EVIDENZE E NUOVE PROSPETTIVE NEL TRATTAMENTO DELLE PATOLOGIE TROMBOEMBOLICHE

Varese, 15/16 marzo 2018

Update sugli studi di profilassi del TEV nel paziente oncologico ambulatoriale

Anna Falanga

ASST Papa Giovanni XXIII - Bergamo

THE ROLE OF PRIMARY PROPHYLAXIS OF VTE IN CANCER PATIENTS

CLINICAL SCENARIO	ROLE OF THROMBOPROPHYLAXIS
SURGICAL PATIENT undergoing major oncological surgery	
MEDICAL INPATIENT hospitalized for acute medical illness	
MEDICAL OUTPATIENT taking anti-cancer drugs	

Profilassi del TEV
nel paziente oncologico
ospedalizzato per problemi acuti internistici

LA TROMBOPROFILASSI NEL PAZIENTE INTERNISTICO

STUDIO ENDORSE *(Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting)*:

- su 37.356 pazienti internistici il 39,5% è sottoposto a profilassi.

- ✓Difficoltà nello stabilire il livello di rischio
- ✓Comorbilità e rischio emorragico
- ✓Scarsa percezione del problema

Cohen AT et al. Lancet 2008

PROFILASSI FARMACOLOGICA *vs* PLACEBO IN MEDICINA INTERNA

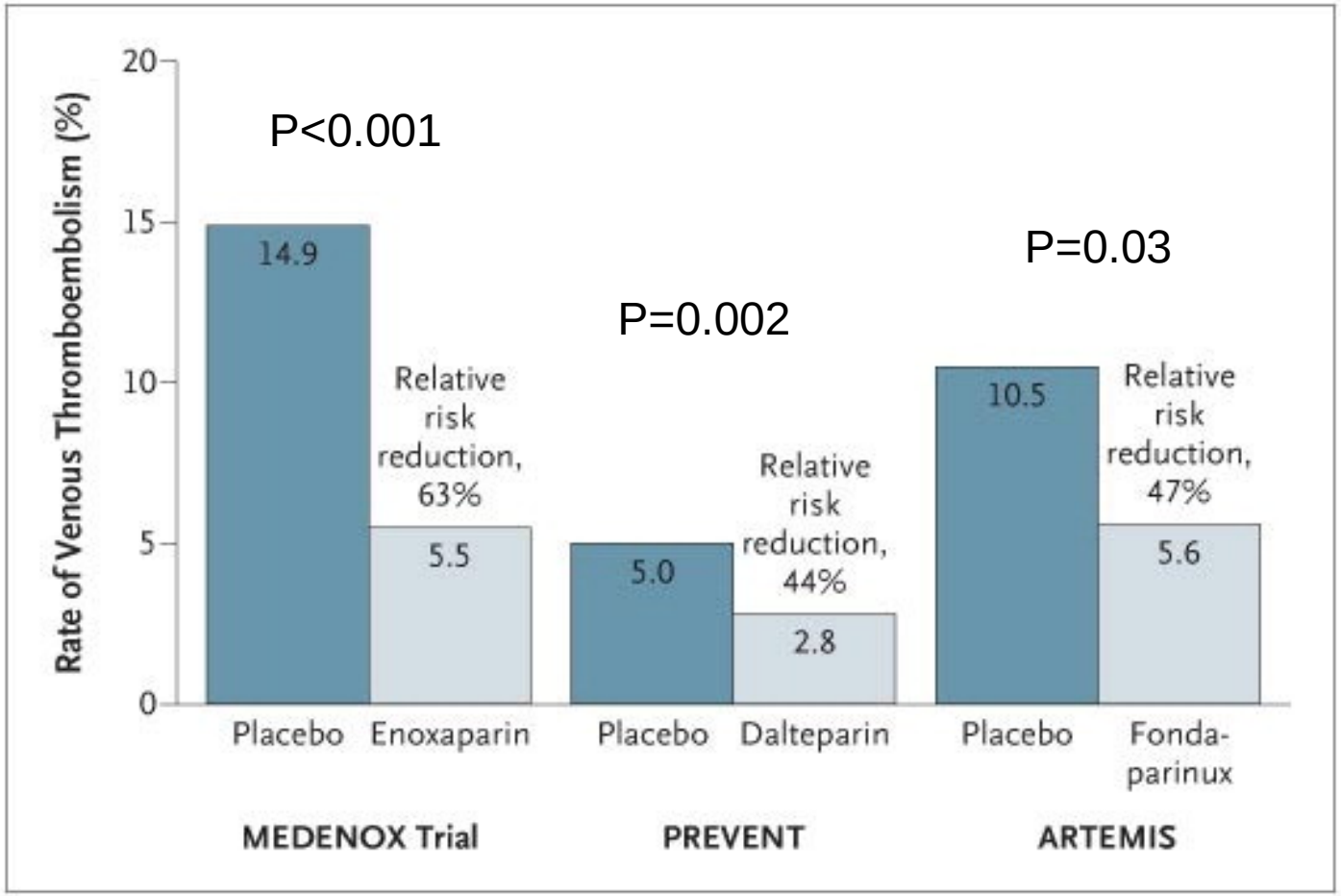
- MEDENOX[1] (enoxaparina):
  - Prophylaxis in **MED**ical patients with **ENOX**aparin trial (n=1102)
- PREVENT[2] (dalteparina):
  - **PR**ospective evaluation of dalt**E**parin efficacy for prevention of **V**tE in immobilized patie**N**ts **T**rial (n=3706)
- ARTEMIS[3] (fondaparinux):
  - **AR**ixtra for **T**hrombo**E**mbolism Prevention in **M**edical **I**ndications **S**tudy (n=849)

[1]Samama MM, et al. N Engl J Med 1999;

[2]Leizorovicz A, et al. Circulation 2004;

[3]Cohen et al, Blood 2003

PROFILASSI FARMACOLOGICA *vs* PLACEBO IN MEDICINA INTERNA



Nei tre studi qui messi a confronto è stata dimostrata una significativa riduzione dell'incidenza di TEV nei pazienti assegnati al braccio di trattamento rispetto a quelli trattati con placebo

Francis CW. N Engl J Med 2007

Modelli di valutazione del rischio *(Risk Assessment Models - RAM)* di TEV

Autore	Riferimento bibliografico
Cohen A et al.	Thromb Haemost, 2005
Samama MM et al.	Haematologica ,2006
Haas SK et al.	Clin Appl Thromb Hemost ,2007
Goldhaber SZ et al.	Am J Cardiol ,2004
Chopard P et al.	J Thromb Haemost, 2006
Kucher N et al.	N Engl J Med, 2005
Lecumberri R et al.	Thromb Haemost, 2008
Barbar et al.	J Thromb Haemost ,2010

MODELLO DI RISCHIO PER TEV NEL PAZIENTE INTERNISTICO: LO SCORE DI PADOVA

Caratteristiche basali	Punti
Neoplasia attiva o in trattamento nei sei mesi precedenti	3
Storia di TEV (con esclusione di trombosi venosa superficiale)	3
Ridotta mobilità (allettamento per ≥ 3 giorni)	3
Condizione trombofilica nota	3
Trauma e/o chirurgia recente (<1 mese)	2
Età ≥ 70 anni	1
Insufficienza respiratoria e/o cardiaca	1
Infarto acuto miocardio e/o ictus ischemico	1
Infezione acuta e/o malattia reumatica	1
Obesità (BMI ≥ 30 negli uomini e ≥ 28 nelle donne)	1
Terapia ormonale in corso	1
TOTALE	

totale < 4: basso rischio di TEV

totale ≥ 4: alto rischio di TEV

Barbar S t al. J Thromb Haemost 2010

GUIDELINES

(Guyatt et al. Chest 2012)

Gruppo di rischio	Profilassi raccomandata	Grado
PAZIENTI INTERNISTICI ACUTI AD ALTO RISCHIO DI TEV (SCORE DI PADOVA ≥4)	In pazienti internistici acuti con: – scompenso cardiaco congestizio – severa malattia respiratoria – allettamento per almeno 3 gg e uno o più fattori di rischio tromboembolico addizionali, compresi: **cancro attivo**, pregresso TEV, sepsi, malattia neurologica acuta, malattie infiammatorie intestinali SI RACCOMANDA PROFILASSI CON EPARINA NON FRAZIONATA O A BASSO PESO MOLECOLARE O FONDAPARINUX	ACCP 2012, Grado 1B

SISET RECOMMENDATIONS: HOSPITALIZEDMEDICAL PATIENTS

- Hospitalized patients with malignancies and concomitant acute medical illness should receive prophylactic doses of LMWH or fondaparinux *[grade A]*

- For those at a high risk of bleeding, or others with contraindications to pharmacological prophylaxis, mechanical prophylaxis with intermittent leg compression or graduated stockings should be provided *[grade C]*

Siragusa et al, Thromb Res 2012

DIRECT ANTICOAGULANTS (DOACs)

- Limited data are available to clearly define the role of DOACs in hospitalized medical patients with cancer, since all trials to date included a minority of patients with malignant disease.
- The role of DOACs, including extending TP for 4 weeks post discharge, has received much attention recently via three randomized trials:
  - MAGELLAN with Rivaroxaban 10 mg (Cohen AT, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med 2013)
  - ADOPT with Apixaban 2,5 mg (Goldhaber SZ, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med 2011)
  - APEX with Betrixaban 80 mg (Cohen AT, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. N Engl J Med 2016)

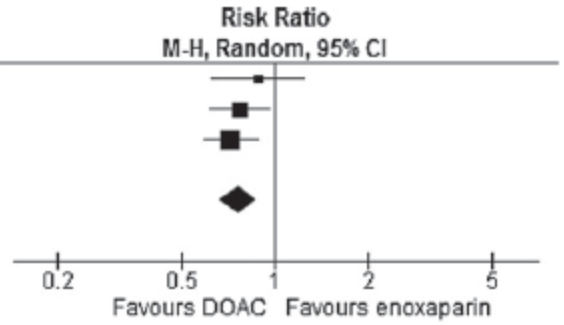
EXTENDED THROMBOPROPHYLAXIS WITH DIRECT ORAL ANTICOAGULANTS FOR MEDICAL PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Total thromboembolic events

Study or Subgroup	DOAC Events	DOAC Total	Enoxaparin Events	Enoxaparin Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT (Apixaban; 2011)	60	2211	70	2284	15.5%	0.89 [0.63, 1.24]
MAGELLAN (Rivaroxaban; 2013)	131	2967	175	3057	36.7%	0.77 [0.62, 0.96]
APEX (Betrixaban; 2016)	165	3112	233	3174	47.9%	0.72 [0.60, 0.88]
Total (95% CI)		**8290**		**8515**	**100.0%**	**0.76 [0.67, 0.87]**
Total events	356		478			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.06$, df = 2 (P = 0.59); $I^2 = 0\%$

Test for overall effect: Z = 3.96 (P < 0.0001)

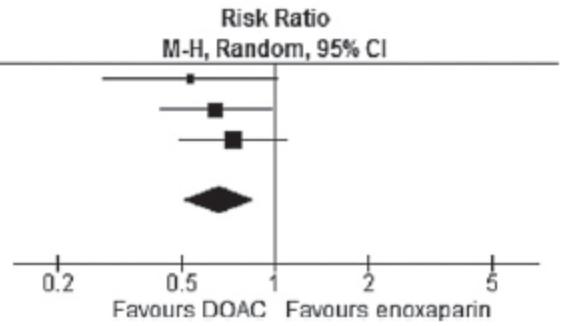


Symptomatic thromboembolic events

Study or Subgroup	DOAC Events	DOAC Total	Enoxaparin Events	Enoxaparin Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT (Apixaban; 2011)	14	2211	27	2284	16.4%	0.54 [0.28, 1.02]
APEX (Betrixaban; 2016)	36	3112	57	3174	39.5%	0.64 [0.43, 0.97]
MAGELLAN (Rivaroxaban; 2013)	42	2967	59	3057	44.1%	0.73 [0.50, 1.09]
Total (95% CI)		**8290**		**8515**	**100.0%**	**0.66 [0.51, 0.86]**
Total events	92		143			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.70$, df = 2 (P = 0.71); $I^2 = 0\%$

Test for overall effect: Z = 3.11 (P = 0.002)



Pooled analysis identified a significant decrease in the rates of total and symptomatic VTE in those who received extended DOAC prophylaxis.

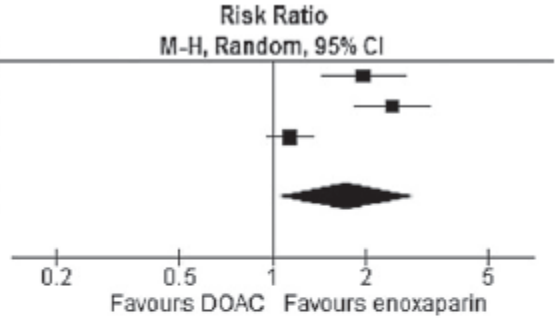
Joseph J. Shatzel et al. Blood 2017

THE POOLED ANALYSIS ALSO IDENTIFIED A SIGNIFICANT INCREASE IN TOTAL AND MAJOR BLEEDING WITH EXTENDED-COURSE DOACs

Total bleeding events

Study or Subgroup	DOAC Events	DOAC Total	Enoxaparin Events	Enoxaparin Total	Weight	Risk Ratio M-H, Random, 95% CI
APEX (Betrixaban; 2016)	116	3716	59	3716	32.1%	1.97 [1.44, 2.68]
MAGELLAN (Rivaroxaban; 2013)	164	3997	67	4001	32.9%	2.45 [1.85, 3.24]
ADOPT (Apixaban; 2011)	246	3184	219	3217	35.0%	1.13 [0.95, 1.35]
Total (95% CI)		**10897**		**10934**	**100.0%**	**1.74 [1.05, 2.90]**
Total events	526		345			

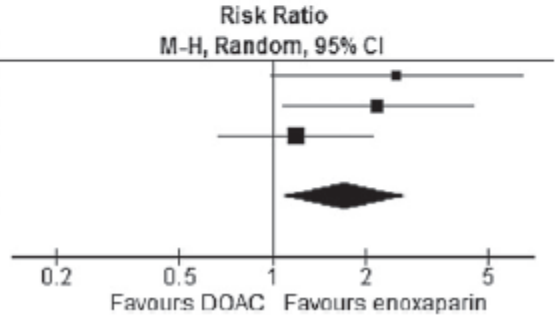
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 24.48$, df = 2 ($P < 0.00001$); $I^2 = 92\%$
Test for overall effect: $Z = 2.14$ ($P = 0.03$)



Major bleeding events

Study or Subgroup	DOAC Events	DOAC Total	Enoxaparin Events	Enoxaparin Total	Weight	Risk Ratio M-H, Random, 95% CI
ADOPT (Apixaban; 2011)	15	3184	6	3217	21.2%	2.53 [0.98, 6.50]
MAGELLAN (Rivaroxaban; 2013)	24	3997	11	4001	33.5%	2.18 [1.07, 4.45]
APEX (Betrixaban; 2016)	25	3716	21	3716	45.3%	1.19 [0.67, 2.12]
Total (95% CI)		**10897**		**10934**	**100.0%**	**1.71 [1.07, 2.75]**
Total events	64		38			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 2.60$, df = 2 ($P = 0.27$); $I^2 = 23\%$
Test for overall effect: $Z = 2.23$ ($P = 0.03$)



The benefit of VTE reduction found in those who received extended prophylaxis with a DOAC must be weighed against the significant increase in both total and major bleeding found in this analysis, suggesting against routine use of extended prophylaxis in the general population of hospitalized medical patients.

Joseph J. Shatzel et al. Blood 2017

Profilassi del TEV
nel paziente oncologico ambulatoriale
in chemioterapia

OUTPATIENTS THROMBOPROPHILAXIS

- Current guidelines have little differences, but **all recommend against the routine use of VTE prophylaxis in all ambulatory patients with cancer.**

- Given the cost and concomitant bleeding risk associated with anticoagulants, administration of VTE prophylaxis in cancer patients is currently not the standard of care.

- A major criticism of the available clinical studies has been the inclusion of patients at lower risk for VTE, which may have diluted the potential beneficial effect of the parenteral thromboprophylaxis.

RCTs OF THROMBOPROPHYLAXIS WITH LMWH IN AMBULATORY CANCER PATIENTS

Trial	N	Treatment	Chemo	Duration	VTE	Major Bleeding
PROTECHT **Solid Tumors (Stage III/IV)**	1166	Nadroparin 2:1 Placebo	100%	≤ 4 months with chemo	1.4% 2.9%	0.7% 0
SAVE-ONCO **(Stage IV)**	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)**	123	Gemcitabine (n=63) Gemcitabine + weight-adjusted dalteparin (n= 60)	100%	12 weeks (therapeutic dose)	31% 12%	27% 22%
CONKO 004 **advanced pancreatic cancer)**	312	Chemo (n=152) Chemo + Enoxaparin (n= 160)	100%	3 months (half a therapeutic dose, than prophylactic dose)	15.1% 6.4%	3.2% 4.3%

1. Agnelli G, et al. Lancet Oncol 2009;
2. Agnelli G, et al. NEJM 2012;
3. Maraveyas A, et al. Europ J Cancer 2012.
4. Pelzer U, et al, JCO 2015

VTE AND MULTIPLE MYELOMA

- There is a well-recognized association between multiple myeloma and VTE, which is further increased in patients treated with thalidomide or lenalidomide [30].
- The risk of VTE in patients receiving thalidomide has been found to range from 17% to 26% in combination with dexamethasone and from 12% to 28% in combination with other chemotherapy agents including anthracyclines
- Prospective studies of thalidomide-containing regimens in patients with MM have suggested the efficacy of LMWH, warfarin at low fixed doses, and aspirin for prophylactic anticoagulation

Larocca et al. Blood 2012; Palumbo et al. J Clin Oncol 2011

DISCUSSION

- The use of VTE prophylaxis in ambulatory patients who have cancer is controversial.

- Even if several important randomized clinical trials showed decreased rates of events among patients who were receiving chemotherapy, the effect of prophylaxis on morbidity, mortality, and cost has not been definitely established.

- It is important to appropriately risk stratify ambulatory cancer patients using a validated scoring system (e.g. Khorana risk score) in order to identify those most likely to benefit from thromboprophylaxis.

IDENTIFICATION OF HIGH RISK PATIENTS

- The identification of *ambulatory* cancer patients who *might benefit from primary thromboprophylaxis* is still one of the most challenging areas
- The rate of VTE in all cancer patients is challenging because not all cancer patients have the same risk for first and recurrent VTE.
- The risk of VTE varies among patients who have cancer, and it depends on a number of factors, including the type of cancer and of treatment, and the presence or absence of coexisting diseases.

RISK FACTORS OF VTE

A number of patient-, treatment-, and tumor-related risk factors contribute to the overall VTE risk in cancer.

Patient-related factors

- Advanced age
- Female gender
- Prior VTE
- Patient co-morbidities (hypertension, infection, obesity, anemia, pulmonary, liver 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 hormone- therapies
- Immunomodulatory agents
- Anti-angiogenic drugs
- Erythropoiesis stimulating agents
- Blood transfusions

Falanga; L. Russo - Hamostaseologie. 2012

RISK ASSESSMENT MODELS

- Khorana and colleagues developed a predictive model to risk-stratify a broad range of ambulatory cancer outpatients potentially allowing for a more favourable risk-to-benefit ratio to be calculated when thromboprophylaxis is being considered
- The model is based on a collection of readily available clinical and biological parameters.
- This RAM was first developed in a prospective cohort of 2,701 ambulatory patients undergoing chemotherapy for cancer and it was then validated in an independent prospective cohort of 1,365 patients.

THE KHORANA's SCORE

- Using Khorana predictive model, cancer patients were considered at VTE low-risk if they had a score of 0, at VTE intermediate-risk if they had a score of 1–2 and at VTE high-risk if they had a score ≥3.

Risk Factors	Risk score
1. Site of cancer	
a) Very high risk cancer (stomach, pancreas)	2
b) High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
2. Platelet count ≥350,000/mm^3	1
3. Hemoglobin level <10 g/dL or use of Red cell growth factors	1
4. Leukocyte count >11,000 /mm^3	1
5. BMI ≥ 35 kg/m^2	1

Low risk: score 0
Intermediate risk: score 1-2
High risk: score ≥3

Khorana AA et al. Blood. 2008

SISET RECOMMENDATIONS – OUTPATIENTS

- Pharmacological prophylaxis is not routinely recommended in patients undergoing chemotherapy or radiotherapy or hormonal therapy [grade C]
- except in the following cases:

  - patients with lung or gastrointestinal cancer should receive nadroparin (3,800 U anti-FXa daily) for no more than 4 months *[grade A]*

  - patients with multiple myeloma treated with thalidomide or lenalidomide plus high-dose dexamethasone should receive LMWH or aspirin or warfarin *[Grade C]*

Siragusa et al, Thromb Res 2012

DOACS FOR PREVENTION OF CAT

- The role of dabigatran, rivaroxaban, apixaban and edoxaban as prophylaxis in ambulatory cancer patients receiving chemotherapy is under determination in phase III randomized clinical trials.

- Only a phase II study (ADVOCATE Study) has been fully published (Levine MN, et al. A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. J Thromb Haemost 2012).

- This pilot study was conducted to evaluate whether apixaban would be well tolerated and acceptable in cancer patients receiving chemotherapy.

DOAC FOR VTE PREVENTION IN HIGH-RISK AMBULATORY CANCER PATIENTS RECEIVING SYSTEMIC CHEMOTHERAPY

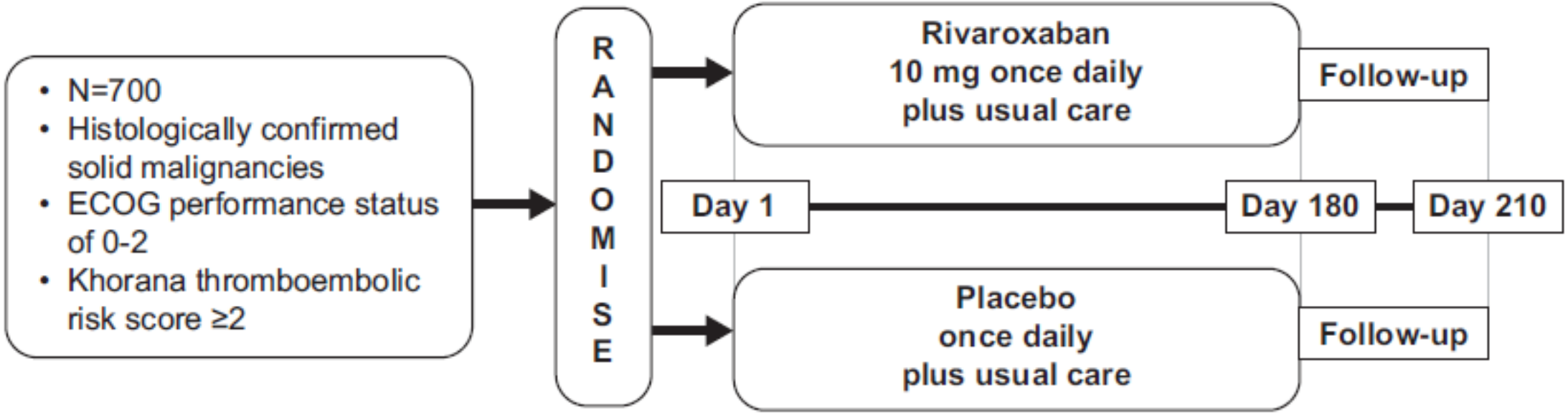
ONGOING RCTs

- **CASSINI TRIAL (Korana AA et al) – 700 pz.**
  - Phase 3, multicenter, randomized, triple-blind, placebo-controlled, superiority study
  - rivaroxaban 10 mg *vs* placebo for 6 months

- **AVERT TRIAL (Carrier M et al) – 574 pz.**
  - phase 2, multicentre, randomized, quadruple-blind trial
  - apixaban 2.5 BID *vs* placebo for 6 months

- **Apixaban in Preventing Secondary Cancer Related Blood Clots in Cancer Patients Who Have Completed Anticoagulation Therapy (6-12 mesi) - 370 pz**
  - Phase 3 A Phase III, Randomized, Controlled, Double-Blind Trial
  - lower dose apixaban PO BID for 365 days vs higher dose apixaban PO BID for 365 days

CASSINI study design



CASSINI (NCT02555878) is a phase 3b, randomized, double-blind, placebo-controlled, parallel-group, multicentre study designed to compare the efficacy and safety of rivaroxaban versus placebo as primary prophylaxis of VTE in ambulatory patients who are receiving systemic cancer treatment and are at an increased risk for VTE

Thromb Haemost 117: 2135, 2017

CASSINI study endpoints

Efficacy	
Primary	• Composite of time from randomization to first occurrence of symptomatic, lower-extremity, proximal DVT; asymptomatic, lower-extremity, proximal DVT; symptomatic, upper-extremity DVT; symptomatic, nonfatal PE; incidental PE; or VTE-related death during the 180-d (±3 d), double-blind treatment period
Key secondary	• Symptomatic VTE events
	• VTE-related deaths
	• All-cause mortality
Other	• Time from randomization to first occurrence of individual components of the composite primary efficacy endpoint
	• Confirmed fatal/non-fatal arterial thromboembolism events
	• Confirmed fatal/non-fatal visceral VTE events
	• Composite of symptomatic, lower-extremity, proximal DVT; asymptomatic, lower-extremity, proximal DVT; symptomatic, upper-extremity DVT; symptomatic, non-fatal PE; incidental PE; and all-cause mortality
Safety	
Primary	• Time to a major bleeding event as defined by the ISTH
Secondary	• Percentages of clinically relevant non-major bleeding, minor bleeding and any bleeding
Exploratory	
	• Inflammation and hypercoagulability biomarkers (e.g., D-dimer, P-selectin and tissue factor)
	• Pharmacokinetics and exposure response to rivaroxaban
	• Health care resource utilization

Abbreviations: DVT, deep-vein thrombosis; ISTH, International Society on Thrombosis and Haemostasis; PE, pulmonary embolism; VTE, venous thromboembolism.

CASSINI Study

Major inclusion and exclusion criteria for patient selection

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

Abbreviations: CrCl, creatinine clearance; CT, computed tomography; CU, compression ultrasonography; ECOG, Eastern Cooperative Oncology Group; PS, performance status; VTE, venous thromboembolism.

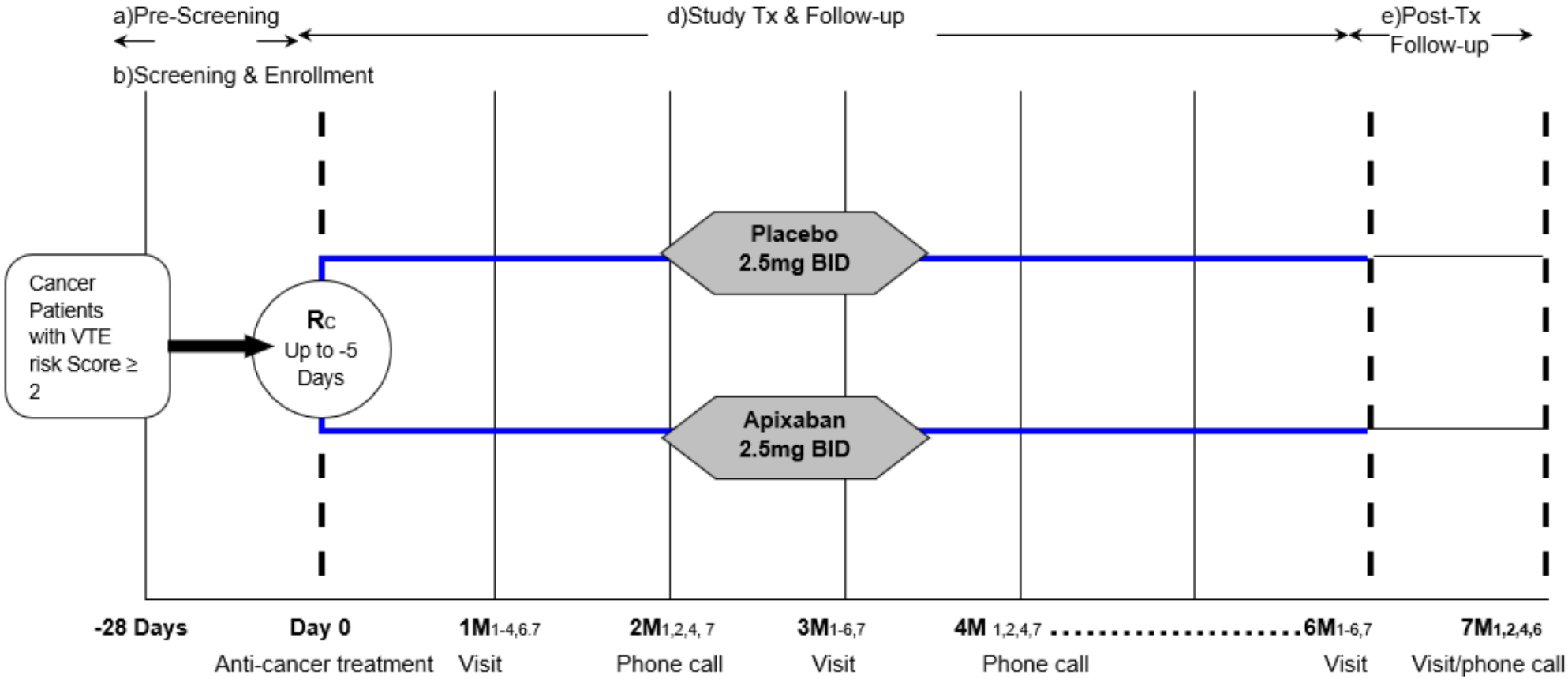
AVERT Trial

Apixaban for the Prevention of Venous Thromboembolism in High-Risk Ambulatory Cancer Patients Receiving Chemotherapy

AVERT will randomize 574 ambulatory cancer patients receiving chemotherapy who are at high-risk for VTE (as defined by a Khorana score of ≥ 2) to Apixaban 2.5mg BID versus placebo for 180 days.

Carrier et al, Thromb Res 2018

AVERT study design



a) Assessment VTE risk by using CBC & BMI within the last 28 days

b) - Eligibility assessment
- Patient's demographics
- Medical history
- Concomitant Medication
- Malignancy characteristics
- Plan of cancer treatment
- Laboratory test
(p-selectin,d-dimer, prothrombin F1+F2, anti-factor Xa)
- Quality of life questionnaire (SF-36)

c) Randomization will occur up to and including 5 days prior to the anti-cancer treatment

d) 1 Surveillance for AEs
2 Assessment of VTE & Bleeding
3 Assessment compliance study drug (patient's diary, pill count at Months 3 and 6)
4 Review concomitant medication and cancer treatment plan
5 Quality of life questionnaire (SF-36)
6 Laboratory test (P-selectin, D-dimer, prothrombin F1+F2, anti-factor Xa)
7 Success of blinding assessment at 6M or if definite study drug discontinuation occurred

Note : all follow-up visits are performed **± 14 days**

Avert: Study Outcome

The **primary efficacy outcome** will be the first episode of objectively documented VTE (DVT and/or PE) within the first 6 months (180 days +/- 3 days) following initiation of the blinded study drug.

VTE is defined as any symptomatic or incidental DVT of the lower limbs**,** any symptomatic or incidental DVT of the upper limbs (including central venous catheter-related thrombosis)**,** any non-fatal symptomatic or incidental PE, and VTE-related deaths (fatal PE or unexplained death).

The **secondary safety outcomes** will be major bleeding, CRNMB, and overall survival rates within the study period in the experimental and placebo arms.

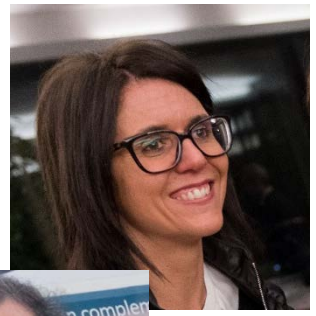
Other VTE sites (e.g. cerebral vein, splenic vein, portal vein, mesenteric vein, hepatic vein, renal vein, gonadal vein) will be considered as secondary outcomes.

Exploratory endpoints including biomarkers (D-Dimer, P-selectin, prothrombin F1+F2, anti-factor Xa, etc.) and health care utilization will also be collected.

Hemostasis and Thrombosis Center Bergamo

Anna Falanga

Teresa Lerede
Luca Barcella
Laura Russo
Marina Marchetti
Alfonso Vignoli
Carmen J. Tartari
Sara Gamba
Cristina Verzeroli
Cinzia Giaccherini
Francesca Schieppati
Shenaz Brevi
Davide Raffaeli
Erika Diani











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