TERZO MEETING DI EMATOLOGIA NON ONCOLOGICA
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Le anemie

Anemia e cancro: un fattore di rischio per trombosi?

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Cancer and VTE

- Patients with cancer have a 4–7 fold increased risk for VTE as compared to non-cancer patients;
- VTE affects 4-20% of cancer patients *antemortem* but has been reported in up to 50% on *postmortem* examination.
- 15–20% of all VTE cases occur in patients with cancer.
- VTE in cancer patients is associated with important complications, including an 8–10% annual risk of bleeding with anticoagulant therapy and an annual 21–27% risk of VTE recurrence.

Falanga et al. Curr Opin Hematol 2014; Agnelli et al. JTH 2011; Lee A., 2013

Thrombotic disorders associated with malignancy

Venous districts

Deep vein thrombosis

Pulmonary embolism

Splanchnic vein thrombosis

Arterial districts

Cerebrovascular occlusion

Peripheral arterial occlusion

Non bacterial thrombotic endocarditis

Systemic syndromes

Disseminated Intravascular Coagulation

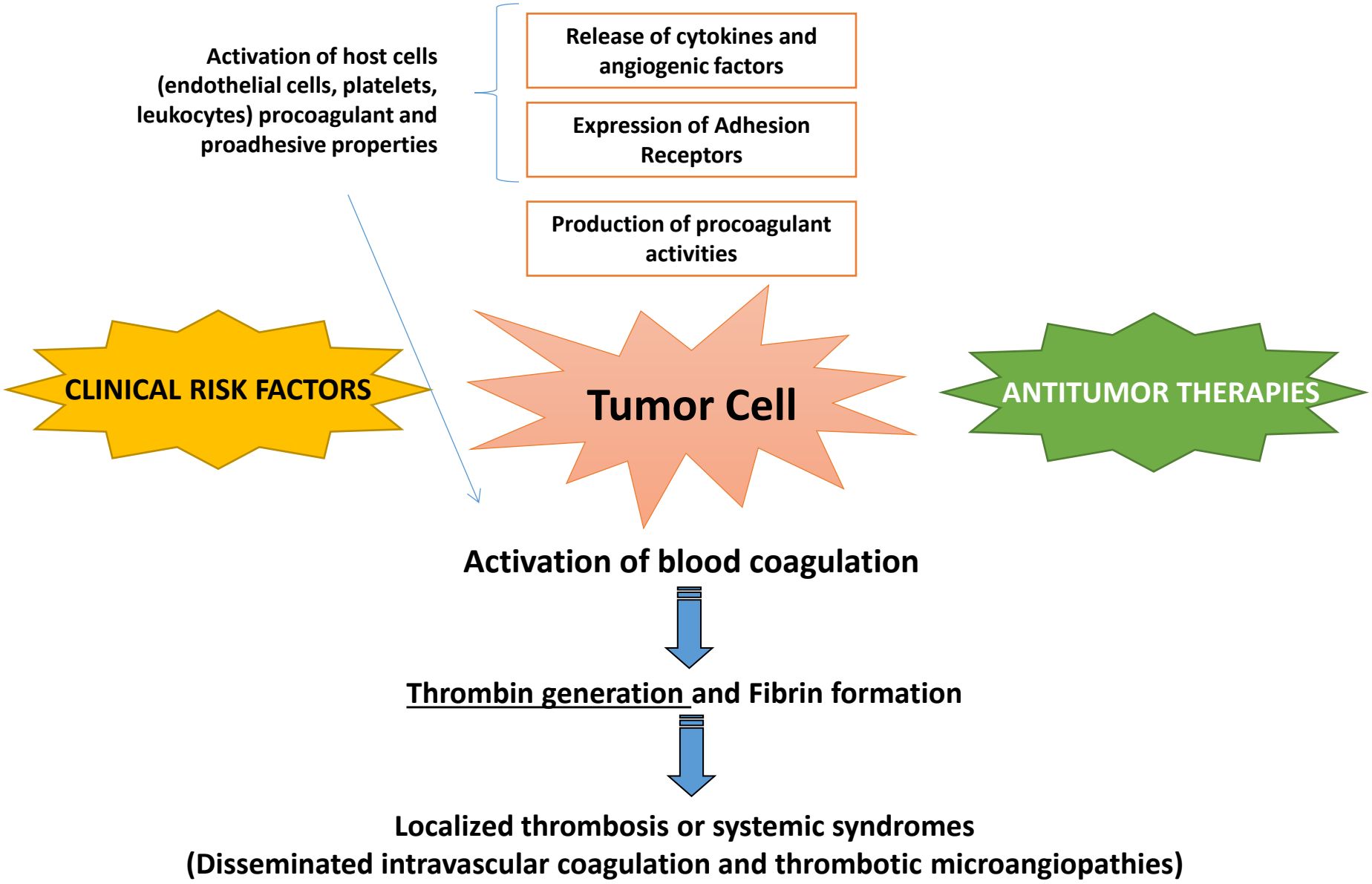
Thrombotic Thrombocytopenic Purpura

Venous occlusive disease

Stato di ipercoagulabilità

- I pazienti neoplastici comunemente presentano uno **stato di ipercoagulabilità** o di coagulazione intravascolare disseminata (CID) di basso grado.
- Lo stato di ipercoagulabilità è rappresentato dal riscontro di laboratorio di anomalie di uno o più test di attivazione dell'emostasi.
- I risultati di questi tests dimostrano che un processo di **continua formazione e rimozione di fibrina** è presente durante lo sviluppo di una neoplasia.
- Differenti gradi di alterazioni dei markers di attivazione della coagulazione sono associati con i vari stadi di avanzamento della malattia tumorale.

Rickles FR, Falanga A. Cancer Treat Res 2009.



Falanga A, Panova-Noeva M, Russo L Best Pract Res Clin Haematol 2009

Important Consequences of VTE in Cancer

- Increased morbidity
  - Hospitalization
  - Anticoagulation
  - Postphlebitic syndrome
- Increased mortality *(worse overall survival outcome)*
- Increased risk of recurrent VTE
- Bleeding complications *(2 times higher during anticoagulation)*
- Cancer treatment delays
- Increased healthcare costs

Anemia and Cancer

- Anemia may frequently occur in patients with cancer.
- Myelosuppressive chemotherapy or radiation therapy are frequent causes of anemia in patients with all types of cancer.
- In addition, anemia can be secondary to bone marrow invasion in leukemias and other blood malignancies, or to metastatic colonization of bone marrow by solid tumor cells
- Supportive treatment with blood transfusions, or treatment with erythropoiesis stimulating factors are the mainstay for anemia treatment in these conditions.

Terapie di supporto

- Le emotrasfusioni
- L’uso di fattori stimolanti l’eritropoiesi (ESA)

Fattori stimolanti l'eritropoiesi (ESA)

- Le terapie di supporto con l'eritropoietina umana ricombinante (EPO) e altri fattori di crescita emopoietici, come il GM-CSF ed il G-CSF, sono sempre più frequentemente utilizzate nei pazienti oncologici.

- L'uso di fattori stimolanti l'eritropoiesi (ESA) durante il trattamento chemioterapico permette una correzione dello stato anemico e una riduzione dell'associata sindrome da affaticamento (fatigue), migliorando di conseguenza la qualità di vita dei pazienti.

- L'ipossia è una caratteristica comune nella maggior parte dei tumori solidi e può determinare resistenza alla chemioterapia e alle radiazioni ionizzanti, deprivando le cellule tumorali dell'ossigeno necessario per l'attività citotossica di questi agenti.

- La riduzione dello stato ipossico a livello dei tessuti tumorali, favorita dall'utilizzo di agenti stimolanti l'eritropoiesi, consente quindi di aumentare la risposta al trattamento chemioterapico e radioterapico con beneficio in termini di sopravvivenza.

Risk Factors for Cancer-associated Thrombosis

Patient-related factors

- Advanced age
- Female gender
- Prior VTE
- Patient comorbidities (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 hormonal therapy
- Anti-angiogenic therapy
- **Erythropoiesis stimulating agents**
- **Blood transfusions**

Biomarkers

- Platelet count (>350,000/µl)
- Leukocyte count (> 11,000/µl)
- D-dimer
- Tissue Factor expression by tumor cells
- Circulating tissue factor (MPs)
- Soluble P-selectin
- C-reactive protein

A. Falanga; L. Russo - Hamostaseologie. 2012

“Thrombotic ***Risk stratification*** in patients with cancer”

“Khorana” Score

- The Khorana score was developed in a study population of 4,066 cancer patients started a new chemotherapy regimen that were enrolled in the “Awareness of Neutropenia in Chemotherapy” (ANC) Study Group Registry.

Khorana AA et al. Blood. 2008

Clinical Risk Model for Chemotherapy-associated VTE

Risk Score Based on Pretreatment Risk Factors

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 $\geq$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 $\geq$ 35 kg/m^2	1

Low risk: score 0
Intermediate risk: score 1-2
High risk: score $\geq$ 3

Khorana AA et al. Blood. 2008

Transfusional treatment and thrombosis in cancer

Blood Transfusions, Thrombosis and Mortality in Hospitalized Cancer Patients

- In a large retrospective cohort study involving 504,208 consecutive hospitalized cancer patients between 1995 and 2003, Khorana et al. evaluated the risk of thrombosis associated with transfusional requirement using a discharge database.

504,208 patients:

- 70,542 patients (14%) received at least 1 RBC transfusion
- 15,237 patients (3%) received at least 1 platelet transfusion

During follow-up:

- 7.2% patients receiving RBC transfusions developed DVT
- 3.8 % non-transfused patients developed DVT
- 5.2% patients developed arterial thromboembolism (ATE)
- 3.1 % non-transfused patients developed ATE

A.A. Khorana et al. Arch Intern Med. 2008

Transfusions	OR (95% CI) Venous thromboembolism	OR (95% CI) Arterial thromboembolism	P Value vs non-transfused
Red blood cell only	1.60 (1.53-1.67)	1.53 (1.46 – 1.61)	<.001
Platelets only	1.20 (1.11-1.29)	1.55 (1.40 – 1.71)	<.001

Transfusions were also associated with an **increased risk of in-hospital mortality** (**RBCs: OR, 1.34;** 95% CI, 1.29-1.38; **Platelets: 2.40**; 2.27-2.52; P<.001)

Both RBC and platelet transfusions are associated with increased risks of venous and arterial thrombotic events and mortality in hospitalized patients with cancer

A.A. Khorana et al. Arch Intern Med. 2008

Association of blood transfusion and venous thromboembolism after colorectal cancer resection

- In this study of 21,943 patients undergoing colorectal resection for cancer, blood transfusion is associated with increased risk of VTE.
  - OR 1.39 (95% CI 1.05 – 1.85) 1 – 2 RBC units
  - OR 1.88 (95% CI 1.19 – 2.99) 3 – 4 RBC units
  - OR 3.19 (95% CI 1.70 – 5.97) 5 - 6 RBC units

- **Malignancy** and **surgery** are known prothrombotic stimuli, the subset of patients receiving intraoperative **RBC transfusion** are even more at risk for VTE, emphasizing the need for sensible use of transfusions and rigorous thromboprophylaxis regimens

Xenos et al. Thrombosis Research 2012

Erythrocytes changes and effects on hemostasis

1. RBC transfusion improves platelet adhesion, shortens bleeding time and reverses the coagulopathy of anemia.

2. RBCs release procoagulant microparticles via phosphatidylserine exposure with thrombogenic potential.

3. Cold storage induces 20-fold increase of RBC MPs and RBCs become more rigid with morphologic changes.

4. RBCs promote platelet aggregation by scavenging nitric oxide although may release simil-NO substances.

G. Castaman. Thrombosis Research 2016

Erythropoiesis stimulating agents (ESA)

ESAs and thrombosis

- Erythropoiesis-stimulating agents (ESAs) such as darbepoetin alfa (DA) are among treatments that can increase serum hemoglobin (Hb) concentrations and thereby reduce the need for blood transfusions, providing benefit to patients and healthcare systems.

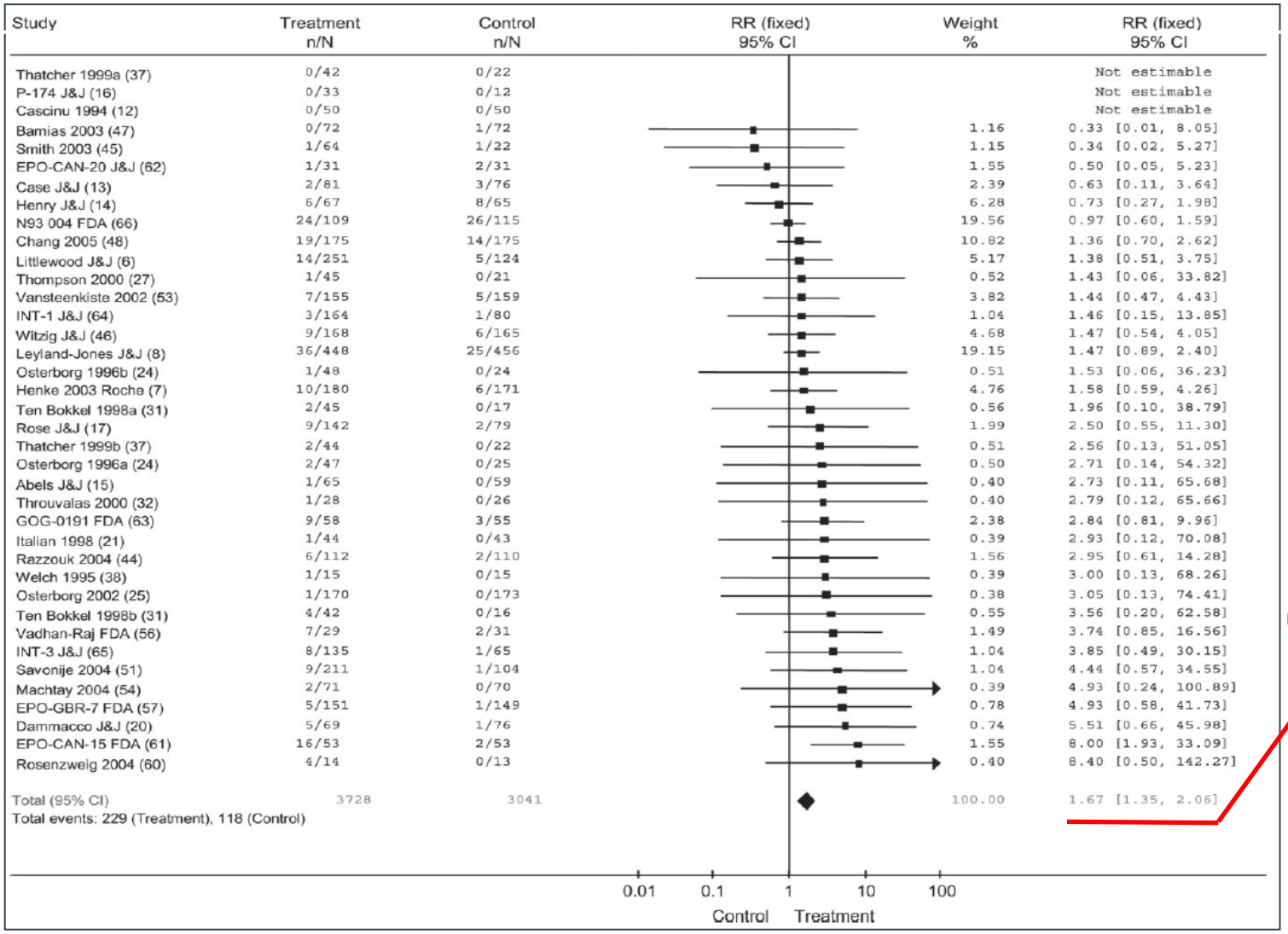
- In 2008, the US FDA and EMA added boxed warning to the labels for ESAs, stating that ESAs may increase the risk of death, myocardial infarction, stroke, VTE, thrombosis of vascular access, and tumor progression or recurrence.

ESAs and thrombosis (cont'd)

- At the same time, the US FDA updated DA's prescribing information, decreasing the Hb treatment initiation threshold to <10 g/dL.

- The EMA made similar changes to DA's summary of product characteristics, decreasing the Hb treatment initiation and discontinuation thresholds to ≤10 g/dL and >12 g/dL, respectively.

Meta-analysis of the relative risk (RR) for thromboembolic complications in cancer patients receiving epoetin or darbepoetin or standard care (35 trials: 6769 patients)



Treatment with epoetin or darbepoetin increased the risk of thromboembolic events (RR = 1.67, 95% CI = 1.35 to 2.06)

1,67

Bohlius et al. JNCI 2006

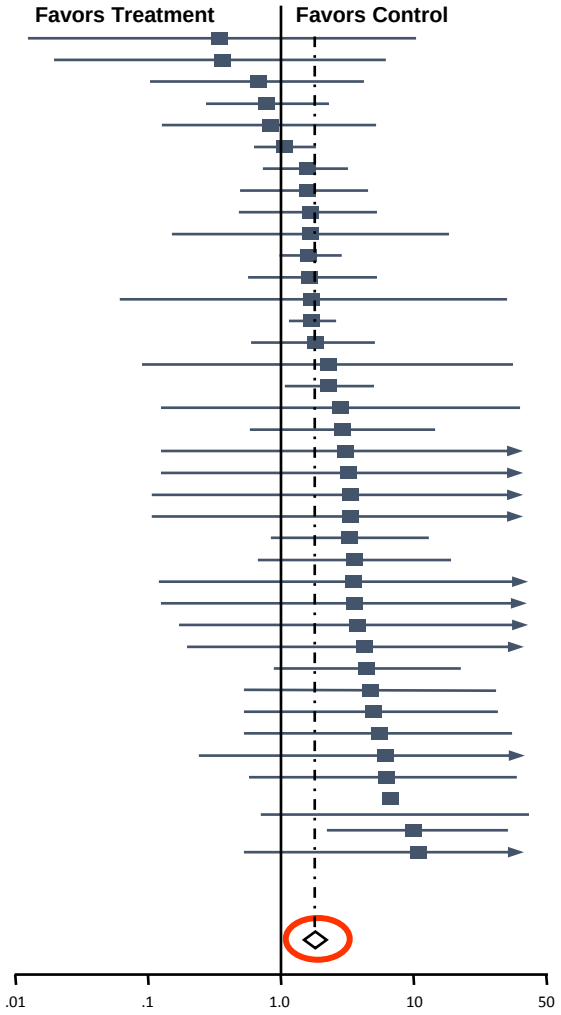
LIMITATIONS

- lack of standard definitions of VTE.
- Events within trials were possibly under-reported because no prospective and uniform screening protocol for thromboembolic events was included in the clinical trials.
- Specific individual patient data on hemoglobin levels preceding a thromboembolic event would be necessary to clarify a possible association between hemoglobin level and thrombo-embolic events

Bohlius et al. JNCI 2006

Venous Thromboembolism and Mortality Associated With Recombinant Erythropoietin and Darbepoetin Administration for the Treatment of Cancer-Associated Anemia.

Source	No. of VTE Events/Total No. (%) Treatment	Control	Weight, %	Relative Risk (95% CI)
Bamias et al, 2003	0/72 (0)	1/72 (1)	0.31	0.33 (0.01-8.05)
Smith et al, 2003	1/64 (2)	1/22 (5)	0.42	0.34 (0.02-5.27)
Case et al, 1993	2/81 (2)	3/76 (4)	1.02	0.63 (0.11-3.64)
Henry and Abels, 1994	6/67 (9)	8/65 (12)	3.14	0.73 (0.27-1.98)
Wright et al, 2007 (EPO-CAN-20)	2/33 (6)	3/37 (20)	1.06	0.75 (0.13-4.20)
Grote et al, 2005 (N93-004)	24/109 (22)	26/115 (23)	13.20	0.97 (0.60-1.59)
EPO-CAN-17, 2007	19/175 (11)	14/175 (8)	7.29	1.36 (0.70-2.62)
Littlewood et al, 2001	14/251 (6)	5/124 (4)	3.17	1.38 (0.51-3.75)
Vansteenkiste et al, 2002	7/155 (2)	5/159 (3)	2.49	1.44 (0.47-4.43)
INT-1, 2004	3/164 (2)	1/80 (1)	0.62	1.46 (0.15-13.85)
Leyland-Jones et al, 2005 (INT-76)	36/448 (8)	25/456 (5)	12.97	1.47 (0.89-2.40)
Witzig et al, 2005	9/168 (5)	6/165 (4)	3.09	1.47 (0.54-4.05)
Osterborg et al, 1996	1/48 (2)	0/24 (0)	0.32	1.53 (0.06-36.23)
Amgen DA 145, 2007	66/296 (22)	43/298 (14)	25.92	1.53 (1.08-2.18)
Henke et al, 2003	10/180 (6)	6/171 (4)	3.22	1.58 (0.59-4.26)
ten Bokkel Huinink et al, 1998	2/45 (4)	0/17 (0)	0.35	1.96 (0.10-38.79)
Debus et al, 2007 (EPO-GER-22)	20/106 (19)	10/107 (9)	6.25	1.98 (0.97-4.03)
Charu et al, 2007			0.37	2.36 (0.13-43.20)
Rose et al, 1994	9/142 (6)	2/79 (3)	1.39	2.50 (0.55-11.30)
Thatcher et al, 1999	2/44 (5)	0/22 (0)	0.35	2.56 (0.13-51.05)
Osterborg et al, 1996	2/47 (4)	0/25 (0)	0.35	2.71 (0.14-54.32)
Abels, 1993	1/65 (2)	0/59 (0)	0.31	2.73 (0.11-65.68)
Throuvalas et al, 2000	1/28 (4)	0/26 (0)	0.32	2.79 (0.12-65.66)
GOG-191, 2007	9/58 (16)	3/55 (5)	2.01	2.84 (0.81-9.96)
Razzouk et al, 2004	6/112 (5)	2/110 (2)	1.27	2.95 (0.61-14.28)
Welch et al, 1995	1/15 (7)	0/15 (0)	0.32	3.00 (0.13-68.26)
Osterborg et al, 2005	1/170 (1)	0/173 (0)	0.31	3.05 (0.13-74.41)
Gordon et al, 2006	4/162 (16)	0/56 (5)	0.37	3.15 (0.17-57.55)
ten Bokkel Huinink et al, 1998	4/42 (10)	0/16 (0)	0.38	3.56 (0.20-62.58)
Vadhan-Raj et al, 2004	7/29 (24)	2/31 (6)	1.43	3.74 (0.85-16.56)
INT-3, 2004	8/135 (6)	1/65 (2)	0.75	3.85 (0.49-30.15)
Wilkinson et al, 2006	12/173 (7)	1/59 (2)	0.77	4.09 (0.54-30.80)
Savonije et al, 2004	9/211 (4)	1/104 (1)	0.75	4.44 (0.57-34.55)
Machtay et al, 2007 (RTOG 99-03)	2/71 (3)	0/70 (0)	0.35	4.93 (0.24-100.89)
EPO-GBR-7, 2007	5/151 (3)	1/149 (1)	0.69	4.93 (0.58-41.73)
Dammacco et al, 2001	5/69 (7)	1/76 (1)	0.70	5.51 (0.66-45.98)
EPO-CAN-15, 2004	16/53 (30)	2/53 (4)	1.57	8.00 (1.93-33.09)
Rosenzweig et al, 2004	4/14 (29)	0/13 (0)	0.39	8.40 (0.50-142.27)
Cascinu et al, 2004	0/50 (0)	0/50 (0)	0	
P-174, 2004	0/33 (0)	0/12 (0)	0	
Thatcher et al, 1999	0/42 (0)	0/22 (0)	0	
Overall I^2=0%; P=.88			**100.00**	**1.57 (1.31-1.87)**



Bennett CL et al JAMA 2008

Results

- Patients with cancer who received ESAs had increased VTE risk
  - **334 VTE events** among 4610 patients treated with ESA *versus* **173 VTE events** among 3562 control patients (**7.5% vs 4.9%**);
  - **RR 1.57** (95% CI, 1.31-1.87) and **increased mortality risk** (HR 1.10; 95% CI, 1.01-1.20).
- These findings raise concern about the safety of ESA administration to patients with cancer.
- However, the VTE definitions varied across trials and VTE rate was not a predefined primary outcome measure in any trials.

Bennett CL et al JAMA 2008

Erythropoietin or darbepoetin for patients with cancer.

- Data from thromboembolic complications were available from a total of 57 trials, including 15,498 participants

- The overall risk ratio to suffer thromboembolic complications was **increased** by 52% for patients receiving ESAs (**RR 1.52**; 95% CI 1.34 to 1.74)

- Results are similar to those from the previous Cochrane review (RR 1.67; 95% CI 1.35 to 2.06, 35 trials, N = 6,769, Bohlius 2006)

Tonia T, Cochrane Review, 2012

Subgroup analyses

- Subgroup analyses for predefined variables did not show robust evidence for statistically significant differences in magnitude or direction of the ESA effect between any of the subgroups tested:
  - baseline Hb level,
  - type of malignancy,
  - duration of treatment,
  - type of anti-cancer therapy,
  - age, iron supplementation,
  - type of publication,
  - epoetin versus darbepoetin,
  - type of data,
  - concealment of allocation and masking

Tonia T, Cochrane Review, 2012

Darbepoetin Alfa for the Treatment of Anemia in Patients With Active Cancer Not Receiving Chemotherapy or Radiotherapy

Adverse events of interest	Placebo N (%)	Darbepoetin N (%)
Cardiovascular and thromboembolic events	36 (7,7)	50 (9,7)
Arrhythmia	17 (3,6)	21 (4,1)
Congestive heart failure	13 (2,8)	12 (2,3)
Cerebrovascular accident	4 (0,9)	7 (1,4)
Myocardial infarction and coronary artery disorders	2 (0,4)	3 (0,6)
Embolism/thrombosis (arterial and venous)	7 (1,5)	12 (2,3)

The incidence of cardiovascular and thromboembolic events was moderately higher in the DA group

Cardiovascular and thromboembolic events did not seem to occur more frequently in patients exceeding hemoglobin 13 g/dL compared with those who did not (hazard ratio [HR] 0.43; 95% CI, 0.13 to 1.41) nor with those with a greater than 1 g/dL increase in hemoglobin in 14 days compared with those who did not (HR 0.81; 95% CI, 0.45 to 1.44)

Smith et al. JCO 2008

Thromboembolic events in patients with colorectal cancer receiving the combination of bevacizumab-based chemotherapy and erythropoietin stimulating agents

- **Retrospective, pilot study of 79 colorectal cancer patients** treated with chemotherapy were divided into 3 groups**:**
  - **bevacizumab (n= 28)**
  - **ESA (n = 21)**
  - **bevacizumab plus ESA (n= 28**)
- Primary end point: incidence of thromboembolic events
- Secondary endpoints: median time-to-event; effect of anticoagulation; and association with concurrent chemotherapy, baseline risk factors, hemoglobin, and performance status.

Roddy VF et al. JCO 2010

Thromboembolic events

	Bevacizumab n = 28	ESA n = 21	Bevacizumab + ESA n = 30	P*
Thromboembolic events	3 (11%)	5 (23.8%)	9 (30%)	0.194
				0.866†
				0.263‡
				0.137§
Type of thromboembolic events	—	—	—	—
Arterial (n = 4)	2	0	2	—
MI	1	—	1	—
Ischemic stroke	1	—	—	—
Abdominal aorta	—	—	1	—
Venous (n = 14)	1	5	8	—
Lower DVT	1	1	2	—
Upper DVT	—	2	1¶	—
Bilateral upper DVTs	—	1	—	—
Bilateral lower DVTs	—	—	1	—
PE	—	1	4	—
Median time-to-event (months)	7.5 (2–10)	3.5 (1–5)	2.5 (1–13.5)	0.060
				0.914†
				0.142‡
				0.045§

*ANOVA was used for median time-to-event (Student *t* test was used to compare between 2 groups). Fisher exact test was conducted for dichotomous variables.
†Comparing ESA only to combination.
‡Comparing bevacizumab only to ESA only.
§Comparing bevacizumab only to combination.
¶This patient had both and upper and lower DVT.
ESA indicates erythropoietin stimulating agents.

Majority (67%) of the thromboembolic events in the **bevacizumab** group were arterial, whereas all the events that occurred in the **ESA** group were venous.

The incidence of thromboembolic events in the **combination group** was increased by 3-fold compared with the bevacizumab group, however this trend was not statistically significant (P = 0.194).

Roddy VF et al. JCO 2010

Association With Baseline Risk Factors.
All Patients Who Experienced a Thromboembolic Event (n= 18)

	Univariate		Multivariable*	
Risk Factor	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Bevacizumab treatment	0.84 (0.25, 2.74)	0.766	0.86 (0.26, 2.90)	0.809
ESA treatment	3.15 (0.82, 12.12)	0.095	3.19 (0.81, 12.62)	0.099
Central venous catheter	1.11 (0.21, 5.79)	0.901	1.22 (0.23, 6.51)	0.816
Hypertension	0.99 (0.34, 2.90)	0.983	0.84 (0.27, 2.62)	0.767
Smoker	0.91 (0.31, 2.70)	0.861	1.09 (0.35, 3.45)	0.879
≥65-yr-old	1.20 (0.37, 3.93)	0.764	1.21 (0.36, 4.03)	0.756
Recent high risk surgery	1.57 (0.47, 5.26)	0.464	2.13 (0.55, 8.21)	0.271
Prior VTE	3.51 (0.83, 14.90)	0.089	3.58 (0.80, 16.09)	0.091
Hyperlipidemia	1.43 (0.39, 5.22)	0.591	1.34 (0.36, 4.93)	0.663
Obesity	8.13 (0.69, 95.77)	0.096	8.87 (0.72, 109.15)	0.663
Diabetes	1.05 (0.20, 5.58)	0.956	1.04 (0.19, 5.68)	0.961
Cardiac disease	6.43 (0.98, 42.17)	0.053	5.91 (0.86, 40.68)	0.071
Prior ATE	0.71 (0.08, 6.54)	0.765	0.63 (0.07, 5.89)	0.688
Nephrotic syndrome	1.88 (0.16, 22.01)	0.617	1.76 (0.15, 21.16)	0.655
Exogenous hormones†	6.48 (0.98, 42.17)	0.053	5.55 (0.80, 38.45)	0.083
Underlying Coagulopathy	0.001 (0.001, 999.99)	0.985	0.001 (0.001, 999.99)	0.985

*Model: thromboembolic event (dependent variable) = constant + age + sex + risk factor (independent variable).
†Megestrol, oral contraceptives, and hormone replacement therapy.
ESA indicates erythropoietin stimulating agents; VTE, venous thromboembolic event; ATE, arterial thromboembolic event.

Roddy VF et al. JCO 2010

Effect of Once-Weekly Epoetin Beta on TE in Metastatic Breast Cancer receiving anthracycline and/ or taxane-based chemotherapy: Results of the Breast Cancer—Anemia and the Value of Erythropoietin (BRAVE) Study

	N° of patients with TE	
	Epoetin beta (n=231)	Control (n= 231)
At least one TE	13%	6%
Serious TE	4%	3%
TE-related death	2%	2%

Patients receiving epoetin beta experienced more thromboembolic events (TE) compared with controls (13% *v 6%; P .012) with no difference in serious TE (4% v 3%).*

Aapro M et al. JCO 2008

Relazione tra il rischio di TEV e i valori di emoglobina

- L’ Agency for Healthcare Research and Quality ha pubblicato dati che evidenziano che i livelli di Hb ai quali negli studi clinici vengono interrotti i trattamenti con ESA hanno una correlazione con il rischio relativo (RR) per gli eventi tromboembolici.

- Infatti il rischio relativo di insorgenza di TEV è:

  - 0.70 quando il target di Hb è 13 g/dl;

  - 1.71 quando il livello target di Hb è compreso tra 13 e 14 g/dl;

  - 1.92 quando i livelli di Hb aumentano sino a 15 g/dl.

Il rischio di TEV è dunque molto superiore se i valori di emoglobina sono elevati e superano i 13 g/dl.

American Society of Clinical Oncology and American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients With Cancer

- **Chemotherapy-Induced Anemia: threshold for Initiating ESA Therapy**
  - The **use of epoetin or darbepoetin** is **recommended** as a treatment option for patients with chemotherapy-associated anemia and an Hb concentration that has decreased to **less than 10 g/dL** to decrease transfusions.
  - **RBC transfusion is also an option**, depending on the severity of the anemia or clinical circumstances
- **Chemotherapy-Induced Anemia: Initiating When Hb is ≥10 g/dL but <12 g/dL**
  - An optimal level at which to initiate ESA therapy in patients with anemia and Hb between 10 and 12 g/dL cannot be definitively determined from the available evidence. Under these circumstances, whether or not to initiate ESA treatment should be determined by clinical judgment, consideration of the risks and benefits of ESAs, and patient preferences
  - RBC transfusion is an option when warranted by clinical conditions.

Rizzo JD, et al JCO 2010

Considerazioni

- L’impiego di eritropoietina deve dunque essere effettuato entro precisi margini di sicurezza vista la particolare condizione dei soggetti candidati che, già di base, sia per il tipo di patologia sia per il tipo di terapia, mostrano una maggiore tendenza all’insorgenza di eventi tromboembolici.

- Al fine di evitare incrementi troppo rapidi di emoglobina con conseguente possibilità di insorgenza di TEV, le indicazioni sottolineano anche la necessità di effettuare aggiustamenti di dose se durante il trattamento con ESA l’Hb aumenta di oltre 2 g/dl al mese.

Patogenesi del TEV associato a EPO

- La patogenesi dell'aumentato rischio di TEV associato all'EPO non è ancora chiara.

- I primi studi, eseguiti nei pazienti uremici trattati con EPO, hanno evidenziato un effetto sulla funzionalità piastrinica e sull'iper-reattività delle piastrine:

    - le piastrine di pazienti trattati con EPO umana ricombinante esprimono maggiori quantità di glicoproteina IIb-IIIa sulla membrana ed hanno un'aumentata aggregabilità *in vitro*.

    - Vi è aumentata espressione della glicoproteina Ib sulla superficie piastrinica, suggerendo un effetto procoagulante in questi soggetti.

- Tuttavia, nei pazienti oncologici, tali effetti non sono stati ancora provati. E' possibile che, come nei pazienti con insufficienza renale cronica, anche nei pazienti con tumore sottoposti a radio- o chemioterapia, il raggiungimento di concentrazioni più alte di emoglobina si associa ad un incrementato rischio di TEV

Conclusioni

- Le nuove direttive sull'uso degli ESA hanno migliorato l'impatto protrombotico di questi farmaci
- Tuttavia il rischio va sempre tenuto presente
- E' infatti sempre da tener presente che il paziente oncologico è ad alto rischio per la patologia di base, per i fattori cardiovascolari generali che possono essere presenti, e per le terapie che si attuano per la guarigione del tumore.