Prophylaxie primaire sur le patient ambulatoire

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Objectifs

- Revoir les scores de risque pour prédire les complications de la thrombo-embolie veineuse (TEV) dans la population oncologique.
- Balancer les risques et bénéfices de la thromboprophylaxie pharmacologique primaire en chimiothérapie ambulatoire.
- Discuter les essais cliniques en cours utilisant les AOD en prophylaxie primaire pour les patients cancéreux.

Incidence

- Annual incidence of VTE in the general population is 117 per 100,000
  - Cancer alone was associated with a 4.1-fold risk of thrombosis
  - Chemotherapy increased the risk 6.5-fold
- Combining these estimates yields an approximate annual incidence of venous thromboembolism (VTE) of 1 per 200 in a population of cancer patients

Heit JA et al. Arch Intern Med. 2000; 160: 809–815.

VTE as a cause of death

- Thromboembolism is the second leading cause of death in cancer patients
- Annual death rate for VTE of 448 per 100,000 patients
  - 47-fold increase over the general population

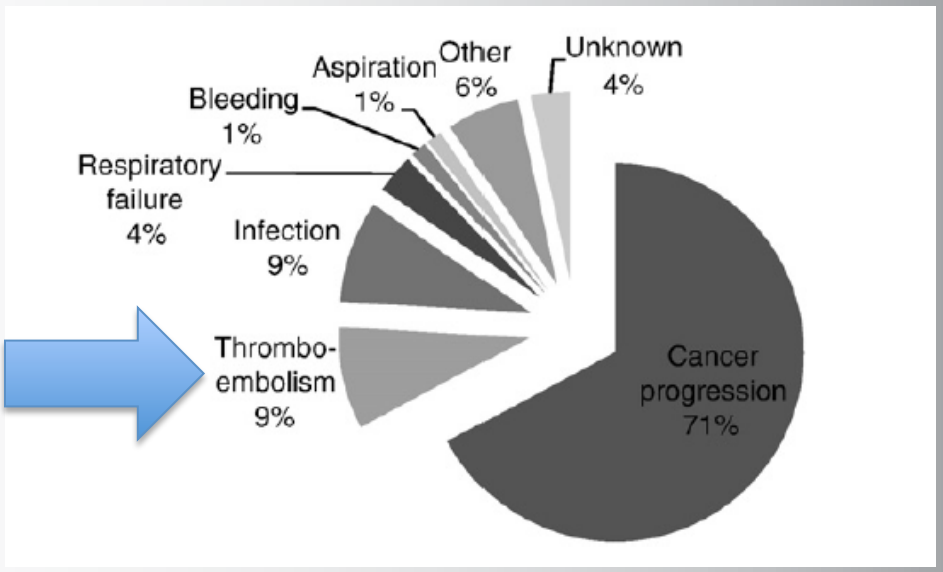


Figure from Khorana AA et al. Thromb Res 2010;e-pub.

Khorana AA et al. J Thromb Haemost 2007;5:632-4.

VTE prophylaxis in cancer patients

- Ambulatory cancer patients receiving chemotherapy

Routine thromboprophylaxis is not recommended for ambulatory patients with cancer. It may be considered for highly select high-risk patients.

Patients with cancer should be periodically assessed for VTE risk.

Oncology professionals should educate patients about the signs and symptoms of VTE.

Lyman GH et al. J Clin Oncol.2015.59.7351

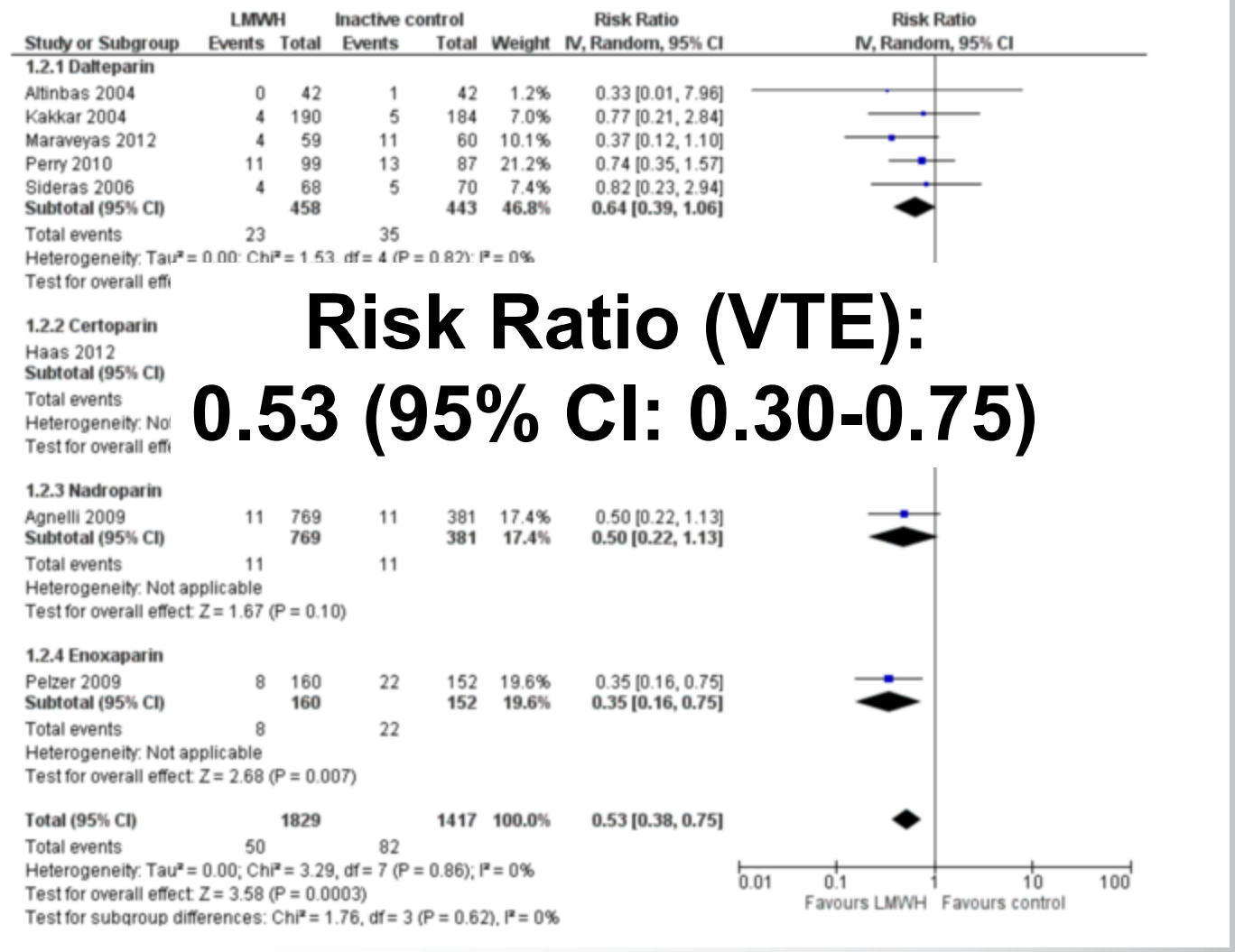
Thromboprophylaxis for ambulatory cancer patients

Table 3
RCTs of thromboprophylaxis with low molecular weight heparin in ambulatory cancer patients

Trial	N	Treatment	Chemo	Duration	VTE	Major Bleeding
PROTECHT Solid Tumors (Stage III/IV) [14]	1166	Nadroparin 2:1 Placebo	100%	≤ 4 months with chemo	1.4% 2.9%	0.7% 0
SAVE-ONCO (Stage IV) [15]	3121	Semuloparin (n= 1608) Placebo (n= 1604)	100%	3.5 months (median)	1.2% 3.4%	1.2% 1.1%
FRAGEM (Locally advanced and metastatic pancreatic cancer) [28]	123	Gemcitabine (n=63) Gemcitabine + weight-adjusted dalteparin (n= 60)	100%	12 weeks (therapeutic dose)	31% 12%	27% 22%
CONKO 004 (advanced pancreatic cancer) [29]	312	Chemo (n=152) Chemo + Enoxaparin (n= 160)	100%	3 months (half a therapeutic dose, then prophylactic dose)	15.1% 6.4%	3.2% 4.3%

Imberti D et al. *Thrombosis Research 140S1 (2016) S103–S108*.

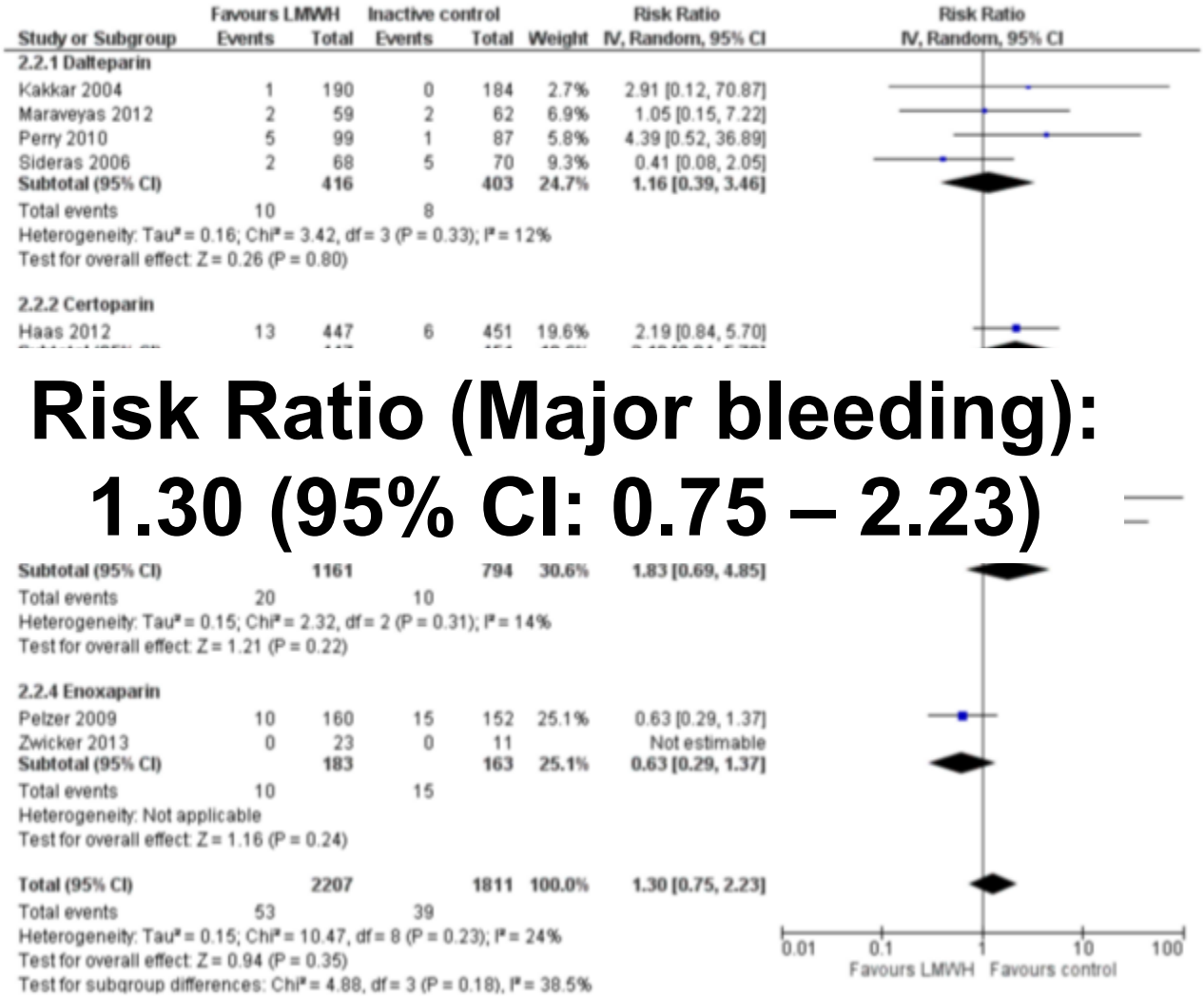
Figure 3. Forest plot of comparison: 1 Anticoagulants versus control: symptomatic VTE, outcome: 1.2 Symptomatic VTE: LMWH versus inactive control.



Risk Ratio (VTE): 0.53 (95% CI: 0.30-0.75)

Di Nisio M et al. Cochrane Database Syst Rev. 2014 Aug 29;8:CD008500.

Figure 5. Forest plot of comparison: 2 Anticoagulants versus control: major bleeding, outcome: 2.2 Major bleeding: LMWH versus inactive control.



Risk Ratio (Major bleeding): 1.30 (95% CI: 0.75 – 2.23)

Di Nisio M et al. Cochrane Database Syst Rev. 2014 Aug 29;8:CD008500.

Favorable risk:benefit ratio but low event rates

Outcomes	Illustrative comparative risk (95% CI)*		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk[1]	Corresponding risk				
	Placebo or no anticoagulant	LMWH				
Symptomatic VTE	52 per 1000	28 per 1000 (20 to 39)	RR 0.53 [0.38, 0.75]	3246 (8)	⊕⊕⊕ moderate[2]	
Major bleeding	14 per 1000	18 per 1000 (11 to 31)	RR 1.30 [0.75, 2.23]	3984 (9)	⊕⊕ low[3]	
Symptomatic PE	12 per 1000	7 per 1000 (3 to 16)	RR 0.59 [0.26, 1.36]	2712 (5)	⊕⊕ low[4]	
1-year mortality	586 per 1000	557 per 1000 (492 to 639)	RR 0.95 [0.84, 1.09]	2268 (7)	⊕⊕⊕⊕ high	

Di Nisio M et al. Cochrane Database Syst Rev. 2014 Aug 29;8:CD008500.

ASCO Guidelines

Routine thromboprophylaxis is not recommended for ambulatory patients with cancer. It may be considered for highly select high-risk patients.

Patients with cancer should be periodically assessed for VTE risk.

Oncology professionals should educate patients about the signs and symptoms of VTE.

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Assessment for VTE risk

Individual risk factors

Patient-related factors

- Advanced age
- Female gender
- Prior VTE
- Patient co-morbidities
- Infection, obesity, anemia, pulmonary or renal disease
- Prolonged immobilization
- Inherited thrombophilic factors

Cancer-related factors

- Site: brain, pancreas, kidney, stomach, lung, bladder, gynecologic, hematologic malignancies
- Stage: advanced stage and initial period after diagnosis
- Hospitalization
- Surgery
- Chemo- and hormonal therapy
- Anti-angiogenic therapy
- Erythropoiesis stimulating agents
- Blood transfusions

Imberti D et al. *Thrombosis Research 140S1 (2016) S103–S108*.

Risk assessment: Biomarkers

Table 1. Select biomarkers predictive of cancer-associated thrombosis

Platelet count (≥ 350 000/mm^3)
Leukocyte count (> 11 000/mm^3)
Hemoglobin (< 10 g/dL)
D-dimer
TF (antigen expression, circulating microparticles, antigen, or activity)*
Soluble P-selectin (> 53.1 ng/mL)*
Factor VIII*
Prothrombin fragment F 1 + 2 (> 358 pmol/L)*

*Investigational or not widely available.

Khorana AA et al. Hematology Am Soc Hematol Educ Program. 2012;2012:626-30.

Risk assessment: Biomarkers

Table 1. Prospective studies investigating potential predictive biomarkers of VTE in cancer patients

First author (ref.)	Variable	Cancer entity	Total number of patients	Cutoff	HR/OR for VTE during follow-up	95% CI
Thaler† (64)	Microparticle-associated tissue factor activity	Pancreas	60	None (per doubling)	1.5 (HR)	1.0-2.4
		Brain	119		1.0 (HR)	0.8-1.2
		Stomach	43		0.7 (HR)	0.4-1.2
		Colorectal	126		0.9 (HR)	0.6-1.6
Zwicker (62)	Tissue factor bearing microparticles	Various	60	>1 × 10^4/μL	3.7 (OR)	1.2-11.8
Tiedje† (71)	Fibrinogen	Various	1079	None (continuous)	1.1 (HR)	0.8-1.3
Vormittag† (80)	Factor VIII activity	Various	840	>232%‖	2.8 (HR)	1.7-4.6
Kanz† (84)	C-reactive protein	Various	705	None (per doubling)	1.0 (HR)	0.9-1.2
Mandalà (24)	Homocysteine	Various	381	None (continuous)	0.9 (OR)	0.9-1.0
	Leukocyte count				0.9 (OR)	0.7-1.1
	Hemoglobin				1.1 (OR)	0.8-1.5
	Platelet count				1.6 (OR)	1.0-2.5
	Protein S			equivalent‖	1.0 (OR)	1.0-1.0

Pabinger I et al. Blood. 2013;122:12:2011-2018

ASCO Guidelines

- Individual risk factors, including biomarkers and cancer site, do not reliably identify patients with cancer at high risk of VTE. In the outpatient setting, risk assessment can be conducted based on a validated risk assessment tool

Lyman G et al. J Clin Oncol. 2013;31:2189-204

VTE risk score for cancer patients

Table 2. Predictive model for chemotherapy-associated VTE[16]

Patient characteristics	Risk score
Site of cancer	
Very high risk: stomach, pancreas	2
High risk: lung, lymphoma, gynecologic, bladder, testicular	1
Prechemotherapy platelet count 350 000/mm^3 or more	1
Prechemotherapy hemoglobin level $<$ 10 g/dL and/or planned use of erythropoiesis-stimulating agents	1
Prechemotherapy leukocyte count $>$ 11 000/mm^3	1
Body mass index 35 kg/m^2 or more	1

High-risk score, $\geq$ 3; intermediate-risk score, 1-2; low-risk score, 0.

Khorana AA et al. Blood 2008;111:4902-7

Validation of Khorana risk score

- Validated in >18 000 patients
- in multiple countries

Table 3. Rates of VTE in select studies validating a risk score for chemotherapy-associated VTE

Study	Type/follow-up	N	Low-risk	Intermediate-risk	High-risk
Ay et al, 2010[27]	Prospective/643 d	819	1.5%	9.6% (score = 2) 3.8% (score = 1)	17.7%
Khorana et al, 2010[12]	Prospective/3 mo	30	†		27%
Moore et al, 2011[1]	Retrospective, cisplatin-based chemotherapy only	932	13%	17.1%	28.2%
Mandala et al, 2011[3]	Retrospective, phase 1 patients only/2 mo	1415	1.5%	4.8%	12.9%
George et al, 2011[28]	Subgroup analysis of SAVE-ONCO,[34]/3.5 mo (placebo arm)	1604	1.3%	3.5%	5.4%
Verso et al, 2012[29]	Subgroup analysis of PROTECHT (placebo arm)	381	3% (scores 0-2)		11.1%

Khorana AA and Francis CW. Thromb Res 2018 Apr;164 Suppl 1:S70-S76.

Vienna risk score

Table 2. Two different risk models for identification of cancer patients at high risk of VTE

Khorana VTE risk assessment score[5]			Points
Site of cancer	Very high risk	Stomach, pancreas	2
	High risk	Lung, lymphoma, gynecologic, bladder, testicular	1
Platelet count		≥350 × 10^9/L	1
Hemoglobin and/or use of erythropoiesis-stimulating agents		<10 g/dL	1
Leukocyte count		>11 × 10^9/L	1
Body mass index		≥35 kg/m^2	1
Vienna VTE risk assessment score,[19] addition of			
D-dimer		≥1.44 μg/mL	1
sP-selectin		≥53.1 mg/mL	1

In the CATS, brain tumors (high-grade glioma) were allocated to the very high risk sites of cancer.

Pabinger I et al. Blood. 2013;122:12:2011-2018

Validation of Khorana risk score

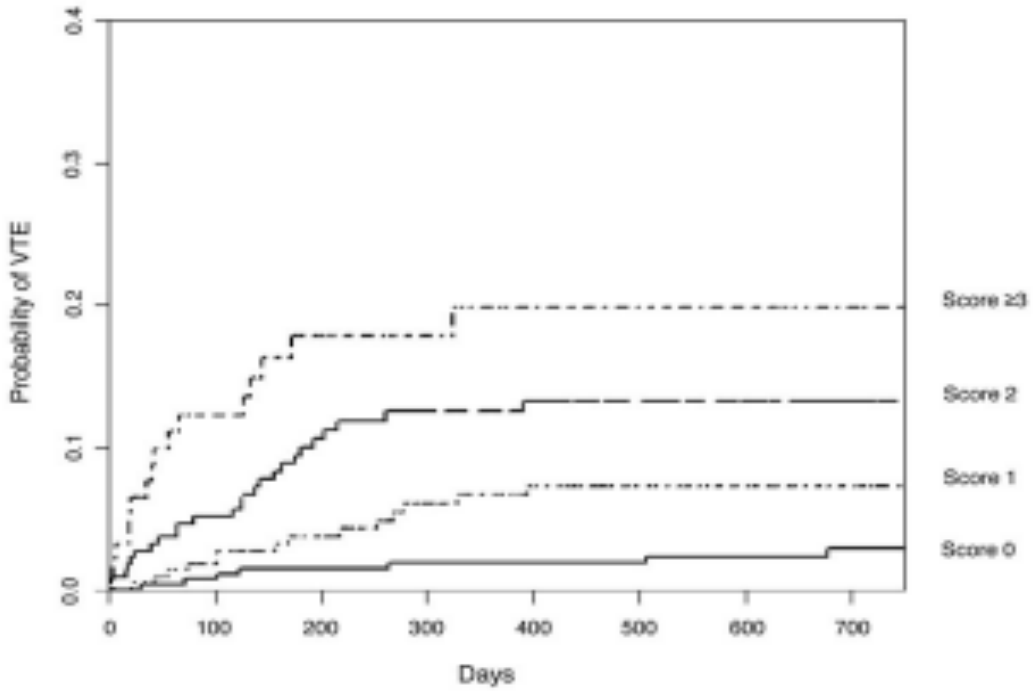


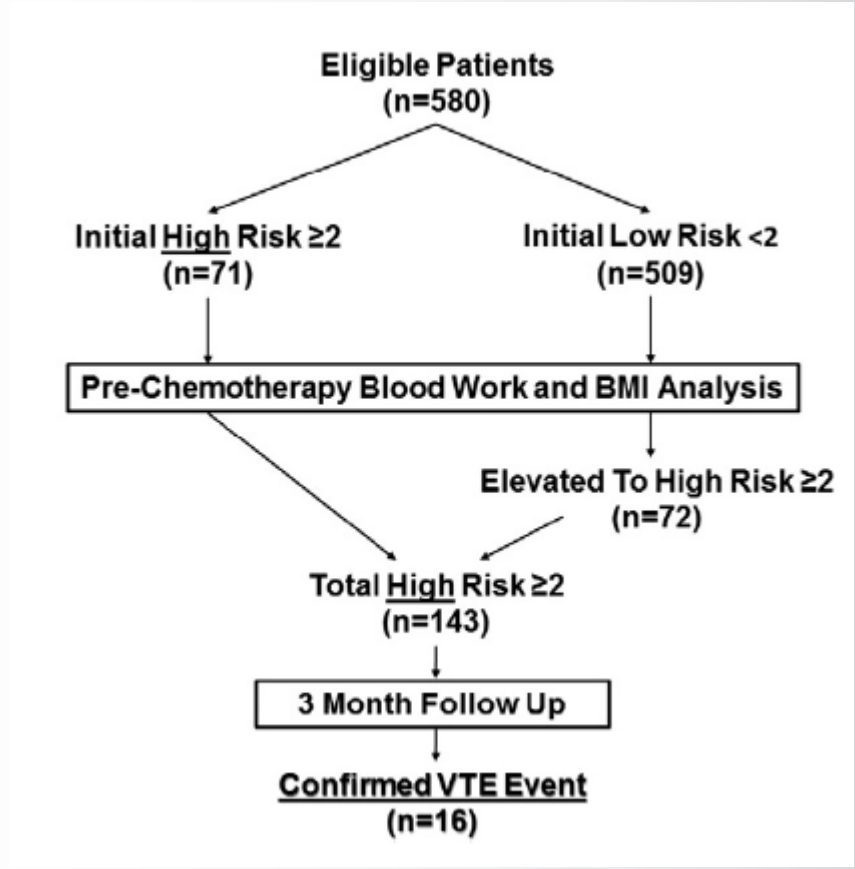
Figure 1. Kaplan-Meier estimates of the risk of VTE in patients with risk scores 0, 1, 2, and ≥ 3 according to the risk scoring model developed by Khorana et al.[16] The cumulative probability of VTE showed statistically significant association with the risk scores (log-rank test, $P < .001$).

Adding glioma and MM

Ay C et al. Blood. 2010;116(24):5377-5382.

Can the Khorana risk score be useful for my practice?

- Prospective observational cohort of 580 patients



Lustig DB et al. Thromb Res. 2015 Dec; 136(6): 1099-102.

Can the Khorana risk score be useful in my practice?

- Khorana risk score (n=143 (25%)) ≥ 2
  - VTE: 16/143 (11%)

- Khorana risk score < 2
  - VTE: 19/437 (4%)

Lustig DB et al. Thromb Res. 2015 Dec; 136(6): 1099-102.

Can risk stratification in combination with thromboprophylaxis decrease the risk of VTE in cancer patients?

PHACS trial

- RCT of cancer patient starting systemic therapy and Khorana risk score ≥ 3
  - Dalteparin 5000 IU SC daily X 12 weeks
  - Observation
- Primary endpoint: All VTE (including screening doppler US at CT at baseline and 12 weeks)

- Terminated early due to poor accrual

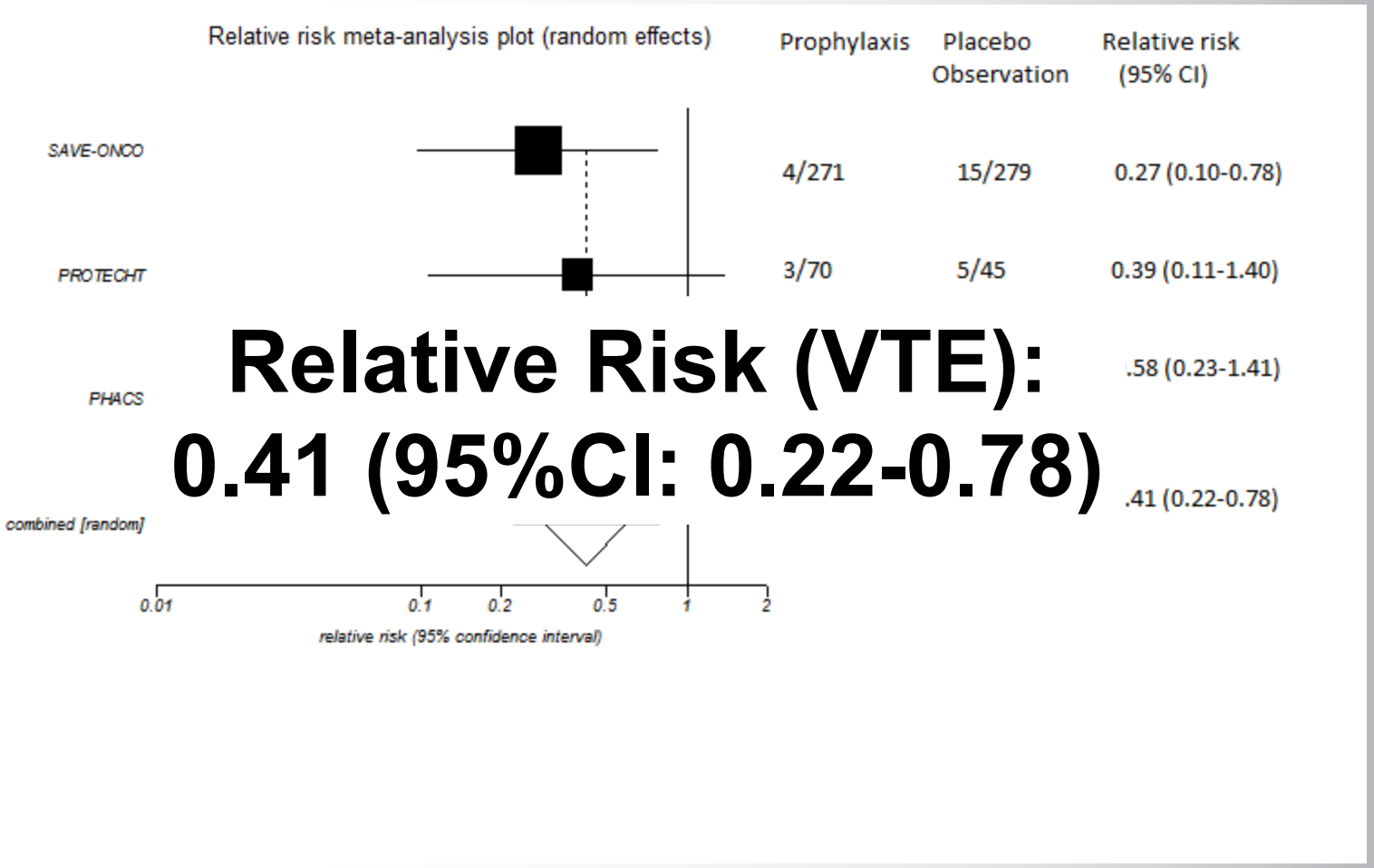
Khorana A et al. Thromb Res. 2017 Mar;151:89-95.

PHACS trial

- 117 patients enrolled
  - 10 (8.5%) had VTE at baseline
- 98 randomized
  - Dalteparin: 6/50 (12%) VTE
  - Observation: 10/41 (21%) VTE
    - HR: 0.69; 95% CI: 0.23-1.89
- Major bleeding: 1 event in both arms
- Clinical relevant non-major bleeding
  - 7 vs 1 (HR: 7.0; 95% CI: 1.2-131.6)

Khorana A et al. Thromb Res. 2017 Mar;151:89-95.

Efficacy of LMWH in high risk patients



Relative Risk (VTE): 0.41 (95%CI: 0.22-0.78)

Khorana A et al. Thromb Res. 2017 Mar;151:89-95.

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Lyman GH et al. J Clin Oncol.2014.59.7351

Other clinical practice guidelines

- NCCN

  Utilizing Khorana predictive risk model: patients with high risk (>3) COULD BE considered for prophylaxis on an individual basis evaluating risk/benefit ratio

- ESMO 2011

  Consider prophylaxis in high risk ambulatory cancer patient (not defined)

The need for additional RCT's

- A universal approach of thromboprophylaxis is not practical and cost effective
- Instead, customized approach of anticoagulation could limit the risk of bleeding in low risk pts.

PROVE trial

- Tinzaparin 4500 IU SC daily vs. observation
- Stage IV lung cancer and elevated D-dimer (> 1,500 IU)
- Primary outcome: Symptomatic and incidental VTE
- Sample size: 800 patients
- Funding: Assistance Publique – Hôpitaux de Paris
- Clinical trial number: NCT03090880

Direct oral anticoagulants

- DOACs (dabigatran, rivaroxaban and apixaban) have numerous indications

Pharmocodynamic Properties of New Oral Anticoagulants

	Apixaban	Dabigatran	Rivaroxaban
Direct factor inhibition	Xa	IIa	Xa
Peak action (t_{max})	1-3 hr	1-3 hr	1-3 hr
Protein binding	84%	35%	92-95%
Renal clearance	25%	80%	33%

DOAC data for VTE prevention in cancer patients

- Phase II trial with apixaban for the prevention of thromboembolism in patients with metastatic cancer

- VTE rate: (0% in each treatment group)

Table 2 Study outcomes

Outcome	Apixaban 5 mg (n = 32)		Apixaban 10 mg (n = 29)		Apixaban 20 mg (n = 32)		Placebo (n = 29)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Major bleeding	0	0.0–11	0	0.0–12	2 (6.3)	0.8–21	1 (3.4)	0.1–18
CRNM bleeding	1 (3.1)	0.1–16	1 (3.4)	0.1–18	2 (6.3)	0.8–21	0	0.0–12
Major and CRNM bleeding	1 (3.1)	0.1–16	1 (3.4)	0.1–18	4 (12.5)	3.5–29	1 (3.4)	0.1–18
DVT ± PE	0	0.0–11	0	0.0–12	0	0.0–11	3 (10.3)	2.2–27
Grade ≥ 3 AEs*	2 (6.3)	0.8–21	0	0.0–12	1 (3.1)†	0.1–16	0	0.0–12
All	3 (9.4)	2.0–25	1 (3.4)	0.1–18	4 (12.5)	3.5–29	4 (13.8)	3.9–32

AE, adverse event; CI, confid[illegible] relevant non-major; DVT, deep vein thrombosis; PE, pulmonary embolism.
*Considered to be related to study drug. †Adjudicated as a major bleed.

Levine M et al. J Thromb Haemost 2012 May;10(5):807-14.

AVERT trial

- Apixaban 2.5 mg PO BID vs. placebo
- Khorana risk score ≥ 2
- FU: 6 months
- Primary outcome: Symptomatic VTE
- Sample size: 574 patients
- Funding: CIHR, BMS
- Clinical trial number: NCT02048865

Rivaroxaban trial

- Rivaroxaban 10 mg PO daily vs. placebo
- Khorana risk score ≥ 2
  - FU: 6 months
- Primary outcome: Symptomatic and asymptomatic VTE
- Sample size: 700
- Funding: Janssen
- Clinical trial number: NCT02555878

CAT-IQ trial

- Phase 2-3 trial
- Isoquercetin vs. placebo:
  - Cohort A: 500 mg, Once daily, 28 days or
  - Cohort B: 1000 mg, Once daily, 28 days
- Pancreas, colo-rectal, NSCLC
- Sample size: 618
- Funding: NHLBI, Quercegen Pharmaceuticals
- Clinical trial number: NCT02195232

Conclusions

- The incidence of VTE is high among cancer patients
- Routine thromboprophylaxis is not recommended for ambulatory patients with cancer.
- Clinicians should periodically assess the risk for VTE in their cancer patients and review signs and symptoms of DVT and PE.
- Future studies might be helpful!!

Thank you

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