

Highlights from EHA

Report dei gruppi di lavoro >>
[Trombosi e cancro]

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Borgo S. Luigi – Monteriggioni (Siena)

Gruppo di lavoro

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[Trombosi e cancro]

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Primary Thromboprophylaxis

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Conditions that increase the thrombotic risk:

- Surgery
- Medical Therapies:
 - Chemotherapy
 - Hormone-therapy
 - Radiotherapy

TROMBOPROFILASSI NEL PAZIENTE ONCOLOGICO

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- PROFILASSI IN CHIRURGIA
 - ▣ PERIOPERATORIA
 - ▣ PROLUNGATA

- PROFILASSI NEL PAZIENTE INTERNISTICO
 - ▣ OSPEDALIZZATO
 - ▣ AMBULATORIALE

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Recommendations for Thromboprophylaxis in oncological patients undergoing surgery

Low doses of UFH

5000 anti-Xa IU administered 2h before surgery, then continued three times/day

or

LMWH

≥ 3.800 anti-Xa IU, administered before surgery and then given once daily post-operatively.

The optimum duration of surgical thromboprophylaxis is controversial

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- *LE LINEE GUIDA AMERICANE INDICANO CAUTELA NEL PROLUNGARE LA PROFILASSI (solo chirurgia addominale pelvica in presenza di fattori di rischio: obesità, pregressa storia di trombosi, chirurgia non eradicante)*
- *LE LINEE GUIDA EUROPEE SONO PIU' CHIARE NELL'INDICARE L'UTILITA' DELLA PROFILASSI PROLUNGATA NELLA CHIRURGIA ADDOMINALE PELVICA*

Primary Thromboprophylaxis: Medical Conditions

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- Hospitalized medical cancer patients are at increased risk for VTE
- Out of hospital cancer patients receiving therapy are at risk for VTE

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Recommendations for VTE Prophylaxis in Hospitalized Cancer Patients

Hospitalized patients with cancer should be considered *candidates for VTE prophylaxis* in the absence of bleeding or other contraindications to anticoagulation

Recommended Dose: Venous Thromboembolism Prophylaxis

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Management	Drug	Regimen
Prophylaxis		
Patients with cancer receiving medical or surgical treatment while staying in hospital	Unfractionated Heparin (UFH)	5000 U q 8 h
	Dalteparin (Fragmin[®])	5000 U daily
	Enoxaparin (Lovenox[®])	40 mg daily
	Fondaparinux (Arixtra[®])	2.5 mg daily

Prophylaxis in Medical Patients: *Ambulatory Cancer Patients*

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- The role of thromboprophylaxis in ambulatory cancer patients during chemotherapy and hormone therapy is not established
- One double-blind placebo-controlled RCT demonstrated the efficacy of low-intensity warfarin (INR 1.3-1.9) in patients receiving chemotherapy for metastatic breast cancer (Levine MN et al, Lancet 1994)

Prophylaxis of VTE in Medical Cancer Patients

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- LMWH benefits
 - Predictable anticoagulant effect
 - Single daily administration
 - Reduced toxicity (thrombocytopenia, osteoporosis)

- Acceptable safety profile in oncological patient (long term use in recent studies: FAMOUS, CLOT)

Primary Prophylaxis During Chemotherapy: *LMWH recent closed studies*

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Study	Cancer
TOPIC-1 ¹	Breast Cancer
TOPIC-2 ¹	Non small cell lung cancer
PRODIGE ²	Malignant glioma (grade III or IV)
PROTECHT	Lung, Breast, Gastrointestinal, Ovarian, Head/Neck cancer

¹ Haas SK, *J Tromb Haemost* 2005, suppl. 1, Abs OR059

² Perry J et al. *Thromb Res* 2007, suppl. 2, Abs PO40

Primary Prophylaxis During Chemotherapy: *LMWH ongoing Studies*

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AUTHOR	STUDY	SCHEDULE
	Pancreatic cancer	
Maraveyas	Prospective randomised	Gemcitabine ± Dalteparin 200U/Kg o.d.
Pelzer	Prospective randomised	Gemcitabine ± Enoxaparin 1 mg/Kg

ASCO 2007 PROCEEDINGS

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Recommendations for Primary VTE Prophylaxis in Ambulatory Cancer Patients

Current guidelines *do not recommend* routine prophylaxis with an antithrombotic agent in ambulatory cancer patients.

Special consideration:

Prophylaxis in Multiple Myeloma patients

ASCO Guidelines, JCO 2007

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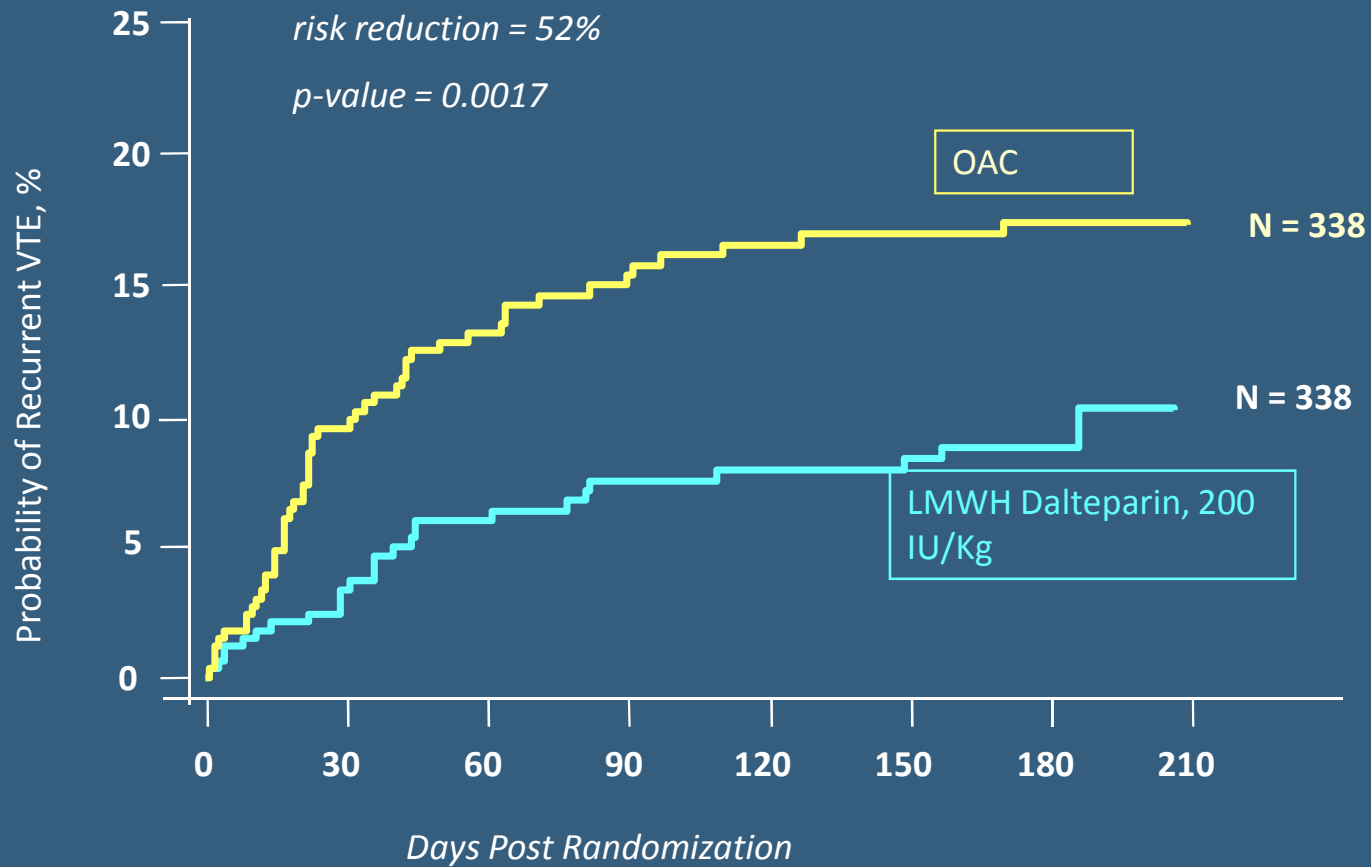
- Prophylaxis with LMWH or adjusted dose warfarin (INR~1.5) is recommended in multiple myeloma patients receiving thalidomide or lenalidomide + chemotherapy or dexamethasone (high VTE risk).
- However:
 - ▣ No RCTs available
 - ▣ Recommendation is based on extrapolation from non-randomized trials or randomized studies in other similar high-risk categories
 - ▣ Well-designed RCTs are urgently needed

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Therapy of established VTE in cancer patients

Clot trial: Recurrent VTE

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Lee et al. *NEJM*, 2003

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Current and future trials to test Anticoagulants to prolong survival

A meta-analysis and systematic review of the efficacy and safety of anticoagulants as cancer treatment:

Impact on survival and bleeding complications

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- *11 studies: Anticoagulation significantly decreased 1-year overall mortality with a relative risk (RR) of 0.905 (95% CI, 0.847-0.967; p = .003).*

- CONCLUSIONS:
 - Anticoagulants, particularly LMWH, significantly improved overall survival in cancer patients without venous thrombosis while increasing the risk for bleeding complications
 - Improved survival with anticoagulation may be dependent on tumor type

- *However, given the limitations of available data, the use of anticoagulants as antineoplastic therapy cannot be recommended until additional RCTs confirm these results.*

Kuderer et al. Cancer 2007

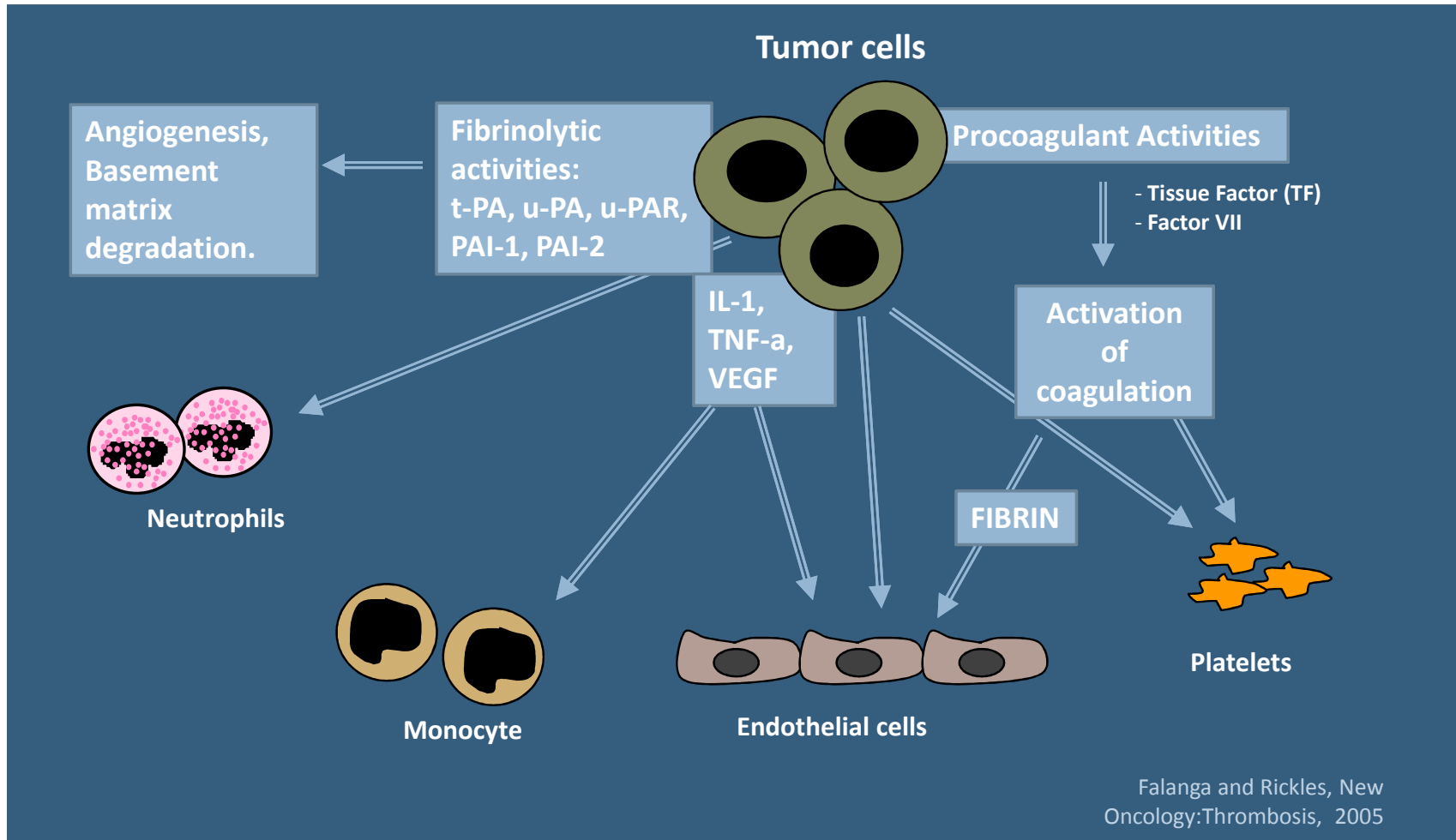
Ongoing Randomized Clinical Trials Testing the Effect of LMWH on Survival in Cancer Patients

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Study	LMWH	Tumor Type	PI
INPACT	Nadroparin	Advanced Prostate, Non-small cell lung, Pancreatic cancers	H. Buller
FOCUS	Fragmin	Ovarian Cancer	A. Lee
FRAGMATIC	Fragmin	Lung Cancer	F. MacBeth
ABEL	Bemiparin	Small Cell Lung Cancer	R. Lecumberri
TILT	Tinzaparin	Non-small cell lung cancer (I, II, III-A)	G. Meyer & P. Girard
GASTRANOX	Enoxaparin	Gastric cancer (III/IV)	A.K. Kakkar

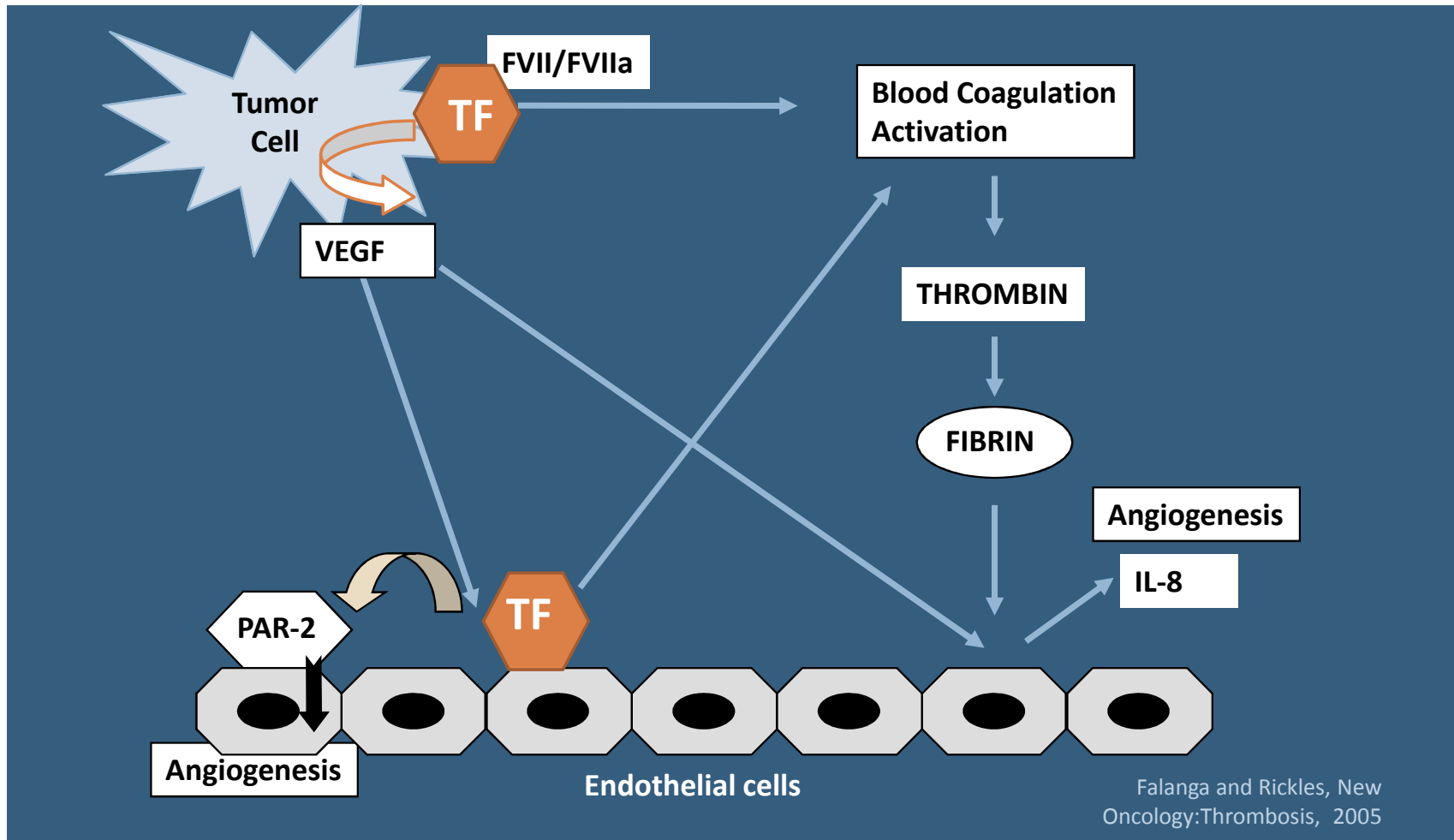
Interface of Tumor Biology and Hemostasis: *Thrombosis +/- Bleeding*

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Interface of Tumor Biology and Hemostasis: *Tumor Growth and Angiogenesis*

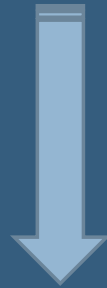
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LMWH in cancer

Antitumor effect

Prevention of thrombosis



Increased cancer patient survival

Antitumor effect of heparin



Anticoagulant
mechanisms



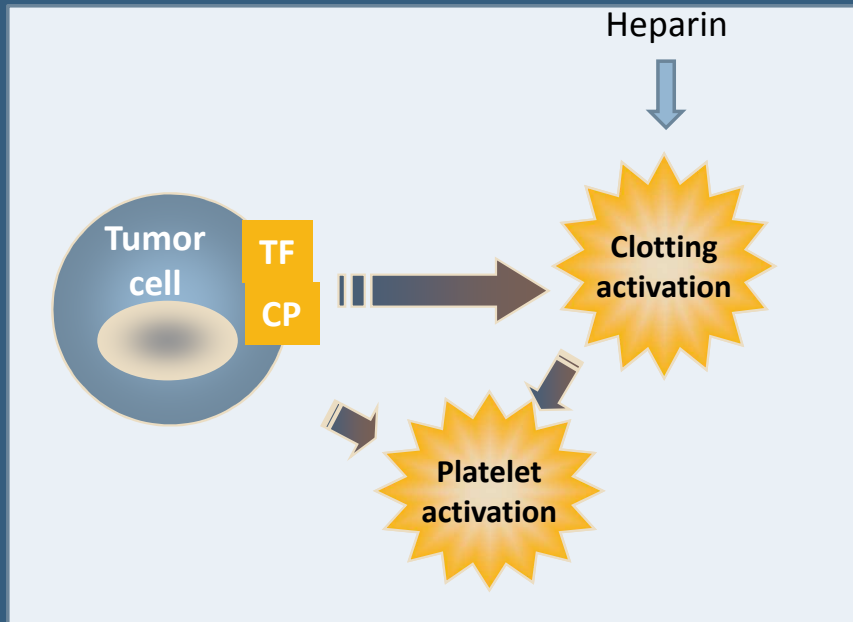
Non-anticoagulant
mechanisms

Antitumor effect of heparin

Anticoagulant mechanisms



Coagulation Protease Inhibition



Tissue
Factor/FVIIa
Factor Xa
Thrombin

Coagulation proteases affect:

- Growth
- Invasion
- Metastasis
- Angiogenesis

Non-Anticoagulant Mechanisms

In vivo studies (animal models) and in vitro studies

- Anti-angiogenic activity
- Anti-metastatic activity
 - Interference with P-Selectin mediated adhesion
 - Heparanase inhibition

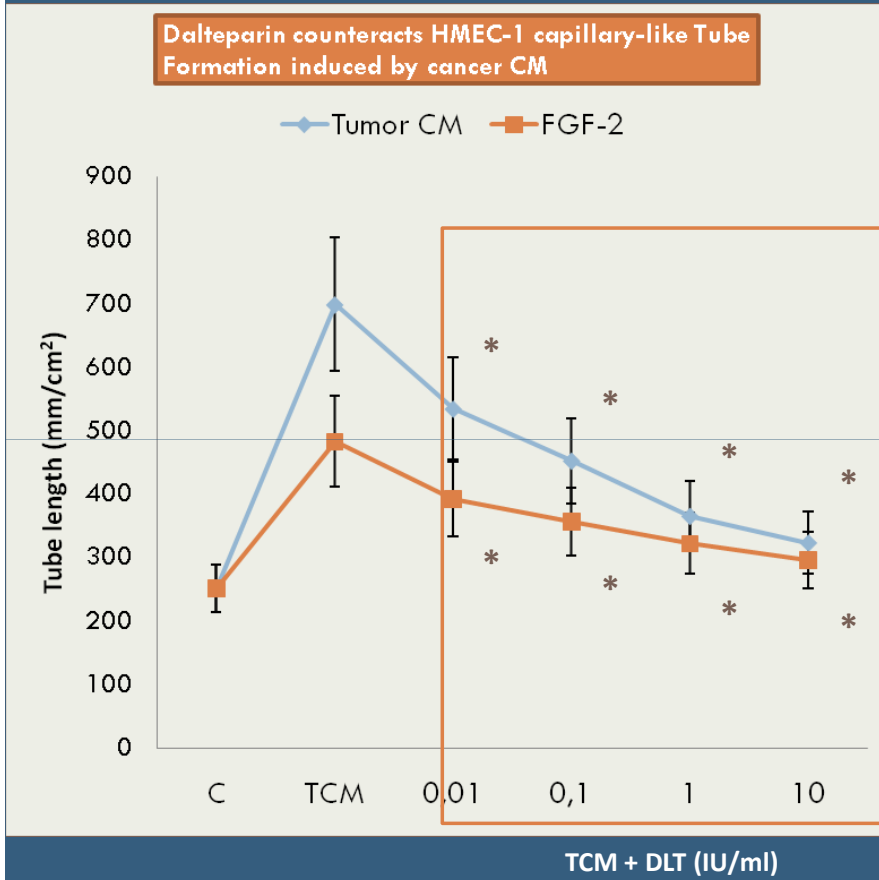
Antitumor effect of heparin

Angiogenesis: In Vitro Assays

- Cell proliferation
- Cell migration
- Capillary tube-formation

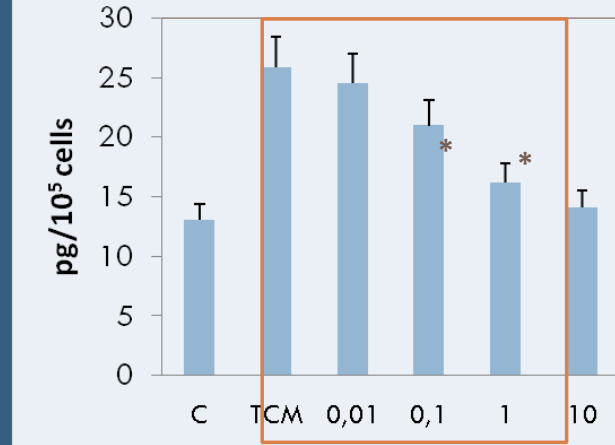
Main Results:

Dalteparin counteracts HMEC-1 capillary-like Tube Formation induced by cancer CM

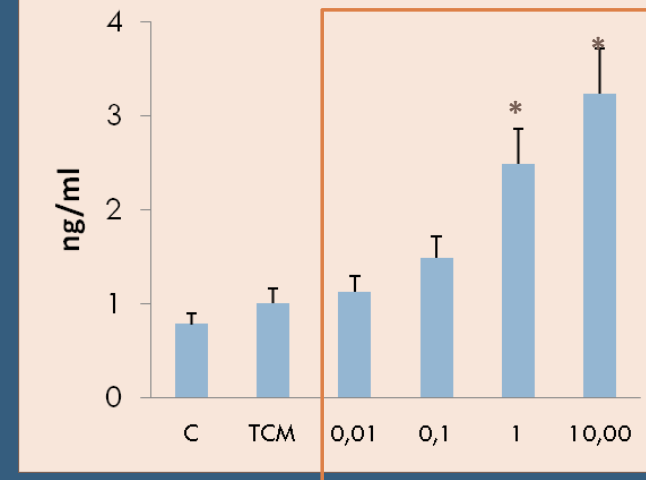


*= $p < 0.05$ vs TCM

TF Activity



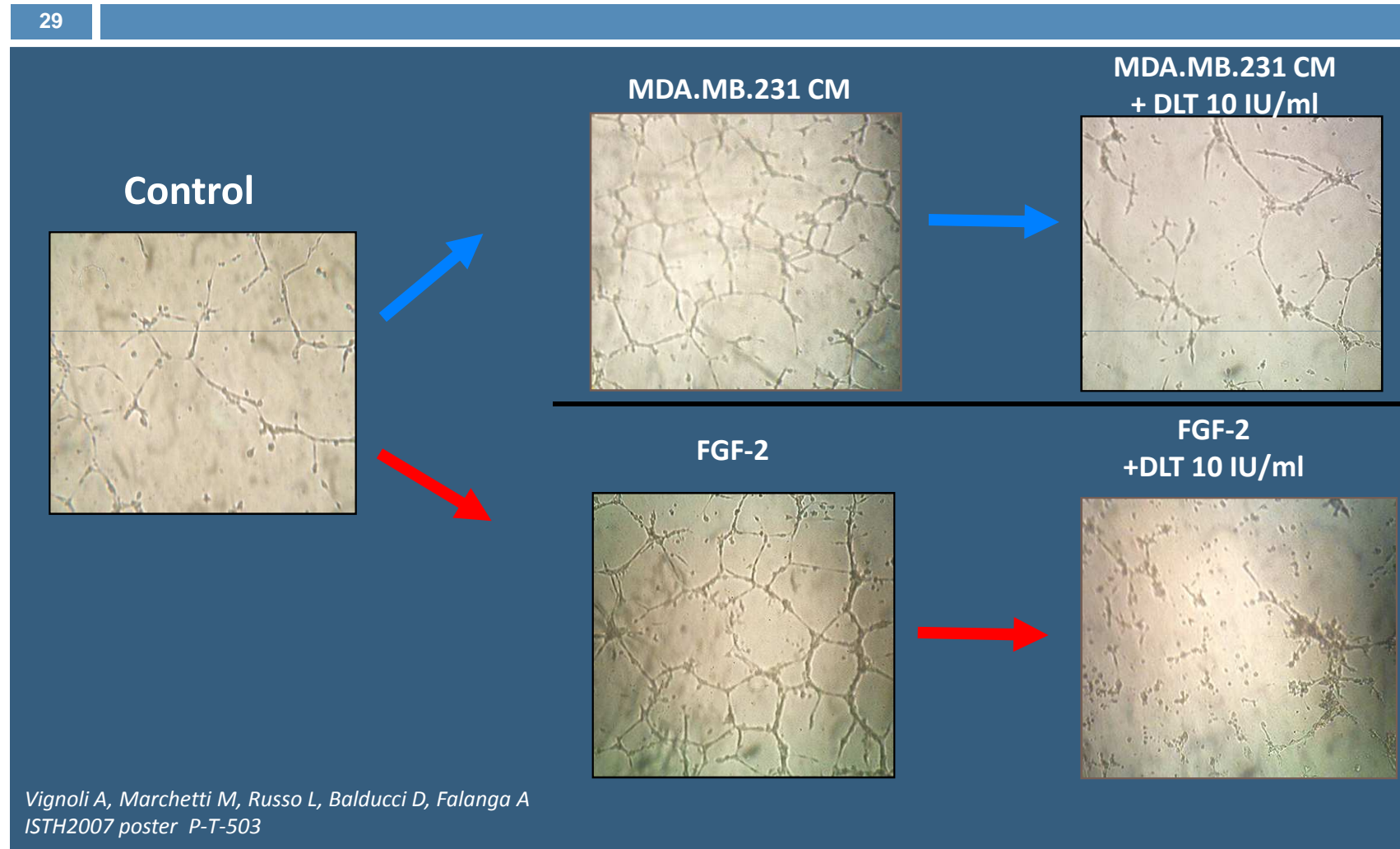
TFPI-1 antigen



Vignoli A, Marchetti M, Russo L, Balducci D, Falanga A
 ISTH2007 poster P-T-503

Representative photos from a Capillary-like Tube Formation assay in Matrigel with MDA.MB.231 CM, or FGF-2, in the presence and absence of Dalteparin

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Discussione