
# Onkoloji Hastasında Venöz Tromboemboli Yönetimi

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**SBÜ Adana Şehir Eğitim ve Araştırma Hastanesi**

# Sunum planı

- Venöz tromboemboli epidemiyoloji-mekanizma-risk faktörleri
- Venöz tromboembolide risk skorlama sistemleri
- Venöz tromboemboli proflaksi ve korunma
- ESMO

Review Series

CANCER-ASSOCIATED THROMBOTIC DISEASE

# Epidemiology of cancer-associated venous thrombosis

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**Table 1. Incidences and risk factors for venous thrombosis as discussed in the review**

| Topic | Study population | Study design | Number of patients | Effect estimate | Reference |
|---|---|---|---|---|---|
| Proportion of cancer-associated VT cases | Olmsted county population | Nested case-control | 625/625 | 18% (PAR) | 5 |
| | California Discharge DataSet | Cohort | 21 002 | 21% | 9 |
| | Worcester metropolitan area, outpatient setting | Cohort | 1399 | 29% | 8 |
| | RIETE Registry | Cohort | 35 539 | 17% | 4 |
| | Tromsø Study | Cohort | 462 | 23% | 3 |
| RR of VT for cancer vs no cancer | MEGA study | Case-control | 2131/3220 | OR 6.7 (95% CI; 5.2-8.6) | 10 |
| | Olmsted county population | Nested case-control | 625/625 | OR 4.1 (95% CI; 1.9-8.5) | 12 |
| | Linked United Kingdom databases | Cohort | 82 203/577 207 | HR 4.7 (95% CI; 4.5-4.9) | 13 |
| | Danish population-based registries | Cohort | 57 591/287 476 | HR 4.7 (95% CI; 4.3-5.1) | 11 |
| Absolute risk of VT in cancer patients | Linkage of California Cancer Registry and California Discharge Dataset | Cohort | 235 149 | 1.6% within 2 y | 14 |
| | Referred patients with solid tumors | Cohort | 1041 | 7.8% (median follow-up 26 mo) | 15 |
| | CATS study | Cohort | 840 | 8% within 1 y | 16 |
| | 38 papers on cohorts with cancer patients | Meta-analysis | NA | 13/1000 PY (95% CI; 7-23) for average-risk patients | 17 |
| | | | | 68/1000 PY (95% CI; 48-96) for high-risk patients | 17 |
| | Linked United Kingdom databases | Cohort | 82 203 | 14/1000 PY (95% CI; 13-14) | 13 |
| Incidence of VT in cancer patients over time | US National Hospital Discharge Survey | Cohort | 40 787 000 | 1.5% in 1989; 3.5% in 1999 | 19 |
| | Discharge Database from University HealthSystem Consortium | Cohort | 1 015 598 | ~3.5% in 1995; ~4.5% in 2002 | 18 |
| | Linked United Kingdom databases | Cohort | 82 203 | 10.3/1000 PY in 1997; 19/1000 PY in 2006 | 13 |
| Risk factors for VT in cancer patients | | | | | |
| Type of cancer | 38 papers on cohorts with cancer patients | Meta-analysis | NA | Pancreatic cancer: ~110/1000 PY | 17 |
| | | | | Brain cancer: ~80/1000 PY | |
| | | | | Lung cancer: ~45/1000 PY | |
| | | | | Haematologic cancer: ~40/1000 PY | |
| | | | | Colorectal cancer: ~30/1000 PY | |
| | | | | Bone cancer: ~30/1000 PY | |
| | | | | Prostate cancer: ~10/1000 PY | |
| | | | | Breast cancer: ~10/1000 PY | |
| Stage of cancer | Danish population-based registries | Cohort | 40 994/204 970 | HRs 2.9, 2.9, 7.5, and 17.1 for stage I, II, III, and IV cancer patients, respectively, vs general population | 11 |
| | Linkage of California Cancer Registry and California Discharge Dataset | Cohort | 235 149 | HRs ranging from 1.1 to 21.5 for different types of cancer, metastatic vs localized cancer | 14 |
| | | | | tumor grade G3+G4 vs G1+G2 | |
| Time since cancer diagnosis | MEGA study | Case-control | 2131/3220 | OR 53.5 (95% CI; 8.6-334.3) in first 3 mo after cancer diagnosis | 10 |
| | | | | OR 14.3 (95% CI; 5.8-35.2) in 3-12 mo after cancer diagnosis | |
| | | | | OR 1.1 (95% CI; 0.6-2.2) > 15 y after cancer diagnosis | |
| | Linkage of California Cancer Registry and California Discharge Dataset, colorectal cancer patients | Cohort | 68 142 | 5.0/100 PY 0-6 mo after cancer diagnosis<br>1.4/100 PY 6-12 mo after cancer diagnosis<br>0.6/100 PY 12-24 mo after cancer diagnosis | 25 |
| | Linked United Kingdom databases | Cohort | 82 203 | Median ratio 3.2 for VT risk in first 3 mo after diagnosis vs whole follow-up period, for cancer types separately | 13 |

Cum. inc., cumulative incidence; NA, not applicable; PAR, population attributable risk; PY, person-years; RCT, randomized controlled trial; VT, venous thrombosis.

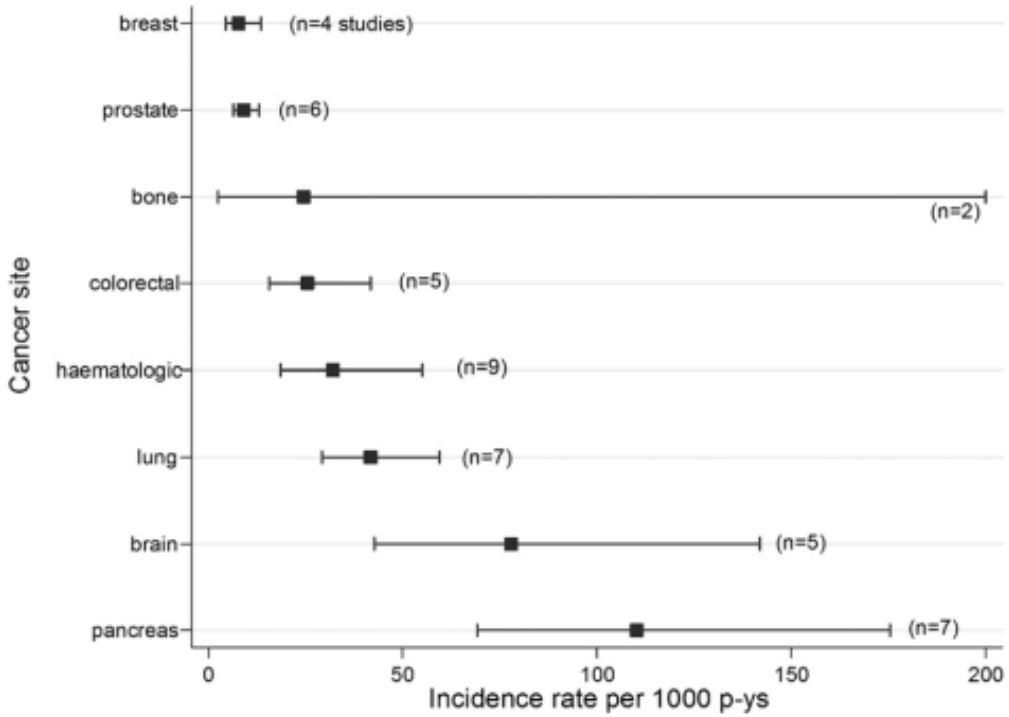



**Table 3. Predictive model for chemotherapy-associated venous thrombosis**

| Patient characteristic | Risk score |
|---|---|
| **Site of cancer** | |
| Very high risk (stomach, pancreas) | 2 |
| High risk (lung, lymphoma, gynecologic, bladder, testicular) | 1 |
| Prechemotherapy platelet count ≥350 × $10^9$/L | 1 |
| Hemoglobin level < 100 g/L or use of red cell growth factors | 1 |
| Prechemotherapy leukocyte count >11 × $10^9$/L | 1 |
| Body mass index ≥ 35 kg/m$^2$ | 1 |

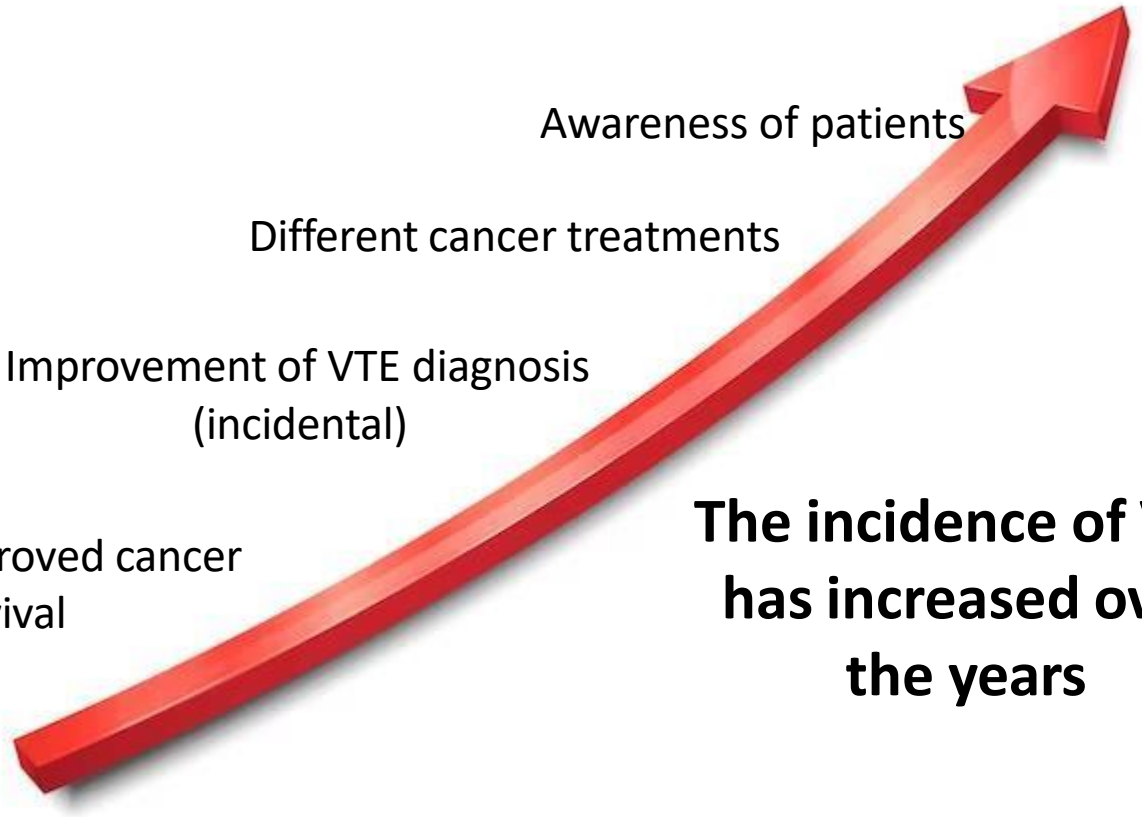
From Khorana et al.[59]

**Table 2. Crude mortality rates and age- and gender-adjusted HRs of death in participants without cancer and without venous thrombosis, with venous thrombosis only, with cancer only, and with cancer-related venous thrombosis (The Tromsø study 1994-2007)**

| Exposure | PY | Deaths (n) | MR per 100 PY (95% CI) | HR (95% CI) |
|---|---|---|---|---|
| None | 277 713 | 1750 | 0.63 (0.60-0.66) | 1.0 (reference) |
| VT only | 1317 | 67 | 5.1 (4.0-6.4) | 2.6 (2.0-3.3) |
| Cancer only | 5650 | 721 | 12.7 (11.9-13.7) | 7.4 (6.8-8.2) |
| Cancer-related VT | 131 | 72 | 55.0 (43.6-69.3) | 31.2 (24.6-39.6) |

HRs were calculated by means of a time-dependent Cox regression analysis. MR, mortality rate; PY, person-years; VT, venous thrombosis.

# CA-VTE INCIDENCE




**The incidence of VTE has increased over the years**

- VTE risk is 4-11 times higher in cancer compared to non-cancer population. Incidence can vary from 1 to 20% per year, depending on
    - Cancer status
        - Active vs non-active
    - Cancer site
    - Cancer Stage
        - Advanced vs limited
    - Concomitant anticancer therapies
    - Surgery
    - Patient-related risk factors
        - Advanced age
        - Previous VTE
        - Hospitalization
        - Immobility
        - Central venous lines
        - Obesity
        - Renal insufficiency

CA-VTE = cancer-associated VTE

# CANCER-ASSOCIATED THROMBOSIS (CAT) – "STABLE" *VS.* "ACTIVE" CANCER

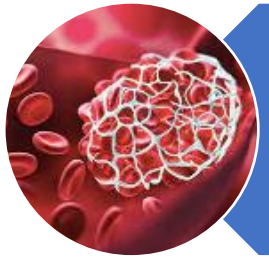
CAT may occur in the presence of stable or active cancer and **has the highest incidence in active cancer**[1]

## Active cancer

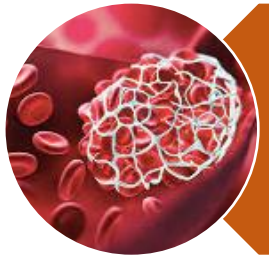
- Diagnosis within the last 6 months
- Therapy within the last 6 months
  - e.g., chemotherapy, radio-hormone-therapy, immunotherapy, surgery
- Active metastatic disease
- Active recurrence of cancer

***1.*** *Cohen AT, et al. Thromb Haemost. 2017;117:57–65*

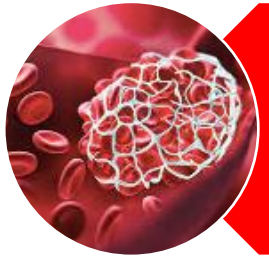
# Virchow’s Triad



Hiperkoagulasyon



Venöz akımın yavaşlaması-staz (RCC)



Endotel hasarı

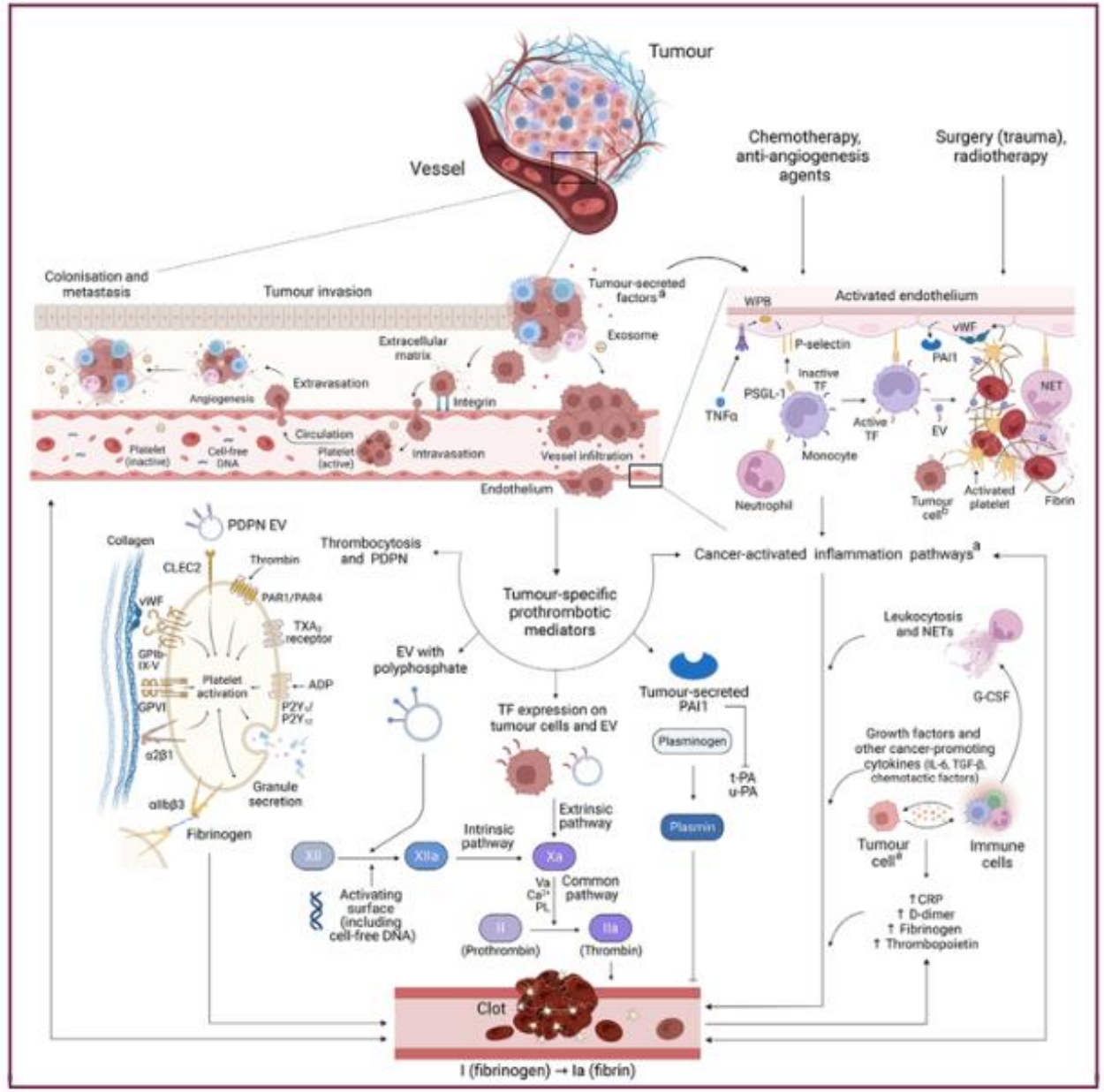



Figure 1. **Cancer-associated hypercoagulability and thrombosis.**

# Prokoagülan proteinler

Tissue factor

TF upregulasyonu

- Colon cancer (KRAS,TP53 mutation)
- NSCLC (PTEN,KRAS,TP53, ALK)
- GBM (EGFR overexpression, IDH wild-type)

Podoplanin

- CLEC-2 → platelets activates

PAI-1

PDI (Protein disulfide isomerase)(JAK2)→ Hypercoagulation

Endotel hücreleri

WBC (Lökosit, nötrofil, monosit)

Trombositler

Hastalıkla ilgili faktörler

- Malignite
- Evre
- Grade
- Zamanlama

## Hastayla ilgili faktörler

- Yaş
- Kalıtsal trombofili
  - -Faktör V leiden
  - -Protrombin G20210A varyant
  - -O grubu dışı kan grubu
- Antifosfolipid antikorlar
- İmmobilite, cerrahi, kalıcı katater
- VTE öyküsü, yüksek BMI, COVID-19

# The CoVID-TE risk assessment model for venous thromboembolism in hospitalized patients with cancer and COVID-19

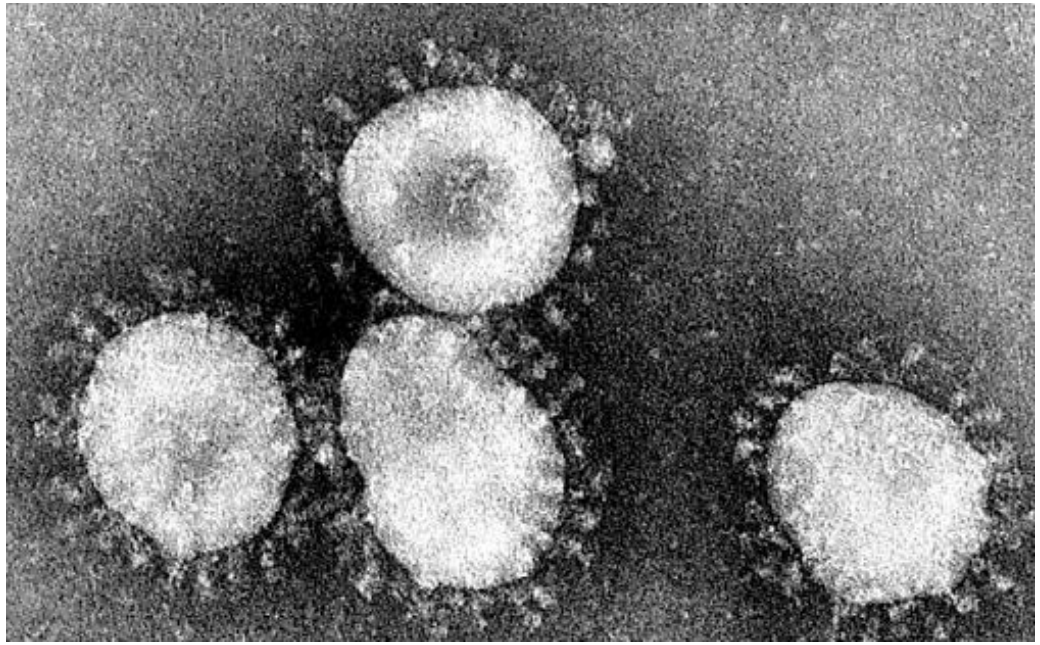


TABLE 3 Simplified risk assessment model for VTE (CoVID-TE thromboembolism score) in hospitalized patients with complete data. (a) CoVID-TE score assignment, (b) CoVID-TE risk category stratification and performance

| Risk assesment model | | |
|---|---|---|
| (a) | | |
| Baseline variables | | Point |
| Cancer subtype by original Khorana score[a] | | +1 |
| VTE history (lifetime) | | +2 |
| ICU triage on admission | | +2 |
| D-dimer elevated[b] | | +1 |
| Therapy (recent systemic last 3 months) | | +1 |
| Ethnicity non-Hispanic[c] | | +1 |
| (b) | | |
| All hospitalized patients ($n = 2457$) | | |
| Risk category ($N$) | VTE % ($N$) | PE % ($N$) |
| Low-risk (0–2) | 4.1% (59) | 2.3% (33) |
| 0–1 (657) | 3.6% (24) | 2.0% (13) |
| 2 (766) | 4.6% (35) | 2.6% (20) |
| High-risk (3+) | 11.3% (117) | 5.5% (57) |
| 3 (529) | 8.9% (47) | 3.6% (19) |
| 4 (317) | 11.7% (37) | 6.3% (20) |
| 5+ (188) | 17.6% (33) | 9.6% (18) |
| $C$ statistic (95% CI) | 0.67 (0.63–0.71) | 0.67 (0.61–0.73) |
| HL test $p$-value | .90 | .77 |

# Post-Discharge Venous Thromboembolism After Cancer Surgery

## *Extending the Case for Extended Prophylaxis*

*Ryan P. Merkow, MD,*†‡ Karl Y. Bilimoria, MD, MS,*‡ Martin D. McCarter, MD,† Mark E. Cohen, PhD,‡ Carlton C. Barnett, MD,† Mehul V. Raval, MD, MS,*‡ Joseph A. Caprini, MD, MS,¶ Howard S. Gordon, MD,§ Clifford Y. Ko, MD, MS, MSHS,‡‡ and David J. Bentrem, MD, MS**

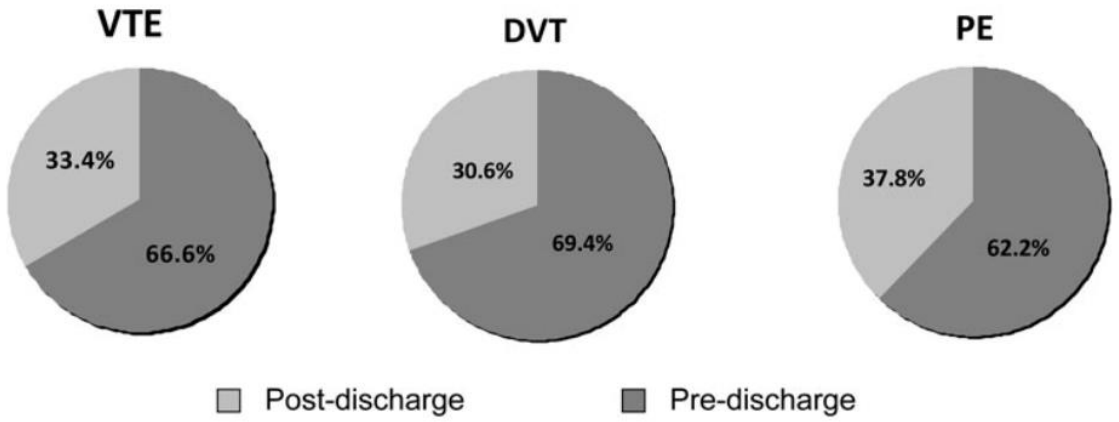



**TABLE 3.** Multivariable Analysis of Risk Factors Associated with Overall VTE

| | Overall Venous Thromboembolism | | |
|---|---|---|---|
| | **OR** | **95% CI** | ***P*** |
| Age (yrs) | | | |
| <65 | Referent | | |
| 65–74 | 1.84 | 1.51–2.24 | <0.0001 |
| 75–84 | 2.29 | 1.85–2.81 | <0.0001 |
| ≥85 | 2.49 | 1.79–3.46 | <0.0001 |
| Cancer site | | | |
| Breast | Referent | | |
| Colon | 5.14 | 3.37–7.82 | <0.0001 |
| Rectum | 6.00 | 3.65–9.87 | <0.0001 |
| Thyroid | 0.512 | 0.20–1.34 | 0.172 |
| Lung | 6.92 | 3.83–12.50 | <0.0001 |
| Esophagogastric | 9.33 | 5.83–14.92 | <0.0001 |
| Hepatopancreaticobiliary | 7.82 | 5.03–12.18 | <0.0001 |
| Ovary/uterus | 6.61 | 3.56–12.28 | <0.0001 |
| Prostate | 4.96 | 2.68–9.18 | <0.0001 |
| Metastatic disease | 1.44 | 1.10–1.90 | 0.009 |
| CHF | 2.88 | 1.66–5.00 | <0.0001 |
| BMI ($kg/m^2$) | | | |
| 18.5–24 | Referent | | |
| 25–29 | 1.36 | 1.11–1.66 | 0.003 |
| 30–34 | 1.55 | 1.23–1.96 | <0.0001 |
| ≥35 | 1.63 | 1.24–2.14 | <0.0001 |
| Ascites | 1.75 | 1.06–2.89 | 0.03 |
| Platelets ($/mm^3$) | | | |
| 150,000–400,000 | Referent | | |
| >400,000 | 1.64 | 1.30–2.07 | <0.0001 |
| <150,000 | 1.05 | 0.76–1.45 | 0.775 |
| Steroids | 1.69 | 1.10–2.60 | 0.016 |
| Albumin (<3.0 g/dL) | 1.75 | 1.36–2.24 | <0.0001 |
| Operation time (hours) | | | |
| <2 | Referent | | |
| 2–4 | 1.41 | 1.11–1.78 | 0.005 |
| 4–6 | 2.21 | 1.70–2.90 | <0.0001 |
| >6 | 3.94 | 2.96–5.24 | <0.0001 |

VTE indicates venous thromboembolism; OR, odds ratio; CI, confidence interval; BMI, body mass index; CHF, congestive heart failure. Hosmer-Lemeshow goodness-of-fit statistic 0.588; c-statistic 0.726.

# Venous thromboembolism in cancer patients: a population-based cohort study

F. I. Mulder,[1-3] E. Horváth-Puhó,[3] N. van Es,[1] H. W. M. van Laarhoven,[4] L. Pedersen,[3] F. Moik,[5] C. Ay,[5,6] H. R. Büller,

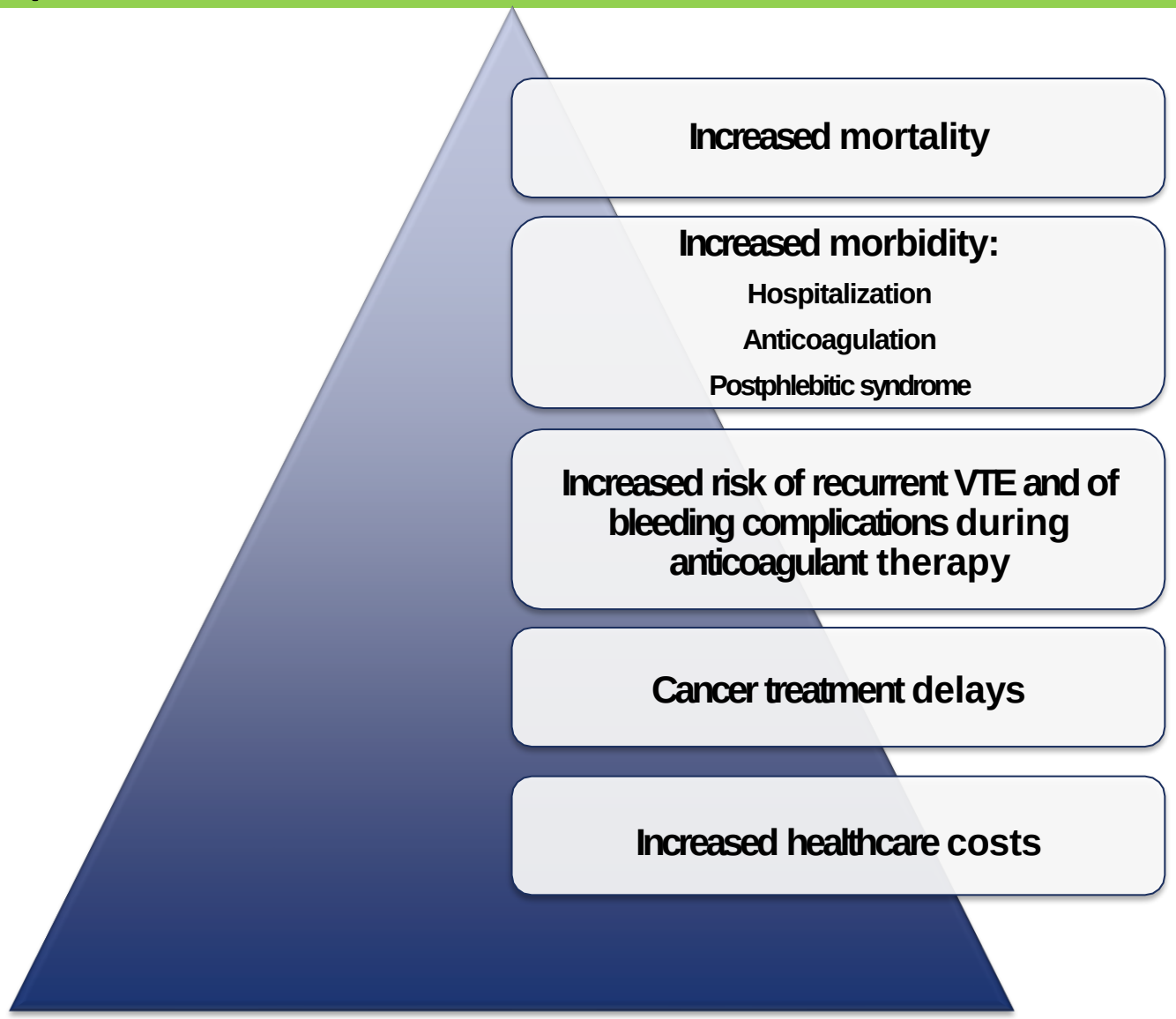
## Table 3. Analysis of risk factors for VTE during the 6-month period following cancer diagnosis

| | SHR (95% CI) | Adjusted SHR* (95% CI) | Cumulative incidence (95% CI) |
|---|---|---|---|
| **Cancer treatment‡** | | | |
| No treatment | Ref | Ref | 1.05 (0.98-1.13) |
| Hormone therapy | 0.87 (0.76-0.99) | 1.18 (0.99-1.41) | 0.92 (0.82-1.03) |
| Surgery | 1.75 (1.62-1.89) | 2.20 (2.02-2.39) | 1.84 (1.79-1.90) |
| Radiotherapy | 1.96 (1.79-2.14) | 2.16 (1.94-2.39) | 2.07 (1.96-2.18) |
| Chemotherapy | 3.33 (3.08-3.60) | 3.35 (3.06-3.66) | 3.50 (3.39-3.61) |
| Targeted therapy | 3.97 (3.60-4.38) | 3.85 (3.43-4.32) | 4.18 (3.91-4.46) |
| Protein kinase inhibitors | 5.40 (4.58-6.38) | 4.07 (3.39-4.90) | 5.69 (4.89-6.56) |
| Antiangiogenic therapy | 5.67 (4.96-6.50) | 4.43 (3.76-5.22) | 5.93 (5.29-6.62) |
| VEGF inhibitors | 5.87 (5.04-6.84) | 4.29 (3.54-5.19) | 6.13 (5.35-6.98) |
| Immunotherapy | 3.84 (3.00-4.91) | 3.56 (2.75-4.59) | 4.08 (3.21-5.10) |
| Checkpoint inhibitors | 3.73 (2.16-6.43) | 2.78 (1.61-4.80) | 4.08 (2.27-6.71) |
| Other targeted therapy | 3.29 (2.93-3.70) | 3.48 (3.03-3.98) | 3.47 (3.17-3.79) |

# Tedavi ajanı

- Sisplatin
- Oxaliplatin
- Asparaginaz
- Tamoxifen vs Raloxifen (1.9 vs 1.56)
- CDK4/6 inhibitörleri (yıllık insidans %10.4)
- Bevacizumab
- Talidomid,lenalidomid
- ICI
- CAR-T cell therapy
- ESA kullanımı

# Important Consequences of VTE in Cancer




Agnelli G and Verso M, J Thromb Haemost 2011; Prandoni et al, Blood 2002; JI Weitz et al, GARFIELD-VTE Investigators. J Thromb Thrombolysis 2020

# Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy

A. A. KHORANA, C. W. FRANCIS, E. CULAKOVA, N. M. KUDERER and G. H. LYMAN
*James P. Wilmot Cancer Center, and the Department of Medicine, University of Rochester, Rochester, NY, USA*

**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.

# Primer proflakside genel yaklaşım

- VTE riski
- Kanama riski
- Yaşam kalitesi (enjeksiyon ihtiyacı)
- Maliyet
- Eğitim

# Yatan hastada VTE proflaksisi

## Kime proflaksi yapılmalı?

- Malignitesi mevcut  ve Hareket kısıtlılığı olan
- Yakın zamanda geçirilmiş cerrahi

OLAN HASTALARA PROFLAKSİ UYGULANABİLİR

- Kanama diyatezi
- PLT<50000

OLMAYAN HASTALARA PROFLAKSİ UYGULANABİLİR

KT infüzyonu için yatan ve günübirlik işlemlerde gerek yok.

# LMW heparin mi? DOAC mı?

## Rivaroxaban for Thromboprophylaxis in Acutely Ill Medical Patients

Alexander T. Cohen, M.D., Theodore E. Spiro, M.D., Harry R. Büller, M.D., Lloyd Haskell, M.D., Dayi Hu, M.D., Russell Hull, M.B., B.S., Alexandre Mebazaa, M.D., Geno Merli, M.D., Sebastian Schellong, M.D., Alex C. Spyropoulos, M.D., and Victor Tapson, M.D., for the MAGELLAN Investigators*

| | | |
|---|---|---|
| Acute medical condition — no. (%) | | |
| Infectious disease | 1854 (45.8) | 1828 (45.1) |
| Heart failure | 1308 (32.3) | 1312 (32.4) |
| Respiratory insufficiency | 1105 (27.3) | 1163 (28.7) |
| Ischemic stroke | 699 (17.3) | 700 (17.3) |
| Active cancer | 296 (7.3) | 296 (7.3) |
| Inflammatory or rheumatic disease | 152 (3.8) | 151 (3.7) |
| Other | 34 (0.8) | 24 (0.6) |
| ≥2 Medical conditions | 1240 (30.6) | 1270 (31.4) |
| Risk factor for VTE — no. (%) | | |
| Age ≥75 yr | 1551 (38.3) | 1565 (38.6) |
| History of heart failure | 1408 (34.8) | 1382 (34.1) |
| History of cancer | 700 (17.3) | 678 (16.7) |
| Acute ischemic stroke with leg paresis | 661 (16.3) | 668 (16.5) |
| Chronic venous insufficiency | 617 (15.2) | 579 (14.3) |
| Body-mass index ≥35 | 612 (15.1) | 618 (15.3) |
| Acute infectious disease | 566 (14.0) | 601 (14.8) |
| Severe varicosis | 501 (12.4) | 461 (11.4) |
| History of DVT or pulmonary embolism | 202 (5.0) | 179 (4.4) |
| Hormone-replacement therapy | 48 (1.2) | 50 (1.2) |
| Major surgery within the previous 6 to 12 wk | 29 (0.7) | 32 (0.8) |
| Hereditary or acquired thrombophilia | 15 (0.4) | 9 (0.2) |
| Serious trauma within the previous 6 to 12 wk | 7 (0.2) | 7 (0.2) |

**Table 2.** Rates of the Composite Primary Efficacy Outcome and Its Components.

| Outcome | Day 10 | | | | Day 35 | | | |
|---|---|---|---|---|---|---|---|---|
| | Rivaroxaban (N=2938) | Enoxaparin (N=2993) | Relative Risk (95% CI)* | P Value† | Rivaroxaban (N=2967) | Enoxaparin–Placebo (N=3057) | Relative Risk (95% CI)* | P Value† |
| | *no. (%)* | | | | *no. (%)* | | | |
| Composite primary efficacy outcome | 78 (2.7) | 82 (2.7) | 0.97 (0.71–1.31) | 0.003 | 131 (4.4) | 175 (5.7) | 0.77 (0.62–0.96) | 0.02 |
| Asymptomatic proximal DVT | 71 (2.4) | 71 (2.4) | — | — | 103 (3.5) | 133 (4.4) | — | — |
| Symptomatic proximal or distal DVT | 7 (0.2) | 6 (0.2) | — | — | 13 (0.4) | 15 (0.5) | — | — |
| Symptomatic nonfatal pulmonary embolism | 6 (0.2) | 2 (<0.1) | — | — | 10 (0.3) | 14 (0.5) | — | — |
| VTE-related death | 3 (0.1) | 6 (0.2) | — | — | 19 (0.6) | 30 (1.0) | — | — |

**Table 4.** Safety Outcomes.*

| Outcome | Rivaroxaban (N=3997) | Enoxaparin–Placebo (N=4001) | Relative Risk (95% CI) | P Value |
|---|---|---|---|---|
| | *no. (%)* | | | |
| Clinically relevant bleeding: principal safety outcome at day 10 | 111 (2.8) | 49 (1.2) | 2.3 (1.63–3.17) | <0.001 |
| Any major bleeding | 24 (0.6) | 11 (0.3) | 2.2 (1.07–4.45) | 0.03 |
| Major bleeding leading to fall in hemoglobin of ≥2 g/dl | 17 (0.4) | 7 (0.2) | — | — |
| Major bleeding leading to transfusion of ≥2 units of blood | 15 (0.4) | 5 (0.1) | — | — |
| Major bleeding at a critical site | 5 (0.1) | 1 (<0.1) | — | — |
| Fatal major bleeding | 5 (0.1) | 1 (<0.1) | — | — |
| Clinically relevant bleeding: principal safety outcome at day 35 | 164 (4.1) | 67 (1.7) | 2.5 (1.85–3.25) | <0.001 |
| Any major bleeding | 43 (1.1) | 15 (0.4) | 2.9 (1.60–5.15) | <0.001 |
| Major bleeding leading to fall in hemoglobin of ≥2 g/dl | 31 (0.8) | 10 (0.2) | — | — |
| Major bleeding leading to transfusion of ≥2 units of blood | 24 (0.6) | 8 (0.2) | — | — |
| Major bleeding at a critical site | 9 (0.2) | 4 (0.1) | — | — |
| Fatal major bleeding | 7 (0.2) | 1 (<0.1) | — | — |
| Other safety outcomes | | | | |
| Any cardiovascular event during treatment† | 51 (1.3) | 49 (1.2) | — | — |
| Any adverse event during treatment, excluding bleeding | 2616 (65.4) | 2607 (65.2) | — | — |
| Any serious adverse event during treatment, excluding bleeding | 616 (15.4) | 569 (14.2) | — | — |

# Standart mı uzatılmış proflaksi mi?

## Extended thromboprophylaxis for medically ill patients with cancer: a systemic review and meta-analysis

Soravis Osataphan,[1,*] Rushad Patell,[2,*] Thita Chiasakul,[2,3] Alok A. Khorana,[4] and Jeffrey I. Zwicker[2]

**Table 1. Designs of the included studies**

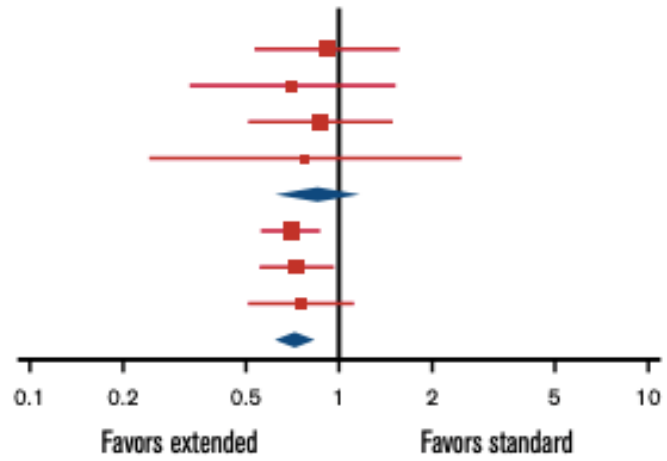
| | EXCLAIM 2010 | MAGELLAN 2013 | APEX 2016 | MARINER 2018 |
|---|---|---|---|---|
| Authors | Hull et al[15] | Cohen et al[14] | Cohen et al[16] | Spyropoulos et al[13] |
| Year of publication | 2010 | 2013 | 2016 | 2018 |
| Setting | International, multicenter | International, multicenter | International, multicenter | International, multicenter |
| Study design | Randomized parallel placebo-controlled trial | Randomized active comparator–controlled trial | Randomized active comparator–controlled trial | Randomized placebo-controlled trial |
| Blinding | Double blind | Double blind | Double blind, double dummy | Double blind |
| Cancer status | Active cancer or history of cancer | History of cancer or active cancer | History of cancer or active cancer | History of cancer in the past 5 y |
| | Excludes intracranial neoplasm or metastasis | Excludes intracranial neoplasm or metastasis | Excludes intracranial neoplasm or metastasis, active lung cancer with residual disease, and nonmelanoma skin cancer | Excludes all active cancers and nonmelanoma skin cancer |
| Intervention | 40 mg enoxaparin SC daily for 10 ± 4 d then enoxaparin 40 mg SC daily for additional 28 ± 4 d | 10 mg rivaroxaban daily for 35 ± 4 d | 80 mg betrixaban orally daily for 35-42 d (loading dose, 160 mg); reduced-dose betrixaban (40 mg) for patients with severe renal insufficiency or receiving concomitant P-glycoprotein inhibitor | 10 mg rivaroxaban daily for 45 d after discharge |
| Control | 40 mg enoxaparin SC daily for 10 ± 4 d then placebo for additional 28 ± 4 d | 40 mg enoxaparin SC daily for 10 ± 4 d | 40 mg enoxaparin SC daily for 10 ± 4 d | Placebo for 45 d after discharge |

**A**

## Venous Thromboembolism

| | Study name | Odds ratio | Lower limit | Upper limit | Event / Total: Extended | Event / Total: Standard | Relative weight |
|---|---|---|---|---|---|---|---|
| Cancer | APEX 2016 | 0.918 | 0.535 | 1.576 | 28 / 492 | 28 / 454 | 36.42 |
| | EXCLAIM 2010 | 0.710 | 0.329 | 1.534 | | | 17.91 |
| | MAGELLAN 2013 | 0.872 | 0.513 | 1.483 | 28 / 405 | 31 / 395 | 37.69 |
| | MARINER 2018 | 0.778 | 0.245 | 2.467 | 5 / 488 | 7 / 533 | 7.97 |
| | | 0.849 | 0.613 | 1.176 | | | |
| No Cancer | APEX 2016 | 0.698 | 0.556 | 0.876 | 134 / 2620 | 195 / 2720 | 48.83 |
| | MAGELLAN 2013 | 0.731 | 0.559 | 0.957 | 95 / 2467 | 133 / 2562 | 34.63 |
| | MARINER 2018 | 0.755 | 0.511 | 1.115 | 45 / 5519 | 59 / 5479 | 16.54 |
| | | 0.719 | 0.613 | 0.842 | | | |

Heterogeneity: df = 1 (P = 0.37)

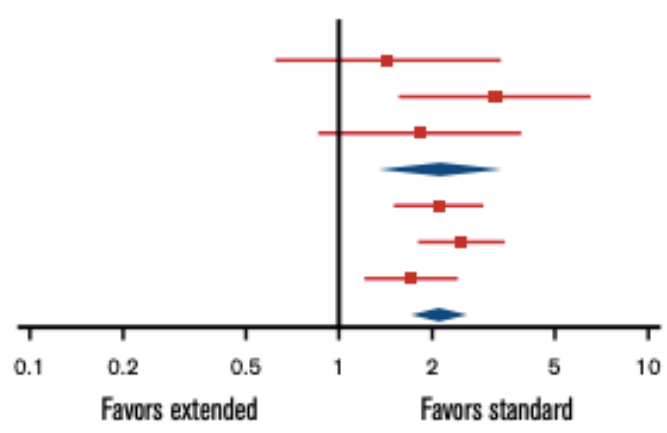



**B**

## Clinically Relevant Bleeding

| | Study name | Odds ratio | Lower limit | Upper limit | Event / Total: Extended | Event / Total: Standard | Relative weight |
|---|---|---|---|---|---|---|---|
| Cancer | APEX 2016 | 1.442 | 0.618 | 3.364 | 14 / 492 | 9 / 452 | 27.99 |
| | MAGELLAN 2013 | 3.182 | 1.549 | 6.538 | 32 / 565 | 10 / 540 | 37.80 |
| | MARINER 2018 | 1.823 | 0.852 | 3.900 | 18 / 483 | 11 / 529 | 34.21 |
| | | 2.107 | 1.325 | 3.350 | | | |
| No Cancer | APEX 2016 | 2.100 | 1.492 | 2.956 | 102 / 3224 | 50 / 3264 | 33.12 |
| | MAGELLAN 2013 | 2.482 | 1.790 | 3.443 | 125 / 3289 | 52 / 3319 | 35.77 |
| | MARINER 2018 | 1.710 | 1.200 | 2.437 | 84 / 5499 | 49 / 5451 | 31.11 |
| | | 2.091 | 1.694 | 2.582 | | | |

Heterogeneity: df = 1 (P = 1.00)



# Postoperatif hastalar

- Malignite
- Cerrahi
- İmmobilizasyon
- Dehidratasyon

**Artan VTE riski**

**%40 HASTADA GÖRÜLÜR**

# The Prophylaxis of Venous Thrombosis in Patients With Cancer Undergoing Major Abdominal Surgery: Emerging Options

GIANCARLO AGNELLI, MD[1]* AND JOSEPH A. CAPRINI, MD, MS, FACS, RVT[2,3,4]

**Add 1 point for each of the following statements that apply now or within the past month:**

- ❑ Lung disease (for example, emphysema or COPD) ____
- ❑ On bed rest or restricted mobility, including a removable leg brace for less than 72 hours ____
- ❑ Other risk factors (1 point each)*** ____

****Additional risk factors not tested in the validation studies but shown in the literature to be associated with thrombosis include BMI above 40, smoking, diabetes requiring insulin, chemotherapy, blood transfusions, and length of surgery over 2 hours.*

**For women only: Add 1 point for each of the following statements that apply:**

- ❑ Current use of birth control or Hormone Replacement Therapy (HRT) ____
- ❑ Pregnant or had a baby within the last month ____
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion (more than 3), premature birth with toxemia or growth restricted infant. ____

**Add 2 points for each of the following statements that apply:**

- ❑ Age 75 or over ____
- ❑ History of blood clots, either Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE) ____
- ❑ Family history of blood clots (thrombosis) ____
- ❑ Personal or family history of positive blood test indicating an increased risk of blood clotting ____

**Add 5 points for each of the following statements that apply now or within the past month:**

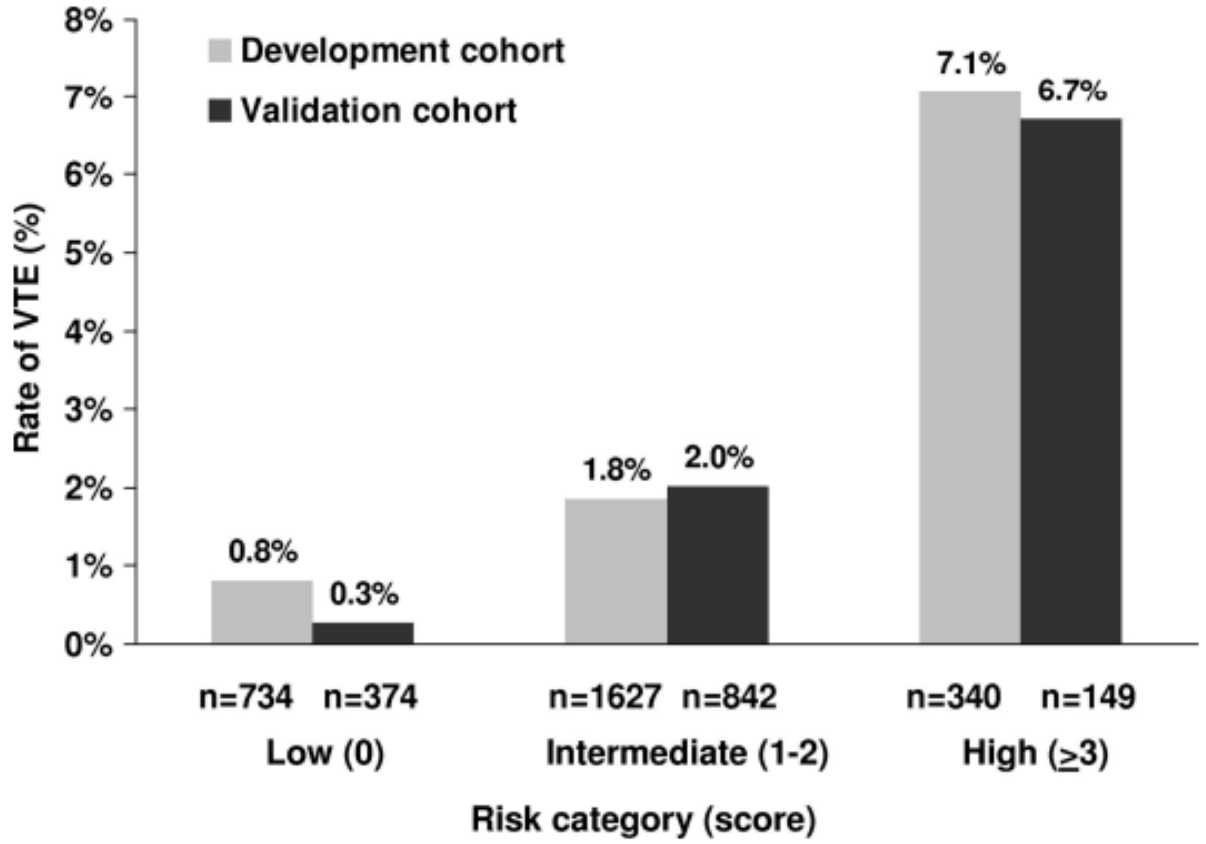
- ❑ Elective hip or knee joint replacement surgery ____
- ❑ Broken hip, pelvis or leg ____
- ❑ Serious trauma (for example, multiple broken bones due to a fall or car accident) ____
- ❑ Spinal cord injury resulting in paralysis ____
- ❑ Experienced a stroke ____

**Interpretation**

| Surgical risk category* | Score | Estimated VTE risk in the absence of pharmacologic or mechanical prophylaxis (percent) |
|---|---|---|
| Very low (see text for definition) | 0 | <0.5 |
| Low | 1 to 2 | 1.5 |
| Moderate | 3 to 4 | 3.0 |
| High | ≥5 | 6.0 |

# Ayakta tedavi gören hastalarda VTE proflaksisi

Development and validation of a predictive model for chemotherapy-associated




r and the Duke

**Table 2. Predictors of venous throm**
**cohort by multivariate logistic regre**

| Patient characteristic | |
|---|---|
| Site of cancer | |
| Very high risk (stomach, pancreas) | |
| High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate) | |
| Low risk (breast, colorectal, head and neck | |
| Prechemotherapy platelet count 350 × $10^9$/L | |
| Hemoglobin level less than 100 g/L or use of growth factors | |
| Prechemotherapy leukocyte count more than 11 × $10^9$/L | |
| BMI 35 kg/$m^2$ or more | |

**iotherapy-associated VTE**

| | Risk score |
|---|---|
| | 2 |
| bladder, testicular) | 1 |
| /L or more | 1 |
| of red cell growth factors | 1 |
| an 11 × $10^9$/L | 1 |
| | 1 |

# Prediction of venous thromboembolism in cancer patients

Cihan Ay,[1] Daniela Dunkler,[2] Christine Marosi,[3] Alexandru-Laurentiu Chiriac,[1] Rainer Vormittag,[1] Ralph Simanek,[1] Peter Quehenberger,[4] Christoph Zielinski,[3] and Ingrid Pabinger[1]

[1]Clinical Division of Haematology and Haemostaseology, Department of Medicine I, [2]Core Unit for Medical Statistics and Informatics, Section of Clinical Biometrics, [3]Clinical Division of Oncology, Department of Medicine I, and [4]Department of Medical and Chemical Laboratory Diagnostics, Medical University of Vienna, Vienna, Austria

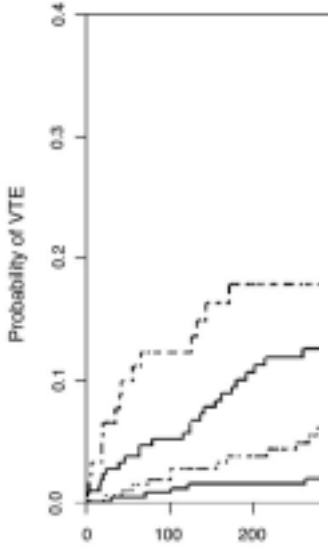



**Table 3. The sensitivity, specificity, PPV, and NPV at the cutoff point of different risk scores and at 6 months in the expanded risk scoring model including sP-selectin and D-Dimer**

| Expanded risk model including sP-selectin and D-Dimer | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
|---|---|---|---|---|
| Score 1 | 95.7 | 29.1 | 8.9 | 99.0 |
| Score 2 | 78.7 | 54.1 | 11.0 | 97.2 |
| Score 3 | 63.8 | 81.3 | 19.7 | 96.9 |
| Score 4 | 38.3 | 94.2 | 32.1 | 95.5 |
| Score ≥ 5 | 19.1 | 98.2 | 42.9 | 94.4 |

PPV indicates positive predictive value; and NPV, negative predictive value.

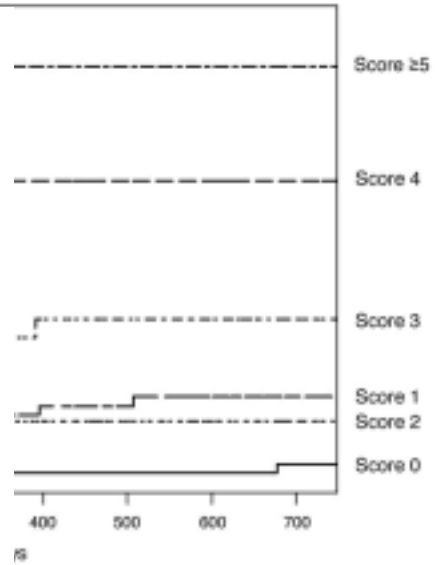



**Figure 1. Kaplan-Meier estimate**
**0, 1, 2, and ≥ 3 according to th**
**al.**[16] The cumulative probability
with the risk scores (log-rank test, $P < .001$).

**e risk of VTE in the expanded risk scoring**
**mer.** The cumulative probability of develop-
its with a high score than in those with a low
score (log-rank test, $P < .001$).

# Evaluation of the Khorana, PROTECHT, and 5-SNP scores for prediction of venous thromboembolism in patients with cancer

Noori A. M. Guman[1,2] | Roos J. van Geffen[1] | Frits I. Mulder[1,2] | Thijs F. van Haaps[1] | Vahram Hovsepjan[1] | Mariette Labots[3] | Geert A. Cirkel[4] | Filip Y. F. L. de Vos[5] |

| | Khorana score[8] (points) | PROTECHT score[19] (points) | 5-SNP score[15] (points) |
|---|---|---|---|
| Clinical risk factors | - | - | - |
| Pancreatic, gastric, or primary brain cancer | 2 | 2 | - |
| Lung, gynecological, lymphoma, bladder, testicular, or renal | 1 | 1 | - |
| Prechemotherapy platelet count ≥350 x $10^9$/L | 1 | 1 | - |
| Prechemotherapy hemoglobin level <6.2 mmol/L | 1 | 1 | - |
| Prechemotherapy leukocyte count >11 x $10^9$/L | 1 | 1 | - |
| Body mass index ≥35 kg/$m^2$ | 1 | 1 | - |
| Gemcitabine therapy | - | 1 | - |
| Platinum-based therapy | - | 1 | - |
| Prothrombotic SNPs | - | - | - |
| rs6025 (F5 gene) | - | - | N*log(3.79) |
| rs8176719 (ABO gene) | - | - | N*log(1.85) |
| rs1799963 (F2 gene) | - | - | N*log(2.78) |
| rs2066865 (FGG gene) | - | - | N*log(1.56) |
| rs2036914 (F11 gene) | - | - | N*log(1.32) |

*Note:* Brain and renal cancer were added, respectively, to the very high- and high-risk sites, as suggested previously.[20,21]

Abbreviations: N, number of risk alleles; SNP, single nucleotide polymorphism; VTE, venous thromboembolism.

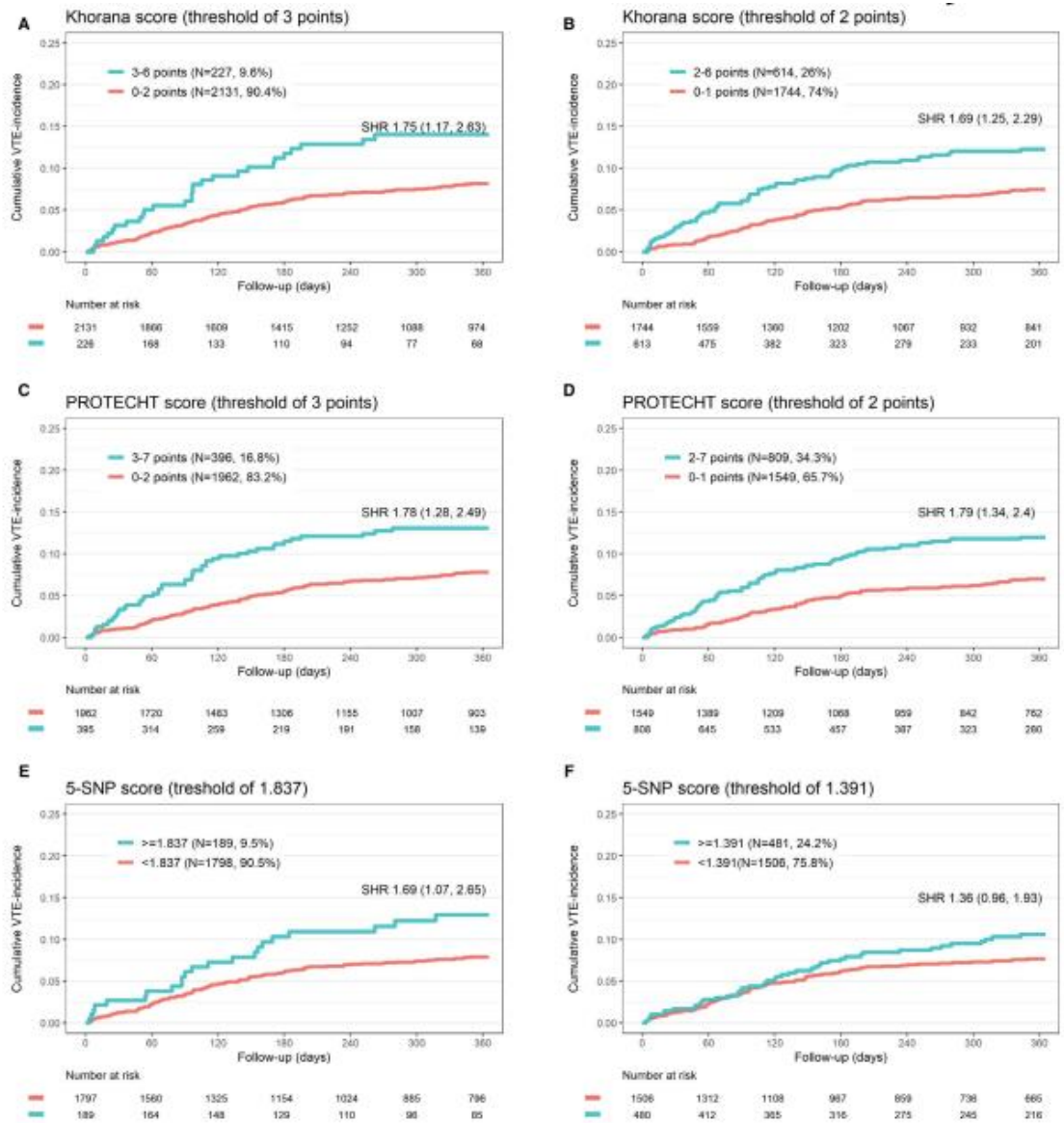
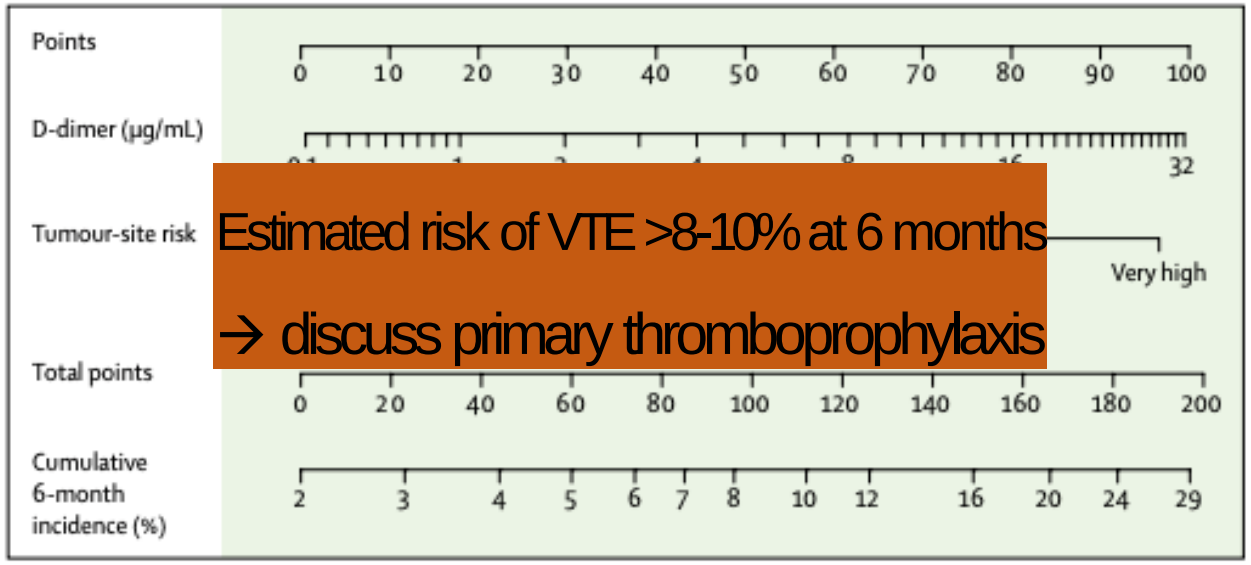



FIGURE 1 Performance of the risk scores during 12-month follow-up. Cumulative incidence of venous thromboembolism in high- and low-risk groups by the (A) Khorana score at the threshold of 3, (B) Khorana score at the threshold of 2, (C) PROTECHT score at the threshold of 3, (D) PROTECHT score at the threshold of 2, (E) 5-SNP score at the threshold of 1.837, and (F) 5-SNP score at the threshold of 1.391 points. Abbreviations: SHR, subdistribution hazard ratio; VTE, venous thromboembolism. [Color figure can be viewed at wileyonlinelibrary.com]

# New-Vienna CATS score

**A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts**

*Ingrid Pabinger, Nick van Es, Georg Heinze, Florian Posch, Julia Riedl, Eva-Maria Reitter, Marcello Di Nisio, Gabriela Cesarman-Maus, Noémie Kraaijpoel, Christoph Carl Zielinski, Harry Roger Büller, Cihan Ay*

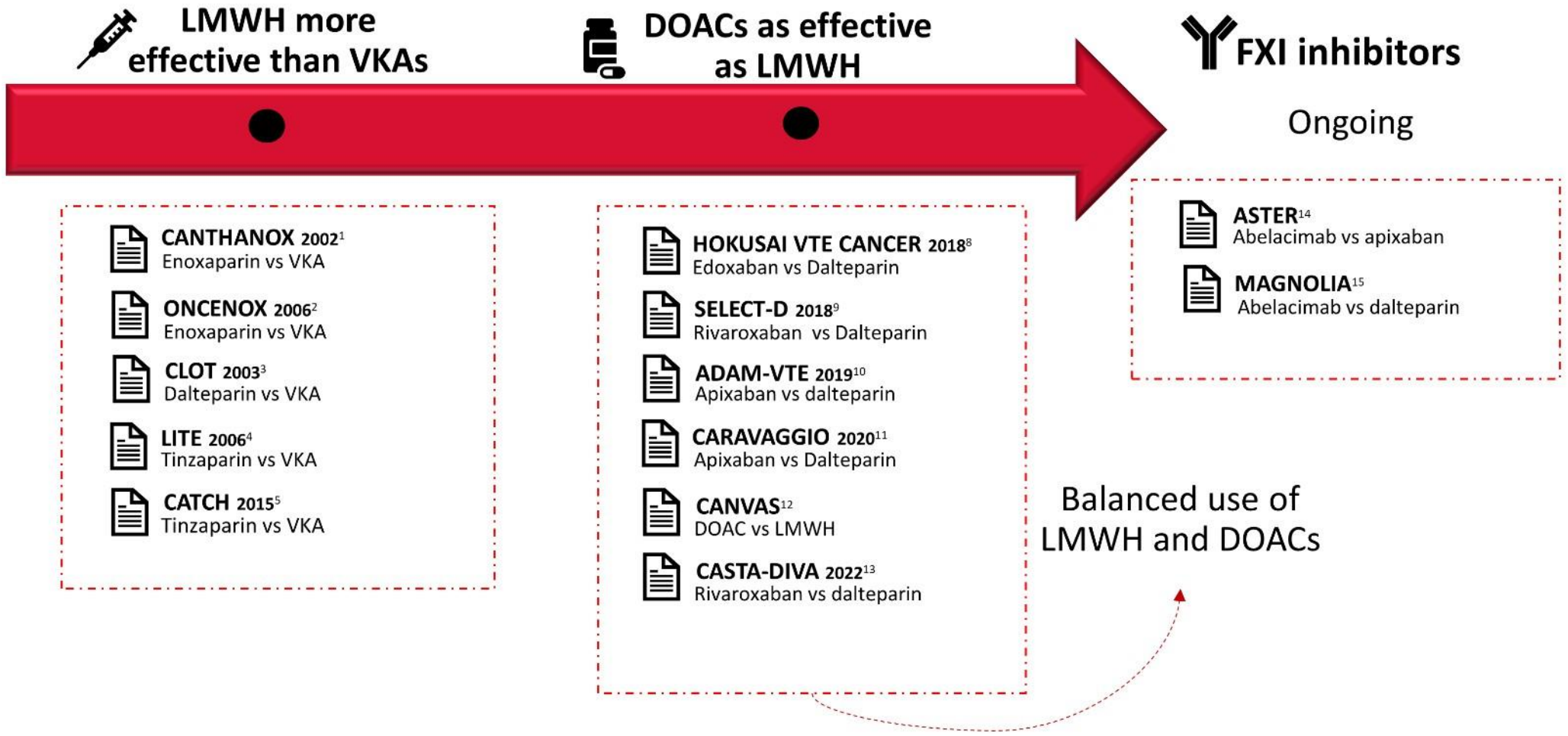



Estimated risk of VTE >8-10% at 6 months

→ discuss primary thromboprophylaxis

***Figure 3*: Nomogram for predicting the 6-month risk of venous thromboembolism**
Points for D-dimer concentration and tumour-site risk category can be obtained by calibrating with the point caliper, and then combined to obtain a total score that can be calibrated with the cumulative 6-month incidence scale. The equation for predicting 6-month risk of venous thromboembolism is provided in the appendix (p 7).

# EVOLVING VTE TREATMENT IN CANCER PATIENTS IN THE LAST 20 YEARS




Falanga A, and Marchetti M., J Thromb Haemost. 2023;1–12

# ESMO önerileri

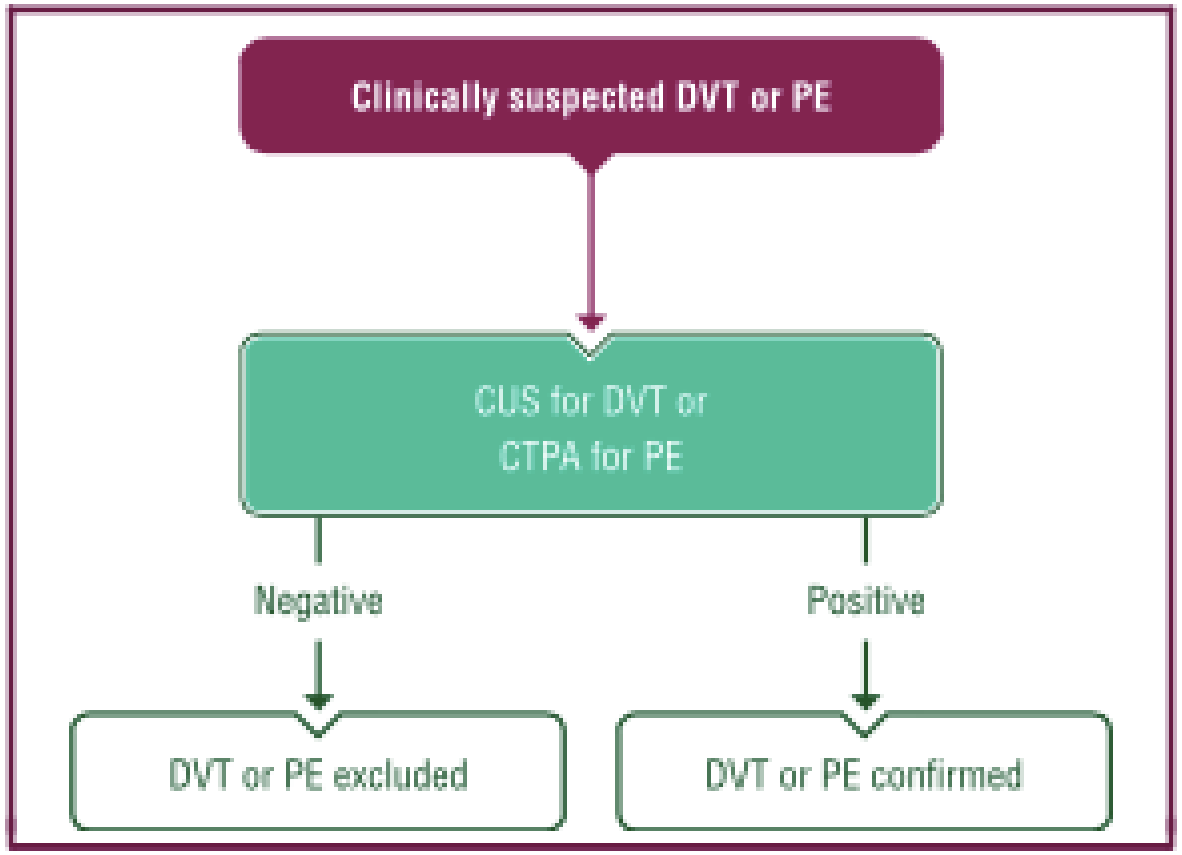



**Figure 2. Diagnostic algorithm for suspected DVT and PE in cancer patients.**

# RISK FACTORS FOR VTE IN CANCER PATIENTS

# Tools for VTE risk assessment in clinical practice

## Khorana risk score

≥ 2

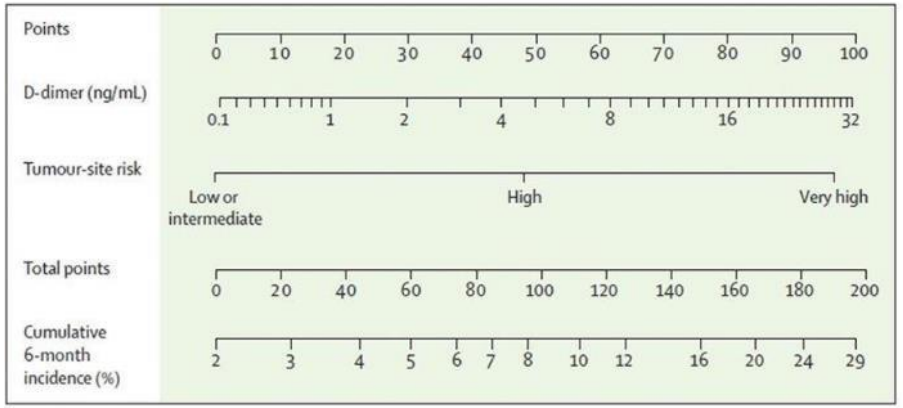
| Variable | | Risk score |
|---|---|---|
| Very high-risk tumour (stomach, pancreas) | | 2 |
| High-risk tumour (lung, gynaecological, genitourinary excluding prostate) | | 1 |
| Haemoglobin level <100 g/l or use of red cell growth factors | | 1 |
| Prechemotherapy leucocyte count >11 x $10^9$/l | | 1 |
| Prechemotherapy platelet count ≥350 x $10^9$/l | | 1 |
| BMI ≥35 kg/$m^2$ | | 1 |
| **Total Score** | **Risk category** | **Risk of symptomatic VTE** |
| 0 | Low | 0.3%-1.5% |
| 1-2 | Intermediate | 1.8%-4.8% |
| ≥3 | High | 6.7%-12.9% |

## COMPASS-CAT score

≥ 7

| Predictors for VTE | Score[a] |
|---|---|
| **Cancer-related risk factors** | |
| Anti-hormonal therapy for women with hormone receptor-positive breast cancer or on anthracycline treatment | 6 |
| Time since cancer diagnosis ≤6 months | 4 |
| CVC | 3 |
| Advanced stage of cancer | 2 |
| **Predisposing risk factors** | |
| Cardiovascular risk factors (composed by at least two of the following predictors: personal history of peripheral artery disease, ischaemic stroke, coronary artery disease, hypertension, hyperlipidaemia, diabetes, obesity) | 5 |
| Recent hospitalisation for acute medical illness | 5 |
| Personal history of VTE | 1 |
| **Biomarkers** | |
| Platelet count ≥350 x $10^9$/l | 2 |

## Vienna-CATS nomogram score




Estimated risk of VTE >8-10% at 6 months

→ discuss primary thromboprophylaxis

*Khorana AA, et al. Blood 2008; Pabinger I, et al. Lancet Haematol 2018; Gerotziafas GT, et al. Oncologist 2017*

# IDENTIFIED RISK FACTORS FOR INCREASED BLEEDING RATES

- Cancer type (GI,GU cancer)
- Metastatic disease
- Obesity (BMI ≥ 40)
- Chronic kidney disease stage III or higher
- Thrombocytopenia

*Data were obtained from Explorys (IBM Watson, Inc.), which pools data from multiple US healthcare organizations*

*Angelini DE, et al. Am J Hematol. 2019*

# Primer proflaksi

**Table 1. VTE prophylaxis options in cancer patients**

| Options | Hospitalised patients | Surgical patients | Ambulatory patients |
|---|---|---|---|
| Heparins[a] | | | |
| UFH | 5000 IU every 8 h | 5000 IU 2-4 h preoperatively and every 8 h thereafter | — |
| Bemiparin | 3500 anti-Xa IU o.d. | 3500 anti-Xa IU starting 2 h preoperatively or 6 h post-operatively and 3500 anti-Xa IU o.d. thereafter | 3500 anti-Xa IU o.d.[b] |
| Dalteparin | 5000 anti-Xa IU o.d. | 5000 anti-Xa IU 12 h preoperatively and 5000 anti-Xa IU o.d. thereafter | 5000 anti-Xa IU o.d.[b,c] |
| Enoxaparin | 4000 anti-Xa IU o.d. | 4000 anti-Xa IU 12 h preoperatively and 4000 anti-Xa IU o.d. thereafter | 4000 anti-Xa IU o.d.[b] |
| Nadroparin | 3800 anti-Xa IU o.d. (if weight >70 kg: 5700 anti-Xa IU/kg o.d.) | 2850 anti-Xa IU 2-4 h preoperatively and 2850 anti-Xa IU o.d. thereafter | 3800 anti-Xa IU o.d. (if weight >70 kg: 5700 anti-Xa IU o.d.)[b] |
| Tinzaparin | 4500 anti-Xa IU o.d. | 4500 anti-Xa IU o.d., beginning 12 h post-operatively | 4500 anti-Xa IU o.d.[b] |
| Selective parenteral indirect factor Xa inhibitor | | | |
| Fondaparinux | 2.5 mg o.d. | 2.5 mg o.d. beginning 6-8 h post-operatively | Not studied in the outpatient prophylaxis setting |
| DOACs | | | |
| Apixaban | Not recommended | Not recommended | 2.5 mg orally b.i.d.[b] |
| Rivaroxaban | Not recommended | Not recommended | 10 mg orally o.d.[b] |
| Mechanical prophylaxis | | | |
| IPC | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |
| Venous foot pump | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |
| GCSs | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |

# Cerrahi işlem uygulanacak hastada proflaksi

## CAPRİNİ skoru risk değerlendirmesi

## Cerrahi türü

- Minör cerrahi-45 dk dan kısa LPS
- Majör cerrahi- 45 dk dan uzun LPS

## Tromboproflaksi kontrendikasyonları

- Acut hepatit, hemofili, kontrolsüz HT, akut SVO, PLT>25000, LP (4 saat önce yapılan veya 12 saat içinde planlanan)

**Table 1. VTE prophylaxis options in cancer patients**

| Options | Hospitalised patients | Surgical patients | Ambulatory patients |
|---|---|---|---|
| Heparins[a] | | | |
| UFH | 5000 IU every 8 h | 5000 IU 2-4 h preoperatively and every 8 h thereafter | — |
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| Dalteparin | 5000 anti-Xa IU o.d. | 5000 anti-Xa IU 12 h preoperatively and 5000 anti-Xa IU o.d. thereafter | 5000 anti-Xa IU o.d.[b,c] |
| Enoxaparin | 4000 anti-Xa IU o.d. | 4000 anti-Xa IU 12 h preoperatively and 4000 anti-Xa IU o.d. thereafter | 4000 anti-Xa IU o.d.[b] |
| Nadroparin | 3800 anti-Xa IU o.d. (if weight >70 kg: 5700 anti-Xa IU/kg o.d.) | 2850 anti-Xa IU 2-4 h preoperatively and 2850 anti-Xa IU o.d. thereafter | 3800 anti-Xa IU o.d. (if weight >70 kg: 5700 anti-Xa IU o.d.)[b] |
| Tinzaparin | 4500 anti-Xa IU o.d. | 4500 anti-Xa IU o.d., beginning 12 h post-operatively | 4500 anti-Xa IU o.d.[b] |
| Selective parenteral indirect factor Xa inhibitor | | | |
| Fondaparinux | 2.5 mg o.d. | 2.5 mg o.d. beginning 6-8 h post-operatively | Not studied in the outpatient prophylaxis setting |
| DOACs | | | |
| Apixaban | Not recommended | Not recommended | 2.5 mg orally b.i.d.[b] |
| Rivaroxaban | Not recommended | Not recommended | 10 mg orally o.d.[b] |
| Mechanical prophylaxis | | | |
| IPC | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |
| Venous foot pump | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |
| GCSs | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |

LMWH→ Hematom riski daha düşük
HIT insidansı daha düşük

Fondaparinux için kanıt düzeyi düşük

DOAC için yeterli veri yok.

Cerrahi sonrası en az 10 gün

Preoperatif proflaksi başlanması VTE oranlarını postoperatif başlanmasına göre azaltır.

Majör cerrahi sonrası 4 hafta→ Benzer kanama oranı daha düşük VTE oranı

# Mekanik tromboproflaksi

IPC, GCS. → Tek başına kullanımını destekleyecek yeterli veri yok.

→ Kanama riski çok düşük

→ Tek başına LMWH IPC'na üstünlüğü kanıtlanmış

→ Büyük cerrahi müdahale sonrası LMWH ile birlikte kullanımı PE riskini azaltır ancak kanama riskini artırır.

→ Kombine proflaksi cerrahi onkoloji hastalarında nadiren kullanılır (IPC)

# Cerrahi dışı ayaktan kanser hastasında tromboproflaksi

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 21, 2019 VOL. 380 NO. 8

Apixaban to Prevent Venous Thromboembolism in Patients with Cancer

Khorana skor ≥2

180 gün 2.5 mg apixaban

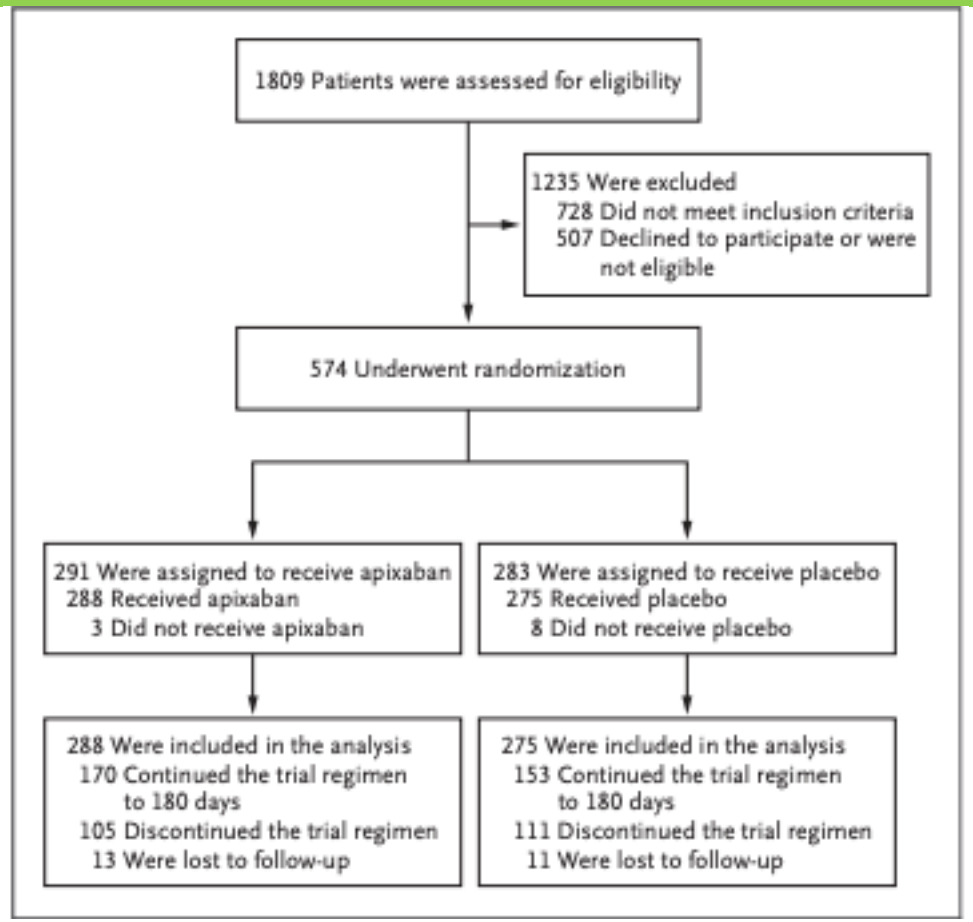
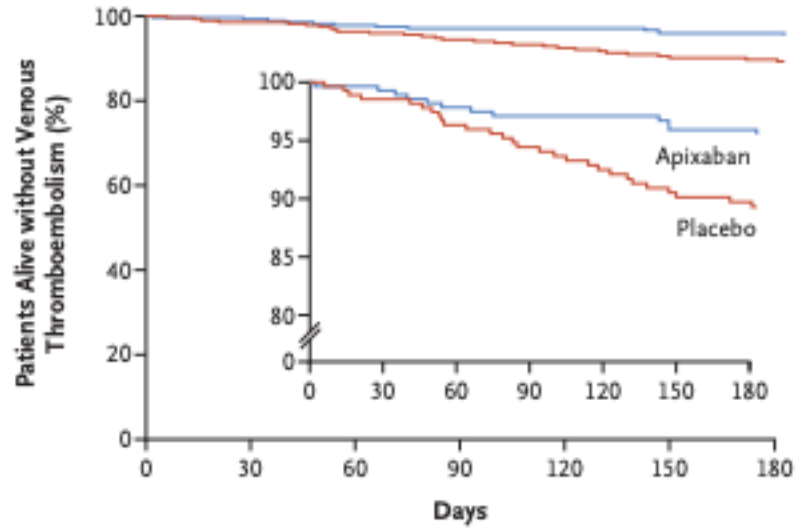


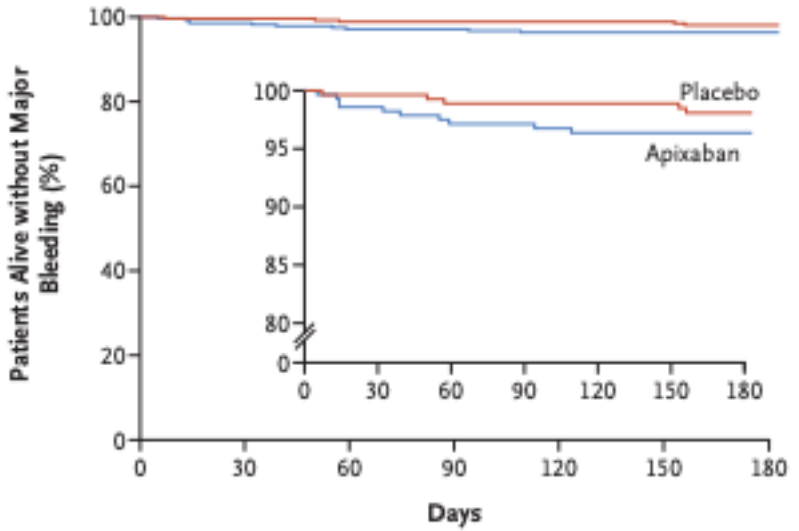
**Table 2.** Efficacy and Safety Clinical Outcomes.

| Outcome | Apixaban (N=288) | Placebo (N=275) | Hazard Ratio (95% CI)* | P Value |
|---|---|---|---|---|
| Venous thromboembolism — no. (%) | 12 (4.2) | 28 (10.2) | 0.41 (0.26–0.65) | <0.001 |
| Deep-vein thrombosis — no. (%) | 7 (2.4) | 12 (4.4) | | |
| Pulmonary embolism — no. (%)† | 5 (1.7) | 16 (5.8)‡ | | |
| Incidental pulmonary embolism — no./total no. | 3/5 | 6/16 | | |
| Major bleeding episode | | | | |
| Any episode — no. (%) | 10 (3.5) | 5 (1.8) | 2.00 (1.01–3.95) | 0.046 |
| Severity of episode — no./total no. (%)§ | | | | |
| Category 1 | 1/10 (10) | 0 | | |
| Category 2 | 8/10 (80) | 3/5 (60) | | |
| Category 3 | 1/10 (10) | 2/5 (40) | | |
| Category 4 | 0 | 0 | | |
| Clinically relevant nonmajor bleeding — no. (%)¶ | 21 (7.3) | 15 (5.5) | 1.28 (0.89–1.84) | |
| Outcome occurred during the treatment period — no. (%) | | | | |
| Venous thromboembolism | 3 (1.0) | 20 (7.3) | 0.14 (0.05–0.42) | |
| Major bleeding episode | 6 (2.1) | 3 (1.1) | 1.89 (0.39–9.24) | |
| Death from any cause — no. (%) | 35 (12.2) | 27 (9.8) | 1.29 (0.98–1.71) | |




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Apixaban | 288 | 276 | 265 | 256 | 249 | 244 | 229 |
| Placebo | 275 | 268 | 259 | 244 | 237 | 228 | 215 |

**Figure 2. Kaplan–Meier Cumulative Event Rates of Venous Thromboembolism.**
The inset shows the same data on an enlarged y axis.




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Apixaban | 288 | 275 | 266 | 258 | 249 | 246 | 233 |
| Placebo | 275 | 269 | 262 | 253 | 249 | 245 | 229 |

**Figure 3. Kaplan–Meier Cumulative Event Rates of Major Bleeding.**
The inset shows the same data on an enlarged y axis.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer

Khorana skor ≥2
180 gün
10 mg Rivaroxaban

**Table 2. Primary Efficacy End Points during the Period up to Day 180 and during the Intervention, According to Trial Group.***

| End Point | Up to Day 180 | | | During Intervention | | |
|---|---|---|---|---|---|---|
| | Placebo (N=421) | Rivaroxaban (N=420) | Hazard Ratio (95% CI) | Placebo (N=421) | Rivaroxaban (N=420) | Hazard Ratio (95% CI) |
| Primary efficacy composite end point | 37 (8.8) | 25 (6.0) | 0.66 (0.40–1.09)† | 27 (6.4) | 11 (2.6) | 0.40 (0.20–0.80) |
| Symptomatic event‡ | 19 (4.5) | 15 (3.6) | — | 12 (2.9) | 5 (1.2) | — |
| Symptomatic proximal DVT in lower limb | 8 (1.9) | 9 (2.1) | 1.12 (0.43–2.91) | 4 (1.0) | 3 (0.7) | 0.72 (0.16–3.22) |
| Symptomatic distal DVT in lower limb | 5 (1.2) | 2 (0.5) | 0.40 (0.08–2.07) | 2 (0.5) | 0 | NA |
| Symptomatic DVT in upper limb | 6 (1.4) | 4 (1.0) | 0.67 (0.19–2.39) | 6 (1.4) | 2 (0.5) | 0.33 (0.07–1.63) |
| Symptomatic nonfatal pulmonary embolism | 5 (1.2) | 5 (1.2) | 1.02 (0.29–3.52) | 0 | 1 (0.2) | NA |
| Asymptomatic event‡ | 18 (4.3) | 9 (2.1) | — | 15 (3.6) | 5 (1.2) | — |
| Asymptomatic proximal DVT in lower limb | 11 (2.6) | 4 (1.0) | 0.35 (0.11–1.11) | 10 (2.4) | 3 (0.7) | 0.29 (0.08–1.07) |
| Incidental pulmonary embolism | 10 (2.4) | 6 (1.4) | 0.59 (0.21–1.62) | 5 (1.2) | 2 (0.5) | 0.38 (0.07–1.98) |
| Venous thromboembolism–related death | 3 (0.7) | 1 (0.2) | 0.33 (0.03–3.18) | 1 (0.2) | 1 (0.2) | 0.97 (0.06–15.55) |

**Table 3. Primary Safety End Points, According to Trial Group.***

| End Point | Placebo (N=404) | Rivaroxaban (N=405) | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of patients with event (%)* | | | |
| Primary safety end point: major bleeding | 4 (1.0) | 8 (2.0) | 1.96 (0.59–6.49) | 0.26 |
| Secondary safety end point: clinically relevant nonmajor bleeding | 8 (2.0) | 11 (2.7) | 1.34 (0.54–3.32) | 0.53 |
| Major and clinically relevant nonmajor bleeding | 12 (3.0) | 19 (4.7) | 1.54 (0.75–3.17) | 0.24 |

# RİVAROXABAN
# APİXABAN

Renal fonksiyon Karaciğer fonksiyon
İlaç-ilaç etkileşimleri
Kanama riskleri (GİS, GÜS)
Opere olmamış hasta

**Table 1. VTE prophylaxis options in cancer patients**

| Options | Hospitalised patients | Surgical patients | Ambulatory patients |
|---|---|---|---|
| Heparins[a] | | | |
| UFH | 5000 IU every 8 h | 5000 IU 2-4 h preoperatively and every 8 h thereafter | — |
| Bemiparin | 3500 anti-Xa IU o.d. | 3500 anti-Xa IU starting 2 h preoperatively or 6 h post-operatively and 3500 anti-Xa IU o.d. thereafter | 3500 anti-Xa IU o.d.[b] |
| Dalteparin | 5000 anti-Xa IU o.d. | 5000 anti-Xa IU 12 h preoperatively and 5000 anti-Xa IU o.d. thereafter | 5000 anti-Xa IU o.d.[b,c] |
| Enoxaparin | 4000 anti-Xa IU o.d. | 4000 anti-Xa IU 12 h preoperatively and 4000 anti-Xa IU o.d. thereafter | 4000 anti-Xa IU o.d.[b] |
| Nadroparin | 3800 anti-Xa IU o.d. (if weight >70 kg: 5700 anti-Xa IU/kg o.d.) | 2850 anti-Xa IU 2-4 h preoperatively and 2850 anti-Xa IU o.d. thereafter | 3800 anti-Xa IU o.d. (if weight >70 kg: 5700 anti-Xa IU o.d.)[b] |
| Tinzaparin | 4500 anti-Xa IU o.d. | 4500 anti-Xa IU o.d., beginning 12 h post-operatively | 4500 anti-Xa IU o.d.[b] |
| Selective parenteral indirect factor Xa inhibitor | | | |
| Fondaparinux | 2.5 mg o.d. | 2.5 mg o.d. beginning 6-8 h post-operatively | Not studied in the outpatient prophylaxis setting |
| DOACs | | | |
| Apixaban | Not recommended | Not recommended | 2.5 mg orally b.i.d.[b] |
| Rivaroxaban | Not recommended | Not recommended | 10 mg orally o.d.[b] |
| Mechanical prophylaxis | | | |
| IPC | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |
| Venous foot pump | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |
| GCSs | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |

VTE tedaviden sonraki ilk 3 ay >%50 den fazla

Progresse hastalıklar Khorona skor ≥2

DOAC → 6 ay
LMWH → 6 ay

# Cerrahi dışı akut medikal problem nedeniyle yatan hastada tromboproflaksi

- Optimal olarak dizayn edilmiş bir çalışma yok.
- Yatan hastaya sıklıkla tromboproflaksi yapılmakta
- PAUDA ve IMPROVE rısk skorlaması mevcut ama spesifik değil
- Khorona skoru kullanılabilir
- Bu grupta DOAC yararı net değil VTE vs Kanama
- Taburculuk sonrası 4 hafta LMWH kullanımı planlanabilir

**Table 1.** VTE prophylaxis options in cancer patients

| Options | Hospitalised patients | Surgical patients | Ambulatory patients |
|---|---|---|---|
| Heparins[a] | | | |
| UFH | 5000 IU every 8 h | 5000 IU 2-4 h preoperatively and every 8 h thereafter | — |
| Bemiparin | 3500 anti-Xa IU o.d. | 3500 anti-Xa IU starting 2 h preoperatively or 6 h post-operatively and 3500 anti-Xa IU o.d. thereafter | 3500 anti-Xa IU o.d.[b] |
| Dalteparin | 5000 anti-Xa IU o.d. | 5000 anti-Xa IU 12 h preoperatively and 5000 anti-Xa IU o.d. thereafter | 5000 anti-Xa IU o.d.[b,c] |
| Enoxaparin | 4000 anti-Xa IU o.d. | 4000 anti-Xa IU 12 h preoperatively and 4000 anti-Xa IU o.d. thereafter | 4000 anti-Xa IU o.d.[b] |
| Nadroparin | 3800 anti-Xa IU o.d. (if weight >70 kg: 5700 anti-Xa IU/kg o.d.) | 2850 anti-Xa IU 2-4 h preoperatively and 2850 anti-Xa IU o.d. thereafter | 3800 anti-Xa IU o.d. (if weight >70 kg: 5700 anti-Xa IU o.d.)[b] |
| Tinzaparin | 4500 anti-Xa IU o.d. | 4500 anti-Xa IU o.d., beginning 12 h post-operatively | 4500 anti-Xa IU o.d.[b] |
| Selective parenteral indirect factor Xa inhibitor | | | |
| Fondaparinux | 2.5 mg o.d. | 2.5 mg o.d. beginning 6-8 h post-operatively | Not studied in the outpatient prophylaxis setting |
| DOACs | | | |
| Apixaban | Not recommended | Not recommended | 2.5 mg orally b.i.d.[b] |
| Rivaroxaban | Not recommended | Not recommended | 10 mg orally o.d.[b] |
| Mechanical prophylaxis | | | |
| IPC | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |
| Venous foot pump | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |
| GCSs | If pharmacological VTE prophylaxis is contraindicated[d] | If pharmacological VTE prophylaxis is contraindicated[d] | Not recommended |

# Multipl myelomlu hastalar

- %8-10 hastalık sürecinde semptomatik VTE
- Paraproteinemi
- Obezite
- İlaçlar
- Santral venöz katater
- G-CSF

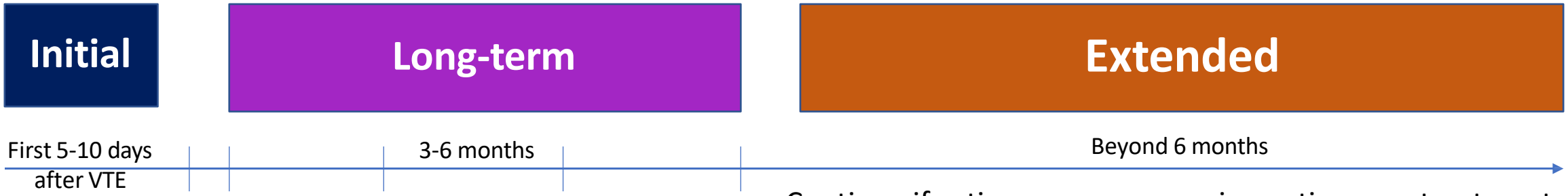
# Multipl myelomlu hastalar

- Düşük doz deksametazon+IMID → 100 mg ASA (IIIB)
- IMWG/NCCN/EMA skoru VTE için yüksek riskli ise

  → 3-6 ay LMAH (IIB)
- VTE proflaksisi hasta durumuna göre uzatılabilir
- LMWH intolerans vea kontrendikasyon varsa

  → 2.5 mg apixaban veya 10 mg rivaroxaban (IVC)

# VTE TREATMENT IN CAT




- Continue if active cancer or ongoing anti-cancer treatment, with periodic reassessment of the risks and benefits

- **Bleeding Risk**
- The risk of clinically relevant bleeding with anticoagulation is highest during the first month of therapy but is lower thereafter

# CAT treatment

ACUTE PHASE → 5-10 day

LONG-TERM PHASE → 3-6 months

EXTENDED PHASE → beyond 6 months

- Tedavisi devam eden hastalar, tekrar riski yüksek hastalarda, tedavi sonrası 3. haftada yüksek D-dimer, CRP düzeyi uzatılabilir

**Table 2. Treatment options for VTE in cancer patients**

| Drug | Initial treatment of established VTE (5-10 days) | Long-term phase (first 3-6 months) and extended phase (beyond 6 months) |
|---|---|---|
| Heparins (LMWH) | | |
| Dalteparin | 100 anti-Xa IU/kg every 12 h, or 200 anti-Xa IU/kg o.d. for the first 30 days | 150 anti-Xa IU/kg o.d. after day 30 |
| Enoxaparin | 100 anti-Xa IU/kg every 12 h, or 150 anti-Xa IU/kg o.d. | 100 anti-Xa IU/kg every 12 h, or 150 anti-Xa IU/kg o.d. |
| Tinzaparin | 175 anti-Xa IU/kg o.d. | 175 anti-Xa IU/kg o.d. |
| Nadroparin | 86 anti-Xa IU/kg every 12 h, or 171 anti-Xa IU/kg o.d. | 86 anti-Xa IU/kg every 12 h, or 171 anti-Xa IU/kg o.d. |
| Bemiparin | 115 anti-Xa IU/kg o.d. | 115 anti-Xa IU/kg o.d. |
| Heparins (UFH) | | |
| UFH | 80 IU/kg i.v. bolus, then 18 IU/kg/h i.v.; adjust dose based on aPTT | — |
| DOACs | | |
| Edoxaban | — | 60 mg, o.d.<br>30 mg, o.d. if: (i) CrCl <50 ml/min, (ii) ≤60 kg or (iii) patients receiving P-glycoprotein inhibitors |
| Rivaroxaban | 15 mg every 12 h for 3 weeks | 20 mg o.d. |
| Apixaban | 10 mg every 12 h for 7 days | 5 mg every 12 h |
| Vitamin K antagonists | | |
| Acenocoumarol | — | Adjust dose to maintain INR 2-3 |
| Phenprocoumon | — | Adjust dose to maintain INR 2-3 |
| Warfarin | — | Adjust dose to maintain INR 2-3 |

Xa, activated coagulation factor X; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; INR, international normalised ratio; i.v., intravenous; LMWH, low-molecular-weight heparin; o.d., once daily; UFH, unfractionated heparin; VTE, venous thromboembolism.

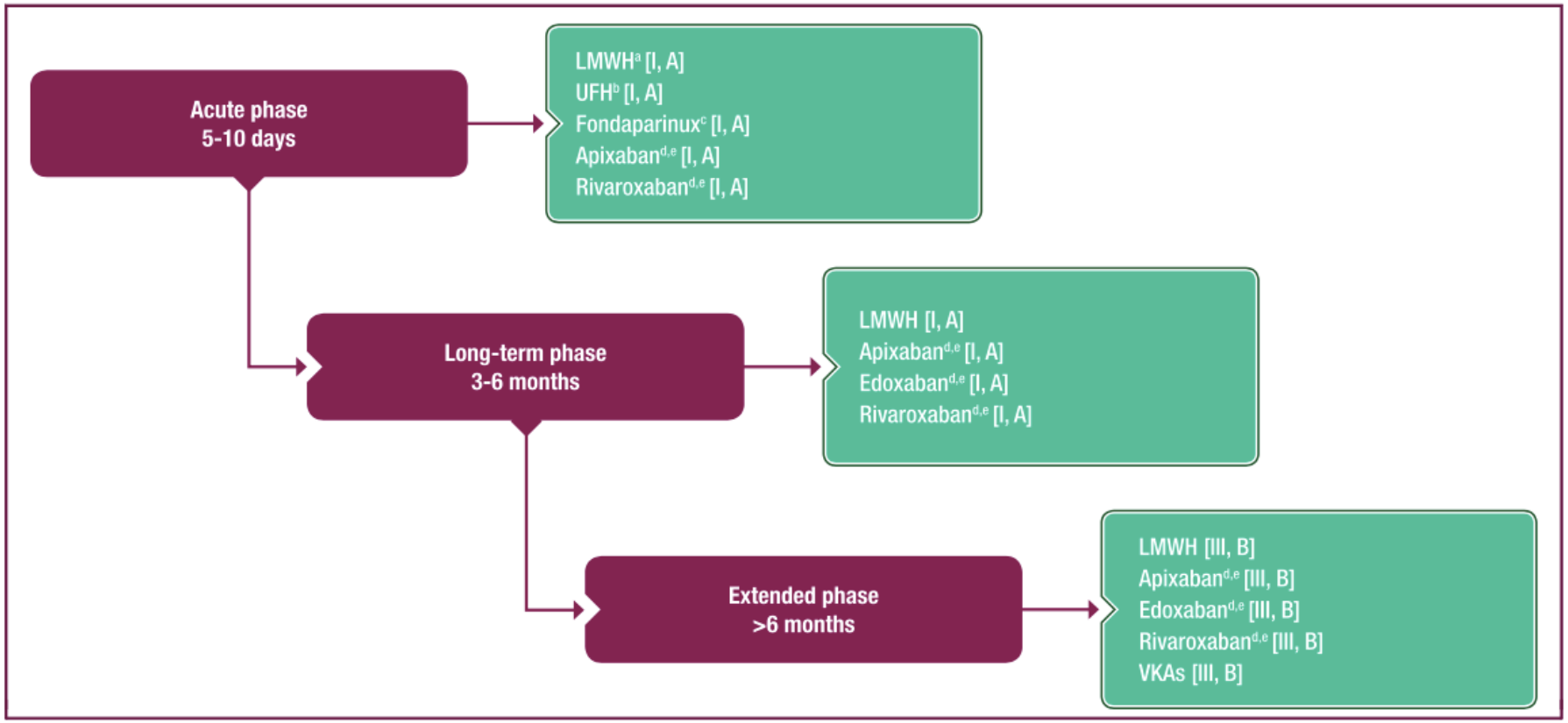



**Figure 3. Treatment of CAT.**

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments.

CAT, cancer-associated thrombosis; CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; GI, gastrointestinal; HIT, heparin-induced thrombocytopaenia; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.

[a]Preferred option over UFH or fondaparinux.

[b]UFH to be considered in patients with renal impairment, defined as CrCL <30 ml/min.

[c]Fondaparinux if previous HIT.

[d]Caution in patients receiving potent inhibitors or inducers of CYP3A4 and P-glycoprotein or with luminal GI cancers.

[e]There are some clinical situations in which DOACs are contraindicated: triple-positive antiphospholipid syndrome, renal failure with CrCl <15 ml/min, pregnancy and lactation. Limited clinical experience in patients with thrombosis of unusual location (upper-limb DVT, CAT, venous sinus thrombosis or splanchnic thrombosis). In patients with brain metastases, LMWH should be used.

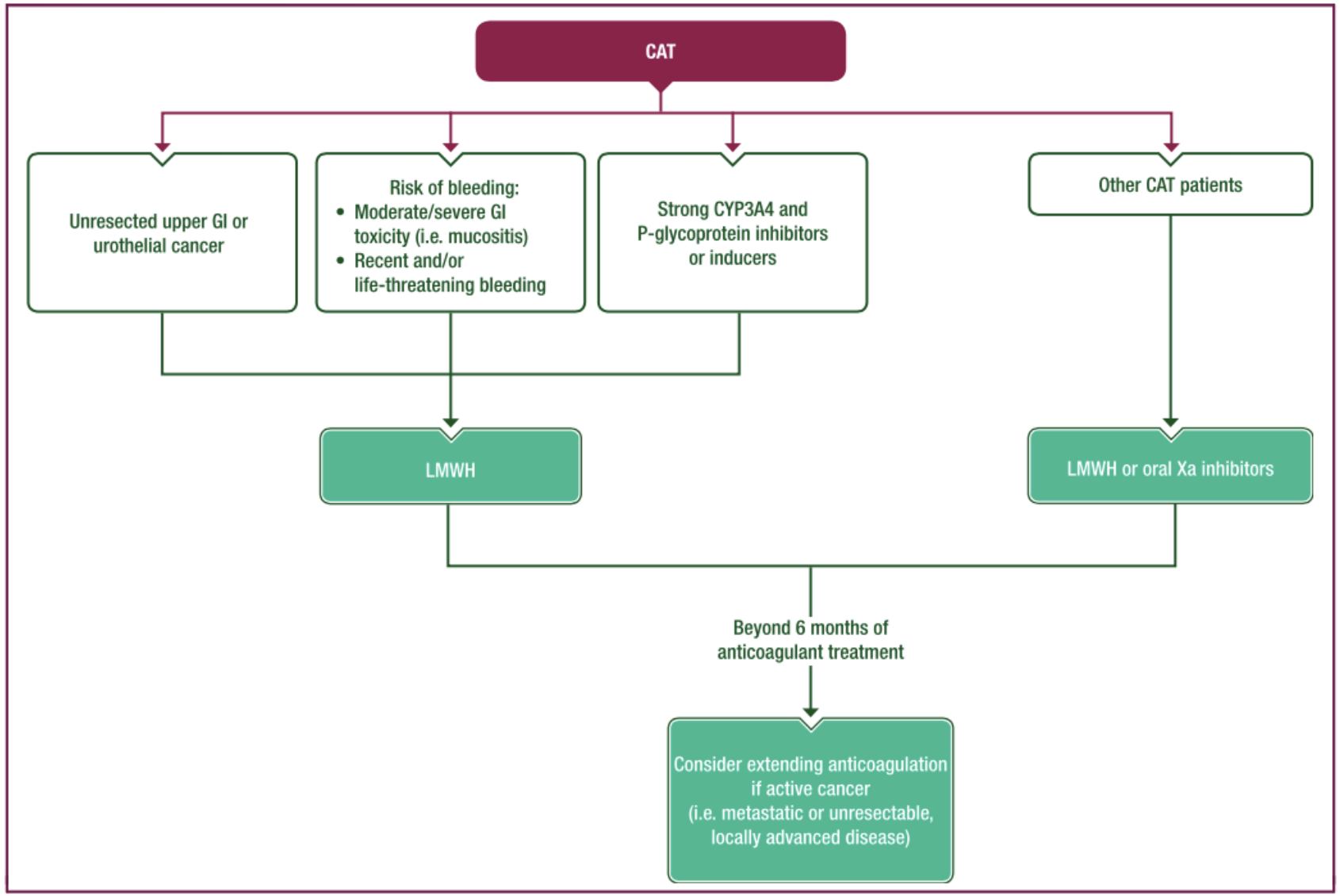



**Figure 4. Treatment of CAT with respect to shared decision making in the ambulatory patient.**
Purple: general categories or stratification; white: other aspects of management; turquoise: combination of treatments or other systemic treatments.
Xa, activated coagulation factor X; CAT, cancer-associated thrombosis; CYP3A4, cytochrome P450 3A4; GI, gastrointestinal; LMWH, low-molecular-weight heparin.

# DOACS FOR THE TREATMENT OF CAT

## Potential therapeutic issues

- Patients receiving potent inhibitors or inducers of CYP3A4 and P-glycoprotein
- Luminal GI cancers, urothelial cancers

**USE WITH CAUTION**

- Triple-positive antiphospholipid syndrome
- Renal failure with CrCl <15 ml/min
- Pregnancy and lactation

**CONTRAINDICATED**

- Patients with thrombosis of unusual location (upper-limb DVT, CAT, venous sinus thrombosis or splanchnic thrombosis)
- Patients with brain metastases (LMWH should be used)

**LIMITED DATA**

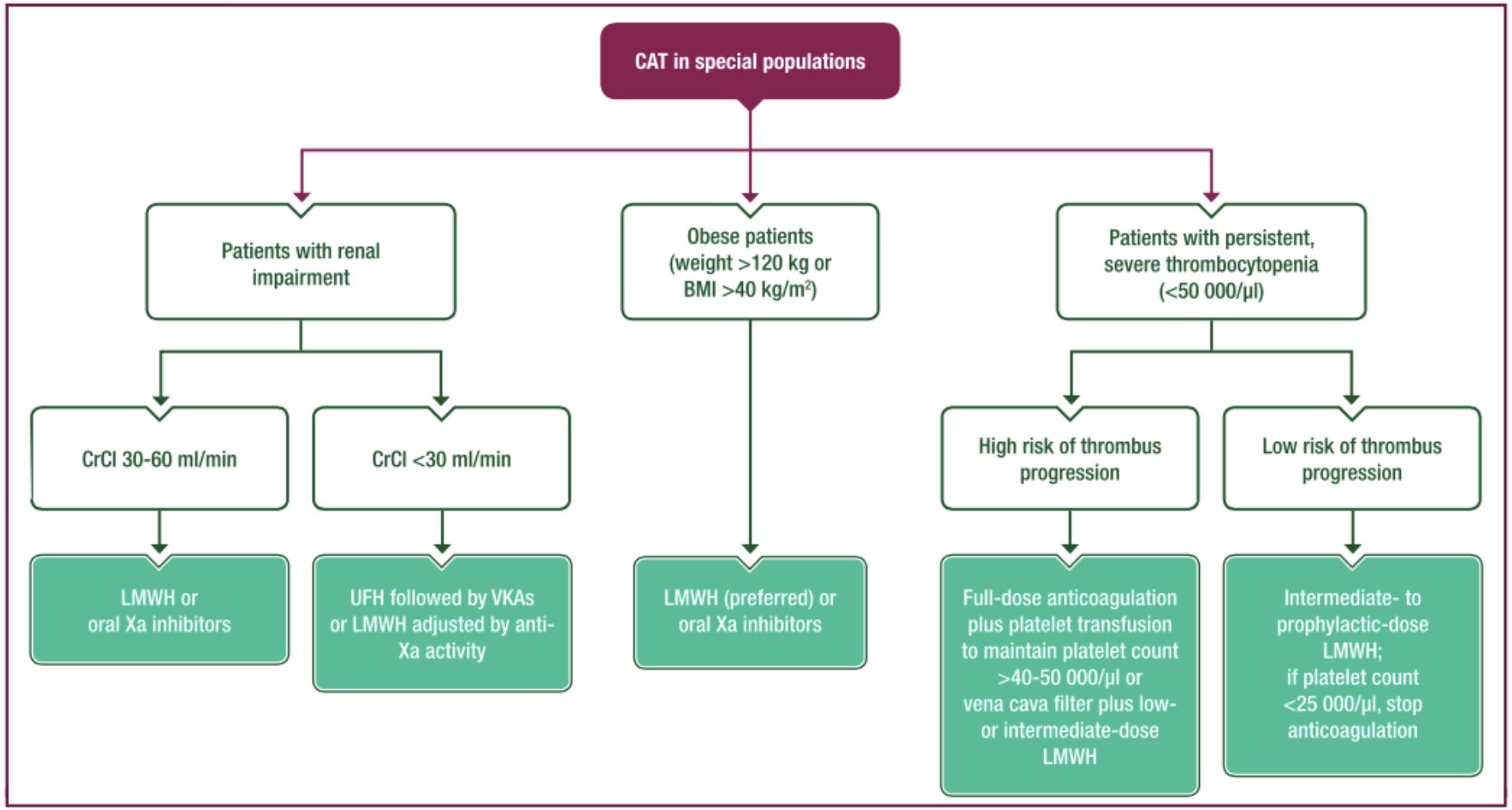



**Figure 5. Treatment of CAT in special populations.**
Purple: general categories or stratification; white: other aspects of management; turquoise: combination of treatments or other systemic treatments.
Xa, activated coagulation factor X; BMI, body mass index; CAT, cancer-associated thrombosis; CrCl, creatinine clearance; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.

Yüksek riskli grup
İlk 30 gün
Segmental-proximal PE
Proximal DVT
Tekrarlayan tromboz

Düşük riskli grup
30 günden sonra
Distal DVT
Subsegmental PE

# CAT vena cava filtresi

- Etkinliği ve güvenliği RKÇ'larda değerlendirilmemiştir.
- Antikoagülan tedaviye ek olarak vena kava filtrelerinin kullanılması
  - → PE insidansını azaltabilir,
  - → DVT riskini artırır
  - → Tek başına antikoagülasyona göre sağkalım faydası yok

**Antikoagülan tedavinin kontrendike olduğu akut faz durumu varsa** DÜŞÜNÜLEBİLİR

# Katater ilişkili tromboz

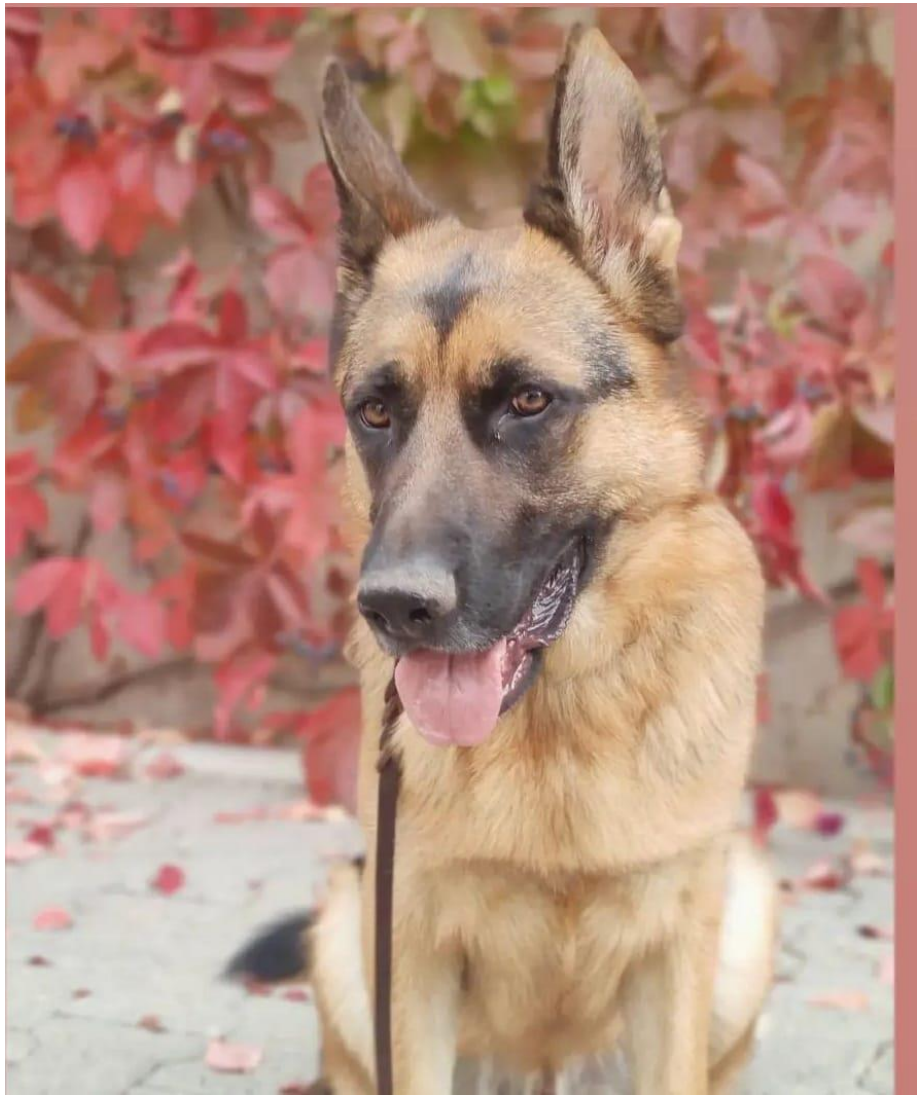
- Genel oran %14-18
- %5 semptomatik
- İmplante portta periferik kataterden daha az
- Tek doz LMWH VKA'ne göre daha az kanama
- 3 aylık proflakside CRT oranı düşük
- Düşük hayat kalitesi
- Rutin proflaksi önerilmez

# Katater ilişkili tromboz

- Tromboz oluşmuşsa
  - → DOAC için yeterli veri yok
  - → Kataterin çıkarılması
    - Enfekte, kullanılmayacaksa
    - Antikoagülan tedaviye rağmen uzamış tromboz
    - Klinik olarak hastanın daha semptomatik olması
  - → LMWH
  - → 3-6 ay için yeterli veri yok
  - → 3 ay LMWH ile tedavi (IIIC)

**TABLE 4.** Estimated Prices for Anticoagulants

| Setting | Agent | Dose | Schedule | HCPCS Dosage | Medicare Payment Limit (US$) | Price Per Dose (US$) | Price Per Day (US$) |
|---|---|---|---|---|---|---|---|
| Pharmacologic (anticoagulant) prophylaxis | | | | | | | |
| Hospitalized medical patients | Unfractionated heparin | 5,000 U | Every 8 hours | 1,000 U | 0.199 | 1.00 | 2.99 |
| | Dalteparin | 5,000 U | Once daily | 2,500 U | 14.982 | 29.96 | 29.96 |
| | Enoxaparin | 40 mg | Once daily | 10 mg | 0.872 | 3.49 | 3.49 |
| | Fondaparinux | 2.5 mg | Once daily | 0.5 mg | 2.283 | 11.42 | 11.42 |
| Surgical patients | Unfractionated heparin | 5,000 U | 2-4 hours preoperatively and every 8 hours thereafter | 1,000 U | 0.199 | 1.00 | 2.99 (postoperatively) |
| | Dalteparin | 2,500 U | 2-4 hours preoperatively and 5,000 U once daily thereafter | 2,500 U | 14.982 | 14.98 | 29.96 (postoperatively) |
| | | or | | | | | |
| | | 5,000 U | 2-4 hours or 10-12 hours preoperatively and 5,000 U once daily thereafter | | | | |
| | Enoxaparin | 40 mg | 2-4 hours or 10-12 hours preoperatively and once daily thereafter | 10 mg | 0.872 | 3.49 | 3.49 (postoperatively) |
| | Fondaparinux | 2.5 mg | Once daily beginning 6-8 hours postoperatively | 0.5 mg | 2.283 | 11.42 | 11.42 |
| Outpatients | Dalteparin | 5,000 U | Once daily | 2,500 U | 14.982 | 29.96 | 29.96 |
| | Enoxaparin | 40 mg | Once daily | 10 mg | 0.872 | 3.49 | 3.49 |
| | Fondaparinux | 2.5 mg | Once daily | 0.5 mg | 2.283 | 11.42 | 11.42 |
| | Apixaban | 2.5 mg | Twice daily | NA | NA | 7.78 | 15.56 |
| | Rivaroxaban | 10 mg | Once daily | NA | NA | 15.69 | 15.69 |



Teşekkürler…

# İnsidental CAT

- Kanser hastalarında VTE, kanser evrelemesi veya kanser tedavisine yanıtın değerlendirilmesi için istenen rutin görüntüleme taramalarında vakaların yaklaşık yarısında tesadüfen teşhis edilir.77 Tesadüfen tespit edilen VTE, göz ardı edilemeyecek bir tekrarlayan tromboz riski ile ilişkili olsa da, yakın zamanda yapılan bir araştırmada, CAT hastalarının meta-analizi, tesadüfi VTE'nin, semptomatik VTE ile karşılaştırıldığında 6 ayda daha düşük VTE nüksü oranıyla ilişkili olduğunu (RR 0.6, %95 CI 0.4-0.9) ve majör kanamada artış eğiliminin olduğunu (RR 1.47, 95% CI 0.4-0.9) bildirmiştir. %95 CI 0,99-2,2).78 12 aylık tekrarlayan VTE insidansı, subsegmental PE'li hastalarda ve daha proksimal PE'li hastalarda (%6,4'e karşı %6,0) benzer görünmektedir.75 Bu nedenle, antikoagülan tedavi önerilmektedir. Subsegmental PE'li çoğu hastada, yeterli kardiyopulmoner sistemin mevcut olması koşuluyla, kanama riski yüksek olduğunda veya eşlik eden DVT olmadan tek bir subsegmental arter tutulumu olduğunda dikkatli bir yaklaşım veya daha kısa süreli antikoagülasyon düşünülebilir

- Doğrudan oral faktör Xa inhibitörleriyle ilgili RKÇ'ler, birincil sonuçlar, çalışma ve tedavi süresi, dahil edilen kanser türleri ve üst gastrointestinal kanserli hastaların oranı açısından heterojendi (Ek Tablo S9, https ://doi. org/10.1016 /j.annonc.2022.12.014). Bire bir karşılaştırmaların olmayışı, bir ajanın diğerlerinden daha iyi performans gösterip gösteremeyeceğine ilişkin sonuçları daha da sınırlamaktadır. Şu anda, direkt trombin inhibitörü dabigatranın CAT tedavisinde kullanımını değerlendiren bir çalışma yok

# Statins Decrease the Occurrence of Venous Thromboembolism in Patients with Cancer

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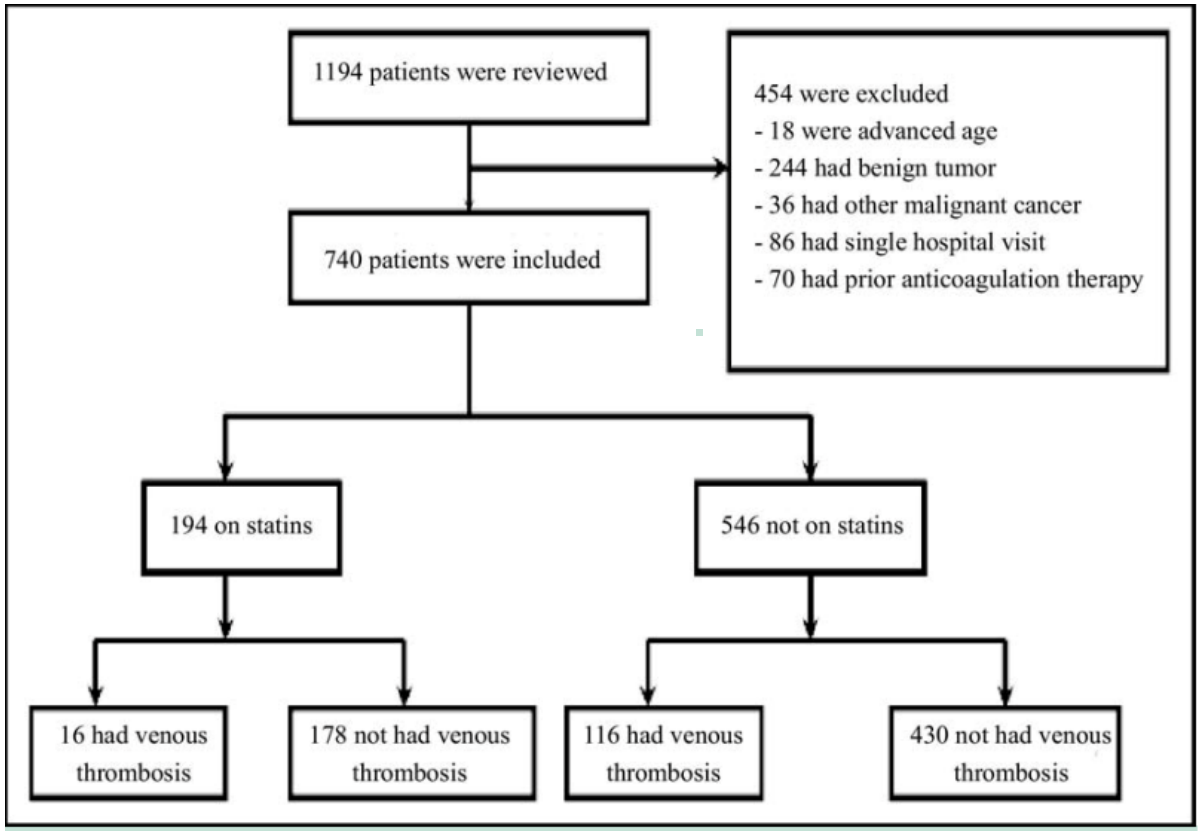


**Figure 1** Study population.

**Table 3** Summary of Statins Used

| Type of Statins Used | Standard Dose (<40 mg) (N = 184) | High Dose (>40 mg) (N = 10) | Total No. of Patients (N = 194) |
|---|---|---|---|
| Simvastatin | 50 | 2 | 52 (27%) |
| Atorvastatin | 103 | 3 | 106 (55%) |
| Lovastatin | 14 | 2 | 16 (8%) |
| Pravastatin | 10 | 2 | 12 (6%) |
| Rosuvastatin/fluvastatin | 7 | 1 | 8 (4%) |

**Table 5** Logistic Regression Analysis of Factors Related to Venous Thromboembolism and Occurrence of Venous Thromboembolism

| Factors | OR | 95% CI | *P* Value |
|---|---|---|---|
| Immobilization | 2.88 | 1.74-4.75 | <.001 |
| Metastatic disease | 2.07 | 1.34-3.18 | .001 |
| Current chemotherapy | 1.77 | 1.10-2.86 | .019 |
| Smoking | 0.63 | 0.39-1.01 | .055 |
| Aspirin use | 0.69 | 0.40-1.20 | .188 |
| Statin use | 0.33 | 0.18-0.59 | <.001 |

OR = odds ratio; CI = confidence interval. $P < .05$.

- Primer ve metastatik beyin tümörlü hastalarda venöz tromboembolizmin (VTE) tedavisi ve önlenmesi birbiriyle çelişen iki konu nedeniyle karmaşık hale gelmektedir. Beyin tümörü olan hastalar, hiper pıhtılaşma durumu, beyin cerrahisi prosedürleri ve sıklıkla bacak parezi nedeniyle VTE geliştirme açısından önemli bir risk taşır. Ancak antitrombotik ajanların nörolojik kötüleşmeyle birlikte tümör içine kanamayı hızlandırabileceğine dair endişeler vardır.

- Beyin tümörlü hastalarda akut VTE'yi yönetme ilkeleri, kanserli ve kansersiz diğer hastalarla aynıdır. Antikoagülasyon tedavinin temel taşıdır ve tedavi kararları, antikoagülasyona bağlı kanama komplikasyonları riski ile tedavi edilmeyen ve tekrarlayan VTE risklerini dengeler.

- Yuksek turoverı olanlar daha fazla kanamaya egılımlı
- Bevacizumab hem kanama hem vte nedeni

**Risk factors for bleeding with anticoagulant therapy and estimated risk of major bleeding in low, moderate, and high risk categories**

| Risk factors* |
|---|
| • Age >65 years<br>• Age >75 years<br>• Previous bleeding<br>• Cancer<br>• Metastatic cancer<br>• Renal failure<br>• Liver failure<br>• Thrombocytopenia<br>• Previous stroke<br>• Diabetes<br>• Anemia<br>• Antiplatelet therapy<br>• Poor anticoagulant control<br>• Comorbidity and reduced functional capacity<br>• Recent surgery¶<br>• Frequent falls<br>• Alcohol abuse |

| | Estimated absolute risk of major bleeding (%) | | |
|---|---|---|---|
| **Categorization of risk of bleedingΔ** | **Low risk◇ (0 risk factors)** | **Moderate risk◇ (1 risk factor)** | **High risk◇ (≥2 risk factors)** |
| **Anticoagulation 0 to 3 months§** | | | |
| Baseline risk (%) | 0.6 | 1.2 | 4.8 |
| Increased risk (%) | 1 | 2 | 8 |
| Total risk (%) | 1.6§ | 3.2 | 12.8¥ |
| **Anticoagulation after first 3 months⁴** | | | |
| Baseline risk (%/years) | 0.3† | 0.6 | ≥2.5 |
| Increased risk (%/years) | 0.5 | 1 | ≥4 |
| Total risk (%/years) | 0.8** | 1.6** | ≥6.5 |

GI: gastrointestinal; UFH: unfractionated heparin; LMWH: low molecular weight heparin; VKA: vitamin K-dependent antagonist (ie, warfarin); VTE: venous thromboembolism.

* The increase in bleeding associated with a risk factor will vary with (1) severity of the risk factor (eg, location and extent of metastatic disease, platelet count), (2) temporal relationships (eg, interval from surgery or a previous bleeding episode), and (3) how effectively a previous cause of bleeding was corrected (eg, upper-GI bleeding).

¶ Important for parenteral anticoagulation (eg, first 10 days), but less important for long-term or extended anticoagulation.

Δ Although there is evidence that risk of bleeding increases with the prevalence of risk factors, this categorization scheme has not been validated. Furthermore, a single risk factor, when severe, will result in a high risk of bleeding (eg, major surgery within the past 2 days, severe thrombocytopenia).

◇ Compared with low-risk patients, moderate-risk patients are assumed to have a 2-fold risk and high-risk patients an 8-fold risk of major bleeding.

§ The 1.6% corresponds to the average of major bleeding with initial UFH or LMWH therapy followed by VKA therapy. We estimated baseline risk by assuming a 2.6 relative risk of major bleeding with anticoagulation (refer to footnote ⁴).

¥ Consistent with frequency of major bleeding observed by Hull et al in high-risk patients[1].

⁴ We estimate that anticoagulation is associated with a 2.6-fold increase in major bleeding based on comparison of extended anticoagulation with no extended anticoagulation. The relative risk of major bleeding during the first 3 months of therapy may be greater than during extended VKA therapy because (1) the intensity of anticoagulation with initial parenteral therapy may be greater than with VKA therapy; (2) anticoagulant control will be less stable during the first 3 months; and (3) predispositions to anticoagulant-induced bleeding may be uncovered during the first 3 months of therapy. However, studies of patients with acute coronary syndromes do not suggest a ≥2.6 relative risk of major bleeding with parenteral anticoagulation (eg, UFH or LMWH) compared with control.

† Our estimated baseline risk of major bleeding for low-risk patients (and adjusted up for moderate- and high-risk groups as per footnote ◇).

** Consistent with frequency of major bleeding during prospective studies of extended anticoagulation for VTE.

*Reference:*

1. Hull RD, Raskob GE, Rosenbloom D, et al. Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. N Engl J Med 1990; 322:1260.

- **Mutlak kontrendikasyonlar** : Antikoagülasyonun mutlak kontrendikasyonları arasında akut (<48 saat) intrakraniyal kanama, kontrolsüz malign hipertansiyon, şiddetli koagülopati, şiddetli trombosit fonksiyon bozukluğu, şiddetli trombositopeni, kalıtsal kanama bozukluğu ve son 7 ila 14 gün içinde yüksek riskli invazif intrakraniyal prosedür yer alır.
- Öneri sırası doac→ lmwh→varfarin
- Kanıt duzeyleri grade 2 c

- Heparinin yarılanma ömrünün kısa olması ve protamin sülfat ile hızlı bir şekilde geri dönüş yapabilmesi nedeniyle klinik olarak stabil olmayan ve kanama riski yüksek olan hastalarda başlangıçta fraksiyone olmayan heparini (bolussuz) kullanmayı tercih ediyoruz .