Novità in coagulazione attraverso i centri emostasi e trombosi
Torino 12-13 novembre 2021

Nuovo approccio alla scoagulazione nel paziente oncologico

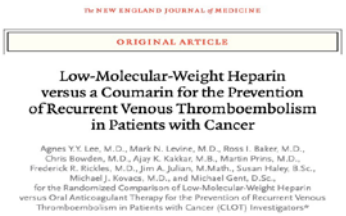
Alessandra Borchiellini
CRR Malattie emorragiche e trombotiche dell'adulto
Ematologia U
Città della Salute e della Scienza
Torino

Cancer associated thrombosis : premesse

- Il rischio di TEV nel paziente con cancro è 4-7 volte maggiore che nella popolazione generale
- Circa il 20% dei casi di TEV sono associati a cancro o alla terapia
- L'evento tromboembolico impatta sulla sopravvivenza e comunque aumenta il carico di malattia nel paziente con cancro
- La terapia anticoagulante rappresenta una sfida per l'aumentato rischio di recidiva di TEV e di sanguinamento; la piastrinopenia e i sintomi gastrointestinali associati alla neoplasia e/o al trattamento rendono necessarie rivalutazioni e modifiche frequenti della terapia anticoagulante

Riess et al Critical Reviews in Oncology / Hematology 157 (2021) 103125

TEV e LMWH

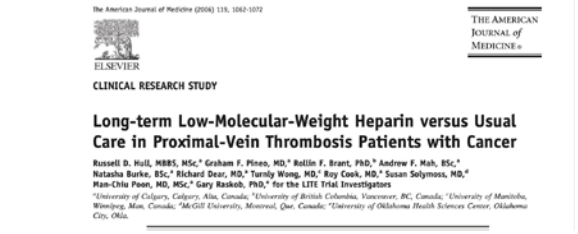


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer

Agnes Y.Y. Lee, M.D., Mark N. Levine, M.D., Ross I. Baker, M.D., Chris Bowden, M.D., Ajay K. Kakkar, M.B., Martin Prins, M.D., Frederick R. Rickles, M.D., Jim A. Julian, M.Math., Susan Haley, B.Sc., Michael J. Kovacs, M.D., and Michael Gent, D.Sc., for the Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators*



The American Journal of Medicine (2006) 119, 1062-1072

THE AMERICAN JOURNAL of MEDICINE

ELSEVIER

CLINICAL RESEARCH STUDY

Long-term Low-Molecular-Weight Heparin versus Usual Care in Proximal-Vein Thrombosis Patients with Cancer

Russell D. Hull, MBBS, MSc,* Graham F. Pineo, MD,* Rollin F. Brant, PhD,† Andrew F. Mah, BSc,* Natasha Burke, BSc,* Richard Dear, MD,* Turnly Wong, MD,* Roy Cook, MD,* Susan Solymoss, MD,‡ Man-Chiu Poon, MD, MSc,§ Gary Raskob, PhD,* for the LITE Trial Investigators

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Correspondence

Evaluation of US prescription patterns: Are treatment guidelines for cancer-associated venous thromboembolism being followed?

Table 1
Percentage of patients with cancer who remained on anticoagulant therapy.

Time from VTE diagnosis, months	LMWH	Warfarin	Rivaroxaban	Fondaparinux
0 to <1	100%	100%	100%	100%
1 to <3	30%	63%	54%	32%
3 to <6	13%	32%	30%	14%

Recidive di TEV 7-8%,
Rischio ridotto di circa il 50-60 % rispetto al gruppo in warfarin
Major bleeding sovrapponibili nei due gruppi (5%)

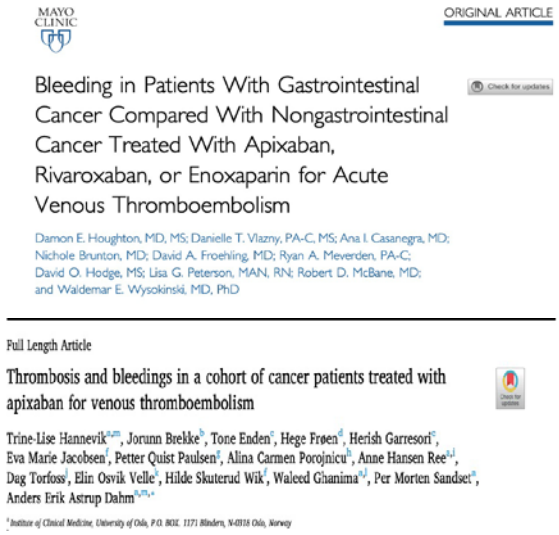
Study name	Year	Treatment allocation*	Baseline characteristics							Study outcomes			
			Male	Age (mean/ median with SD/ IQR), y	Index event PE ± DVT	Incidental VTE	Prior VTE	Metastatic disease¶	Gastro-intestinal cancer	Recurrent VTE†	Major bleeding	Clinically relevant nonmajor bleeding	All-cause mortality
Hokusai VTE Cancer	2018	Edoxaban, n = 522‡	277 (53.1)	64 ± 11	328 (62.8)	167 (32.0)	49 (9.4)	274 (52.5)	165 (31.6)	34 (6.5)	29 (5.6)	64 (12.3)	140 (26.8)
		Dalteparin, n = 524	263 (50.2)	63 ± 12	329 (62.8)	173 (33.0)	63 (12.0)	280 (53.4)	140 (26.7)	46 (8.8)	17 (3.2)	43 (8.2)	127 (24.2)
Select-D	2018	Rivaroxaban, n = 203	116 (57.1)	67 (22-87)	150 (73.9)	108 (53.2)	NR	118 (58.1)	94 (46.3)	7 (3.4)	11 (5.4)	25 (12.3)	48 (23.6)
		Dalteparin, n = 203	98 (48.3)	67 (34-87)	145 (71.4)	105 (51.7)	NR	118 (58.1)	86 (42.4)	17 (8.4)	6 (3.0)	7 (3.5)	56 (27.6)
ADAM-VTE§	2020	Apixaban, n = 150	72 (48.0)	64 ± 11	81 (54.0)	NR	8 (5.3)	96 (64.0)	48 (32.0)	0 (0)	0 (0)	9 (6.2)	23 (15.9)
		Dalteparin, n = 150	73 (48.7)	64 ± 11	75 (50.0)	NR	12 (8.0)	97 (64.7)	57 (38.0)	5 (3.5)	2 (1.4)	7 (4.9)	15 (10.6)
CARAVAGGIO	2020	Apixaban, n = 576	292 (50.7)	67 ± 11	304 (52.8)	116 (20.1)	45 (7.8)	389 (67.5)	188 (32.6)	32 (5.6)	22 (3.8)	52 (9.0)	135 (23.4)
		Dalteparin, n = 579	276 (47.7)	67 ± 11	334 (57.7)	114 (19.7)	61 (10.5)	396 (68.4)	187 (32.3)	46 (7.9)	23 (4.0)	35 (6.0)	153 (26.4)

Blood. 2020;136(12):1433-1441)

Outcome	No. of participants (studies)	Certainty of the evidence (GRADE)	RR (95% CI)	Observed risk with LMWH	Anticipated absolute effects	
					Risk with DOACs*	Absolute risk difference
Recurrent VTE	2607 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	0.68 (0.39 to 1.17)	8.3%	5.6%	−2.7% (–5.1 to 1.4)
Major bleeding	2607 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	1.36 (0.55 to 3.35)	3.5%	4.8%	1.3% (–1.6 to 8.3)
Composite outcome of first recurrent VTE and major bleeding	2607 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	0.86 (0.60 to 1.23)	11.1%	9.5%	−1.6% (–4.4 to 2.6)
Clinically relevant nonmajor bleeding	2607 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	1.63 (0.73 to 3.64)	6.5%	10.6%	4.1% (–1.8 to 17.2)
All-cause mortality	2607 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	0.96 (0.68 to 1.36)	25.7%	24.7%	−1.0% (–8.2 to 9.3)
On-treatment analyses						
Recurrent VTE (on-treatment)	2440 (3 RCTs)	⊕⊕⊕⊕ HIGH	0.60 (0.38 to 0.95)	8.1%	4.9%	−3.2% (–5.0 to −0.4)
Major bleeding (on-treatment)	2440 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	1.43 (0.46 to 4.45)	3.2%	4.6%	1.4% (–1.7 to 11.0)
Clinically relevant nonmajor bleeding (on-treatment)	2440 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	1.93 (0.70 to 5.31)	4.6%	8.9%	4.3% (–1.4 to 19.7)

Blood. 2020;136(12):1433-1441)

CAT e DOAC : i dati della real life



MAYO CLINIC

ORIGINAL ARTICLE

Bleeding in Patients With Gastrointestinal Cancer Compared With Nongastrointestinal Cancer Treated With Apixaban, Rivaroxaban, or Enoxaparin for Acute Venous Thromboembolism

Damon E. Houghton, MD, MS; Danielle T. Vlazny, PA-C, MS; Ana I. Casanegra, MD; Nichole Brunton, MD; David A. Froehling, MD; Ryan A. Meverden, PA-C; David O. Hodge, MS; Lisa G. Peterson, MAN, RN; Robert D. McBane, MD; and Waldemar E. Wysokinski, MD, PhD

Full Length Article

Thrombosis and bleedings in a cohort of cancer patients treated with apixaban for venous thromboembolism

Trine-Lise Hannevik, Jorunn Brekke, Tone Enden, Hege Frøen, Herish Garresori, Eva Marie Jacobsen, Petter Quist Paulsen, Alina Carmen Porojnicu, Anne Hansen Ree, Dag Torfoss, Elin Osvik Velle, Hilde Skuterud Wik, Waleed Ghanima, Per Morten Sandset, Anders Erik Astrup Dahm

RESEARCH ARTICLE

AJH WILEY

Comparison of apixaban to rivaroxaban and enoxaparin in acute cancer-associated venous thromboembolism

Waldemar E. Wysokinski | Damon E. Houghton | Ana I. Casanegra | Danielle T. Vlazny | Dalene M. Bott-Kitslaar | David A. Froehling | David O. Hodge | Lisa G. Peterson | Robert D. Mcbane

Sci Immunol. 2019 September 20; 4(39): . doi:10.1126/sciimmunol.aaw8405.

Myeloid cell-synthesized coagulation Factor X dampens anti-tumor immunity

Claudine Graf[1,2,3], Petra Wilgenbus[1], Sven Pagel[1], Jennifer Pott[1], Federico Marini[1,4], Sabine Reyda[1], Maki Kitano[2], Stephan Macher-Göppinger[5], Hartmut Weiler[6], Wolfram Ruf[1,2,*]

Immune evasion in the tumor microenvironment (TME) is a crucial barrier for effective cancer therapy and plasticity of innate immune cells may contribute to failures of targeted immunotherapies. Here, we show that rivaroxaban, a direct inhibitor of activated coagulation factor X (FX) promotes antitumor immunity by enhancing infiltration of dendritic cells and cytotoxic T cells at the tumor site. Profiling FX expression in the TME identifies monocytes and macrophages as crucial sources of extravascular FX. By generating mice with immune cells lacking the ability to produce FX, we show that myeloid cell-derived FX plays a pivotal role in promoting tumor immune evasion. In mouse models of cancer, we report that the efficacy of rivaroxaban is comparable to anti-PD-L1 therapy and that rivaroxaban synergizes with anti-PD-L1 in improving anti-tumor immunity. Mechanistically, we demonstrate that FXa promotes immune evasion by signaling through protease activated receptor 2 and that rivaroxaban specifically targets this cell-autonomous signaling pathway to reprogram tumor-associated macrophages. Collectively, our results have uncovered the importance of coagulation factor X produced in the TME as a regulator

CAT : le raccomandazioni internazionali

8.6 Recommendations for the regimen and the duration of anticoagulation after pulmonary embolism in patients with active cancer

Recommendations	Class[a]	Level[b]
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 6 months over VKAs.[360–363]	IIa	A
Edoxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.[366]	IIa	B
Rivaroxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.[367]	IIa	C
For patients with PE and cancer, extended anticoagulation (beyond the first 6 months)[c] should be considered for an indefinite period or until the cancer is cured.[378]	IIa	B
In patients with cancer, management of incidental PE in the same manner as symptomatic PE should be considered, if it involves segmental or more proximal branches, multiple subsegmental vessels, or a single subsegmental vessel in association with proven DVT.[376,377]	IIa	B

CAT : aggiornamenti (ACCP guidelines 2021)

- ***In patients with acute VTE in the setting of cancer we recommend an oral Xa inhibitor over LMWH for the initiation and treatment phases of therapy (strong recommendation; moderate –certainty evidence)***

Gli unmet needs : la profilassi Iaria . Gli scores I

Table 1. Risk prediction scores for venous thromboembolism in cancer patients.

Item	Khorana score (points)	Vienna CATS score (points)	PROTECHT score (points)	CONKO score (points)
Pancreatic or gastric cancer (very high-risk tumors)	+2	+2	+2	+2
D-dimer >1.44 µg/L	–	+1	–	–
Soluble P-selectin >53.1 ng/L	–	+1	–	–
Gemcitabine chemotherapy	–	–	+1	–
Platinum-based chemotherapy	–	–	+1	–
WHO performance status ≥2	–	–	–	+1

WHO: World Health Organization.

IDENTIFICAZIONE DEL 13-34% DEI PAZIENTI CON VTE

Haematologica 2017 Volume 102(9):1494-1501

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, ischemic stroke, coronary artery disease, hypertension, hyperlipidemia, diabetes, obesity)	5
Recent hospitalization for acute medical illness	5
Personal history of VTE	1
Biomarkers	
Platelets count ≥ 350 × 10^9/L	2

[a]Low/Intermediate risk: 0–6; high risk: ≥7.

The Oncologist

Symptom Management and Supportive Care

A Predictive Score for Thrombosis Associated with Breast, Colorectal, Lung, or Ovarian Cancer: The Prospective COMPASS–Cancer-Associated Thrombosis Study

Grigoris T. Gerotziafas,[a,b] Ali Taher,[c] Hikmat Abdel-Razeq,[d] Essam AboElnazar,[e] Alex C. Spyropoulos,[f] Salem El Shemmari,[g] Annette K. Larsen,[a] Ismail Elalamy,[a,b] on behalf of the COMPASS–CAT Working Group

[a]Cancer Biology and Therapeutics, INSERM U938, Institut Universitaire de Cancérologie (IUC), Faculté de Médecine Pierre et Marie Curie, Université Pierre et Marie Curie (UPMC), Sorbonne Universités, Paris, France; [b]Service d'Hématologie Biologique Hôpital Tenon, Hôpitaux Universitaires Est Parisien, Assistance Publique Hôpitaux de Paris, Paris, France; [c]Department of Internal Medicine, Division of Hematology/Oncology, American University of Beirut, Lebanon; [d]Department of Internal Medicine, King Hussein Cancer Center, Amman, Jordan; [e]Surgery Department, Umm Al-Qura University, Mecca, Saudi Arabia; [f]Department of Medicine, Anticoagulation and Clinical Thrombosis Services, Hofstra Northwell School of Medicine, Northwell Health System, Manhasset, New York, USA; [g]Department of Medical Oncology, Kuwait Cancer Control Center, Kuwait City, Kuwait

Disclosures of potential conflicts of interest may be found at the end of this article.

Gli unmet needs : la profilassi Iaria . Gli scores II

Review Article

Check for updates

blood

Cancer-associated pathways and biomarkers of venous thrombosis

Yohei Hisada[1,2] and Nigel Mackman[1]

[1]Division of Hematology and Oncology, Department of Medicine, Thrombosis and Hemostasis Program, University of North Carolina at Chapel Hill, Chapel Hill, NC; and [2]K.G. Jebsen Thrombosis Research and Expertise Center, University of Tromsø, Tromsø, Norway

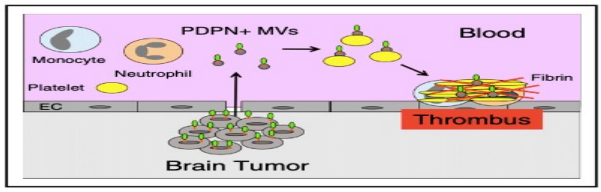


Figure 4. Tumor-derived, PDPN$^+$ MVs trigger thrombosis in brain cancer. Brain tumor cells may release PDPN$^+$ MVs that activate circulating platelets and increase thrombosis in patients with brain cancer.

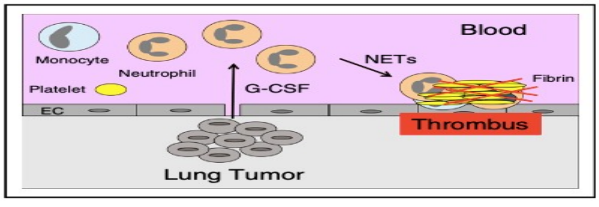


Figure 1. Neutrophilia increases thrombosis in lung cancer. Tumor-derived G-CSF leads to increased levels of neutrophils, and these neutrophils release NETs that increase thrombosis in patients with lung cancer. EC, endothelial cell.

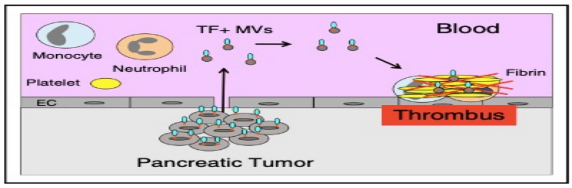


Figure 3. Tumor-derived TF$^+$ MVs trigger thrombosis in pancreatic cancer. Pancreatic tumor cells release TF$^+$ MVs into the circulation that trigger thrombosis in patients with pancreatic cancer.

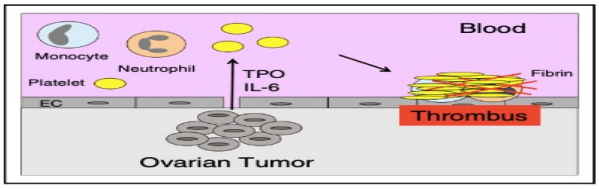
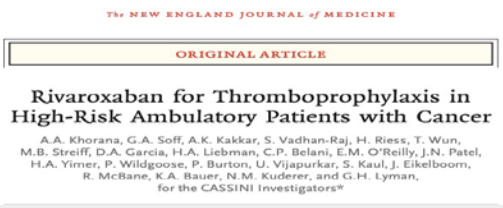


Figure 2. Thrombocytosis increases thrombosis in ovarian cancer. Tumor-derived IL-6 stimulates hepatocytes to express thrombopoietin (TPO), which increases platelet production and enhances thrombosis in patients with ovarian cancer.

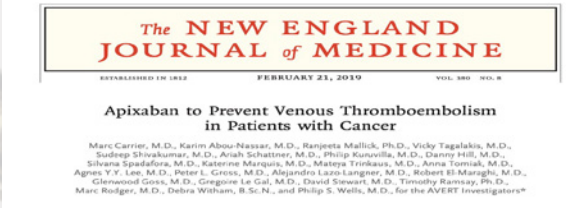
PROFILASSI IARIA E DOAC:


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*


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*

841 pazienti ambulatoriali con Khorana score >2
Rivaroxaban 10 mg vs placebo per 180 gg
US allo screening e regolarmente alle visite sett 8, 16, 180

Incidenza VTE 2,6 % vs 6,4%
Major bleeding 2 vs 1%

563 pazienti ambulatoriali con Khorana score > 2
Apixaban 2,5 mg x2/d vs placebo per 180 gg

Incidenza VTE 4,2% vs 10% p< 0,001
Major bleeding 2,1% vs 1,1 %

Prevenzione laria : efficacia e sicurezza

	Prophylaxis	Comparator	Duration	Outcomes	Prophylaxis	Comparator	RR (95% CI)
Hass et al. [19, 44] (2012)	Certoparin	Placebo	6 months	Symptomatic VTE Major Bleeding	1.8% (8/442) 2.9% (13/447)	3.2% (14/441) 1.3% (6/451)	0.57 (0.24, 1.35) 2.19 (0.84, 5.70)
Kakkar et al. [19, 45] (2004)	Dalteparin	Placebo	12 months	Symptomatic VTE Major Bleeding	2.1% (4/190) 0.5% (1/190)	2.7% (5/184) 0.0% (0/184)	0.77 (0.21, 2.84) 2.91 (0.12, 70.87)
Pelzer et al. [19, 46] (2015)	Enoxaparin	No Treatment	3 months	Symptomatic VTE Major Bleeding	6.3% (10/160) 8.1% (13/160)	14.5% (22/152) 6.6% (10/152)	0.43 (0.21, 0.88) 1.24 (0.56, 2.73)
Agnelli et al. [18, 19] (2012)	Semuloparin	Placebo	3.5 months (median)	Symptomatic VTE Major Bleeding	0.7% (11/1608) 1.2% (19/1589)	2.1% (34/1604) 1.1% (18/1583)	0.32 (0.15–0.62)^ 1.05 (0.55, 2.04)+
Agnelli et al. [17, 19] (2009)	Nadroparin	Placebo	3 months (median)	Symptomatic VTE Major Bleeding	1.4% (11/769) 0.7% (5/769)	2.9% (11/381) 0.0% (0/381)	0.50 (0.22, 1.13)^ 5.46 (0.30, 98.43)^
Carrier et al. [20] (2019)	Apixaban	Placebo	6 months	Major VTE Major Bleeding	4.2% (12/288) 3.5% (10/288)	10.2% (28/275) 1.8% (5/275)	0.41 (0.26, 0.65)^ 2.00 (1.01, 3.95)^
Khorana et al. [21] (2019)	Rivaroxaban	Placebo	6 months	Major VTE Major Bleeding	5.7% (24/420) 2.0% (8/405)	8.1% (34/421) 1.0% (4/404)	0.71 (0.43, 1.17) 1.96 (0.59, 6.49)^

Sanfilippo et al Curr Treat Options Cardio Med (2019) 21: 70

ASCO speci

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

Clinical Question 2. Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?

Recommendation 2.1. Routine pharmacologic thromboprophylaxis should not be offered to all outpatients with cancer (Type: evidence based; Evidence quality: intermediate to high; Strength of recommendation: strong).

Recommendation 2.2. 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).

ASCO speci

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

Clinical Question 6. What is known about risk prediction and awareness of VTE among patients with cancer?

Recommendation 6.1. There is substantial variation in risk of VTE between individual patients with cancer and cancer settings. Patients with cancer should be assessed for VTE risk initially and periodically thereafter, particularly when starting systemic antineoplastic therapy or at the time of hospitalization. Individual risk factors, including biomarkers or cancer site, do not reliably identify patients with cancer at high risk of VTE. In the ambulatory setting among patients with solid tumors treated with systemic therapy, risk assessment can be conducted based on a validated risk assessment tool (Khorana score; Table 1) (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

.....Il nostro ambulatorio ....

- 4000 visite /anno
- 400 nuove diagnosi di TEV

  Circa 25% con neoplasia

  il 50% in trattamento con DOAC , 30% con LMWH e 8% in AVK

CONCLUSIONI

- L'evoluzione e la diversificazione delle terapie disponibili necessita sempre più di competenze sensibili , di tempo e luoghi adeguati affinchè le risorse disponibili siano utilizzate al meglio , rendendo più forte la sanità e più protetto il paziente .

GRAZIE A...

- Carola Sella
- Marco Bardetta
- Cristina Dainese
- Federica Valeri
- Stefania Arminio

- Grazie !