LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
CAMPUS GROSSHADERN
CAMPUS INNENSTADT
NAME DER EINRICHTUNG

Thromboseprophylaxe in der Hämatologie und Onkologie

Wer profitiert?

Und wer nicht?

Helmut Ostermann





Offenlegung Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition keine

2. Beratungs- bzw. Gutachtertätigkeit – Astra Zeneca, Basilea, Gilead, Leo, MSD, Pfizer, TEVA

3. Besitz von Geschäftsanteilen, Aktien oder Fonds keine

4. Patent, Urheberrecht, Verkaufslizenz keine

1.5. Honorare – Astra Zeneca, Basilea, CSL, Janssen, Leo, MSD, Roche, TEVA

6. Finanzierung wissenschaftlicher Untersuchungen Cerus, Gilead, MSD

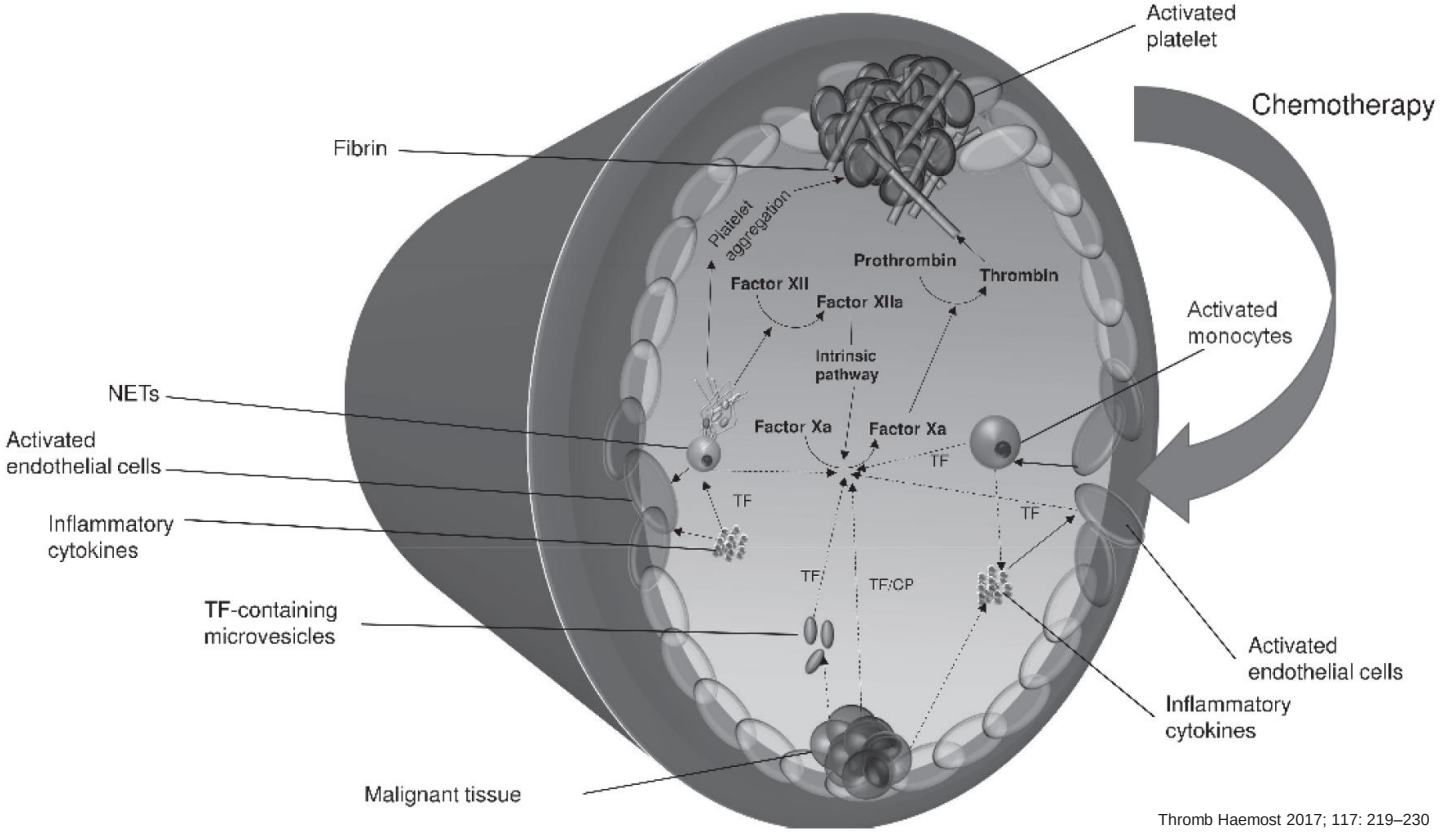
7. Andere finanzielle Beziehungen keine

8. Immaterielle Interessenkonflikte keine

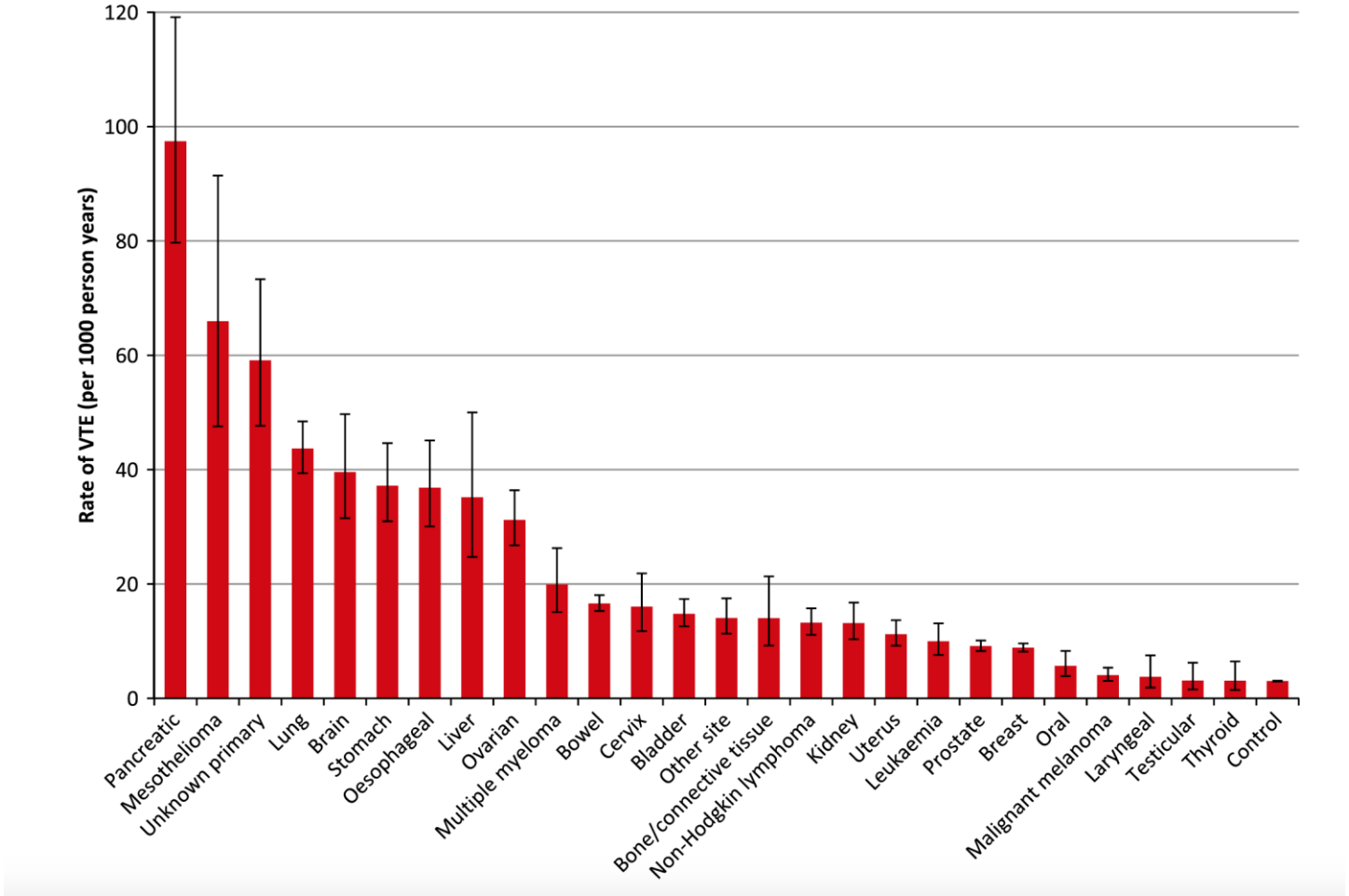
Agenda

- Epidemiologie
- Risikofaktoren
- Risikoscores
- Datenlage
  - Prophylaxe ambulant
  - Prophylaxe stationär
  - Prophylaxe perioperativ
- Guidelines

Risikofaktoren für die Tumorassoziierte Thrombose



Thromb Haemost 2017; 117: 219–230



Walker et al European Journal of Cancer (2013) 49, 1404– 1413

Tumorstadium und Thromboserisiko

Cancer	Incidence rate of VTE in year after diagnosis of cancer (events/100 patients)		
	Local stage	Regional stage	Remote stage
Pancreas	4.3	5.3	19.7
Stomach	2.7	3.9	12.9
Kidney	1.2	3.9	8.0
Bladder	0.7	2.7	7.6
Uterus	0.9	1.6	6.2
Lung	1.1	2.3	5.2
Colon/rectum	0.9	2.3	4.6
Melanoma	0.2	1.0	4.6
Ovary	0.6	2.1	3.8
Lymphoma	2.0	3.5	2.9
Breast	0.6	1.0	2.8

Wun & White, Cancer Investigation, 2009, 27:su

Risiko Scores

- Khorana
- Vienna – Biomarker
- Protecht – Chemotherapie
- CONKO – Performance Status

Development and validation of a predictive model for chemotherapy-associated thrombosis

Alok A. Khorana,[1] Nicole M. Kuderer,[2] Eva Culakova,[2] Gary H. Lyman,[2] and Charles W. Francis[1]

Blood. 2008;111:4902-4907

Table 3. Predictive model for chemotherapy-associated VTE

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 $\times$ 10^9/L or more	1
Hemoglobin level less than 100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count more than 11 $\times$ 10^9/L	1
BMI 35 kg/m^2 or more	1

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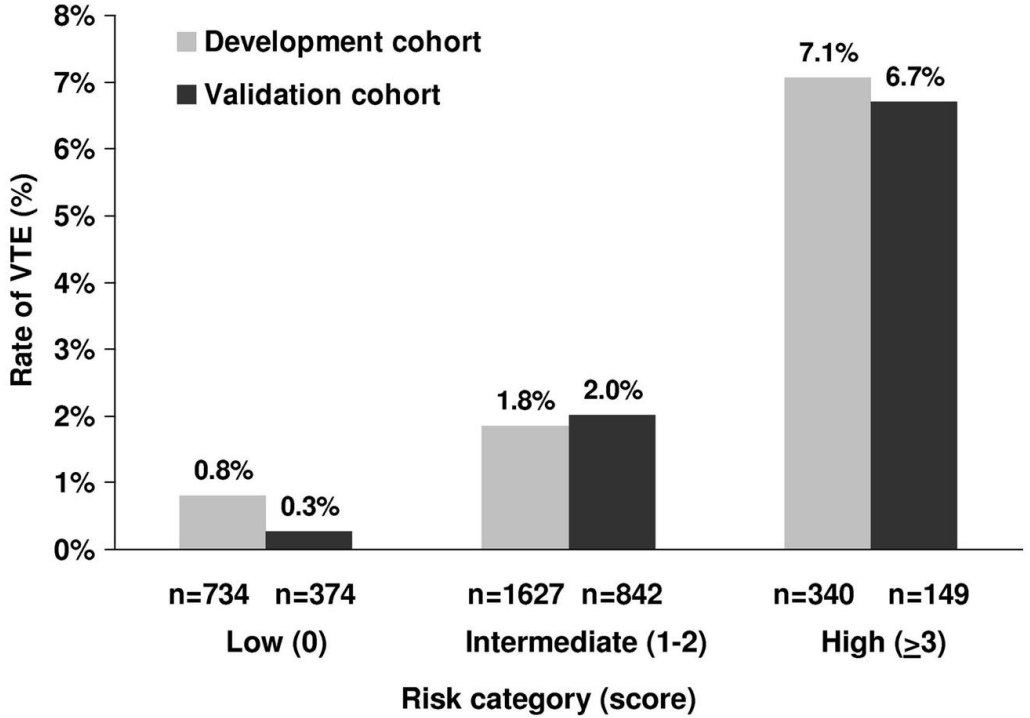


Protecht Score
Verso et al, Intern Emerg Med 2012; 7:291

- Khorana Score
- Jeweils 1 Punkt für
  - Cisplatin, Carboplatin, Gemcitabin
- 2 Punkte für Kombination
- Hochrisiko > 2 Punkte

Protecht Score
Verso et al, Intern Emerg Med 2012; 7:291

Table 1 Efficacy of nadroparin by VTE risk according to Khorana and Protecht scores

	VTE			
	Nadroparin *n/N* (%)	Placebo *n/N* (%)	RR (95 % CI)	NNT
All patients	15/769 (2.0)	15/381 (3.9)	0.49 (0.24–1.00)	50
Khorana score				
VTE risk score 0–2	12/699 (1.7)	10/336 (3.0)	0.57 (0.25–1.32)	77
VTE risk score $\geq$3	3/70 (4.3)	5/45 (11.1)	0.38 (0.09–1.53)	15
Protecht score				
VTE risk score 0–2	10/540 (1.9)	5/254 (2.0)	0.94 (0.32–2.72)	–
VTE risk score $\geq$3	5/225 (2.2)	10/124 (8.1)	0.27 (0.09–0.78)	17

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]

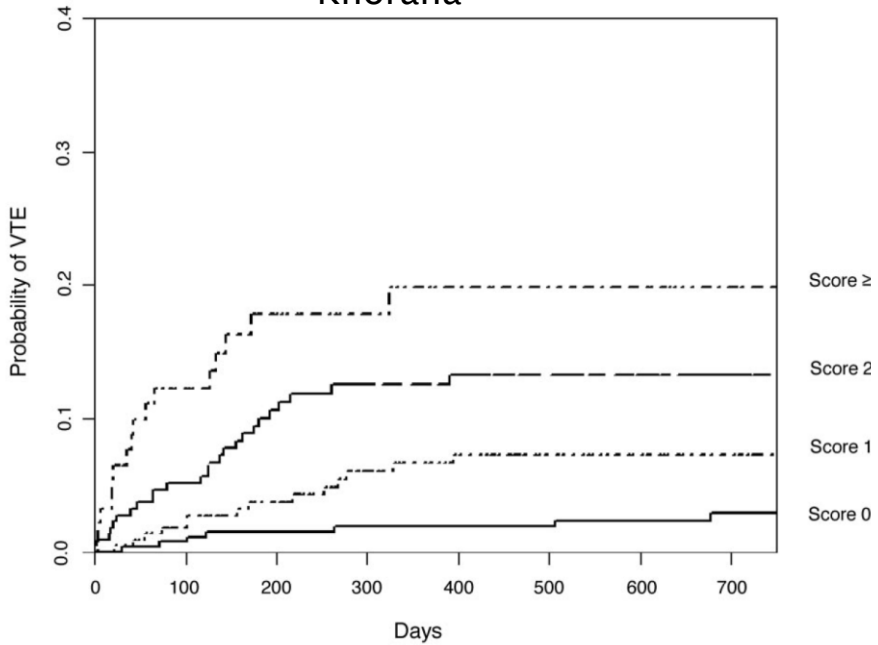
- Khorana Score und
- Lösliches P-Selectin
- D-Dimer
- 819 Patienten, 61 venöse Thromboembolien

Blood. 2010;116(24):5377-5382

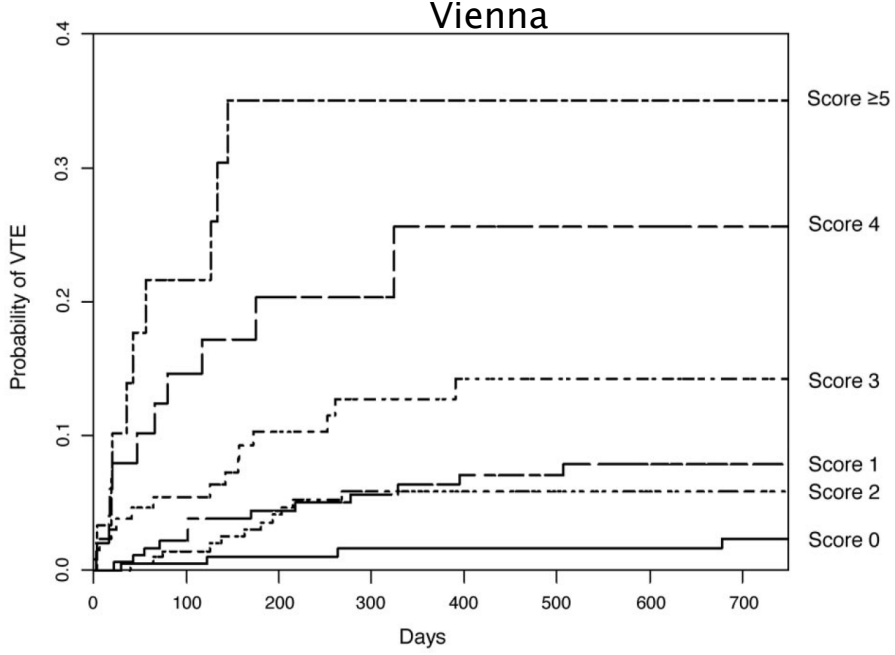
Prediction of venous thromboembolism in cancer patients

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]

Khorana



Vienna



Blood. 2010;116(24):5377-5382

EUROPEAN HEMATOLOGY ASSOCIATION

haematologica

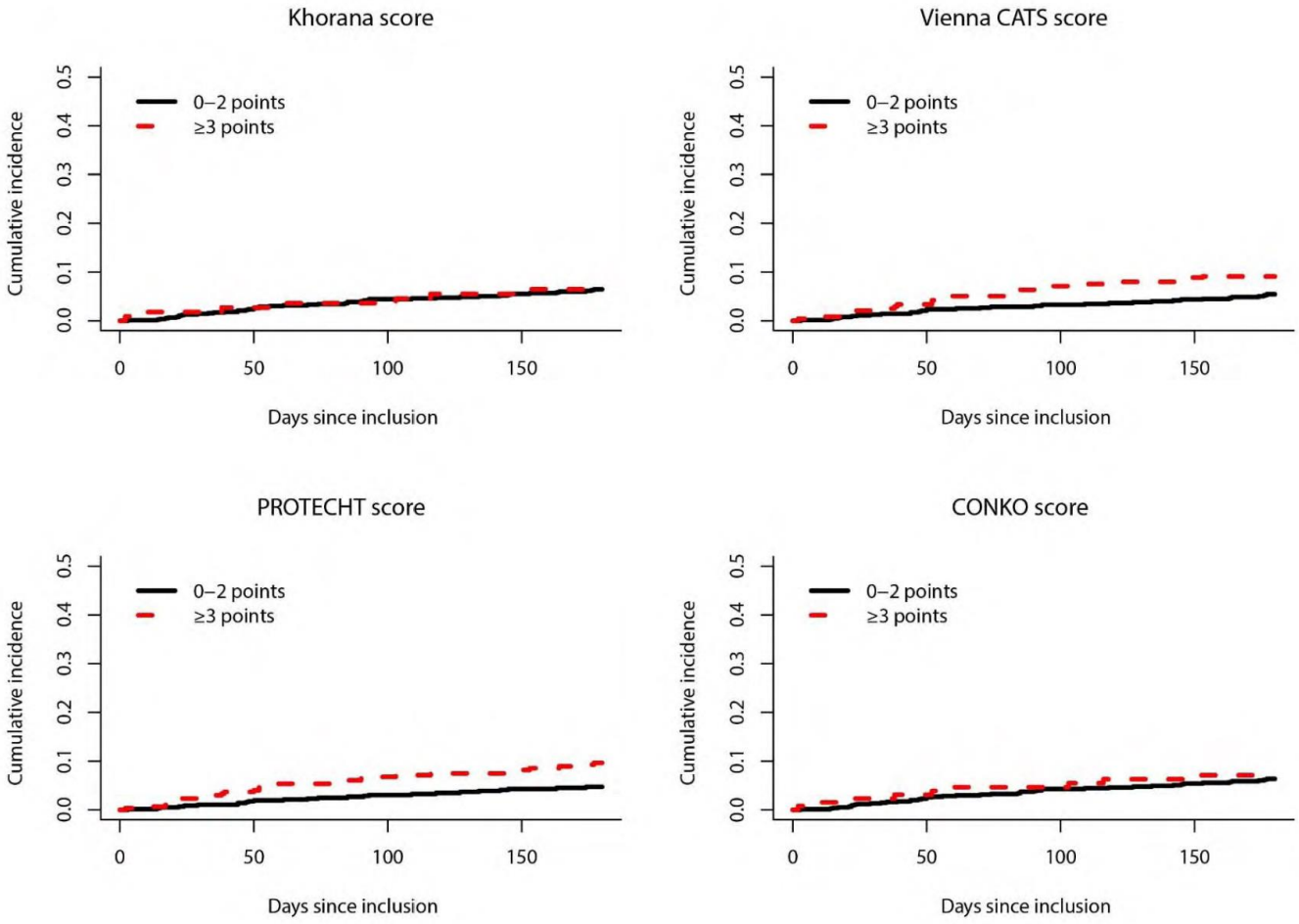
Journal of the European Hematology Association

Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study

by Nick van Es, Marcello Di Nisio, Gabriela Cesarman, Ankie Kleinjan, Hans-Martin Otten, Isabelle Mahé, Ineke T. Wilts, Desirée C. Twint, Ettore Porreca, Oscar Arrieta, Alain Stépanian, Kirsten Smit, Michele De Tursi, Suzanne M. Bleker, Patrick M. Bossuyt, Rienk Nieuwland, Pieter W. Kamphuisen, and Harry R. Büller

Haematologica 2017 [Epub ahead of print]

Appendix 4. Cumulative VTE incidence in high vs low risk patients for the four scores in all patients (N=876)



	Khorana score	Vienna CATS score	PROTECHT score	CONKO score
Patients enrolled prior to chemotherapy (n=260)				
Time-dependent c-index at 180 days (95% CI)	0.50 (0.42-0.57)	0.57 (0.48-0.66)	0.54 (0.45-0.63)	0.50 (0.44-0.57)
High-risk patients (≥3 points), % (95% CI)	13 (9.5-18)	31 (26-37)	34 (28-40)	15 (11-20)
6-month VTE risk in low-risk patients (≤2 points), % (95% CI)	8.4 (5.1-13)	7.9 (4.4-13)	7.4 (4.0-12)	8.6 (5.3-13)
6-month VTE risk in high-risk patients (≥3 points), % (95% CI)	6.0 (1.0-18)	8.4 (3.5-16)	9.5 (4.4-17)	5.2 (0.9-16)
Subhazard ratio for high- (≥3 points) *vs.* low-risk patients (≤2 points)	0.69 (0.17-2.9)	1.1 (0.41-2.7)	1.3 (0.53-3.15)	0.58 (0.14-2.4)

Haematologica 2017; 102(9):1494-1501

Empfehlungen zur Prophylaxe

CHEST Supplement

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

Prevention of VTE in Nonsurgical Patients

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Susan R. Kahn, MD; Wendy Lim, MD; Andrew S. Dunn, MD; Mary Cushman, MD; Francesco Dentali, MD; Elie A. Akl, MD, MPH, PhD; Deborah J. Cook, MD, MSc(Epi); Alex A. Balekian, MD, MSHS; Russell C. Klein, MD; Hoang Le, MD, FCCP; Sam Schulman, MD; and M. Hassan Murad, MD, MPH

4.2.1. In outpatients with cancer who have no additional risk factors for VTE, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) **and recommend against the prophylactic use of vitamin K antagonists** (Grade 1B)**.**

Remarks: Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

4.2.2. In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic-dose LMWH or LDUH over no prophylaxis (Grade 2B)**.**

Remarks: Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

4.4. In outpatients with cancer and indwelling central venous catheters, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) **and suggest against the prophylactic use of vitamin K antagonists** (Grade 2C)**.**

Studien

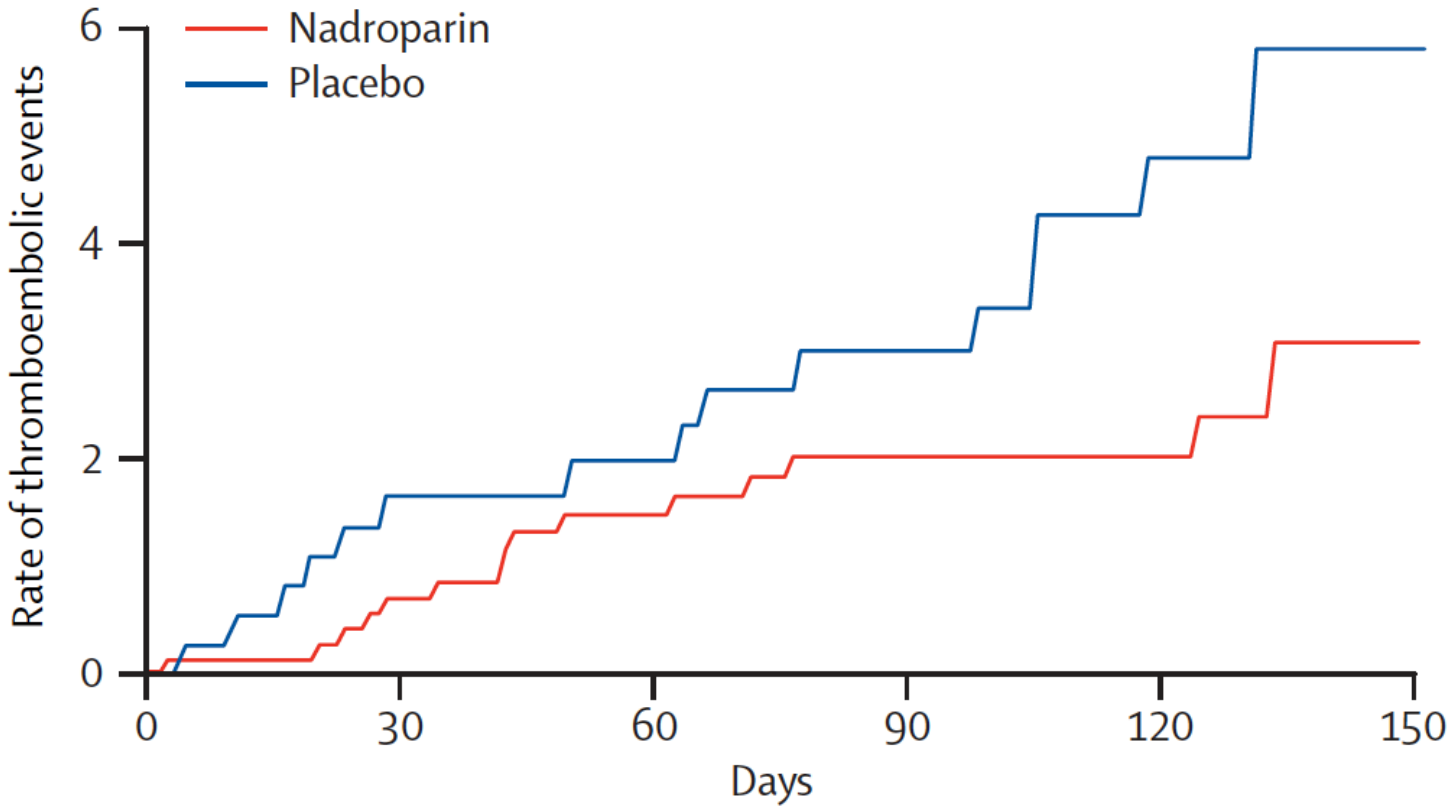
- 2009 PROTECHT
- 2012 SAVE-ONCO
- 2012 FRAGEM
- 2015 CONCO-004

Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study

*Giancarlo Agnelli, Gualberto Gussoni, Carlo Bianchini, Melina Verso, Mario Mandalà, Luigi Cavanna, Sandro Barni, Roberto Labianca, Franco Buzzi, Giovanni Scambia, Rodolfo Passalacqua, Sergio Ricci, Giampietro Gasparini, Vito Lorusso, Erminio Bonizzoni, Maurizio Tonato, on behalf of the PROTECHT Investigators**

- Chemotherapie bei lokal fortgeschrittenem oder metastasiertem
  - Lungenkarzinom
  - GI-Tumor
  - Mammakarzinom
  - Ovarialkarzinom
  - Kopf-Halstumor
- Nadroparin 3800 IU vs Plazebo 2:1
- Beginn mit Chemotherapie bis Ende oder maximal 120 Tage

Lancet Oncol 2009; 10: 943–49



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	Nadroparin	Plazebo
Major bleeding	6 (0.8%)	0
Minor bleeding	57 (7.4%)	30 (7.9%)

Lancet Oncol 2009; 10: 943–49

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

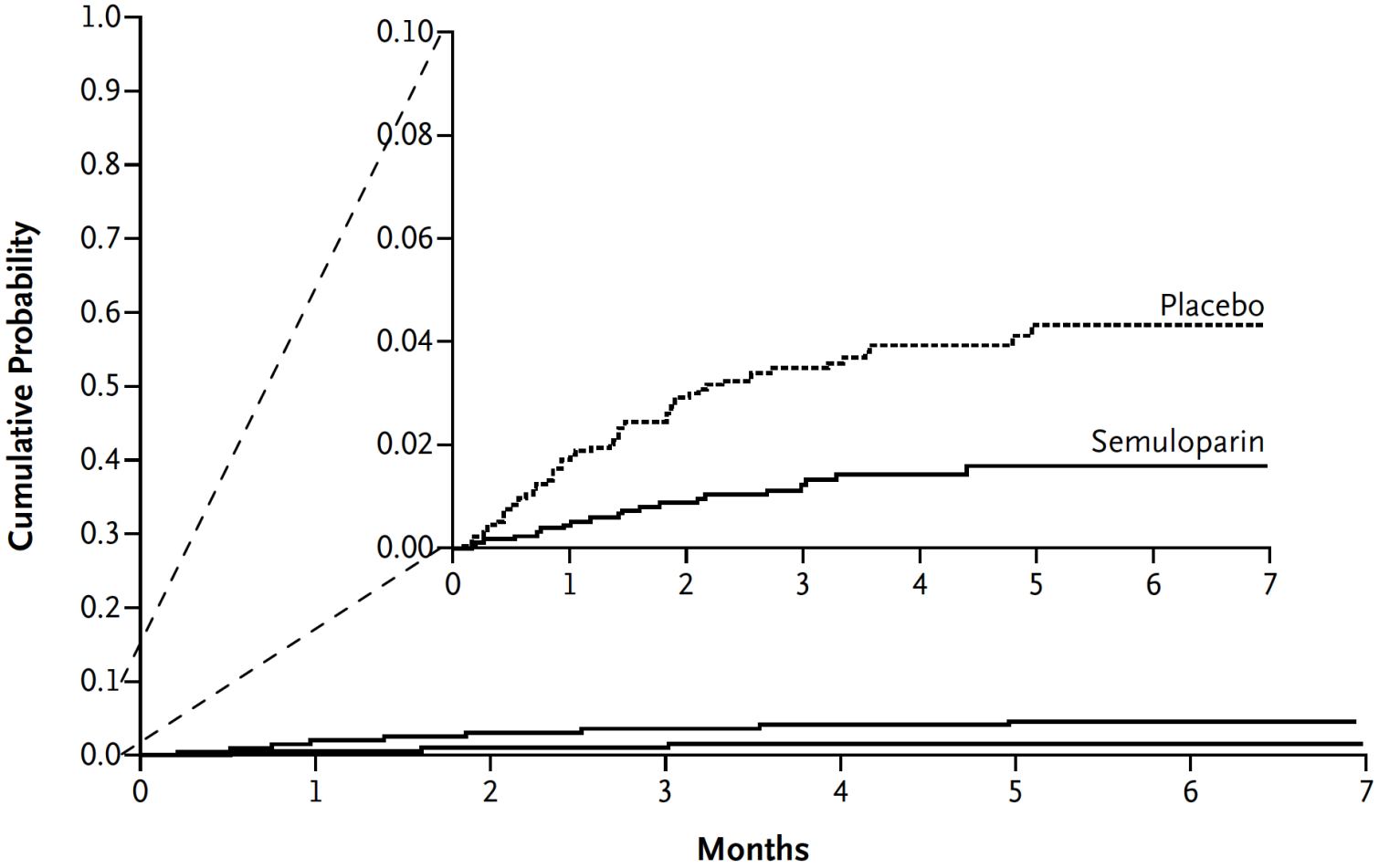
Semuloparin for Thromboprophylaxis in Patients Receiving Chemotherapy for Cancer

Giancarlo Agnelli, M.D., Daniel J. George, M.D., Ajay K. Kakkar, M.B., B.S., Ph.D., William Fisher, M.D., Michael R. Lassen, M.D., Patrick Mismetti, M.D., Patrick Mouret, M.D., Umesh Chaudhari, M.D., Francesca Lawson, M.D., and Alexander G.G. Turpie, M.D., for the SAVE-ONCO Investigators*

N Engl J Med 2012;366:601-9

- Chemotherapie bei lokal fortgeschrittenem oder metastasiertem
  - Lungenkarzinom
  - GI-Tumor
  - Blasenkarzinom
  - Ovarialkarzinom
- Semuloparin 20 mg vs Plazebo
- Beginn mit Chemotherapie bis Ende mindestens 90 Tage

N Engl J Med 2012;366:601-9


Cumulative Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
7
Months
0.10
0.08
0.06
0.04
0.02
0.00
Placebo
Semuloparin

Outcome according to primary cancer site — no./total no. (%)	Semuloparin (N = 1608)	Placebo (N = 1604)	Hazard Ratio (95% CI)†
Lung	9/591 (1.5)	25/589 (4.2)	0.36 (0.17–0.77)
Pancreas	3/126 (2.4)	14/128 (10.9)	0.22 (0.06–0.76)
Stomach	1/204 (0.5)	4/207 (1.9)	0.25 (0.03–2.20)
Colon or rectum	5/464 (1.1)	9/461 (2.0)	0.54 (0.18–1.60)
Bladder	1/32 (3.1)	3/31 (9.7)	0.30 (0.03–2.95)
Ovary	1/191 (0.5)	0/188	NE

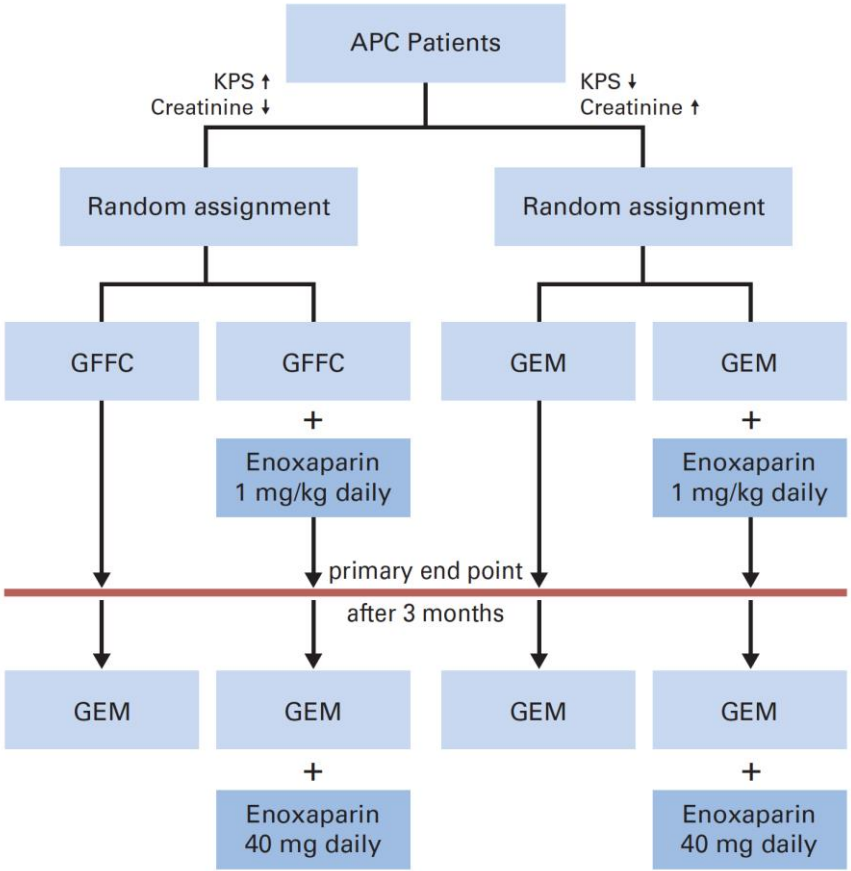
Bleeding Events	Semuloparin (N=1589)	Placebo (N=1583)	Odds Ratio (95% CI)
	no. (%)		
Clinically relevant bleeding	45 (2.8)	32 (2.0)	1.41 (0.89–2.25)
Major bleeding†	19 (1.2)	18 (1.1)	1.05 (0.55–2.04)
Clinically relevant nonmajor bleeding‡	26 (1.6)	14 (0.9)	1.86 (0.98–3.68)

Patrick Mouret, M.D., Umesh Chaudhari, M.D., Francesca Lawson, M.D.,
and Alexander G.G. Turpie, M.D., for the SAVE-ONCO Investigators*

Efficacy of Prophylactic Low–Molecular Weight Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From the CONKO-004 Trial

Uwe Pelzer, Bernhard Opitz, Gerd Deutschinoff, Martina Stauch, Peter C. Reitzig, Sabine Hahnfeld, Lothar Müller, Martina Grunewald, Jens M. Stieler, Marianne Sinn, Timm Denecke, Sven Bischoff, Helmut Oettle, Bernd Dörken, and Hanno Riess

J Clin Oncol 33:2028-2034



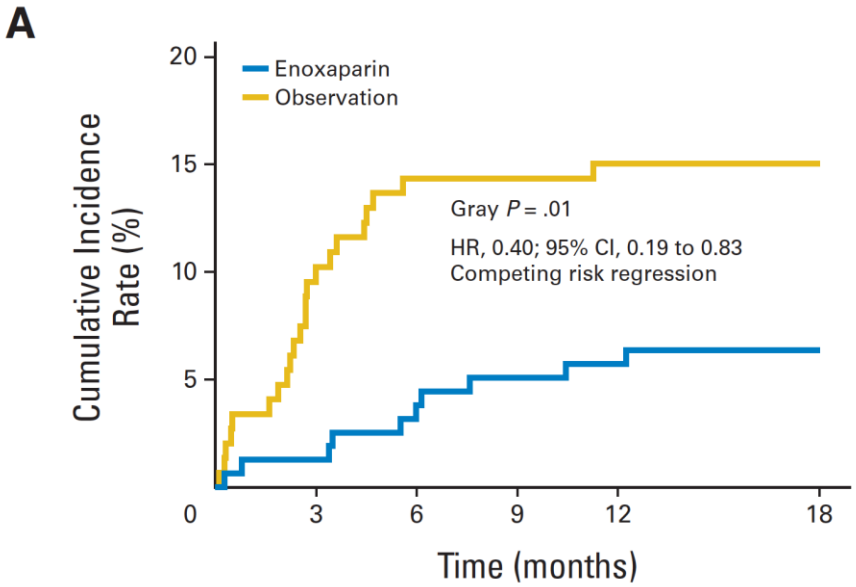
- Enoxaprin 3 Monate halbtherapeutisch, dann 40 mg fix bis Progress

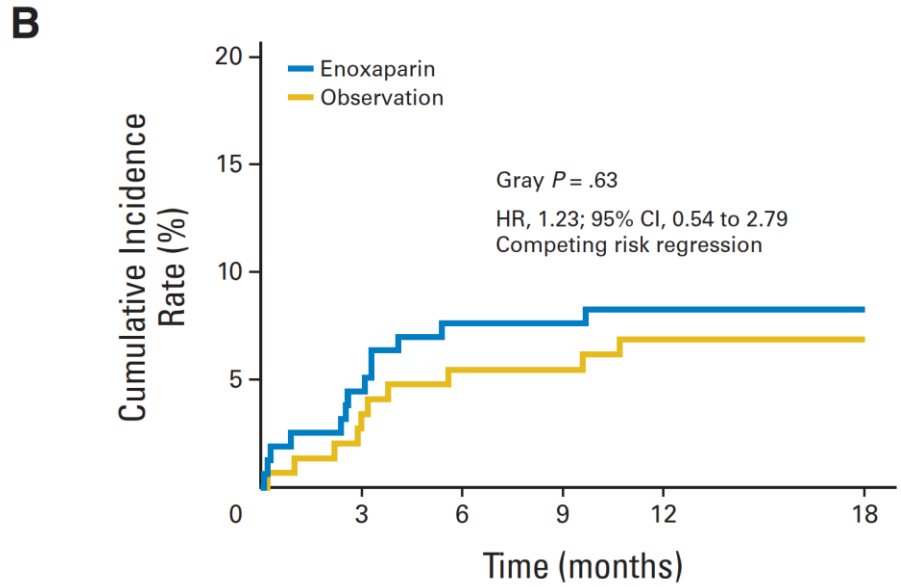
J Clin Oncol 33:2028-2034

Efficacy of Prophylactic Low–Molecular Weight Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From the CONKO-004 Trial

venöse Thromboembolien

Blutungen





J Clin Oncol 33:2028-2034

Fazit aus klinischen Studien

- Thromboseprophylaxe effektiv in der Verminderung der Anzahl an VTE
- Mehr Blutungen?

Fazit aus klinischen Studien

- Welche Patienten?
- Welche Risikofaktoren?
- Welche Dosis?
- Welche Dauer

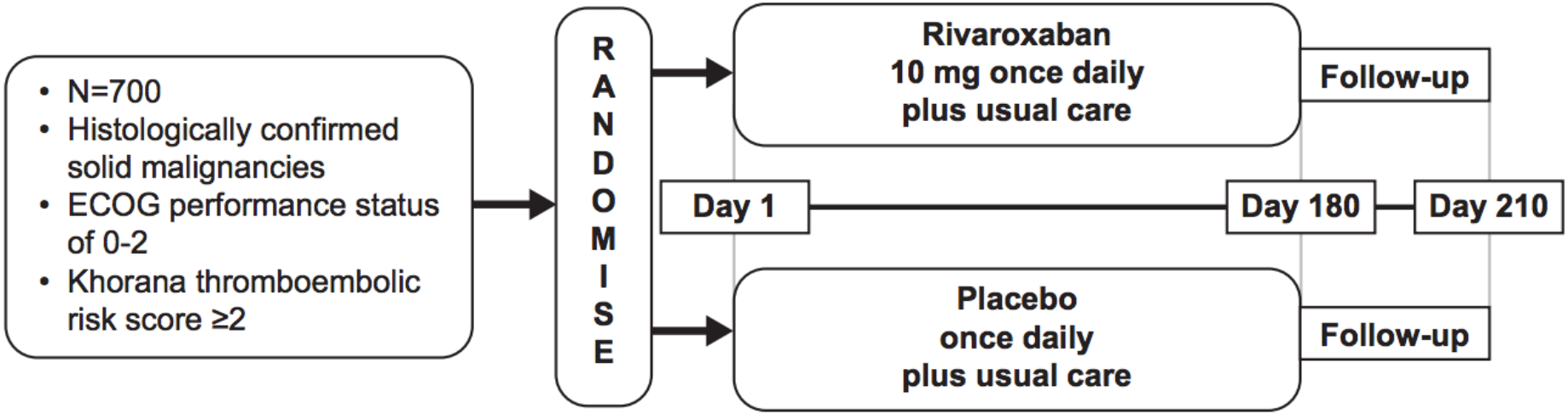
DOAC ?

Rivaroxaban for Preventing Venous Thromboembolism in High-Risk Ambulatory Patients with Cancer: Rationale and Design of the CASSINI Trial

Alok A. Khorana[1] Saroj Vadhan-Raj[2] Nicole M. Kuderer[3] Ted Wun[4] Howard Liebman[5] Gerald Soff[6] Chandra Belani[7] Eileen M. O'Reilly[6] Robert McBane[8] John Eikelboom[9] C.V. Damaraju[10] Karen Beyers[10] Flavia Dietrich[10] Ajay Kakkar[11] Hanno Riess[12] Renata D'Alpino Peixoto[13] Gary H. Lyman[14]

Thrombosis and Haemostasis ahead of print 2017-09-21

Inclusion criteria	Exclusion criteria
1. ≥18 y of age	1. Diagnosis of primary brain tumour
2. Histologically confirmed solid malignancy including, but not limited to, pancreas, lung, stomach, colon, rectum, bladder, breast, ovary, renal or lymphoma (haematologic), with locally advanced or metastatic disease	2. Known history of brain metastases
3. ECOG PS 0–2	3. Haematologic malignancies with the exception of lymphoma
4. Khorana score ≥2	4. Bleeding diathesis, haemorrhagic lesions, active bleeding and other conditions with a high risk for bleeding
5. Adequate renal function: CrCl ≥ 30 mL/min	5. Life expectancy of ≤6 mo
6. Plan to initiate systemic cancer therapy within ± 1 wk of receiving first dose of study drug with the intent of continuing systemic cancer therapy with study drug during the double-blind treatment period	6. Evidence of VTE on screening CU or incidental VTE identified on spiral CT scans ordered primarily for staging or restaging of malignancy ≤30 d prior to randomization



Thrombosis and Haemostasis ahead of print 2017-09-21

Leitlinien

Leitlinien

- ASCO 2015
- BSH 2015
- ESMO 2010
- International Practice Guideline 2013
- ISTH 2014
- NCCN 2016
- EMN 2015

	Ambulant
ASCO	Keine Empfehlung, evtl. selektionierte Risikopatienten
BCSH	Patienten mit aktiver Tumorerkrankung: Risikobestimmung, falls hohes Risiko kann Thromboseprophylaxe überlegt werden
ESMO	Prophylaxe bei fortgeschrittener Tumorerkrankung nicht empfohlen, kann bei Hochrisikopatienten überlegt werden
International Practice Guideline	Keine generelle Empfehlung, bei Patienten mit lokal fortgeschrittenem oder metastasiertem Pankreas/Magenkarzinom und niedrigem Blutungsrisiko kann Prophylaxe indiziert sein
ISTH	Niedrig Risiko: kein Prophylaxe Hohes Risiko: LMWH bei soliden Tumoren und Khorana >2
NCCN	----
EMN	----

	Stationär
ASCO	Pharmakologische Prophylaxe empfohlen falls keine Kontraindikation
BCSH	Thromboseprophlaxe empfohlen falls keine Kontraindikation
ESMO	UFH, LMWH oder Fondaparinux falls immobilisierter Patient
International Practice Guideline	LMWH, UFH oder Fondaparinux bei reduzierter Mobilität
ISTH	-----
NCCN	LMWH, Fondaparinux, UFH oder Warfarin
EMN	----

	Perioperativ
ASCO	UFH oder LMWH wenn keine Kontraindikation
BCSH	Bei abdominellen oder pelvinen Eingriffen verlängerte Thromboseprophylaxe empfohlen
ESMO	----
International Practice Guideline	Die höchste prophylaktische Dosis LMWH einmal täglich oder 3 x täglich UFH, Beginn 2-12 Stunden präoperativ, bis 7-10 Tage postoperativ, verlängerte Prophylaxe (4 Wochen) bei Risikopatienten mit niedrigem Blutungsrisiko möglich
ISTH	----
NCCN	LMWH, Fondaparinux, UFH oder Warfarin
EMN	----

	Chemotherapie
ASCO	LMWH bei selektierten ambulanten Patienten; Myelom bei Thalidomid oder Lenalidomid Regime mit Chemotherapie und/oder Dexamethason: Niedrigrisiko ASS oder LMWH, Hochrisiko LMWH
BCSH	Myelom falls Thalidomid oder Lenalidomid, Risikoabschätzung und Thromboseprophylaxe falls nicht kontraindiziert.
ESMO	Myelom falls Thalidomid in Kombination mit Chemotherapie oder Dexamethason: LMWH oder Warfarin
International Practice Guideline	Keine generelle Prophylaxe, empfohlen bei Immunmodulatoren mit Steroiden oder Chemotherapie, kann indiziert sein bei lokal fortgeschrittenem oder metastasiertem Pankreas- oder Lungenkarzinom die mit Chemotherapie behandelt werden und ein niedriges Blutungsrisiko haben.
ISTH	LMWH oder Aspirin bei Patienten mit Myelom die ein Thalidomid oder Lenalidomid haltiges Schema erhalten.
NCCN	LMWH oder Aspirin bei Patienten mit Myelom die ein Thalidomid oder Lenalidomid haltiges Schema erhalten.
EMN	Patienten mit niedrigem Risiko für eine Thromboembolie die eine Therapie mit einem Imid beginnen, sollten Aspirin einnehmen, ansonsten LMWH oder Warfarin

Fazit

- Prophylaxe bei stationären Patienten gut etabliert
- Prophylaxe bei ambulanten Patienten:

  risikoadaptiert