Profilassi del TEV nel paziente internistico e nel paziente oncologico

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PREVENTION OF VTE IN MEDICAL PATIENTS

- ✓ Why?
  - ✓ When?
    - ✓ How?
      - ✓ How long?

PREVENTION OF VTE IN CANCER PATIENT

- ✓ Cancer and VTE relation
  - ✓ Thromboprophylaxis in hospitalized patients with cancer
    - ✓ Thromboprophylaxis in ambulatory patients with cancer who are receiving anticancer therapy

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Why?

- ✓ Over 1 million estimated symptomatic venous thromboembolism (VTE) per annum within six European countries (France, Germany, Italy, Spain, Sweeden and UK) Cohen AT, Agnelli G et al. Thromb Haemost 2007; 98:756-64
- ✓ Approximately half of new VTE cases occur during a hospital stay or within 90 days of an inpatient admission or surgical procedure Streiff MB, Brady PJ et al. MMWR March 7,2014 Vol 63 No.9
- ✓ Hospital - associated venous thromboembolism (HA-VTE) is a common source of morbidity and mortality. Pulmonary embolism (PE), with an estimated death rate of 15%, is the most common preventable cause of in-hospital death Behnood Bikdeli and Babak Sharif- Kashani Semin Thromb Hemost 2012; 38:144-155
- ✓ VTE costs. 160 patients with VTE and 160 patients receiving prophylaxis and without VTE were retrospectively evaluated within 26 IM units in Italy. The total median costs for VTE management were around four-times higher than those for prophylaxis (€1348.68 vs €373.03) Gussoni G, Foglia E et al. Thromobosis Research 131 (2013) 17-23

When?

CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Prevention of VTE in Nonsurgical Patients

5.1. In chronically immobilized persons residing at home or at a nursing home, we suggest against the routine use of thromboprophylaxis (Grade 2C).

American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients

Recommendation 15. In chronically ill medical patients, including nursing home patients, the ASH guideline panel *suggests* not using VTE prophylaxis compared with using any VTE prophylaxis

Recent studies among **hospitalized medically ill** patients suggest that a universal approach to prevention has minimal impact on reducing VTE Heit JA, Crusan DJ et al. Blood, 13 July 2017. Volume 130, number 2

This may be due to:

1. Shorter lenghts of stay and truncated thromboprophylaxis regimens compared with older studies
2. Overprophylaxis of low-risk patients
3. Underutilization of appropriate prophylaxis in hospitalized medical patients due to clinical concern for bleeding

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Risk-assessment models (RAMs)

Table 2. Padua Prediction Score Risk Assessment Model[a]

Baseline Features	Score[b]
Active cancer[c]	3
Previous VTE (excludes superficial vein thrombosis)	3
Reduced mobility[d]	3
Already known thrombophilic condition[e]	3
Recent (≤1 month) trauma and/or surgery	2
Elderly age (≥70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥30 kg/m^2)	1
Ongoing hormonal treatment	1

Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost*. 2010;8(11):2450-2457.

A total score ≥4 indicates a high risk of VTE

In a prospective observational study of 1,180 medical inpatients, 60.3% of patients were low risk and 39.7% were high risk. Among patients who did not receive prophylaxis, VTE occurred in 11.0% of high-risk patients vs 0.3% of low-risk patients (HR 32.0; 95% CI, 4.1-251.0).

IMPROVE VTE RAM	point
Previous VTE	3
Known thrombophilia	2
Lower limb paralysis	2
Active cancer	2
Immobilization	1
ICU/CCU stay	1
Age > 60 anni	1

Predictive and Associative Models to Identify Hospitalized Medical Patients at Risk for VTE *CHEST 2011; 140(3):706–714*

A total score of 2 or more indicates increased VTE risk

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How?

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients

- In **acutely ill medical patients**, the panel suggests using **UFH, LMWH, or fondaparinux** rather than no parenteral anticoagulant *(conditional recommendation, low certainty)*
- The panel suggests using LMWH *(low certainty)* or fondaparinux *(very low certainty)* rather than UFH *(conditional recommendation)*

Parenteral anticoagulant compared with **no parenteral anticoagulant**:

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with no parenteral anticoagulant	*Risk difference with parenteral anticoagulant*
Mortality	**0.97** (0.91 to 1.04)	69 per 1,000	**2 fewer deaths per 1,000** (6 fewer to 3 more)
PE	**0.59** (0.45 to 0.78)	10 per 1,000	**4 fewer PE per 1,000** (6 fewer to 2 fewer)
Symptomatic proximal DVT	**0.28** (0.06 to 1.37)	4 per 1,000	**3 fewer DVT per 1,000** (4 fewer to 1 more)
Major bleeding	**1.48** (0.81 to 2.71)	7 per 1,000	**3 more bleeds per 1,000** (1 fewer to 12 more)

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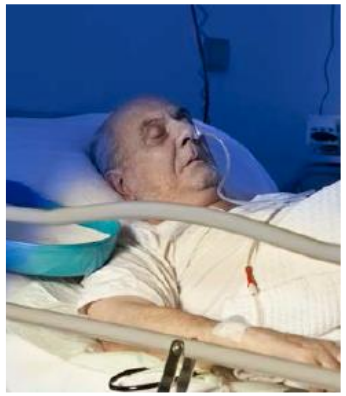
Quality of Evidence (GRADE): Low Moderate Strong

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients

In **acutely or critically ill medical patients**, the panel suggests using **pharmacological VTE prophylaxis over mechanical prophylaxis** *(conditional recommendation, very low certainty)*



Pharmacologic prophylaxis compared with **mechanical prophylaxis**
(graduated compression stockings or pneumatic compression devices):

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with pharmacologic prophylaxis	*Risk difference with mechanical prophylaxis*
● Mortality	**0.95** (0.42 to 1.13)	18 per 1,000	**1 fewer death per 1,000** (11 fewer to 21 more)
● PE	**1.54** (0.48 to 4.93)	1 per 1,000	**1 more PE per 1,000** (1 fewer to 4 more)
● Symptomatic proximal DVT	**2.20** (0.22 to 22.09)	2 per 1,000	**2 more DVT per 1,000** (1 fewer to 38 more)
● Major bleeding	**0.87** (0.25 to 3.08)	28 per 1,000	**4 fewer bleeds per 1,000** (21 fewer to 58 more)

Quality of Evidence (GRADE): Low ● Moderate ● Strong ●

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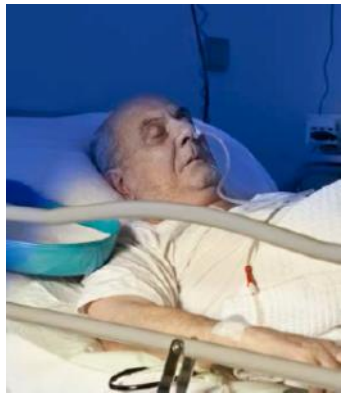

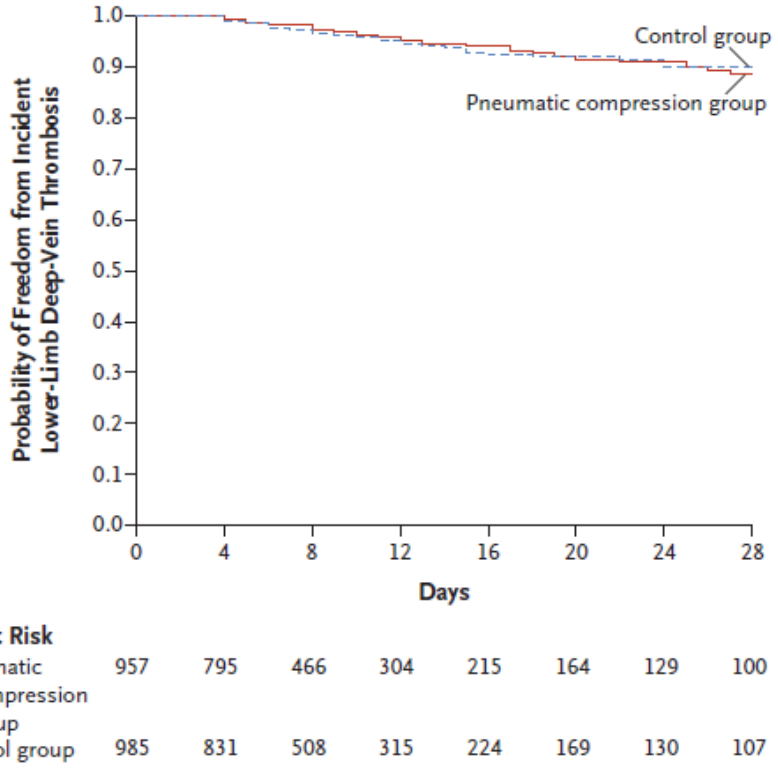

No. at Risk								
Pneumatic compression group	957	795	466	304	215	164	129	100
Control group	985	831	508	315	224	169	130	107

Figure 1. Kaplan–Meier Time-to-Event Curves for Freedom from Incident Lower-Limb Deep-Vein Thrombosis in the Modified Intention-to-Treat Population.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 4, 2019 VOL. 380 NO. 14

Adjunctive Intermittent Pneumatic Compression for Venous Thromboprophylaxis

In the PREVENT trial, adjunctive intermittent pneumatic compression had no effect on the incidence of proximal deep-vein thrombosis among critically ill patients who were receiving pharmacologic thromboprophylaxis. The addition of intermittent pneumatic compression to pharmacologic thromboprophylaxis did not result in a lower incidence of pulmonary embolism or a composite outcome of venous thromboembolism or death from any cause at 28 days than pharmacologic thromboprophylaxis alone.

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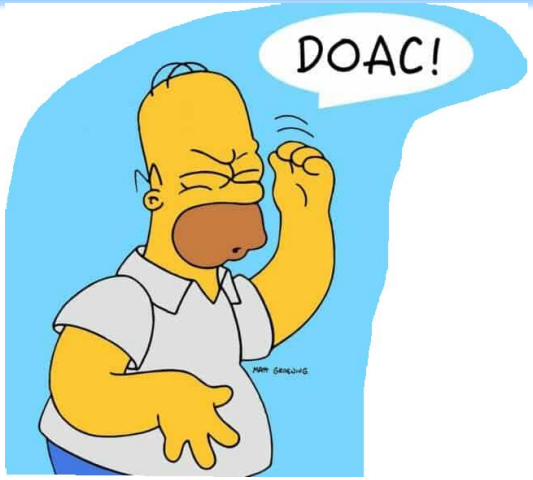

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients

In acutely ill hospitalized **medical patients**, the panel recommends using **LMWH over DOACs** for VTE prophylaxis *(strong recommendation, moderate certainty)*

Any DOAC compared with **prophylactic LMWH**:

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with prophylactic LMWH	*Risk difference with any DOAC*
Mortality	**0.64** (0.21 to 1.98)	1 per 1,000	**0 fewer deaths per 1,000** (1 fewer to 1 more)
PE	**1.01** (0.29 to 3.53)	1 per 1,000	**0 fewer PE per 1,000** (1 fewer to 3 more)
Symptomatic proximal DVT	**1.03** (0.34 to 3.08)	2 per 1,000	**0 fewer DVT per 1,000** (1 fewer to 4 more)
Major bleeding	**1.70** (1.02 to 2.82)	2 per 1,000	**2 more bleeds per 1,000** (0 fewer to 4 more)*

*these estimates apply to low baseline bleeding risk

Quality of Evidence (GRADE): Low Moderate Strong

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ADOPT

Apixaban 2.5 mg twice daily for 30 days

VS

Enoxaparin 40 mg once daily for 6-14 days

2011 — 2013

MAGELLAN

Rivaroxaban 10 mg once daily for 35 days

VS

Enoxaparin 40 mg once daily for 10 days

Betrixaban (Bevyxxa®)

- FDA approval: June 23, 2017
  - New Molecular Entity
  - Priority review drug
- Marketed by: Portola Pharmaceuticals
- Website information: http://www.bevyxxa.com

Bevyxxa® betrixaban capsules

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How long?

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients

In acutely ill hospitalized medical patients, the panel recommends **inpatient over inpatient plus extended duration outpatient VTE prophylaxis** *(strong recommendation, moderate certainty).*

Extended prophylaxis (30-40 days) compared with **in-hospital prophylaxis** (any agent):

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)
		Risk difference with extended prophylaxis
🔴 Mortality	1.00 (0.89 to 1.12)	0 fewer deaths per 1,000 (5 fewer to 5 fewer)
🔴 PE	0.63 (0.39 to 1.03)	1 fewer PE per 1,000 (3 fewer to 0 fewer)
🟠 Symptomatic proximal DVT	0.54 (0.32 to 0.91)	3 fewer DVT per 1,000 (4 fewer to 1 fewer)
🟠 Major bleeding	2.09 (1.33 to 3.27)	4 more bleeds per 1,000 (1 more to 8 more)

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Quality of Evidence (GRADE): Low 🔴 Moderate 🟠 Strong 🟢

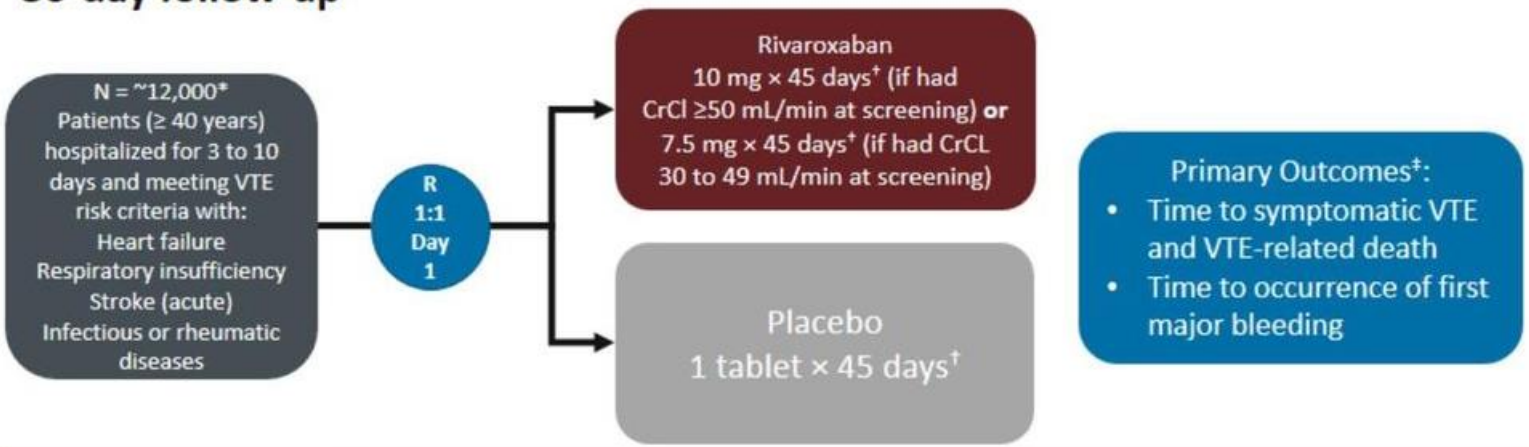
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban for Thromboprophylaxis after Hospitalization for Medical Illness

N Engl J Med 2018;379:1118-27.
DOI: 10.1056/NEJMoa1805090

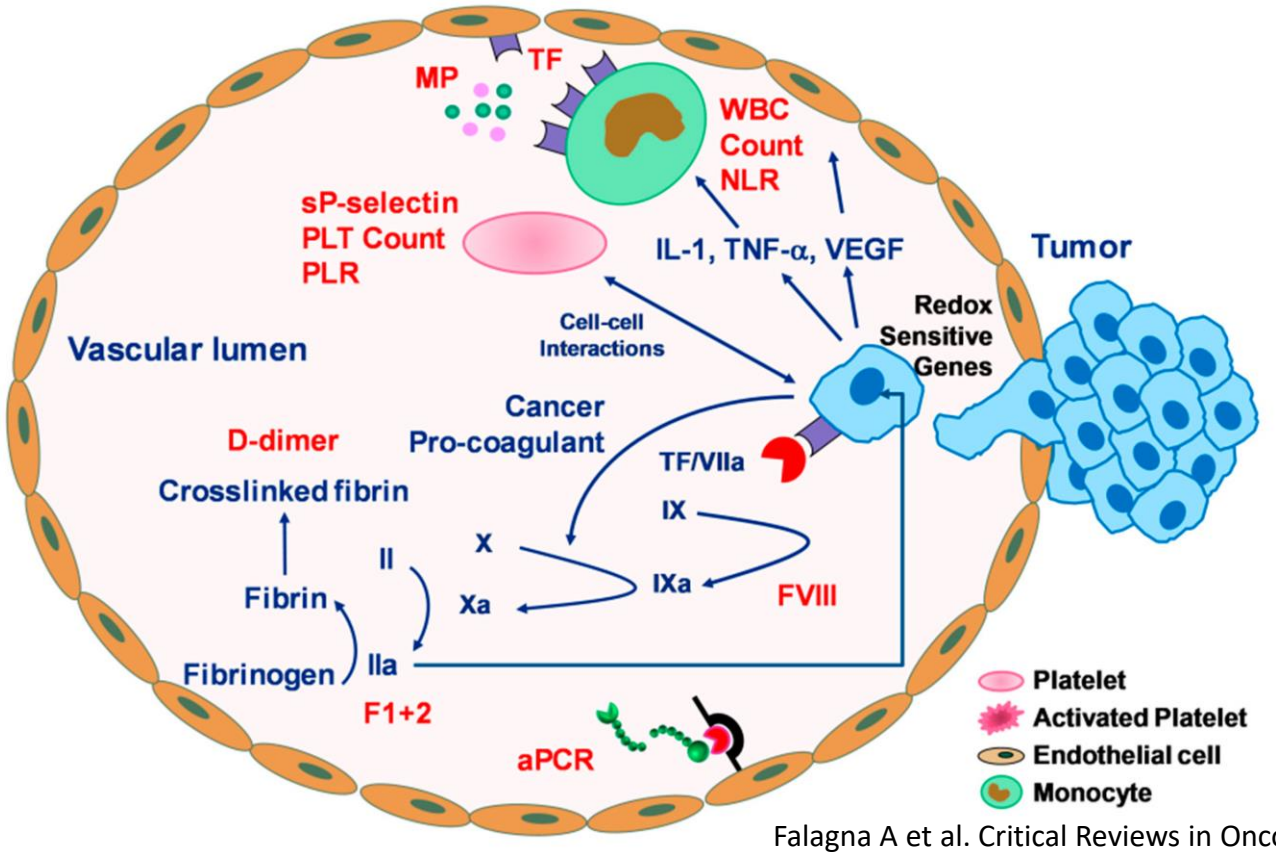
Phase 3, randomized trial evaluating the efficacy and safety of rivaroxaban vs placebo on reducing post-discharge VTE in high-risk, medically ill patients with 30-day follow-up



Key Inclusion Criteria	Key Exclusion Criteria
• Duration of index hospitalization: 3 to 10 consecutive days • Total IMPROVE VTE score ≥4 or score of 2 or 3 with elevated Dd >2 × ULN	• Any serious bleeding ≤ 3 months prior to randomization or index hospitalization • Serious trauma ≤4 weeks before randomization • History of hemorrhagic stroke • Need for parenteral or oral anticoagulation

« Rivaroxaban was not associated with a significantly lower risk of symptomatic venous thromboembolism and death due to venous thromboembolism than placebo. The incidence of major bleeding was low.”

PREVENTION OF VTE IN CANCER PATIENT: AN UNMET CLINICAL NEED



- Patients with cancer are six times more likely to devolop VTE than their noncancer counterparts and account for more than 20% of all newly diagnosed case of VTE
- VTE is the second leading cause of death in cancer patients after cancer itself
- A reciprocal cancer-thrombosis connection exists, by which cancer cell support clot formation and clotting proteins support cancer growth and dissemination

Falagna A et al. Critical Reviews in Oncology/Hematology 118 (2017) 79-83
Donnellan, Khorana. The Oncologist 2017; 22:00-00

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Thromboprophylaxis in hospitalized patients with cancer

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update

Journal of Clinical Oncology®

Nigel S. Key, MB ChB[1]; Alok A. Khorana, MD[2]; Nicole M. Kuderer, MD[3]; Kari Bohlke, ScD[4]; Agnes Y.Y. Lee, MD, MSc[5]; Juan I. Arcelus, MD, PhD[6]; Sandra L. Wong, MD, MS[7]; Edward P. Balaban, DO[8]; Christopher R. Flowers, MD, MS[9]; Charles W. Francis, MD[10]; Leigh E. Gates[11]; Ajay K. Kakkar, MBBS, PhD[12]; Mark N. Levine, MD, MSc[13]; Howard A. Liebman, MD[14]; Margaret A. Tempero, MD[15]; Gary H. Lyman, MD, MPH[16]; and Anna Falanga, MD[17]

Hospitalized patients who have active malignancy and acute medical illness or reduced mobility should be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications *(Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).*

Hospitalized patients who have active malignancy without additional risk factors may be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications *(Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).*

Routine pharmacologic thromboprophylaxis should not be offered to patients admitted for the sole purpose of minor procedures or chemotherapy infusion, nor to patients undergoing stem-cell/bone marrow transplantation *(Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).*

Thromboprophylaxis in hospitalized patients with cancer

2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer *Lancet Oncol 2019*

Dominique Farge, Corinne Frere*, Jean M Connors, Cihan Ay, Alok A Khorana, Andres Munoz, Benjamin Brenner, Ajay Kakkar, Hanadi Rafii, Susan Solymoss, Dialina Brilhante, Manuel Monreal, Henri Bounameaux, Ingrid Pabinger, James Douketis, and the International Initiative on Thrombosis and Cancer (ITAC) advisory panel*

We recommend prophylaxis with LMWH or fondaparinux when creatinine clearance is ≥30 mL/min, or with unfractionated heparin in hospitalised patients with cancer and reduced mobility (grade 1B). In this setting, direct oral anticoagulants are not recommended routinely

ITAC CME
International Initiative on Thrombosis and Cancer

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4° Congresso Nazionale 2019

Thromboprophylaxis in ambulatory patients with cancer who are receiving anticancer therapy

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update

Journal of Clinical Oncology®

Nigel S. Key, MB ChB[1]; Alok A. Khorana, MD[2]; Nicole M. Kuderer, MD[3]; Kari Bohlke, ScD[4]; Agnes Y.Y. Lee, MD, MSc[5]; Juan I. Arcelus, MD, PhD[6]; Sandra L. Wong, MD, MS[7]; Edward P. Balaban, DO[8]; Christopher R. Flowers, MD, MS[9]; Charles W. Francis, MD[10]; Leigh E. Gates[11]; Ajay K. Kakkar, MBBS, PhD[12]; Mark N. Levine, MD, MSc[13]; Howard A. Liebman, MD[14]; Margaret A. Tempero, MD[15]; Gary H. Lyman, MD, MPH[16]; and Anna Falanga, MD[17]

Routine pharmacologic thromboprophylaxis **should not** be offered to all outpatients with cancer (*Type: evidence based; Evidence quality: intermediate to high; Strength of recommendation: strong*)

KHORANA SCORE

Ri

Patient characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Pre-chemotherapy platelet count $\geq 350 \times 10^9$/L	1
Hemoglobin level < 10 g/dL or use of red cell growth factors	1
Pre-chemotherapy leukocyte count $>11.0 \times 10^9$/L	1
Body mass index ≥ 35 kg/m^2	1

Notes: High-risk score ≥ 3; intermediate-risk score $= 1$ or 2; low-risk score $= 0$.

Adapted from Lyman GH, *et al. ASCO Update. J Clin Oncol.* 2013;31:2189-204.

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Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update

Journal of Clinical Oncology®

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Patients with **multiple myeloma** receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients *(Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong)*

High-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) **may be** offered thromboprophylaxis with apixaban, rivaroxaban, or low molecular- weight heparin (LMWH) provided there are no significant risk factors for bleeding and no drug interactions. Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and duration of prophylaxis in this setting (*Type: evidence based; Evidence quality: intermediate to high for apixaban and rivaroxaban, intermediate for LMWH; Strength of recommendation: moderate)*

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The NEW ENGLAND JOURNAL of MEDICINE

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

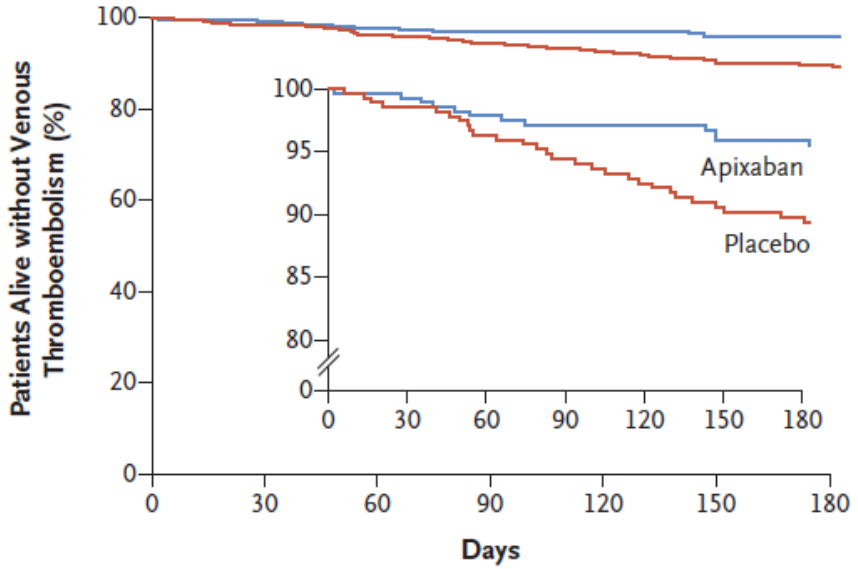
Apixaban to Prevent Venous Thromboembolism in Patients with Cancer

Marc Carrier, M.D., Karim Abou-Nassar, M.D., Ranjeeta Mallick, Ph.D., Vicky Tagalakis, M.D., Sudeep Shivakumar, M.D., Ariah Schattner, M.D., Philip Kuruvilla, M.D., Danny Hill, M.D., Silvana Spadafora, M.D., Katerine Marquis, M.D., Mateya Trinkaus, M.D., Anna Tomiak, M.D., Agnes Y.Y. Lee, M.D., Peter L. Gross, M.D., Alejandro Lazo-Langner, M.D., Robert El-Maraghi, M.D., Glenwood Goss, M.D., Gregoire Le Gal, M.D., David Stewart, M.D., Timothy Ramsay, Ph.D., Marc Rodger, M.D., Debra Witham, B.Sc.N., and Philip S. Wells, M.D., for the AVERT Investigators*

A randomized, placebo-controlled, double blind clinical trial assessing the efficacy and safety of apixaban (2.5 mg twice daily) for thromboprophylaxis in ambulatory patients with cancer who were at intermediate-to-high risk for venous thromboembolism (Khorana score, ≥2) and were initiating chemotherapy

The **primary efficacy outcome** - first episode of objectively documented major venous thromboembolism within the first 180 days - occurred in 12 of 288 patients (4.2%) in the apixaban group and in 28 of 275 patients (10.2%) in the placebo group (hazard ratio, 0.41; 95% confidence interval [CI], 0.26 to 0.65; P<0.001)

Major bleeding occurred in 10 patients (3.5%) in the apixaban group and in 5 patients (1.8%) in the placebo group (hazard ratio, 2.00; 95% CI, 1.01 to 3.95; P = 0.046)



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.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

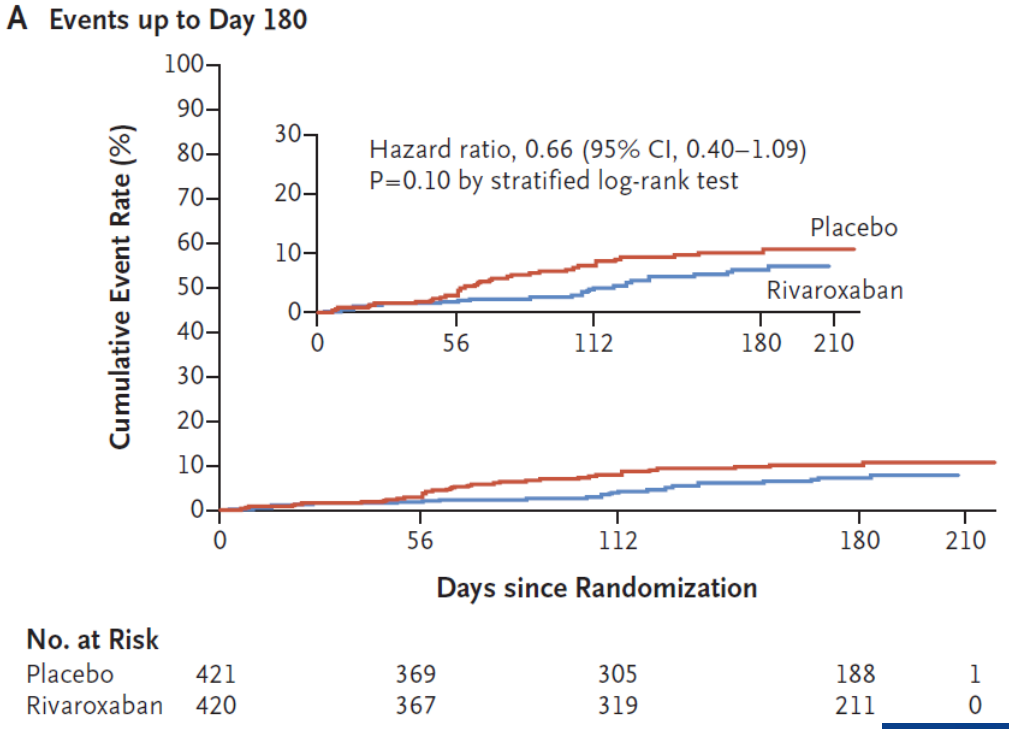
Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer

A.A. Khorana, G.A. Soff, A.K. Kakkar, S. Vadhan-Raj, H. Riess, T. Wun, M.B. Streiff, D.A. Garcia, H.A. Liebman, C.P. Belani, E.M. O'Reilly, J.N. Patel, H.A. Yimer, P. Wildgoose, P. Burton, U. Vijapurkar, S. Kaul, J. Eikelboom, R. McBane, K.A. Bauer, N.M. Kuderer, and G.H. Lyman, for the CASSINI Investigators*

In a double-blind, randomized trial involving high-risk ambulatory patients with cancer (Khorana score of ≥2) we randomly assigned patients without deep-vein thrombosis at screening to receive rivaroxaban (at a dose of 10 mg) or placebo daily for up to 180 days

The **primary efficacy end point** was a composite of objectively confirmed proximal deep-vein thrombosis in a lower limb, pulmonary embolism, symptomatic deep vein thrombosis in an upper limb or distal deep-vein thrombosis in a lower limb, and death from venous thromboembolism. The primary end point occurred in 25 of 420 patients (6.0%) in the rivaroxaban group and in 37 of 421 (8.8%) in the placebo group (hazard ratio, 0.66; 95% confidence interval [CI], 0.40 to 1.09; P = 0.10)

Major bleeding occurred in 8 of 405 patients (2.0%) in the rivaroxaban group and in 4 of 404 (1.0%) in the placebo group (hazard ratio, 1.96; 95% CI, 0.59 to 6.49)



AVERT

- ✓ Routine ultrasonographic testing was not performed
- ✓ The most common types of primary cancer were gynecologic (25.8%), lymphoma (25.3%) and pancreatic (13.6%)
- ✓ The rate of adherence was high in both groups, at 83.6% in the apixaban group and 84.1% in the placebo goup
- ✓ A small proportion of patients affected by brain tumors were included

CASSINI

- ✓ Enrolled patients underwent venous duplex compression ultrasonography of both legs to rule out preexisting proximal deep-vein thrombosis (4.5% excluded)
- ✓ The most common primary cancer was pancreatic cancer (32.6%)
- ✓ Nearly 47% of enrolled patients prematurely discontinued the trial regimen
- ✓ No brain tumor patients included

The NEW ENGLAND JOURNAL of MEDICINE

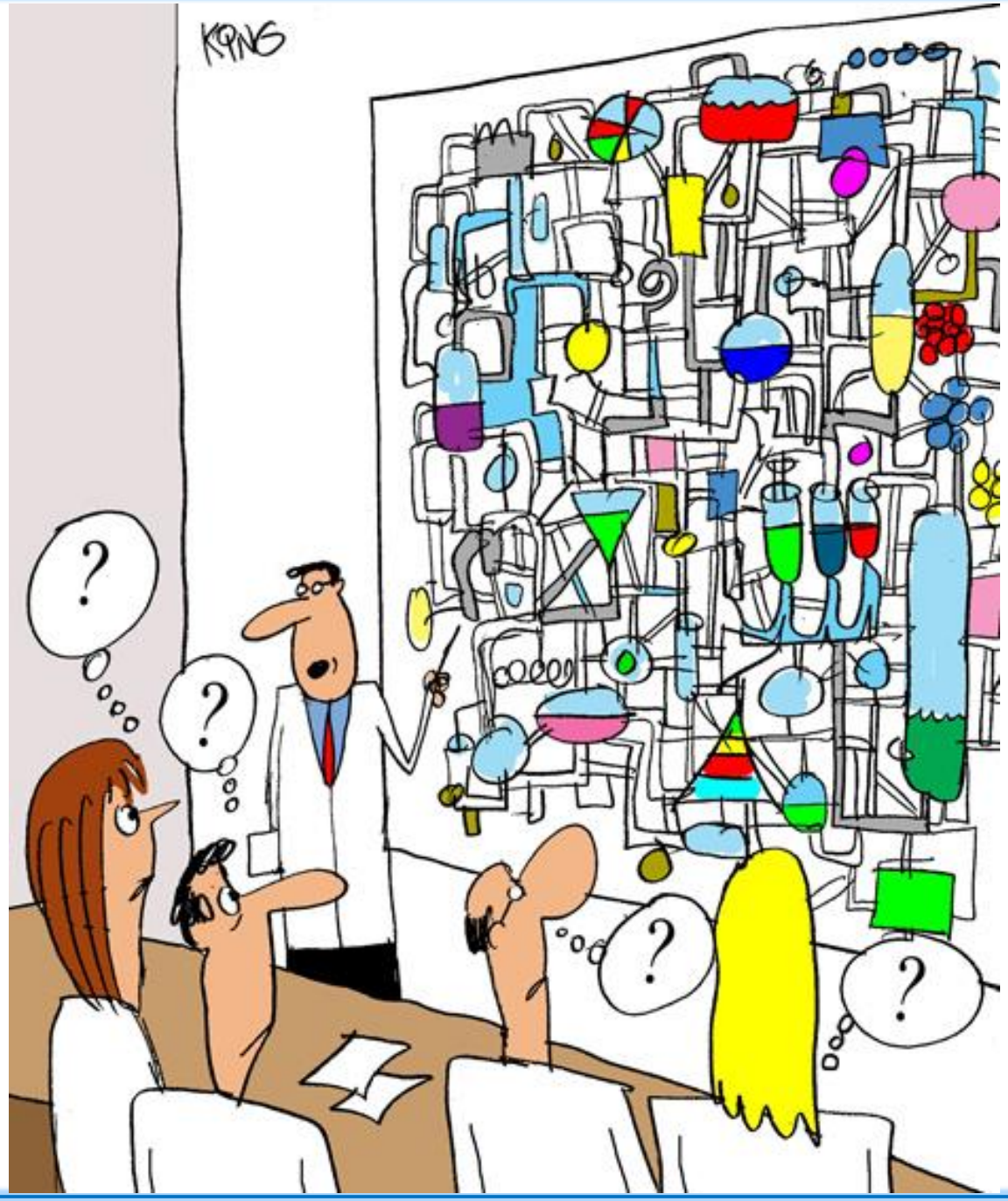
EDITORIALS

Direct Oral Anticoagulants for Thromboprophylaxis in Ambulatory Patients with Cancer

Giancarlo Agnelli, M.D.

Table 1. Cumulative Analysis of the AVERT and CASSINI Trials.*

Outcome	CASSINI Trial		AVERT Trial		Cumulative Values				
	Rivaroxaban	Placebo	Apixaban	Placebo	DOACs	Placebo	Relative Risk (95% CI)	Absolute Difference	No. Needed to Treat or Harm†
	number/total number (percent)							*percentage points*	
Primary efficacy outcome									
ITT analysis	25/420 (6.0)	37/421 (8.8)	12/288 (4.2)	28/275 (10.2)	37/708 (5.2)	65/696 (9.3)	0.56 (0.38–0.83)	–4.1	24
Analysis during treatment period	11/420 (2.6)	27/421 (6.4)	3/288 (1.0)	20/275 (7.3)	14/708 (2.0)	47/696 (6.8)	0.29 (0.16–0.53)	–4.8	21
Symptomatic VTE: ITT analysis	15/420 (3.6)	19/421 (4.5)	9/288 (3.1)	22/275 (8.0)	24/708 (3.4)	41/696 (5.9)	0.58 (0.35–0.94)	–2.5	40
Major bleeding	8/405 (2.0)	4/404 (1.0)	10/288 (3.5)	5/275 (1.8)	18/693 (2.6)	9/679 (1.3)	1.96 (0.88–4.33)	1.3	77
Death from any cause	84/420 (20.0)	100/421 (23.8)	35/288 (12.2)	27/275 (9.8)	119/708 (16.8)	127/696 (18.2)	0.92 (0.73–1.16)	–1.4	71



Any questions ?

AMGE Associazione Multidisciplinare di Geriatria
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