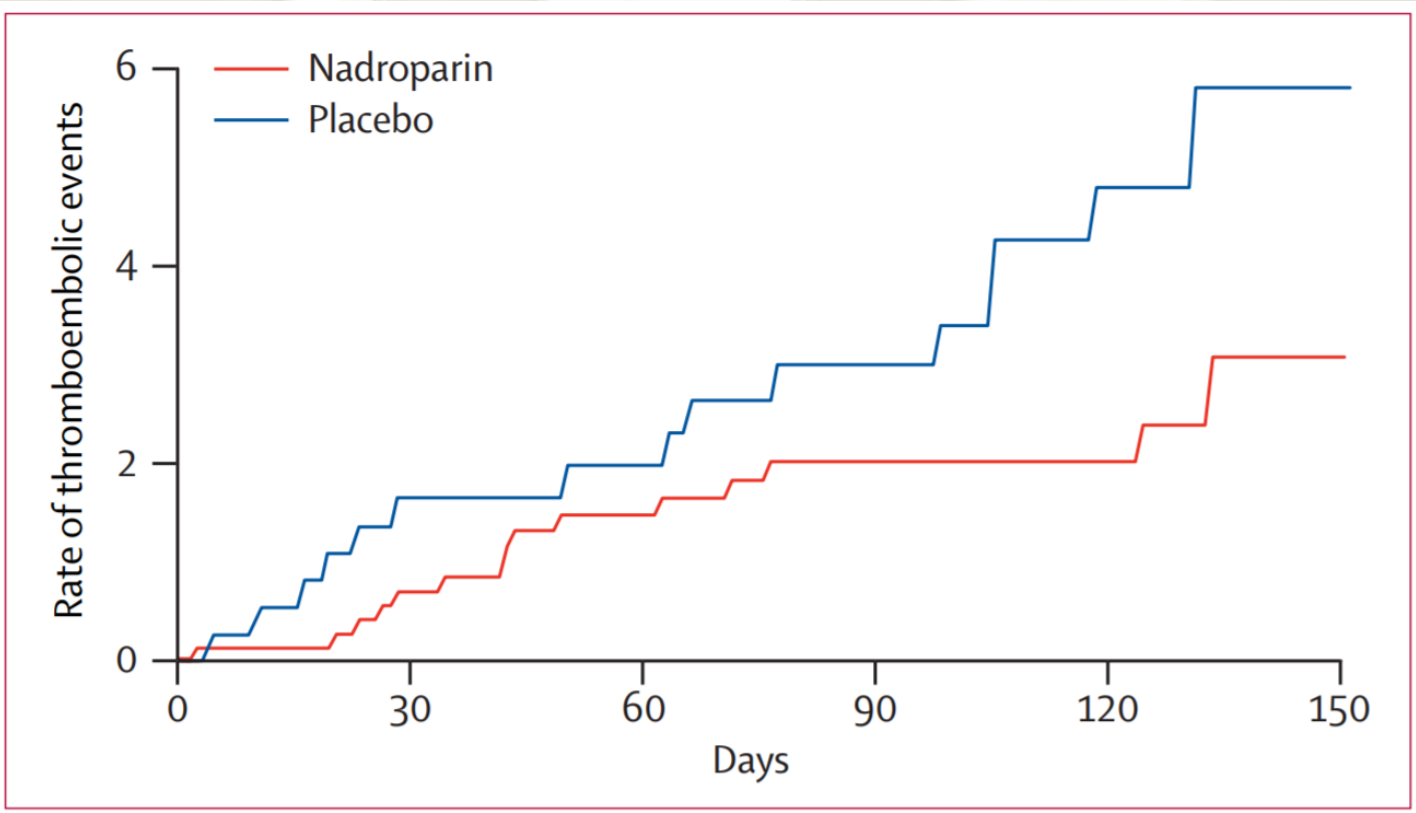


Figure 2: **Cumulative hazard of thromboembolic events by treatment**

(Agnelli, Gussoni et al. 2009)

CONTRAINDICATIONS TO VTE PROPHYLAXIS

Contraindications to Prophylactic Anticoagulation

- Active bleeding
- Thrombocytopenia (platelet count <50,000/μL or clinical judgment)[2]
- Underlying hemorrhagic coagulopathy (eg, abnormal PT or aPTT excluding a lupus inhibitor/anticoagulant) or known bleeding disorder in the absence of replacement therapy (eg, hemophilia, von Willebrand disease)
- Indwelling neuraxial catheters (contraindication for apixaban, dabigatran, edoxaban, fondaparinux, rivaroxaban, or enoxaparin dose exceeding 40 mg daily)
- Neuraxial anesthesia/lumbar puncture[3,4]
- Interventional spine and pain procedures[5]

Contraindications to Mechanical Prophylaxis

- Absolute
  - Acute DVT (unless on therapeutic anticoagulation)
  - Severe arterial insufficiency (pertains to graduated compression stockings [GCS] only)
- Relative
  - Large hematoma
  - Skin ulcerations or wounds[6]
  - Mild arterial insufficiency (pertains to GCS only)
  - Peripheral neuropathy (pertains to GCS only)

VTE PROPHYLAXIS OPTIONS FOR **HOSPITALIZED** MEDICAL ONCOLOGY PATIENTS

Agent	Standard Dosing[a,b]	Renal Dose	Obesity Dosing (BMI ≥40 kg/m²)[c]
Dalteparin[1,2,3,4]	5,000 units SC daily (category 1)	Avoid if CrCl <30 mL/min	Consider 7,500 units SC daily OR 5,000 units every 12 hours SC daily OR 40–75 units/kg SC daily
Enoxaparin[3,4,5,6]	40 mg SC daily (category 1)	Recommend 30 mg SC daily if CrCl <30 mL/min	Consider 40 mg SC every 12 hours OR 0.5 mg/kg SC daily
Fondaparinux[4,7,8,10]	2.5 mg SC daily (category 1) Avoid in patients weighing <50 kg	Caution if CrCl 30–49 mL/min Avoid if CrCl <30 mL/min	Consider 5 mg SC daily
Unfractionated Heparin[9,10] (UFH)	5,000 units SC every 8–12 hours (category 1)	Same as standard dose	Consider 7,500 units SC every 8 hours

CrCl = estimated creatinine clearance; SC = subcutaneous

VTE PROPHYLAXIS OPTIONS FOR **AMBULATORY** MEDICAL ONCOLOGY PATIENTS

Agent	Standard Dosing[d]	Renal Dose	Other Dose Modifications
Apixaban[f,11]	2.5 mg PO twice daily	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/μL Avoid if weight <40 kg
Rivaroxaban[g,12]	10 mg PO once daily	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/μL

CrCl = estimated creatinine clearance, PO = oral

VTE PROPHYLAXIS OPTIONS FOR HOSPITALIZED **SURGICAL ONCOLOGY** PATIENTS

Agent	Standard Dosing[h,i]	Renal Dose	Obesity Dosing (BMI ≥40 kg/m^2)[j]
Dalteparin[1,2,3,4]	5,000 units SC the evening prior to surgery, then 5,000 units SC daily OR 2,500 units SC 1–2 hours pre-operation and then 2,500 units SC 12 hours later and then 5,000 units SC daily beginning post-op Day 1	Avoid if CrCl <30 mL/min	Consider 7,500 units SC daily OR 5,000 units every 12 hours SC daily OR 40–75 units/kg SC daily
Enoxaparin[3,4,5,6]	Pre-operation: 40 mg SC 10–12 hours pre-operation Post-operation: 40 mg SC daily or 40 mg SC daily with first dose 6–12 hours post-operation	30 mg SC once daily if CrCl <30 mL/min	Consider 40 mg SC every 12 hours
Fondaparinux[3,4,6,7,8]	2.5 mg SC daily no earlier than 6–8 hours post-operation Avoid in patients weighing <50 kg	Caution if CrCl 30–49 mL/min Avoid if CrCl <30 mL/min	Consider 5 mg SC daily
UFH[13,14]	Pre-operation: 5,000 units SC 2–4 hours prior to surgery Post-operation: 5,000 units SC every 8 hours	Same as standard dose	Consider 7,500 units SC every 8 hours post-operation

CrCl = estimated creatinine clearance, SC = subcutaneous

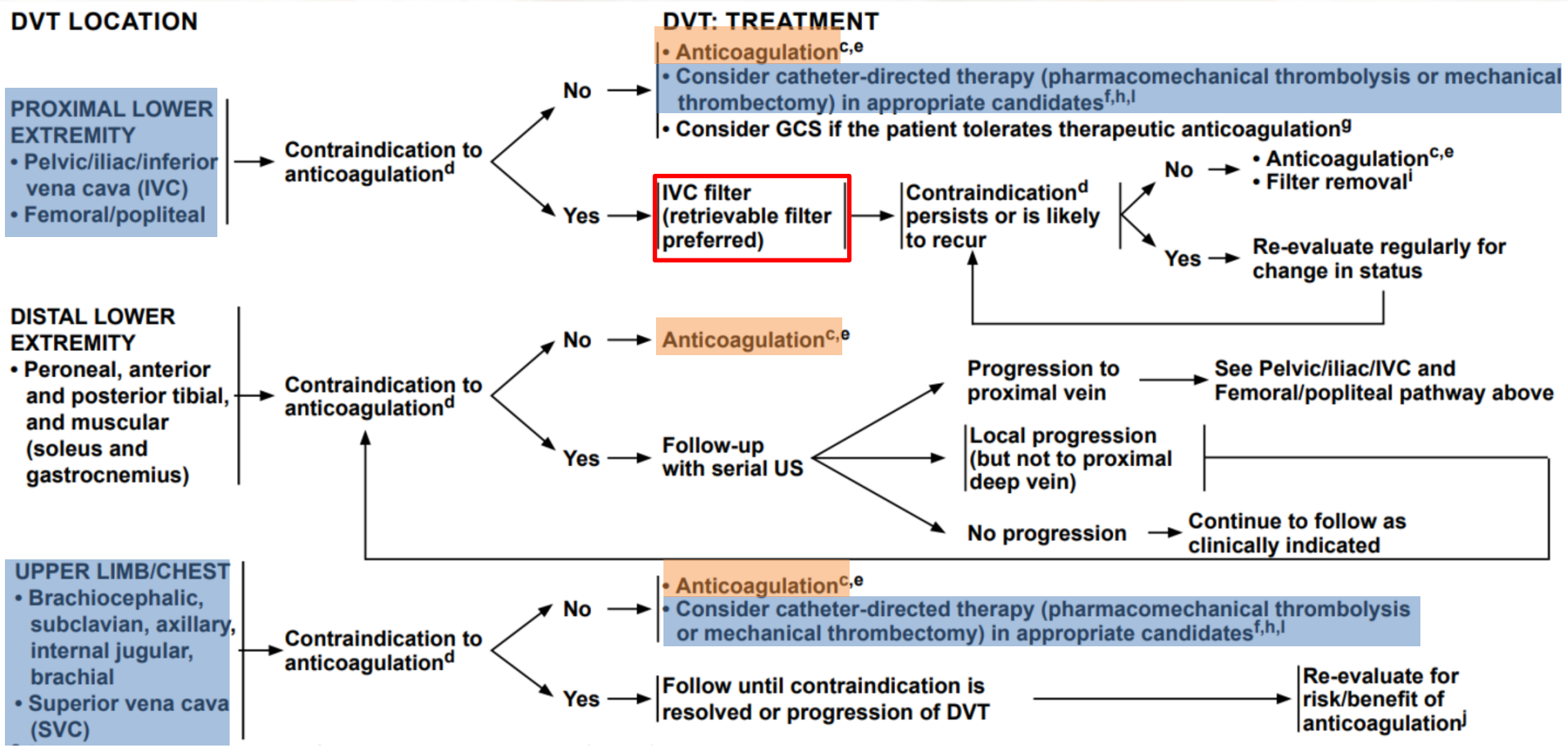
Mechanical Prophylaxis

- Intermittent pneumatic compression (**IPC**) devices and Graduated compression stockings (**GCS**) are mechanical prophylaxis options that are principally used in patients with **CIx. to pharmacologic prophylaxis** or in conjunction with pharmacologic agents in patients at very high risk for VTE

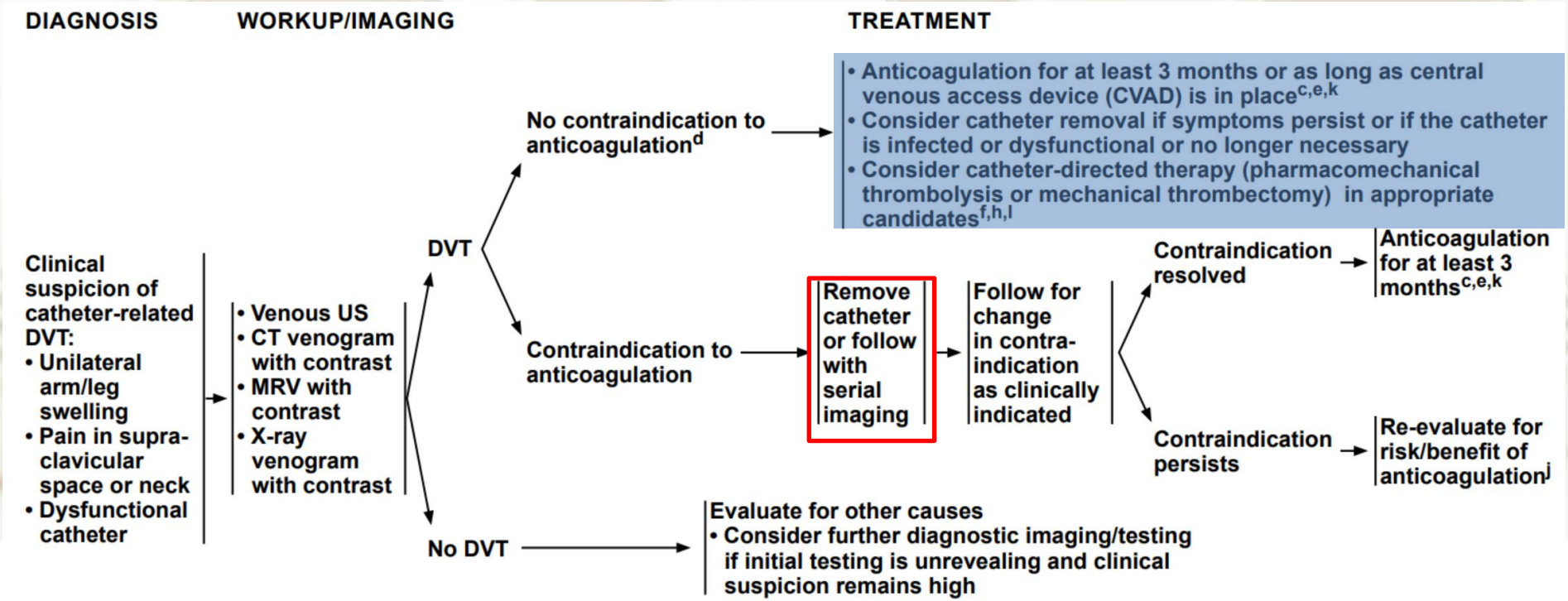
- Cf) Vena Cava Filters

  : placement of an IVC filter does **not prevent DVT** and has been associated with an increased risk for recurrent DVT

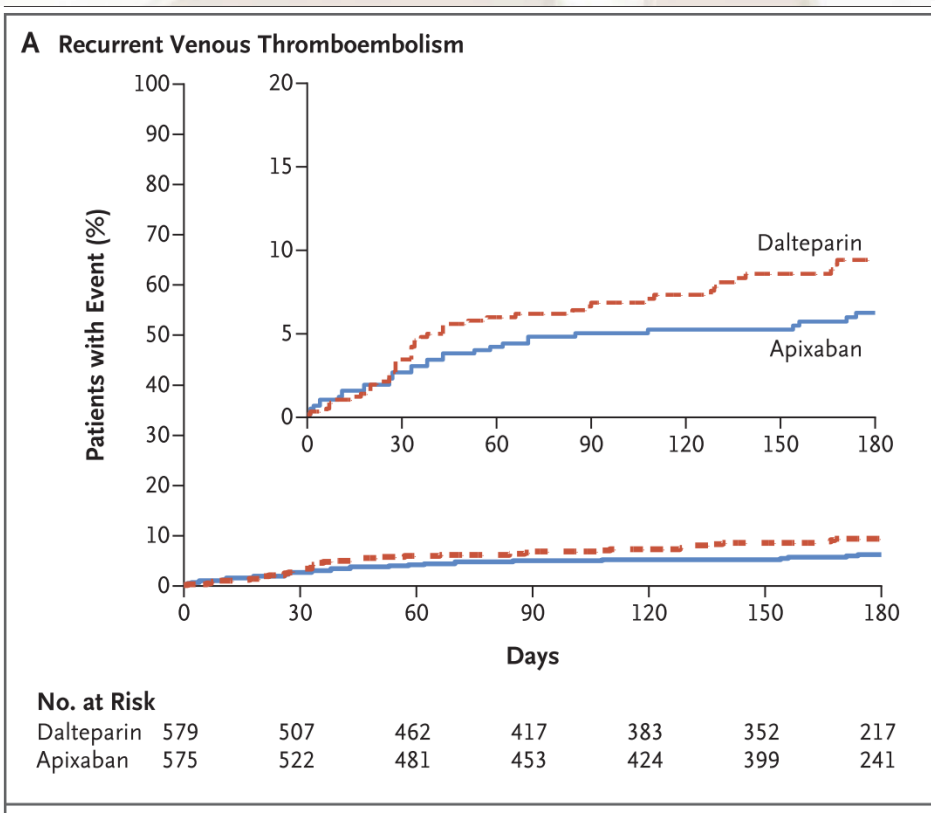
Acute Deep Vein Thrombosis (DVT) Tx

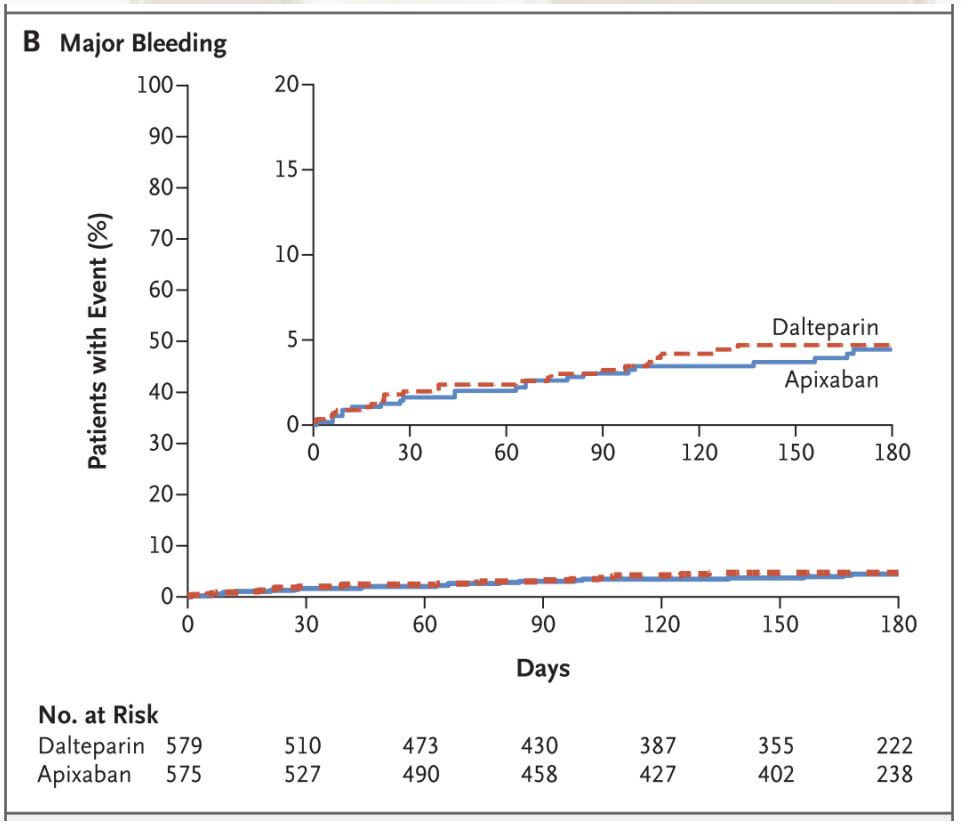


CATHETER-RELATED DVT : DIAGNOSIS AND TREATMENT



Tx.: **Oral apixaban** was **noninferior** to subcutaneous dalteparin for the treatment of CAVT without major bleeding (multinational, randomized, investigatorinitiated, open-label, noninferiority trial with blinded : 585 for apixaban, 585 for dalteparin)





(Agnelli, Becattini et al. 2020)

THERAPEUTIC **ANTICOAGULATION** FOR VENOUS THROMBOEMBOLISM

- **General Guidelines**

  1. Anticoagulation options recommended for involving only one agent (monotherapy) as well as regimens that use more than one type of agent (combination therapy).
     - Duration
       - ◇ At least 3 months or as long as active cancer or cancer therapy
       - ◇ For non–catheter-associated DVT or PE
         : indefinite anticoagulation while cancer is active, under treatment, or if risk factors for recurrence persist
       - ◇ For catheter-associated thrombosis, anticoagulate as long as catheter is in place.

THERAPEUTIC ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM

2. Select regimen based on these factors
   : [CrCl] <30 mL/min), hepatic disease (elevated transaminases or bilirubin, Child-Pugh B and C liver impairment, or cirrhosis), inpatient/outpatient, FDA approval, cost, patient preference, ease of administration, monitoring, bleeding risk assessment, and ability to reverse anticoagulation.
3. DOACs
   : absorbed primarily in the stomach and proximal small bowel (cf: exception of apixaban, partially absorbed in the colon)
   => in case of Pts who have had significant resections of these portions of the intestinal tracts.

THERAPEUTIC ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM

- **DOACs**

  : preferred for patients without gastric or gastroesophageal lesions

  => gastric and gastroesophageal tumors are at **increased risk for hemorrhage** with direct oral anticoagulants

  1) **Apixaban (category 1)** : 10 mg PO every 12 hours for 7 days followed by 5 mg PO every 12 hours

  2) **Edoxaban (category 1)** : Initial therapy **with LMWH or UFH** for at least 5 days followed by edoxaban 60 mg PO daily (30 mg PO daily in patients with CrCl 30–50 mL/min or weight <60 kg or concomitant potent p-glycoprotein inhibitors)

THERAPEUTIC ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM

- **LMWH**

  : preferred for patients **with** gastric or astroesophageal lesions

  Dalteparin (category 1)

  : 200 units/kg SC daily for 30 days,

  then switch to 150 units/kg once daily

THERAPEUTIC ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM

- DOACs (if above regimens not appropriate or unavailable) : **Dabigatran**
- Fondaparinux
- UFH (**category 2B**)

  : IV 80 units/kg bolus, followed by 18 units/kg/h adjusted to target aPTT of 2–2.5 X control or per hospital SOPs, followed by SC 250 units/kg every 12 hours

  : SC 333 units/kg load, followed by 250 units/kg every 12 hours25
- Warfarin

  : Start warfarin concurrently with LMWH, fondaparinux, or UFH (see dosing below)

  LMWH + warfarin options:

  ◇ Dalteparin 200 units/kg SC daily4 or 100 units/kg SC every 12 hours

  ◇ Enoxaparin 1 mg/kg SC every 12 hours3

  Fondaparinux + warfarin

  UFH5 + warfarin options:

  ◇ IV 80 units/kg bolus, followed by 18 units/kg/h adjusted to target aPTT of 2–2.5 X control or per hospital SOPs

  ◇ SC 333 units/kg load, followed by 250 units/kg every 12 hours

THROMBOLYTIC AGENTS

Indications for Thrombolysis

- Limb-threatening/life-threatening acute proximal DVT
- Symptomatic iliofemoral thrombosis
- Massive/life-threatening PE
- Intestinal SPVT with high risk of ischemia

- Deep Vein Thrombosis:[1,2]
  - Pharmacomechanical devices[2,3]
    - ◊ Alteplase 10 mg to 25 mg per session
  - Infusion catheters[2,3]
    - ◊ Alteplase 0.5 mg to 1 mg per hour for 12–24 hours
    - ◊ Reteplase 0.5 units to 1 units per hour for 12–24 hours

- Splanchnic Vein Thrombosis
  - Thrombolysis with catheter-directed therapies is limited to case reports and small studies. Follow local institutional protocols.

- Pulmonary Embolism
  - Systemic thrombolysis
    - ◊ Alteplase 100 mg IV over 2 hours[5]
    - ◊ Alteplase 50 mg as a 10 mg bolus followed by 20 mg per hour for 2 hours[4,5]
    - ◊ Reteplase 10 unit IV bolus followed 30 minutes later by a second 10 unit IV bolus injection, both doses administered over 2 minutes[6]
    - ◊ Tenecteplase (category 2B)[7]

Weight (kg)	Tenecteplase Dose
<60	30 mg
≥60 – <70	35 mg
≥70 – <80	40 mg
≥80 – <90	45 mg
≥90	50 mg

  - US-assisted, catheter-directed thrombolysis[8]
    - ◊ Alteplase 1 mg per hour per lung for 12–24 hours[9]

NCCN 2021

ANTICOAGULANT OPTIONS: **CONTRAINDICATIONS** AND WARNINGS

1. LMWH

- caution in patients with renal dysfunction.
- Consider dose adjustments or alternative therapy for patients with CrCl <30 mL/min
- Follow package insert for renal dysfunction and body weight dosing
- **Anti-Xa monitoring** (peak and trough) of LMWH has been recommended for patients with severe renal dysfunction
- Absolute contraindication: recent/acute HIT
- Relative contraindication: past history of HIT

ANTICOAGULANT OPTIONS: **CONTRAINDICATIONS** AND WARNINGS

2. DOACS; Apixaban, Dabigatran, edoxaban, rivaroxaban

- Stage IV/V chronic kidney disease:
  - Apixaban: CrCl <30 mL/min
  - Dabigatran, edoxaban, and rivaroxaban: CrCl <30 L/min
- Significant liver disease:
  - Apixaban or edoxaban
    - : ALT/AST >2 x ULN; TB bilirubin >1.5 x ULN
  - Dabigatran or rivaroxaban: ALT/AST >3x ULN
- Strong dual inhibitors/inducers of CYP3A4 and P-lycoprotein
- Inducers/inhibitors of P-lycoprotein

MANAGEMENT OF ANTICOAGULATION FOR VTE IN PATIENTS WITH **CTx-INDUCED THROMBOCYTOPENIA**

- **Thrombocytopenia is a common** occurrence in cancer patients receiving therapeutic anticoagulation for cancer-associated thrombosis
- Generally, anticoagulation is considered safe with platelet counts ≥50,000/μL
- **High risk of recurrent thromboembolism**
  (includes recent proximal DVT or PE [**within 1 month**], **recurrent** thromboembolism) management options
  : Continuation of therapeutic dose anticoagulation while maintaining platelet count ≥50,000/μL with **platelet transfusions**
  : Placement of a **retrievable IVC filter** and discontinuation of anticoagulation until platelet recovery

MANAGEMENT OF ANTICOAGULATION FOR VTE IN PATIENTS WITH **CTx-INDUCED THROMBOCYTOPENIA**

- **Lower risk for recurrent thromboembolism** (includes chronic DVT/PE [>1 month of treatment, central venous catheter-associated DVT, upper extremity DVT, acute distal DVT) management options
  : Use lower dose anticoagulation as **outlined below in table**
  : Remove central venous catheter in patients with central venous catheter-associated DVT
  : Monitor distal DVT with serial US surveillance while patient is off anticoagulation (if clot extends to proximal venous system then manage as acute high-risk patient)

Enoxaparin Dose Modification in the Setting of Thrombocytopenia

Platelet Count	Dose Adjustment	Suggested Dose of Enoxaparin	Alternative Once-Daily Dosing Regimen
>50,000/μL	Full-dose enoxaparin	1 mg/kg twice daily	1.5 mg/kg daily
25,000–50,000/μL	Half-dose enoxaparin	0.5 mg/kg twice daily	—
<25,000/μL	Temporarily hold enoxaparin		

Summary

- **Recognizing** the increased **risk for VTE in cancer patients** is the first step
- **VTE thromboprophylaxis for all hospitalized patients with cancer** who do not have contraindications to such therapy is emphasized.
- **Cancer patients in a high-risk setting** for VTE continue to receive **VTE prophylaxis**
- Careful evaluation of cancer patients in whom **VTE is suspected and prompt treatment** and follow-up for patients diagnosed with VTE is recommended

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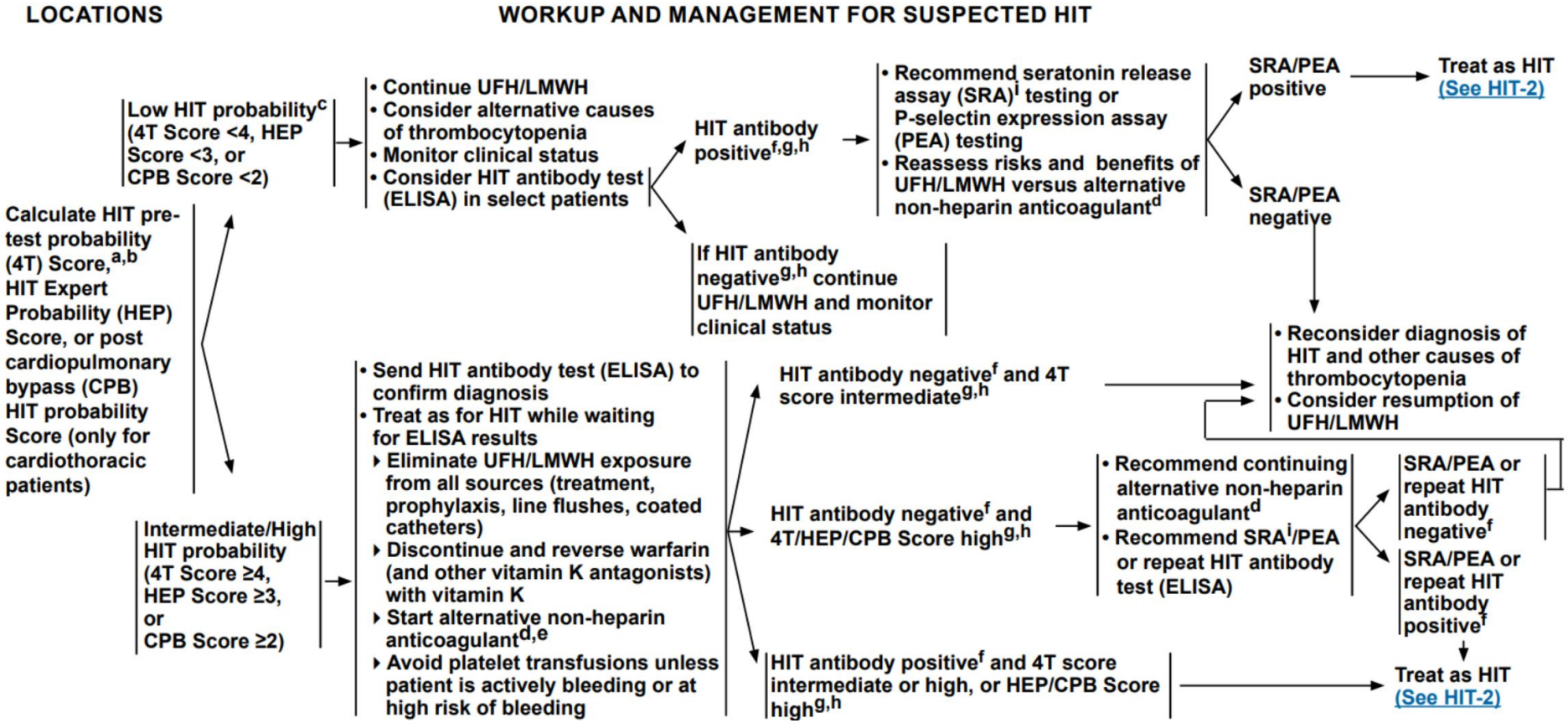
LOCATIONS
WORKUP AND MANAGEMENT FOR SUSPECTED HIT
Calculate HIT pre-test probability (4T) Score,[a,b] HIT Expert Probability (HEP) Score, or post cardiopulmonary bypass (CPB) HIT probability Score (only for cardiothoracic patients)
Low HIT probability[c] (4T Score <4, HEP Score <3, or CPB Score <2)
• Continue UFH/LMWH
• Consider alternative causes of thrombocytopenia
• Monitor clinical status
• Consider HIT antibody test (ELISA) in select patients
HIT antibody positive[f,g,h]
• Recommend seratonin release assay (SRA)[i] testing or P-selectin expression assay (PEA) testing
• Reassess risks and benefits of UFH/LMWH versus alternative non-heparin anticoagulant[d]
SRA/PEA positive
Treat as HIT (See HIT-2)
SRA/PEA negative
If HIT antibody negative[g,h] continue UFH/LMWH and monitor clinical status
Intermediate/High HIT probability (4T Score ≥4, HEP Score ≥3, or CPB Score ≥2)
• Send HIT antibody test (ELISA) to confirm diagnosis
• Treat as for HIT while waiting for ELISA results
▸ Eliminate UFH/LMWH exposure from all sources (treatment, prophylaxis, line flushes, coated catheters)
▸ Discontinue and reverse warfarin (and other vitamin K antagonists) with vitamin K
▸ Start alternative non-heparin anticoagulant[d,e]
▸ Avoid platelet transfusions unless patient is actively bleeding or at high risk of bleeding
HIT antibody negative[f] and 4T score intermediate[g,h]
HIT antibody negative[f] and 4T/HEP/CPB Score high[g,h]
HIT antibody positive[f] and 4T score intermediate or high, or HEP/CPB Score high[g,h]
• Reconsider diagnosis of HIT and other causes of thrombocytopenia
• Consider resumption of UFH/LMWH
• Recommend continuing alternative non-heparin anticoagulant[d]
• Recommend SRA[i]/PEA or repeat HIT antibody test (ELISA)
SRA/PEA or repeat HIT antibody negative[f]
SRA/PEA or repeat HIT antibody positive[f]
Treat as HIT (See HIT-2)

TREATMENT FOR HIT

- Global assessment of bleeding and clotting should be performed prior to treatment.

Initial Treatment for Patients with Suspected or Confirmed HIT

- Start/continue alternative non-heparin anticoagulant
  - There are no data from randomized controlled trials comparing different non-heparin anticoagulants to inform anticoagulant selection for treatment of HIT (with or without thrombosis). Therefore, an intravenous direct thrombin inhibitor (DTI) is preferred for initial treatment of hospitalized patients with suspected HIT (ie, patients awaiting test results) or confirmed HIT as many of these patients are critically ill and have contraindications to fondaparinux or (DOACs).[j]
  - DOACs or fondaparinux are considered reasonable options for the initial treatment of clinically stable patients without hemodynamically unstable pulmonary embolism or limb-threatening thrombosis or planned invasive procedures who do not have contraindications to the use of these agents as listed on VTE-D, 3 of 4.[k]
  - Full-dose anticoagulation is generally preferred, depending on assessment of bleed and clot risks.
  - For more information on agent selection and dosing, see Therapeutic Options for HIT (HIT-B).

Additional Recommendations for Patients with Confirmed HIT

- Lower-extremity US is recommended to identify asymptomatic DVT; consider upper-extremity US based on clinical situation.
- For patients who are stabilized on initial HIT treatment and have no procedures planned, consider transitioning to an oral agent:
  - DOACs (preferred): For patients with adequate renal and hepatic function and no other contraindications (listed on VTE-D, 2 of 4).
  - Fondaparinux
  - Warfarin
  - For more information on agent selection and administration, see Therapeutic Options for HIT (HIT-B).
- Duration of therapy:
  - HIT without thrombosis: At least 4 weeks (in the absence of serious bleeding risk)
  - HIT with thrombosis: At least 3 months as indicated for thrombotic event