TEV: il punto di vista del medico internista

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Le osservazioni di Trousseau (1865)

Sindrome della tromboflebite migrante associata al cancro

In pazienti affetti da tumore…
'si verifica nella cachessia…
una particolare condizione del sangue che lo predispone ad una coagulazione spontanea…'

- *1801-1867*

Trousseau A. Phlegmasia alba dolens. Clinique médicale de l'Hôtel-Dieu de Paris. 2nd ed. Paris: JB Balliere et Fils; 1865. p. 654-712.

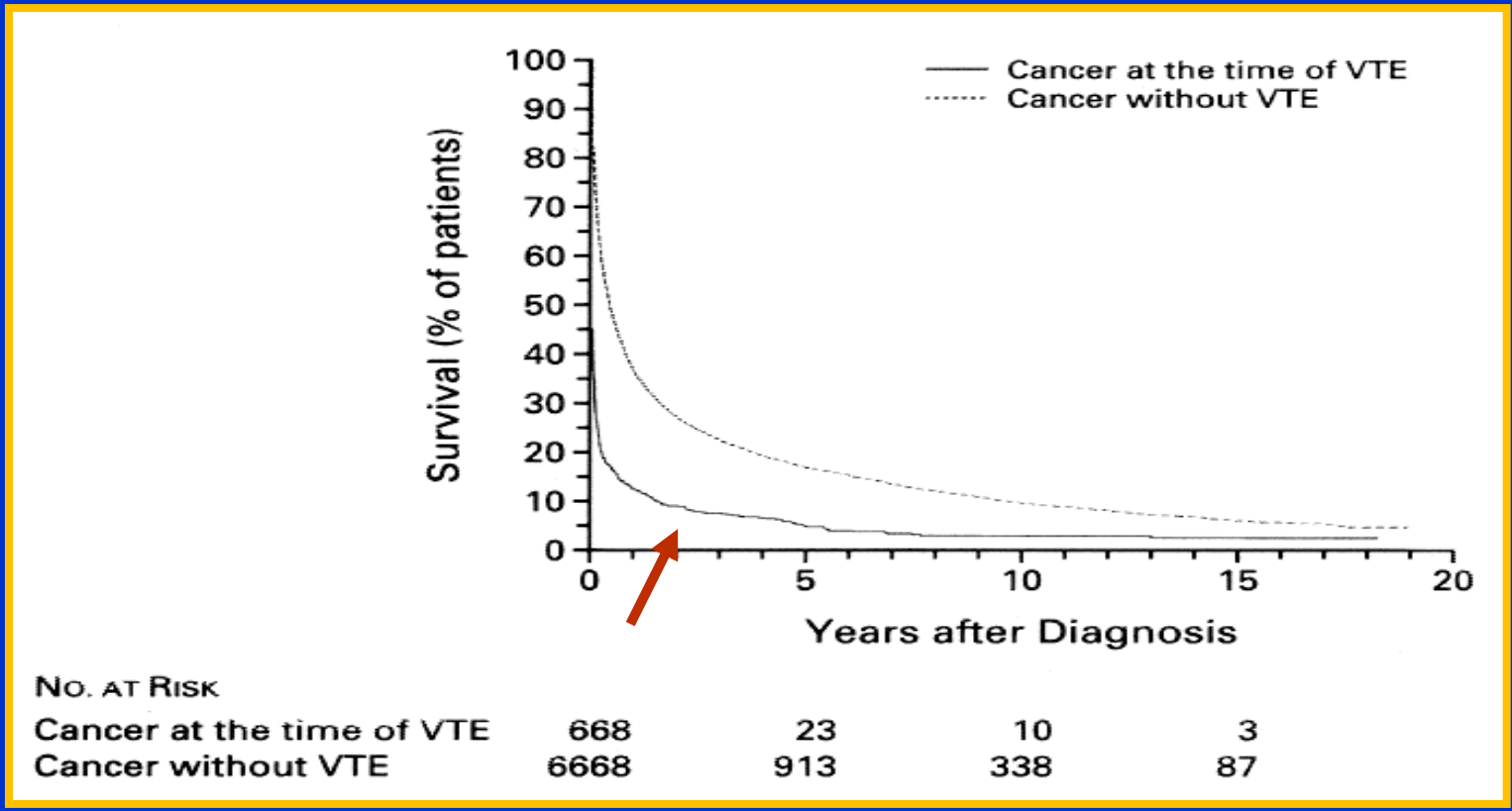
"Trombosi e cancro"

- Si è stimato che circa il 15% dei pazienti neoplastici presenta una complicanza tromboembolica nel corso della sua malattia.
- La TEP fatale è la seconda causa di morte nel paziente oncologico.
- La TEP è la primaria causa di morte nell' 8-35% dei pazienti con cancro ed è una concausa in un ulteriore 43% dei pazienti.
- È noto che i pazienti oncologici presentano una più significativa "ricorrenza" di eventi tromboembolici rispetto ai pazienti non neoplastici.

TROMBOSI E CANCRO

- Prognosi
- Profilassi
- Terapia

Prognosi nei pazienti oncologici con TEV



Sorensen et al. *N Engl J Med* 2000

Nei pazienti con cancro la prevenzione del TEV è una priorità superiore che non negli altri pazienti, perché:

- **Spesso la diagnosi di TEV è più difficile.**
- **Spesso è più elevato il rischio emorragico.**
- **Spesso il trattamento della TEV ha meno successo.**

- **Profilassi nel paziente medico**
- **Profilassi nel paziente chirurgico**
- **Profilassi nel paziente in chemioterapia**

La profilassi antitrombotica deve considerare:

- Tipo di tumore
- Stadio clinico
- Farmaci utilizzati
- Fasi di trattamento
- Condizioni cliniche associate

Tumori più frequentemente associati a TEV distinti per sesso

MASCHI:

- **Prostata**
- **Polmone**
- **Pancreas.**

FEMMINE:

- **Mammella**
- **Pancreas.**

Glioblastoma (7 -28% TEV / anno)

Levine et al.

Patient-Associated Risk Factors

- Older age
- Race
- Gender
- Medical comorbidities
- Obesity
- History of thrombosis

Cancer-Associated Risk Factors

- Primary site
- Stage
- Cancer histology (higher for adenocarcinoma than squamous cell)
- Time after initial diagnosis (highest in first 3–6 months)

Treatment-Associated Risk Factors

- Chemotherapy
- Antiangiogenic agents (thalidomide, lenalidomide)
- Hormonal therapy
- Erythropoiesis-stimulating agents
- Transfusions
- Indwelling venous access devices
- Radiation
- Surgery

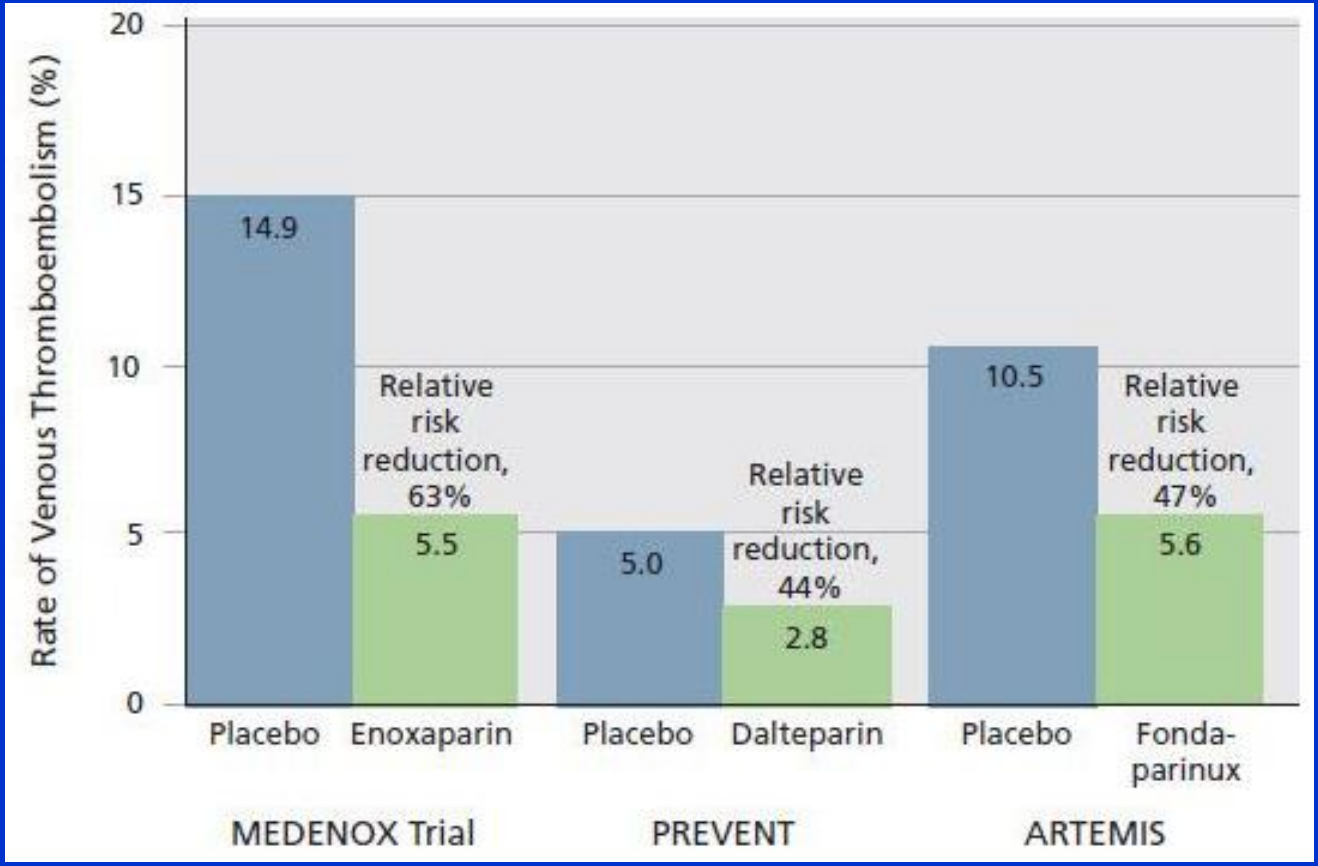
Guidelines for VTE Prophylaxis and Treatment in Patients with Cancer Released by National and International Scientific Societies

- AIOM (Italian Society Medical Oncology)
- ASCO (American Society of Clinical Oncology)
- NCCN (National Comprehensive Cancer Network)
- ESMO (European Society of Medical Oncology)
- ACCP (American College of Chest Physicians)
- IUA (International Union of Angiology)
- SISET (Italian Society Study Haemostasis and Thrombosis)

PROFILASSI PRIMARIA

		Cancer Pt		Placebo events		Treatment events	
Reference	N° TOTAL PATIENTS	No	%	No.	%	No.	%
MEDENOX	579	72	12.4	43/288	14.9	16/291	5.5
PREVENT	3.706	190	5.1	73/1473	4.96	42/1518	2.77
ARTEMIS	849	131	15.4	34/323	10.5	18/321	5.6

Trials di prevenzione nei pazienti medici ricoverati per patologie acute


Rate of Venous Thromboembolism (%)
20
15
10
5
0
14.9
Relative risk reduction, 63%
5.5
5.0
Relative risk reduction, 44%
2.8
10.5
Relative risk reduction, 47%
5.6
Placebo
Enoxaparin
Placebo
Dalteparin
Placebo
Fonda-parinux
MEDENOX Trial
PREVENT
ARTEMIS

Profilassi nel paziente oncologico sottoposto ad intervento

TVP distali	**40-80%**
• TVP prossimali	**20-30%**
• EP clinicamente evidente	**4-10%**
• EP fatale	**1-5%**

Consensus statement on antithrombotic therapy
ACCP CHEST 1998

La TVP post-chirurgica è 3-5 volte più frequente nei pazienti sottoposti a chirurgia oncologica rispetto ai pazienti non oncologici sottoposti allo stesso intervento

Walsh JJ et al J Obstet Gynaecol Br Commonw 1974

età avanzata

- procedure chirurgiche lunghe e demolitive
- post-operatorio prolungato con lunga immobilizzazione

40% delle EP fatali si manifestano nella seconda settimana dopo l'intervento

Lindbad B et al. Am J Surg 1995;169(2):214-6

- **tutti i pazienti sottoposti ad intervento chirurgico per una neoplasia maligna devono essere considerati per una profilassi del TEV**
- **pazienti sottoposti a laparatomia, laparoscopia e toracotomia per un periodo superiore a 30' devono ricevere una profilassi farmacologica con EBPM se non sono presenti controindicazioni assolute per un'elevato rischio di sanguinamento o per un'emorragia in corso**
- **la profilassi deve essere iniziata nel pre-opratorio o prima possibile**
- **i mezzi meccanici non devono essere usati in monoterapia**
- **un trattamento combinato farmacologico e con mezzi meccanici migliora l'efficacia nei pazienti ad alto rischio**
- **la profilassi deve essere continuata per 7-10 giorni dopo l'intervento. Una profilassi prolungata deve essere riservata ai pazienti sottoposti a chirurgia pelvica o addominale per un cancro con alto rischio di malattia residua dopo l'operazione o nei pazienti obesi o in quelli con precedenti di TEV**

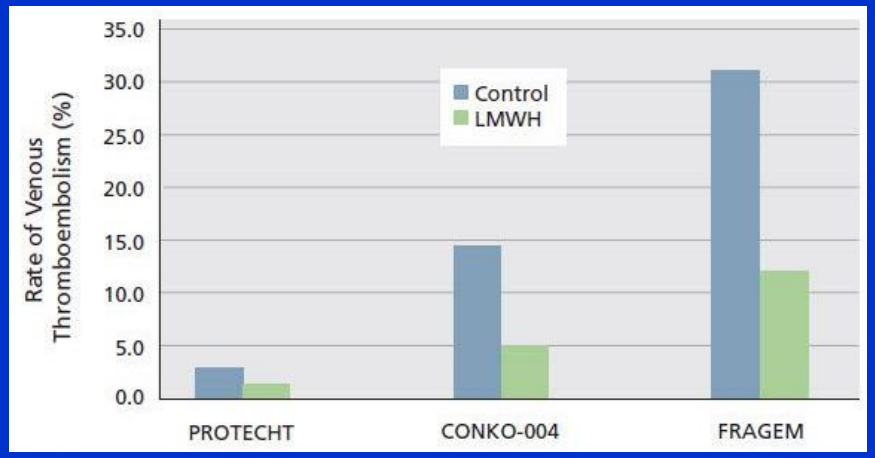
TEV e CHEMIOTERAPIA

il rischio di TEV varia dal 15-20% a seconda del tipo di **chemioterapia**

- **Chemioterapia determina effetti trombogeni** attraverso:
  - **attivazione aggregazione piastrinica**
  - **tossicità endoteliale**
  - **espressione di TF da parte monociti/macrofagi, cellule endoteliali**
  - **riduce attività fibrinolitica**
  - **aumenta apoptosi cellule endoteliali**

Agnelli G. Thrombosis Research 2007, 120 (Suppl 2); S128-S132

Thromboembolic events: cumulative event rate



PROTECHT

Thromboembolic events by treatment and cancer site

	Nadroparin (15/769)	Placebo (15/381)	All (30/1150)
Lung *	7/199 (3.5%)	7/80 (8.8%)	15/279 (5.4%)
GI	4/272 (1.5%)	4/148 (2.7%)	8/420 (1.9%)
Pancreas	3/36 (8.3%)	1/17 (5.8%)	4/53 (7.5%)
Other	1/262 (0.4%)	3/136 (2.2%)	4/398 (1.0%)

* NNT = 18.7

PROTECHT

Main Secondary Study Outcomes

	Nadroparin (n=769)	Placebo (n=381)	p
Major bleedings	5 (0.7%)	0	NS
Minor bleedings	57 (7.4%)	30 (7.9%)	NS
Death (EOT *)	33 (4.3%)	16 (4.2%)	NS
Death (at 12-mo)	333 (43%)	155 (41%)	NS

* EOT: end of treatment

PROTECHT

Venous Thromboembolism in Non-Small Cell Lung Cancer Patients: Retrospective Analysis of Cases Treated at the Oncology Day Hospital of Novara, Italy

Roberta Buosi[1]
Gloria Borra[1]
Oscar Alabiso[1]
Alessandra Galetto[1]
Giovanni Pappagallo[2]
Mauro Campanini[3]

355 pazienti con NSCLC

36 casi: incidenza TEV 12%

31 casi TEV in CT

Table 1.

Patients' characteristics.

	Number (%)
Patients' characteristics	
Median age (range)	68 (31-84 years), distance-IQ 14
>65 years	58% (177)
Male	80% (245)
Female	20% (62)
Adenocarcinoma	60% (186)
Squamous-cell carcinoma	31% (95)
Large-cell carcinoma	2% (5)
NOS	7% (21)
TNM stage	
I	2% (7)
II	9% (29)
IIIa	6% (16)
IIIb	22% (68)
IV	61% (187)
BMI	
<25%	69% (153)
>25%	31% (70)
N.D.	(84)
Baseline LMWH	
Yes	13% (39)
No	87% (268)
Ongoing ASA	
Yes	81% (249)
No	19% (58)

Italian Journal of Medicne 2013;7:113-118

VTE RISK PREDICTION TOOL (KHORANA)

Patient characteristic (site of cancer)	Risk score*
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynaecological, bladder, testicular)	1
Prechemotherapy platelet count 350×10^9/l or more	1
Haemoglobin level less than 110 g/l or use of red cell growth factors	1
Prechemotherapy leucocyte count more than 11×10^9/l	1
BMI 35 kg/m^2 or more	1

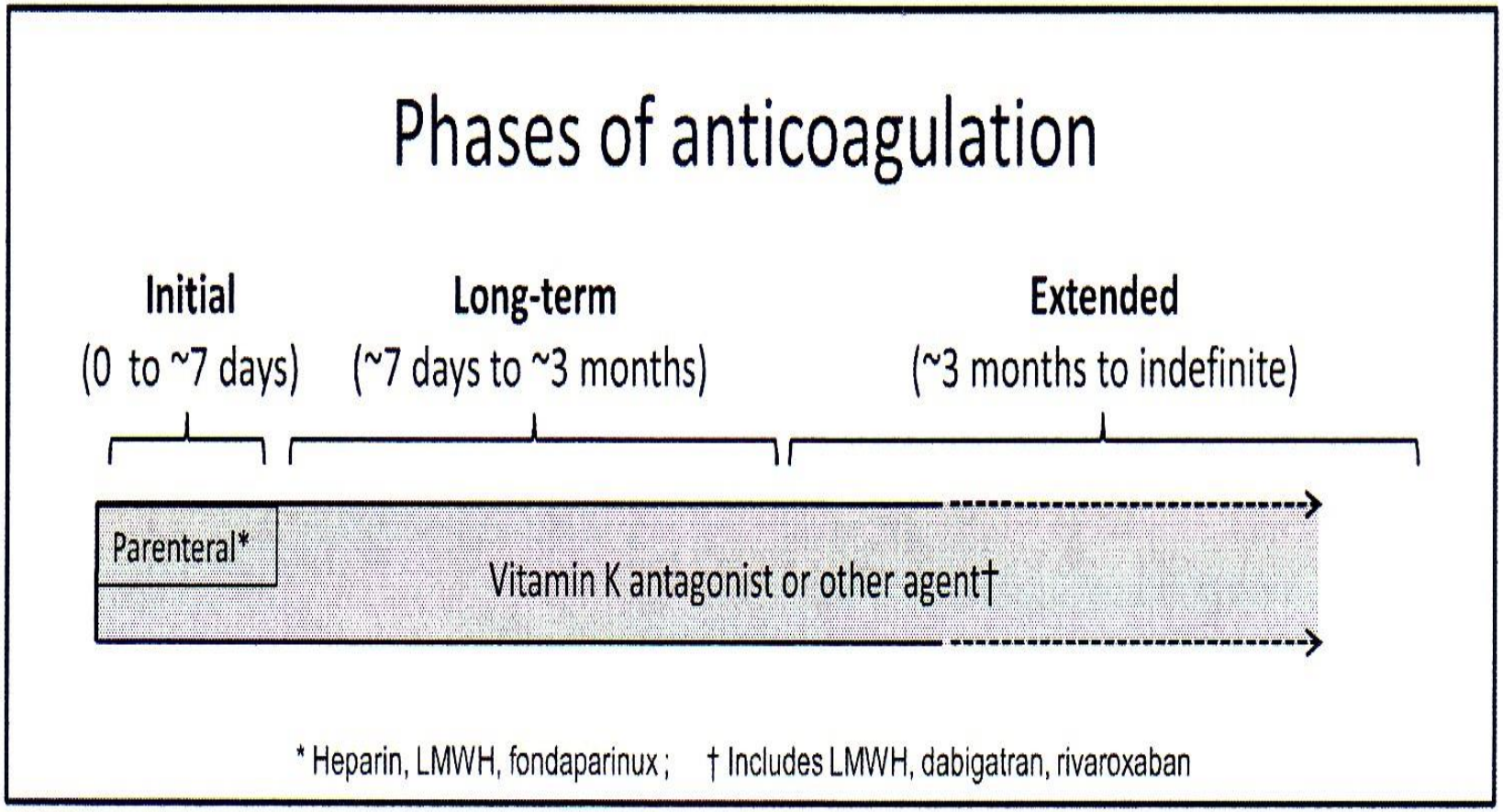
The Khorana risk assessment tool is the best way of assessing risk for VTE in cancer patients.

* 0 points = low risk; 1–2 points = intermediate risk and ≥3 points = high risk

Source: AA Khorana et al. *Blood* (2008) 111:4902–07, published with permission from American Society of Hematology

Terapia del TEV nel paziente con cancro

Initial and long term treatment of VTE



Kearon, Chest, 2012

4 convinzioni (sbagliate) sulla terapia del TEV associata a neoplasia

La definizione è chiara

Tutti devono fare lo stesso dosaggio

La durata è uguale per tutti

Tutti la devono fare per un lungo periodo

Oral anticoagulant therapy in cancer patients

La terapia con warfarin è complicata nei pazienti con cancro

- difficile mantenere un valore di INR stabile ed idoneo (anoressia, vomito, interazione con i farmaci)
- Problema degli accessi venosi
- Frequenti interruzioni per trombocitemia e procedure invasive
- Aumentato rischio di ricorrenza e sanguinamento

Oral anticoagulant therapy and **VTE recurrence**

Author	Cancer	Non-cancer	P
Hutten, 2000	27.1 %	9.0 %	0.003
Palareti, 2000	6.8 %	2.5 %	0.06
Prandoni, 2002	20.7 %	6.8 %	<0.001

Hutten, J Clin Oncol, 2000
(Data from Koopman & Columbus)
Palareti, Thromb Haemost, 2000
Prandoni, Blood, 2002

Oral anticoagulant therapy and **major bleeding**

Author	Cancer	Non-cancer	P
Hutten, 2000	13.3 %	2.1 %	0.002
Palareti, 2000	21.6 %	4.5 %	0.001
Prandoni, 2002	12.4 %	4.9 %	0.019

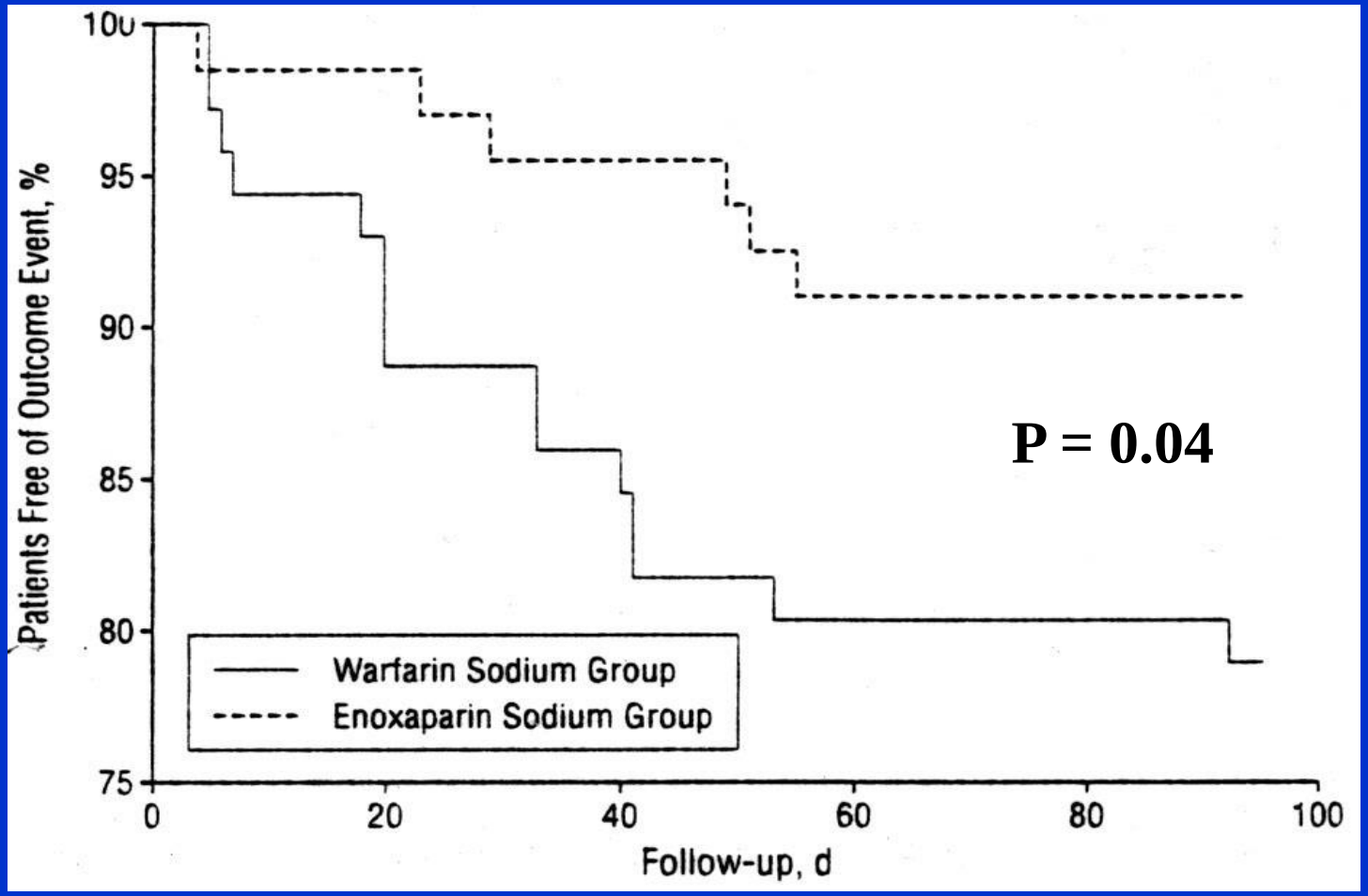
Hutten, J Clin Oncol, 2000
(Data from Koopman & Columbus)
Palareti, Thromb Haemost, 2000
Prandoni, Blood, 2002

LMWH for secondary prophylaxis of VTE in cancer patients

STUDY	THERAPY	PATIENTS (n)	LMWH DAILY DOSE	DURATION (months)
Meyer 2002	Enoxaparin OA	71 75	1.5 mg/kg	3
Lee 2003	Dalteparin OA	336 336	200 (150) UI/kg	6
Hull, 2006	Tinzaparin OA	100 100	175 UI/kg	3
Deitcher, 2006	Enoxaparin OA	31 /36 34	a) 1.5 mg/kg b) 1 mg/kg	6

Randomized, open-label, multicenter trials

Recurrent venous thromboembolism or major haemorrage during 3 months treatment in 138 patients with cancer and VTE



Meyers, Arch Intern Med, 2002

***3. In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy** (Grade 2C), **dabigatran** (Grade 2C), **rivaroxaban** (Grade 2C), **apixaban** (Grade 2C), **or edoxaban** (Grade 2C).

AT10. CHEST 2016;149(2):315-352

Recommendations for pulmonary embolism in cancer

Recommendations	Class[a]	Level[b]	Ref[c]
Incidental PE in patients with cancer should be managed in the same manner as symptomatic PE.	IIa	C	447–449, 463
Negative D-dimer levels have the same negative diagnostic value as in non-cancer patients.	IIa	B	98, 443
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 3–6 months.	IIa	B	278, 376, 377
For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C	

LMWH = low molecular weight heparin; PE = pulmonary embolism.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

ESC Guidelines. Eur Heart J 2014;35

Vascular Medicine

Development of a Clinical Prediction Rule for Risk Stratification of Recurrent Venous Thromboembolism in Patients With Cancer-Associated Venous Thromboembolism

Martha L. Louzada, MD, MSc; Marc Carrier, MD, MSc; Alejandro Lazo-Langner, MD, MSc;

Table 2. Ottawa Score for Recurrent VTE Risk in Cancer-Associated Thrombosis

Variable	Regression Coefficient	Points
Female	0.59	1
Lung cancer	0.94	1
Breast cancer	−0.76	−1
TNM* stage I	−1.74	−2
Previous VTE	0.40	1
Clinical probability		
Low (≤0)	. . .	−3 to 0
High (≥1)	. . .	1 to 3

VTE indicates venous thromboembolism.
*TNM (tumor-nodes-metastasis staging system) for solid tumors only.

retrospective cohort and a validation study to derive a clinical prediction rule that stratifies VTE recurrence risk.
543 patients
-included 4 independent predictors (sex, primary tumor site, stage, and prior VTE)
-the score sum ranged between - 3 and 3 points. Patients with a **score 0 had low risk (4.5%)** for recurrence and **patients with a score 1 had a high risk (19%)** for VTE recurrence.

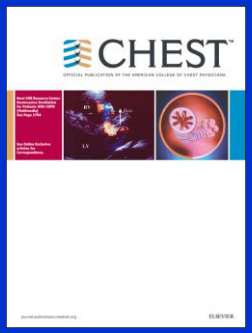
Circulation. 2012;126:448-454

In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who:

(i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B),

(ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B).

***Remarks*: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g. annually).**



Antithrombotic Therapy for VTE Disease: CHEST Guideline, *CHEST* (2016), doi: 10.1016/j.chest.2015.11.026.

Predicting recurrences or major bleeding in cancer patients with venous thromboembolism

Findings from the RIETE Registry

Javier Trujillo-Santos[1], José Antonio Nieto[2], Gregorio Tiberio[3], Andrea Piccioli[4], Pierpaolo Di Micco[5], Paolo Prandoni[4], Manuel Monreal[6]

Bleeding
Older age (>65 years)
Higher intensity anticoagulation
Prior gastrointestinal bleeding
Thrombocytopenia
Overdosing
Bleeding diathesis (eg, elevated INR in cirrhosis)
Immobilization
Presence of metastases
Creatinine clearance <30 mL/min

Table 2: Multivariate analysis on the risk to develop recurrent PE, recurrent DVT, or major bleeding.

	Odds ratio (95% CI)	P-value
Major bleeding		
Recent major bleeding	2.4 (1.1–5.1)	0.03
CrCl <30 ml/min	2.2 (1.5–3.4)	<0.001
Immobility ≥4days	1.8 (1.2–2.7)	0.005
Metastatic cancer	1.6 (1.1–2.3)	0.03

PE, pulmonary embolism; DVT, deep-vein thrombosis; CrCl, creatinine clearance; CI, confidence intervals.

Patients with immobility (OR: 1.8; 95% CI: 1.2–2.7), metastases (OR: 1.6; 95% CI: 1.1–2.3), recent bleeding (OR: 2.4; 95% CI: 1.1–5.1), or with creatinine clearance <30 ml/ min (OR: 2.2; 95% CI: 1.5–3.4), had an **increased incidence of major bleeding**

Thromb Haemost 2008; 100: 435–439

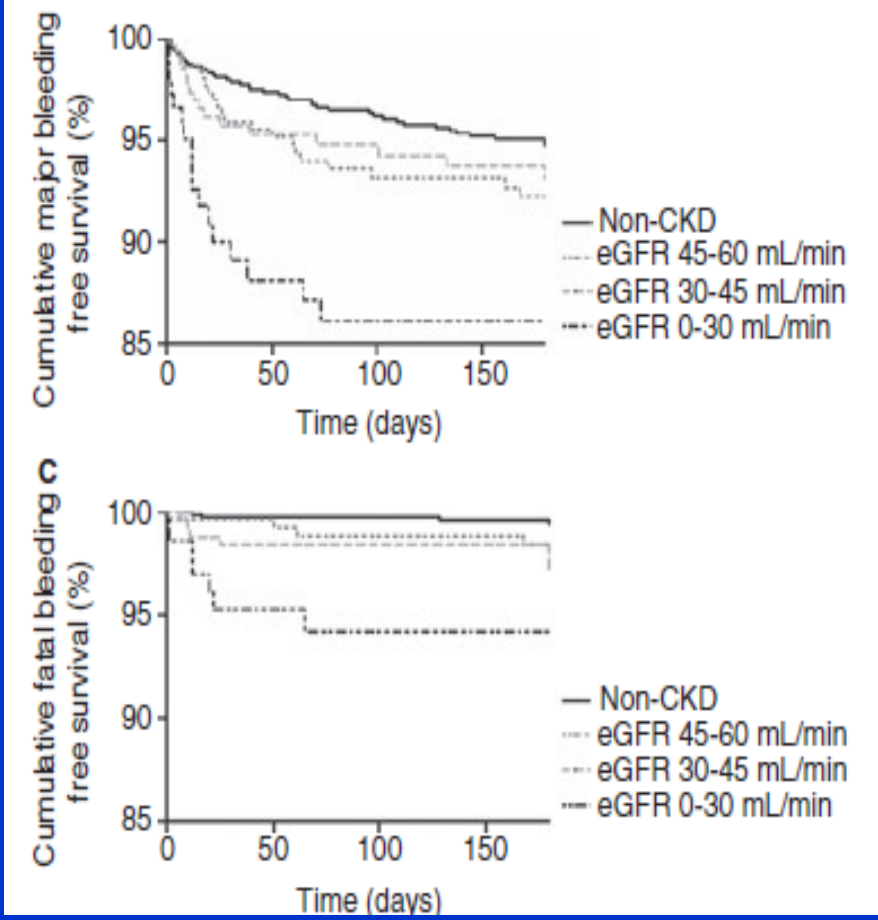
ORIGINAL ARTICLE

Impact of chronic kidney disease on the risk of clinical outcomes in patients with cancer-associated venous thromboembolism during anticoagulant treatment

J. KOOIMAN,* P. L. DEN EXTER,* S. C. CANNEGIETER,† S. LE CESSIE,† J. DEL TORO,‡

14.9% of cancer patients have concomitant moderate CKD (eGFR) 30–60 mL min and 1.2% severe CKD (eGFR < 30 mL min)

Cancer patients with VTE and CKD on anticoagulant treatment are at **increased risk of major and fatal bleeding** compared with non-CKD patients, and was most prominent in those treated with LMWH and an **eGFR < 30 mL min**. **These increased bleeding risks in CKD patients were mainly driven by the group treated with LMWH, not VKA**.



J Thromb Haemost 2013; 11: 1968–76.

4 nuove convinzioni (giuste?) sul TEV associato a cancro

Ci sono tante ‘VTE-associated cancer’

La terapia/dose varia a seconda del paziente

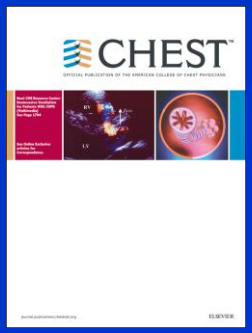
La durata non è uguale per tutti …

… qualcuno la può fare per un periodo breve

1. **Superficiale o profonda**
2. **TVP/EP o sede inusuale (cerebrale, splancnica, OVR)**
3. **Catheter-related o no**
4. **CHT-associata o no**
5. **Chirurgia-associata o no**
6. **Sintomatica o incidentale**

In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C) or edoxaban (Grade 2C).

***Remarks*: Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy.**



Antithrombotic
Therapy for VTE Disease: CHEST Guideline, *CHEST* (2016), doi: 10.1016/j.chest.2015.11.026.

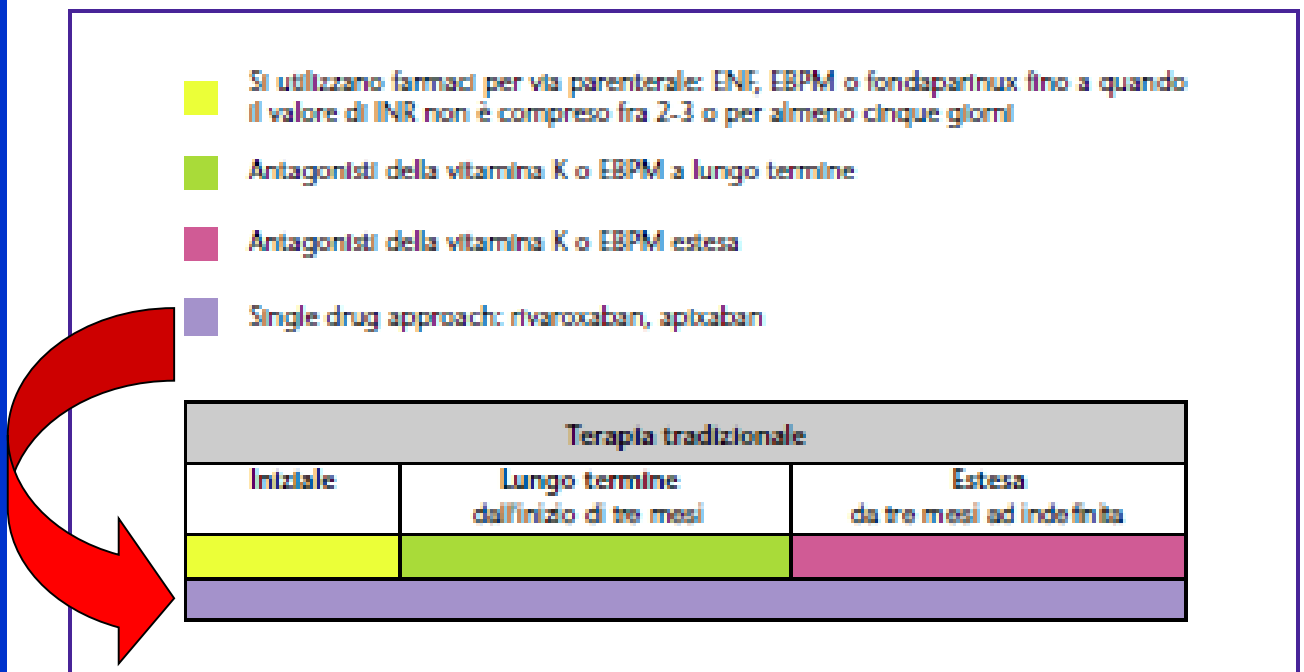


Figura 3.1 Schema della terapia anticoagulante secondo i protocolli tradizionali e secondo il nuovo approccio del "single drug approach". ENF, eparina non frazionata; EBPM, eparina a basso peso molecolare; INR, International normalized ratio.

Mauro Campanini, Michelangelo Di Salvo. La trombosi venosa profonda e l'embolia polmonare: dalle tecniche diagnostiche alla nuova strategia terapeutica del "single drug approach". 2013

American Society of Clinical Oncology Clinical Practice Guideline Update

- LMWH is recommended for the initial 5 to 10 days of treatment for patients with established DVT and PE, as well as for long-term (6 months) secondary prophylaxis
- Use of NOACs is not currently recommended for patients with malignancy and VTE
- Oncology professionals should provide patient education about the signs and symptoms of VTE

Lyman GH, et al. *J Clin Oncol.* 2013;31:2189-2204.[2]

NOA for VTE: pooled analyses

Recurrent VTE	NOAC	Conv. Treat.	RR (95% CI), p
Body weight ≥ 100 kg	2.4%	2.7%	0.92 (0.64-1.32), 0.65
Age ≥ 75 years	2.1%	3.8%	0.56 (0.38-0.82), 0.003
CrCl 30-49 ml/min	2.9%	4.4%	0.70 (0.43-1.15), 0.16
Cancer	3.8%	5.9%	0.63* (0.37-1.10),

* OR

Van Es Blood 2014; Vedovati Chest 2014

NOA for VTE: pooled analyses

Major Bleeding	NOAC	Conv. Treat.	RR (95% CI), p
Major GI bleeding	0.5%	0.6%	0.78 (0.47-1.31), 0.35
Age ≥ 75 years	2.0%	4.1%	0.49 (0.25-0.96), 0.04
CrCl 30-49 ml/min	1.8%	3.8%	0.51 (0.26-0.99), 0.05
Cancer	3.2%	4.2%	0.77 (0.41-1.44),

* OR

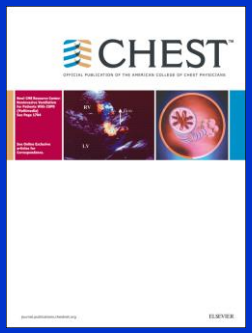
Van Es Blood 2014; Vedovati Chest 2014

NOACs
Limitations in Cancer Patients

- Paucity of clinical trial data
  - Cancer patients constituted <10% of the population
- No comparison with LMWHs
  - Comparisons with warfarin in clinical trials
- Patients were not representative of cancer patients
- Drug interactions with chemotherapy agents may be clinically important
- Liver and renal dysfunction is common in cancer patients
  - NOACs are cleared renally to varying extent
  - NOACs are metabolized in the liver to varying extent

In patients with acute DVT or PE who are treated with anticoagulants, we recommend against the use of an IVC filter (Grade 1B).

In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE we suggest clinical surveillance over anticoagulation (Grade 2C)**, and (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance** (Grade 2C)**.**



Antithrombotic Therapy for VTE Disease: CHEST Guideline, *CHEST* (2016), doi: 10.1016/j.chest.2015.11.026.

- La diagnosi di EP subsegmentale è spesso un falso positivo rispetto alla diagnosi di EP segmentale o prossimale
- La EP subsegmentale è probabile che abbia avuto origine da una TVP di minore entità, il rischio di un TEV ricorrente o progressivo è ridotto.
- US bilaterale per escludere TVP prossimale
- Se TVP presente il paziente deve essere scoagulato
- Non esistono trials randomizzati sulle EP subsegmentarie

Fattori di rischio per ricorrenza:

- ospedalizzazione o ridotta mobilità
- cancro in fase attiva
- non sono presenti fattori di rischio reversibili e chirurgia recente

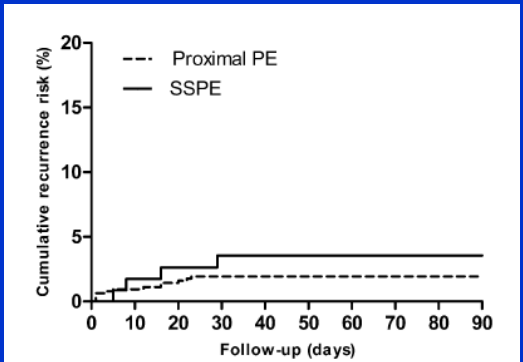


Figure 1. Cumulative recurrence risk SSPE vs proximal PE. Cumulative risk of recurrent VTE for patients with SSPE vs patients with proximal (defined as segmental or central) PE ($P = .42$ from the log-rank test).

AT10. CHEST 2016;149(2):315-352

La diagnosi di EP subsegmentale è probabile che sia corretta se:

1. Le immagini TC sono di alta qualità
2. Difetti intraluminali multipli
3. I difetti comprendono arterie subsegmentali prossimali
4. Pazienti sono sintomatici
5. Elevato rischio pre-test di probabilità
6. Livelli di D-dimero elevati
7. I difetti emergono con il contrasto piuttosto che immagini aderenti alla perete del vaso
8. Sono presenti in più immagini

AT10. CHEST 2016;149(2):315-352

International clinical practice guidelines for the treatment and prophylaxis of VTE in patients with cancer

- **In cancer patients with thrombocytopenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is > 50 G L^{-1} and there is no evidence of bleeding**

- **For patients with a platelet count below 50 G L^{-1}, decisions on treatment and dosage should be made on a case-by-case basis with the utmost caution**

Farge, J Thromb Haemost, 2013

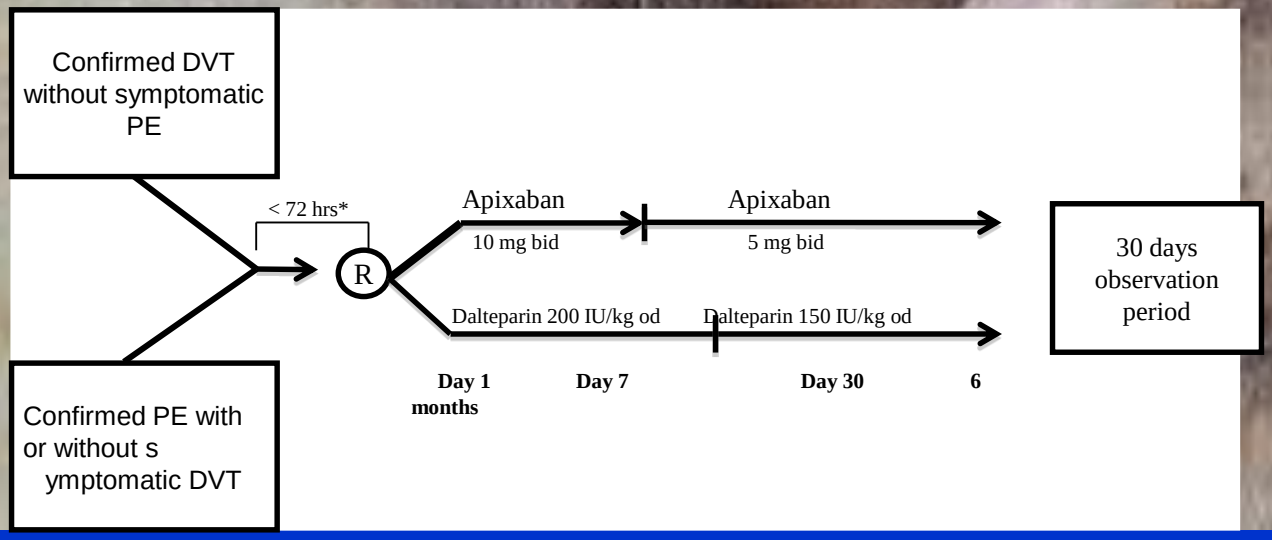
La Ricerca Clinica FADOI: Promotore di uno studio Investigator-Initiated internazionale

Giancarlo Agnelli – Mauro Campanini

- **Ricerca promossa e coordinata da FADOI, con collaborazione scientifica dell'Università di Perugia (Coordinatore Prof. G. Agnelli)**
- **Studio randomizzato controllato con utilizzo di un DOAC (Apixaban) per il trattamento del tromboembolismo venoso in pazienti con cancro, vs terapia standard (EBPM)**
- **Arruolamento di circa 1200 Pazienti in 8 Paesi Europei + Israele + USA+ Canada**
- **Inizio studio previsto IIIQ-2016**

STUDIO CARAVAGGIO

APIXABAN FOR THE TREATMENT OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER: A PROSPECTIVE RANDOMIZED OPEN BLINDED END-POINT (PROBE) STUDY



Parma Marathon 16 ottobre 2016

Il Campa è “tornato”

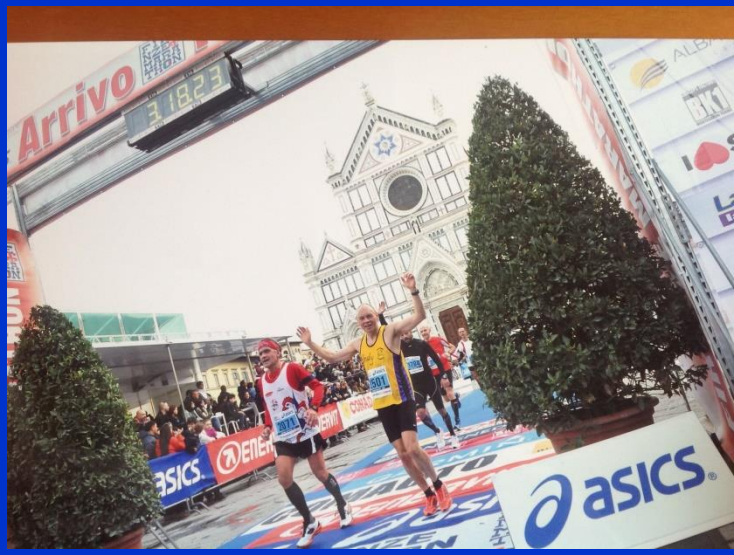
Nizza Cannes Marathon **13 nov 2016 ?**

Trino Marathon 26 nov 2016 ?

Venice marathon 2011

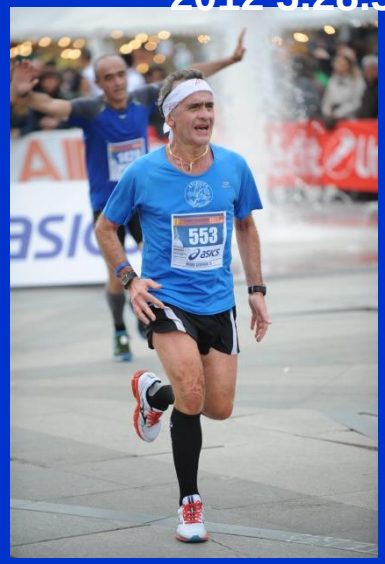
3.38.43

Venice marathon 2012 3.28.34



Firenze marathon 2013

3.18.00



Turin marathon 2014

3.16.34

Roma marathon 15 marzo 2015

Lago Maggiore marathon

18 ottobre 2015

3.14’28”

Verona marathon 15 novembre 2015

3.29’.51’’

Trino marathon 29 novembre 2015

3.26.16”