Workshop

SISET

POST-ISTH: Novità dal meeting di Toronto 2015

25°ISTH and 61°SSC-ISTH Congress

Cancro e Trombosi

Anna Falanga

Divisione di Immunoematologia e Medicina Trasfusionale

ASST Papa Giovanni XXIII, Bergamo

SISET

Cancro e Trombo-Embolismo Venoso (TEV)

- Il cancro è un fattore di rischio indipendente per TEV
  - I pazienti oncologici hanno un **rischio di TEV** (trombosi venosa profonda, embolia polmonare) di **4–7 volte maggiore** rispetto alla popolazione non oncologica.
  - L'**incidenza** di TEV nei pazienti oncologici è compresa tra l'**1 e il 20%.**
  - Studi autoptici hanno documentato la presenza di TEV fino al **50%** di questi pazienti .
- L'incidenza del TEV in oncologia **è in aumento per:**
  - L'aumento della sopravvivenza dei pazienti
  - L'aumento del grado di sospetto e di diagnosi di TEV da parte dei medici
  - L'introduzione di nuovi schemi di terapie anti-tumorali

Falanga A et al, Anticancer treatment and thrombosis. Thromb Res 2012.
Timp JF et al, Epidemiology of cancer-associated venous thrombosis. Blood 2013

Fattori di rischio associati al paziente

- Età
- Etnia (rischio più alto negli afro-americani, più basso nelle etnie asiatiche)
- Comorbilità (infezioni, malattie renali, malattie polmonari, tromboembolismo arterioso)
- Obesità
- Precedente TEV
- Basso performance status
- Trombofilia ereditaria

Fattori di rischio specifici della malattia neoplastica e del suo trattamento

- Tipo di tumore
- Caratteristiche istologiche (rischio più alto negli adenocarcinomi che nei carcinomi squamocellulari)
- Periodo intercorso dalla diagnosi (rischio più alto nei primi 3-6 mesi)
- Chemioterapia
- Farmaci antiangiogenici (talidomide, lenalidomide)
- Fattori di crescita eritrocitari, trasfusioni di sangue
- Catetere venoso centrale
- Radioterapia
- Chirurgia oncologica maggiore

Marcatori biologici di trombosi (in corso di studio)

- Piastrinosi (conta piastrinica >350,000/µl)
- Leucocitosi (conta leucocitaria > 11,000/µl)
- Anemia (Hb < 10 g/dL)
- D-dimero, Fattore Tissutale, P selectina solubile, Proteina C reattiva

Falanga A, Russo L. Epidemiology, risk and outcomes of venous thromboembolism in cancer. Hamostaseologie. 2012

ISTH CONGRESS - Toronto 2015

ABSTRACT SYMPOSIA Total = 2

Cancer and thrombosis- clinical

Cancer and thrombosis- basic

ORAL SESSIONS Total = 6

Cancer and thrombosis- clinical (**3 oral sessions**)

Platelet and cancer (**1 oral session**)

Cancer and thrombosis- basic (**2 oral sessions**)

POSTER SESSIONS Total = 4

Cancer and thrombosis/hemostasis (**3 poster session**)

Platelet and cancer (**1 poster session**)

SSC-ISTH MEETING

SSC on Hemostasis and Malignancy

- Education Session (n= 1)

- Working Session (n= 2)

Hot topics in cancer and thrombosis

Clinical

- Incidental VTE
- Treatment of VTE
- Recurrent VTE
- VTE and mortality
- Occult cancer

Biomarkers

- Predictive and diagnostic markers in Cancer Associated Thrombosis

Mechanisms

- Platelets and cancer

INCIDENTAL VTE

Trombosi venose diagnosticate in modo incidentale nei pazienti con tumore: "Incidental VTE in cancer"

- Il TEV *incidentale* si riferisce a una TVP o EP che è clinicamente non sospettata , evidenziata dall'esecuzione di esami strumentali effettuati per ragioni cliniche diverse (ad esempio la stadiazione del tumore).
- Riguarda principalmente le EP (incidenza 2.6%), ma anche TVP in altri distretti, come il circolo splancnico o le vene degli arti superiori o inferiori
- Nella maggior parte dei casi, i riscontri incidentali avvengono dopo tomografie assiali computerizzate (TC), ma non sono rari i casi di riscontro ecografico, soprattutto a livello addominale
- Anche se l'EP incidentale è asintomatica, ben due terzi dei pazienti affetti riferiscono di avere sintomi compatibili con EP, come la stanchezza o la mancanza di respiro. Tuttavia, questi sintomi non specifici sono spesso attribuiti al tumore o agli effetti collaterali del trattamento.
- ***Pertanto, i medici devono esaminare attentamente il quadro clinico per valutare se un paziente con TEV incidentale ha avuto sintomi compatibili con la diagnosi di TVP o EP***

Dentali et al, Tromb Res 2010; Ageno W et al, JTH 2012; Di Nisio et al, JTH 2015

Incidental VTE in cancer

Diagnosis and treatment of incidental venous thromboembolism in cancer patients

Guidance from SSC of ISTH
SSC on malignancy and thrombosis

Incidental VTE at thoraco-abdominal staging CT in colorectal cancer
Oral presentation-230: Rasmussen MS

Risk factors for incident VTE in active cancer patients: a population based case–control study.
Oral presentation-128: Ashrani AA

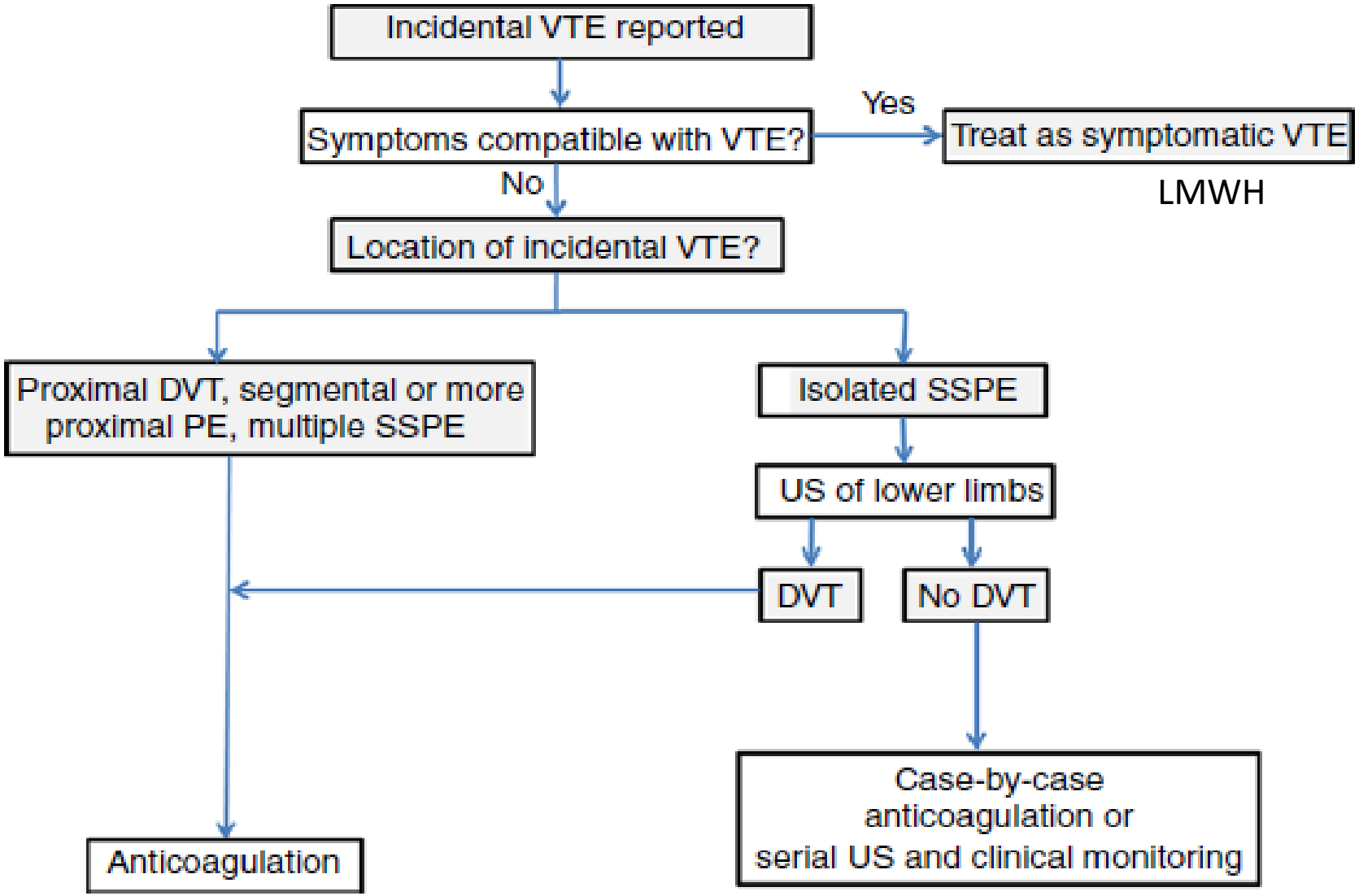
RECOMMENDATIONS AND GUIDELINES

Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH

M. DI NISIO,*† A. Y. Y. LEE,‡ M. CARRIER,§ H. A. LIEBMAN¶ and A. A. KHORANA,** FOR THE SUBCOMMITTEE ON HAEMOSTASIS AND MALIGNANCY

Journal of Thrombosis and Haemostasis, **13**: 880–883

La gestione delle trombosi venose diagnosticate incidentalmente



Di Nisio et al., JTH 2015

Incidental VTE at Thoraco-abdominal staging CT in colorectal cancer (*OR 230 - Rasmussen MS*)

810 colorectal cancer patients: **23** (2.8%) **had a manifest VTE**:

- **15 (1.9%) PE**
- **6 (0.7%) splanchnic VTE**
- **4 (0.5%) iliofemoral VTE**

- **VTE significantly associated with:**
  - **Synchronous metastatic disease** (SMD) (adjusted **OR 2.70**,95% CI:1.15–6.27, P = 0.020), but not with gender, age, index tumor location or comorbidity.
  - **Impaired 30-day survival** (adjusted **HR= 7.20**, 95% CI:2.04–25.47, P = 0.002), but not on long-term survival beyond 30 days

Incidental VTE can be detected at routine thoraco-abdominal CT scan in the primary staging of nearly 3% of CRC patients and is associated with synchronous metastatic disease. The radiologist should endeavor to detect VTE, as they have major impact on 30-day survival.

Risk factors for incident VTE in active cancer patients: a population based case–control study (*OR128: Ashrani AA*)

All Olmsted County, MN residents with active cancer (1973 and 2000)
→ **604 Controls *vs* 570** objectively diagnosed incident **VTE cases (excluding arm DVT)**
On multivariate analysis**:**

higher cancer site score (OR = 1.4 per 2-fold increase)
higher cancer stage (OR = 2.1)
liver metastasis (OR = 2.6)
stage progression (OR = 1.6)
chemotherapy (OR = 1.7)
hospitalization (OR = 7.2)
nursing home confinement (OR = 6.7)
CVC (OR = 6.3)
any recent infection (OR = 1.6)

were independently associated with VTE

Cancer site, advanced cancer stage, liver metastasis, stage progression, chemotherapy, hospitalization/nursing home confinement, CVC, and infection are independent risk factors for incident VTE in cancer patients

TREATMENT OF VTE IN CANCER

Treatment of VTE in cancer

- Treatment with **low-molecular-weight heparin (LMWH) is effective and is recommended** over vitamin K antagonist therapy by clinical practice guidelines.
- **These recommendations are largely based on results from a single, large randomized trial (i.e. CLOT) with supportive evidence from additional smaller studies** that were conducted over a decade ago in academic centers primarily in North America and Western Europe.
- **These limitations may partly explain why vitamin K antagonists remain frequently** used worldwide in patients with cancer-associated thrombosis.

(Lee AY et al .N Engl J Med. 2003 Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer (CLOT study).

JAMA. 2015;314(7):677-686. doi:10.1001/jama.2015.9243

Research

Original Investigation

Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer
A Randomized Clinical Trial

Agnes Y. Y. Lee, MD, MSc; Pieter W. Kamphuisen, MD, PhD; Guy Meyer, MD; Rupert Bauersachs, MD; Mette S. Janas, MD, PhD; Mikala F. Jarner, MSc; Alok A. Khorana, MD; for the CATCH Investigators

Characteristics and risk factors of major and clinically relevant non-major bleeding in cancer patients receiving anticoagulant treatment for acute venous thromboembolism – the CATCH study
Oral presentation-228: *Kamphuisen PW et al*

Tissue factor (TF) as predictor of recurrent venous thromboembolism (VTE): risk factor and biomarker analysis from the catch trial of treatment of cancer associated VTE with tinzaparin or warfarin.
Symposia-081: *Khorana AA et al*

Long-term tinzaparin versus warfarin for treatment of venous thromboembolism (VTE) in cancer patients – analysis of renal impairment (RI) in the catch study
Symposia-214 *Bauersachs et al*

The CATCH study

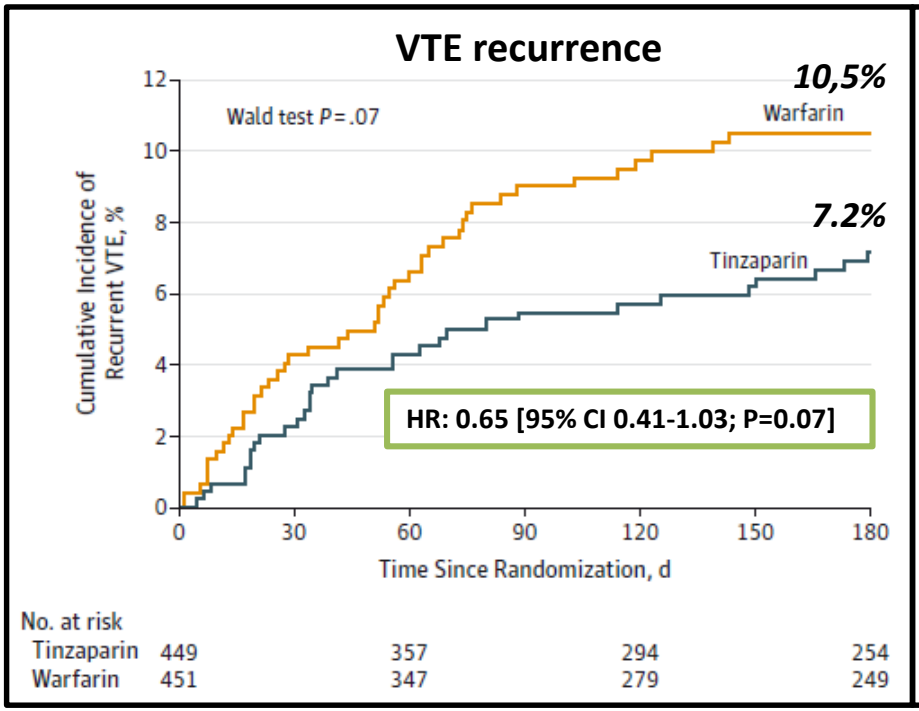
- Randomized, open label, multicenter, phase III trial aimed to assess the efficacy of tinzaparin in preventing recurrent VTE compared with warfarin:
  - 449 patients: **tinzaparin 175 IU/kg o.d. for 6 months**
  - 451 patients: **initial tinzaparin 175 IU/kg o.d. for 5–10 days overlapped and followed by dose-adjusted warfarin (target INR 2.0–3.0) for 6 months**
- ***Primary efficacy***: recurrent VTE verified by objective, standard imaging
- ***Primary safety***: major bleeding

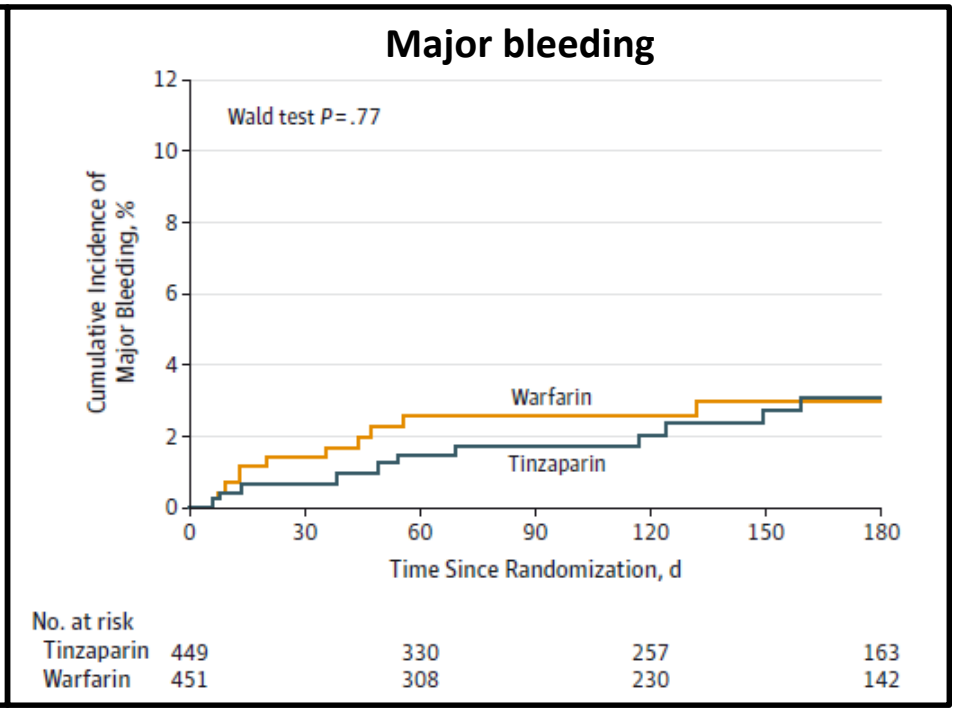
JAMA. 2015;314(7):677-686. doi:10.1001/jama.2015.9243

CATCH study: Results

Full-dose **tinzaparin** (175 IU/kg daily) *versus* **warfarin** for 6 months:

- did not significantly reduce recurrent VTE (7.2 *vs* 10.5%: p=0.07)
- was not associated with reduction in overall mortality (34.7 vs 32.2%: p=ns) or major bleeding (2.7 *vs* 2.4%: p=ns)
- was associated with a lower rate of clinically relevant non major bleeding (10.9 *vs* 15.3%: p=0.004)





A.Y.Y. Lee et al. JAMA 2015

Results of studies from the CATCH population

Characteristics and risk factors of major and clinically relevant non-major bleeding in cancer patients receiving anticoagulant treatment for acute venous thromboembolism – the CATCH study

OP-228: Kamphuisen PW et al

- Clinically relevant non major bleeding (CRB) occurs in 16% of cancer patients with symptomatic VTE during anticoagulant treatment and is associated with metastatic disease, older age, and intracranial lesions.
- Treatment with full-dose tinzaparin seems safe in patients with renal impairment

Long-term tinzaparin versus warfarin for treatment of venous thromboembolism (VTE) in cancer patients – analysis of renal impairment (RI) in the CATCH study

***AS-214 Bauersachs et* al**

- Renal impairment leads to a significant increase in the risk of recurrent VTE
- but not clinically relevant bleeding in cancer patients on anticoagulation for VTE compared with Warfarin.

Nonvitamin-K-antagonist oral anticoagulants (NOAC)

- Nonvitamin-K-antagonist oral anticoagulants (NOAC) are approved as novel VTE treatment.
- However, their role in the cancer setting, particularly in comparison with the current standard of care, which is LMWH, remains unclear

Tissue factor (TF) as predictor of recurrent VTE: risk factor and biomarker analysis from the CATCH trial of treatment of cancer associated VTE with tinzaparin or warfarin. (*AS 081 Khorana AA*)

Studio biologico per valutare l'associazione fra i livelli di TF antigene, F-VIII, D-dimero, sP-selettina e proteina C-reattiva (CRP), misurati al momento della diagnosi iniziale di TEV, e la comparsa di recidive di *TEV.*

RESULTS

- **72/805 patients with recurrent VTE**.
- **Recurrent VTE was associated with:**
  - **elevated TF levels in the highest quartile** (> 64.6 pg/ml: RR 3.3, 95% CI 2.1-5.1, p < 0.0001)
  - **elevated CRP levels** (> 75 mg/L: RR 2.3, 95% CI 1.3-4.2, p = 0.007)
- **At regression analysis elevated TF levels remained significantly associated with risk for recurrent VTE** (HR 3.4, 95% CI 2.1-5.5, p < 0.001).
- Baseline D-dimer, FVIII and sP-selectin levels did not appear to confer additional risk in this study.

TF is a clinically significant biomarker predictive for recurrent VTE in malignancy. A biomarker based strategy could help identify high-risk patients benefiting from longer or more intense anticoagulation strategies.

XXV ISTH Congress – Toronto, June 20-25, 2015

SSC Hemostasis and Malignancy

Hypercoagulation screening as a marker of early diagnosis and disease prognosis in cancer: The HYPERCAN study

(supported by a Grant 5x1000 of the Italian Association for Cancer Research)

Anna Falanga, PI, for the HYPERCAN Investigators

Hospital Papa Giovanni XXIII (Bergamo), National cancer Institute (Milan), Humanitas Institute (Milan), Hospital San Filippo Neri (Rome), Hospital Sant'Eugenio (Rome), Humanitas Gavazzeni Institute (Bergamo), Hospital Alzano (Bergamo), Hospital Treviglio-Caravaggio (Bergamo), Policlinico San Marco (Bergamo), Institute Neuromed (Pozzilli, Isernia), and

The Blood donors associations Bergamo

ITALY

International Advisory Board:
Pieter I. Reitsma (The Netherlands)
Frederick R. Rickles (United States)

The HYPERCAN is an ongoing prospective Italian, multicenter, observational study structured in **two sub-projects** that involve:

1. non-cancer, and **2. cancer subjects**

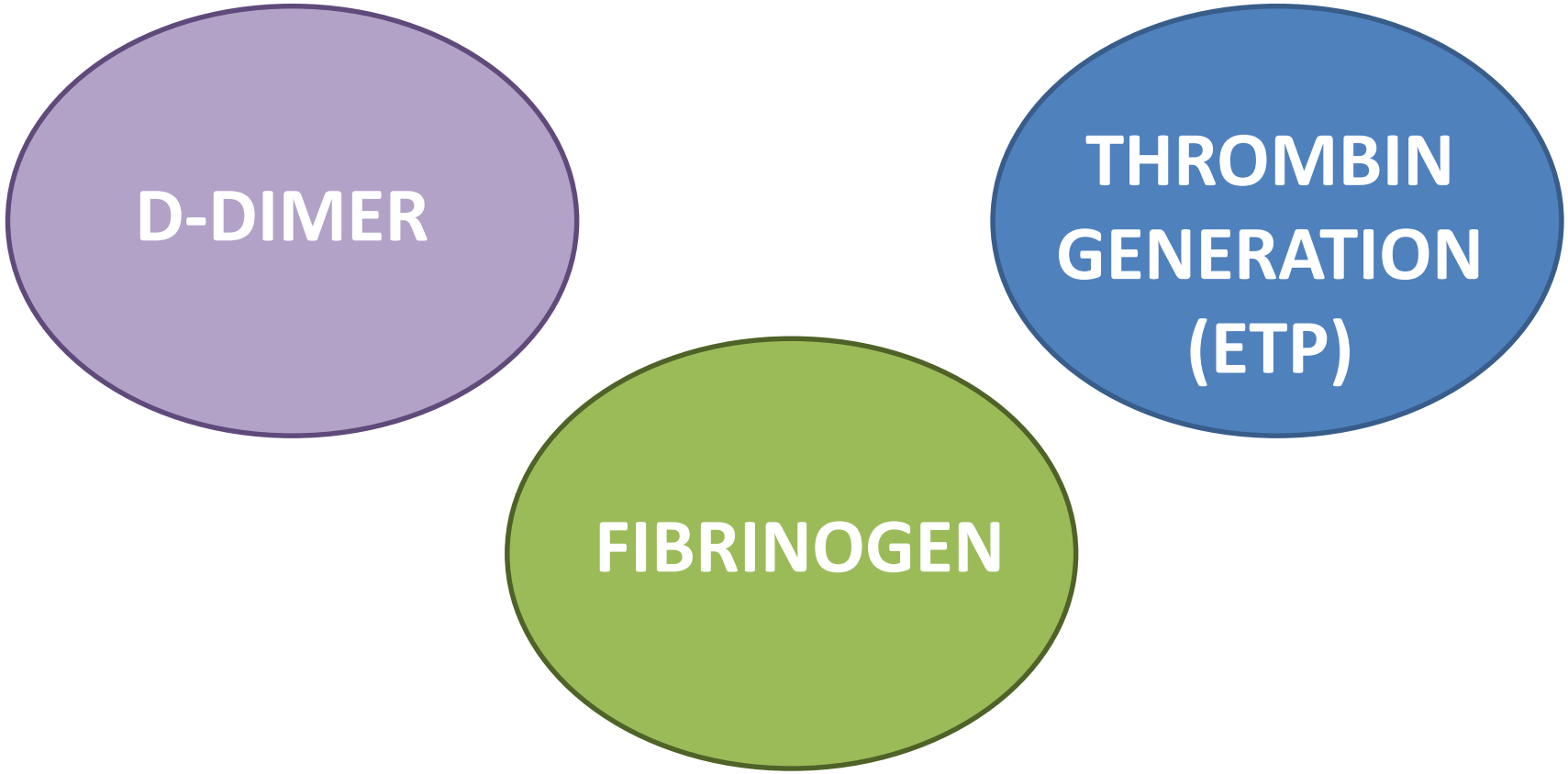
PROJECT 1 . Assessment of thrombotic markers as a tool for cancer risk prediction in healthy subjects

- To establish whether the persistence of a hypercoagulable state, as detected by laboratory thrombosis markers on 2 different samples (at enrollment and after 6-12 months), may predict for an increased risk of cancer diagnosis.

PROJECT 2. Evaluation of thrombotic markers in patients with newly diagnosed cancer in relation with cancer survival and VTE

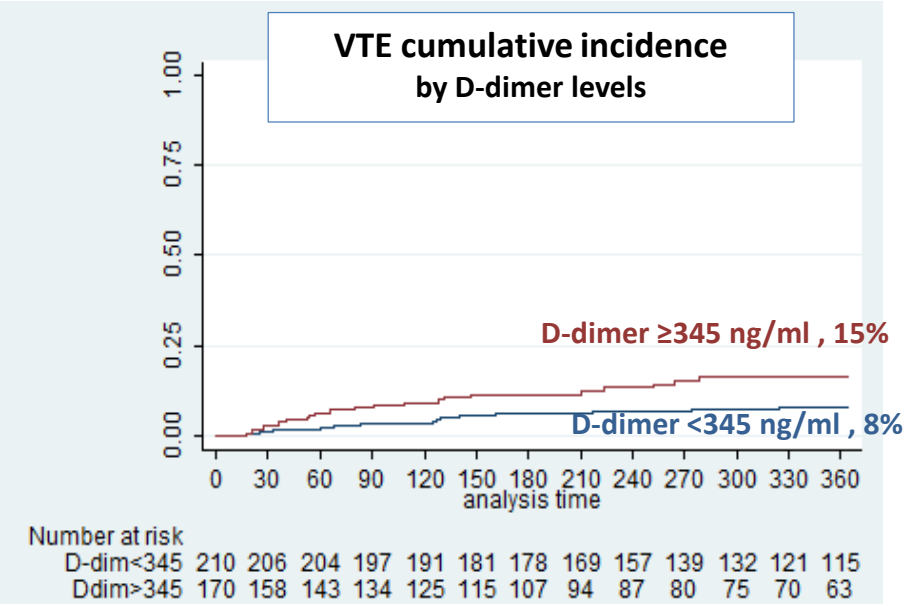
- To assess whether the occurrence of a hypercoagulable state may be a marker of cancer prognosis, response to therapy, and/or VTE in patients with **breast**, **lung**, **gastro-intestinal** cancers.

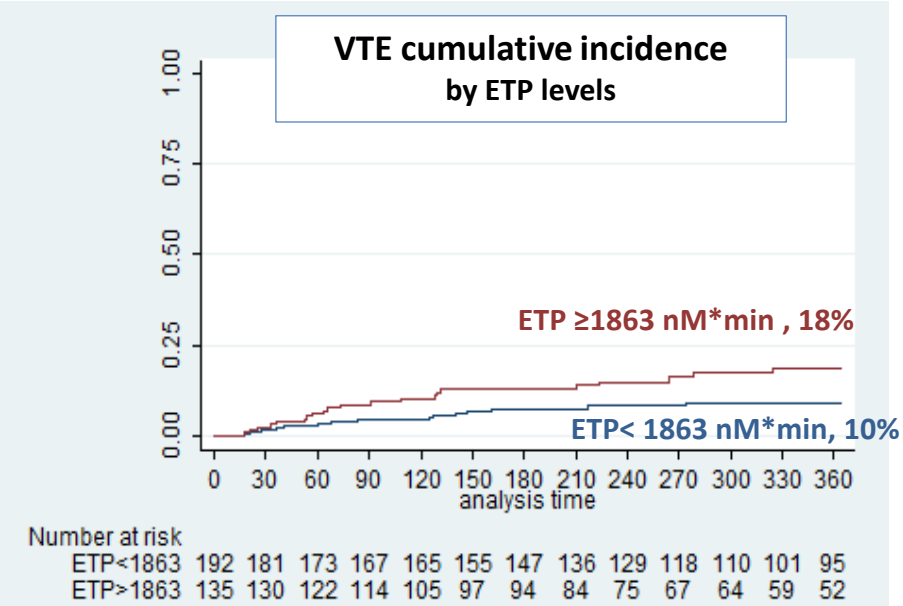
Project 2:
Biomarker Study in the cancer population



Biomarkers were analyzed by commercial assays: D-DIMER (Werfen), Fibrinogen (Werfen), Thrombin Generation (Stago)

Pre-chemotherapy levels of D-dimer or ETP greater than cut-off values are associated with significant increased VTE risk

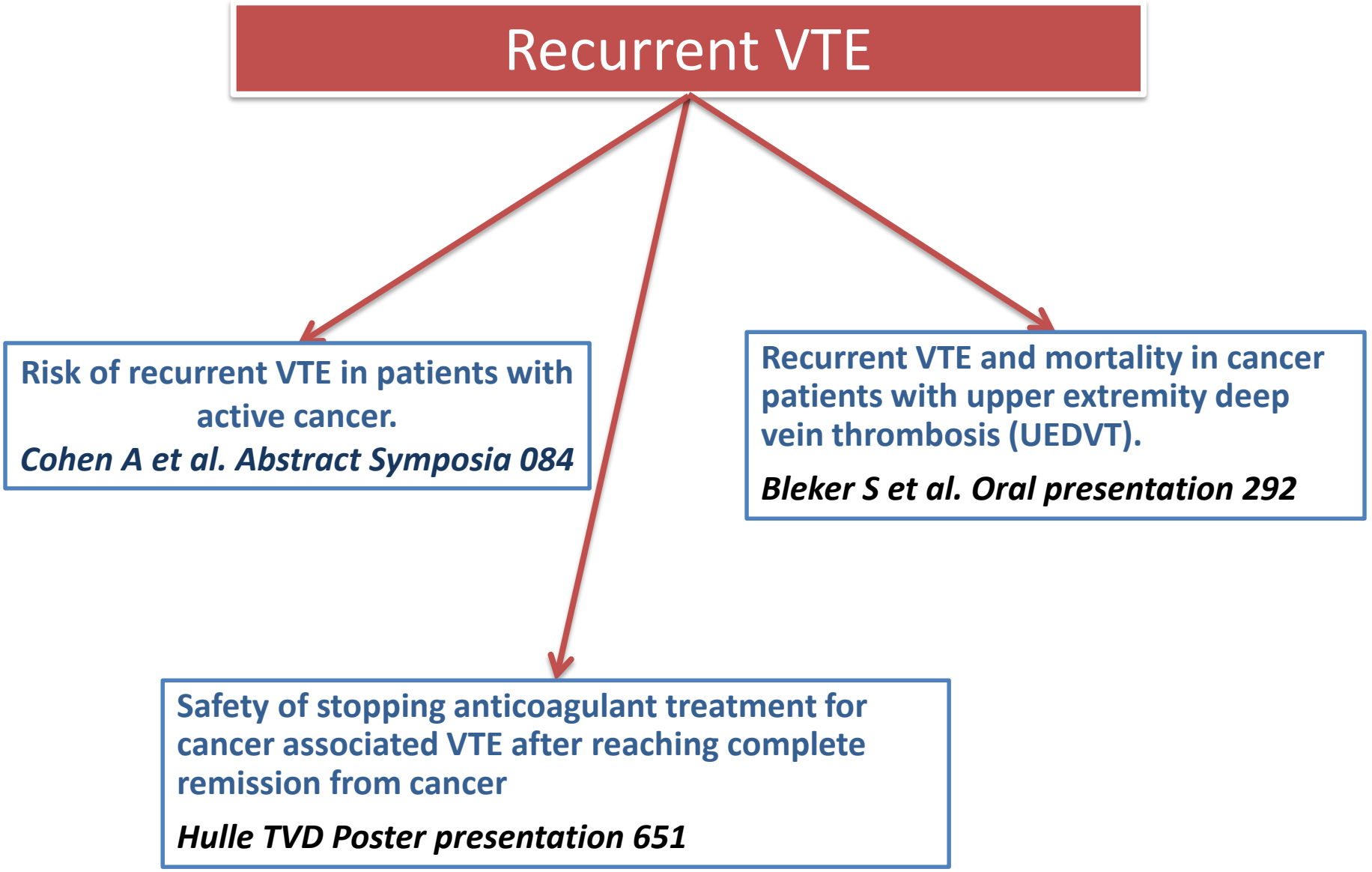




15% vs 8%
HR: 2.18 (95% CI 1.13-4.21)
p<0.05

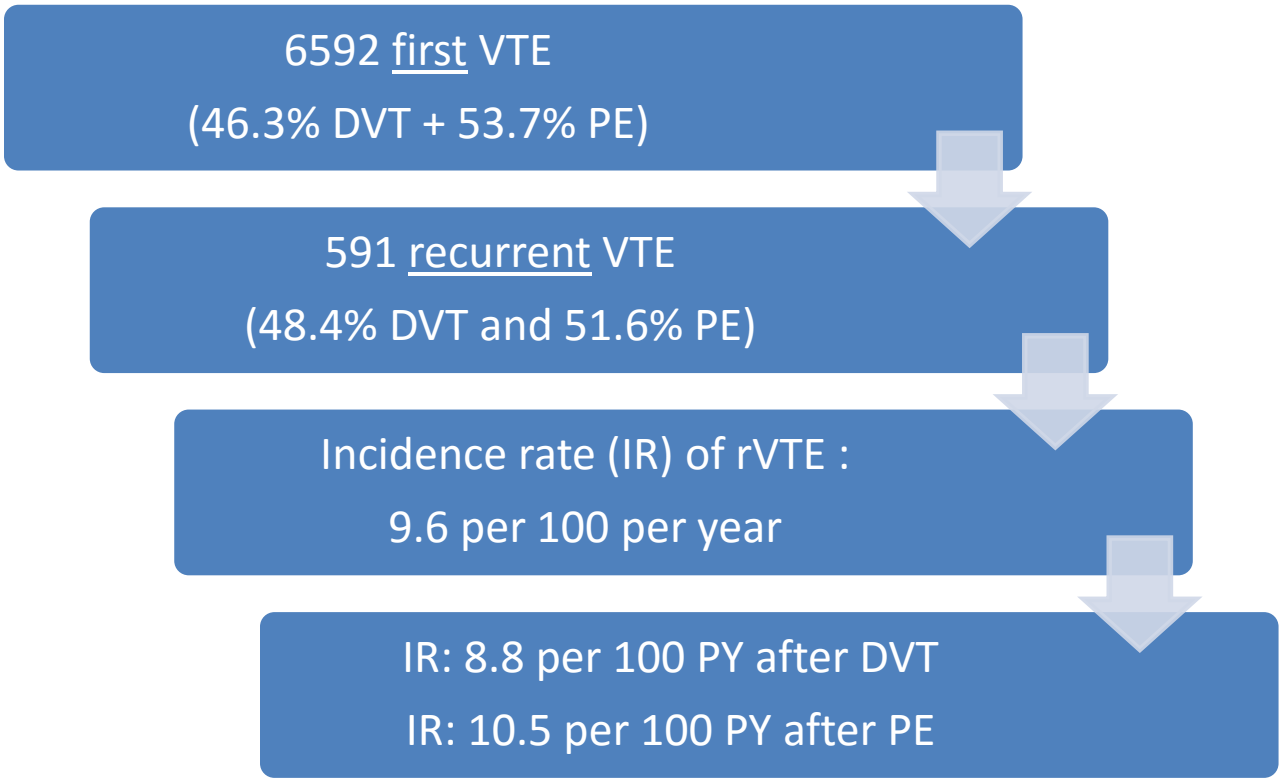
18% vs 10%
HR: 2.11 (95% CI 1.09-4.10)
p<0.05

Fibrinogen levels are not associated with significant increased VTE risk (HR: 2.91, 95% CI 0.99-3.67, p=ns)


Recurrent VTE
Risk of recurrent VTE in patients with active cancer.
Cohen A et al. Abstract Symposia 084
Recurrent VTE and mortality in cancer patients with upper extremity deep vein thrombosis (UEDVT).
Bleker S et al. Oral presentation 292
Safety of stopping anticoagulant treatment for cancer associated VTE after reaching complete remission from cancer
Hulle TVD Poster presentation 651

Risk of recurrent VTE in patients with active cancer

Population based observational cohort study 2001-2011

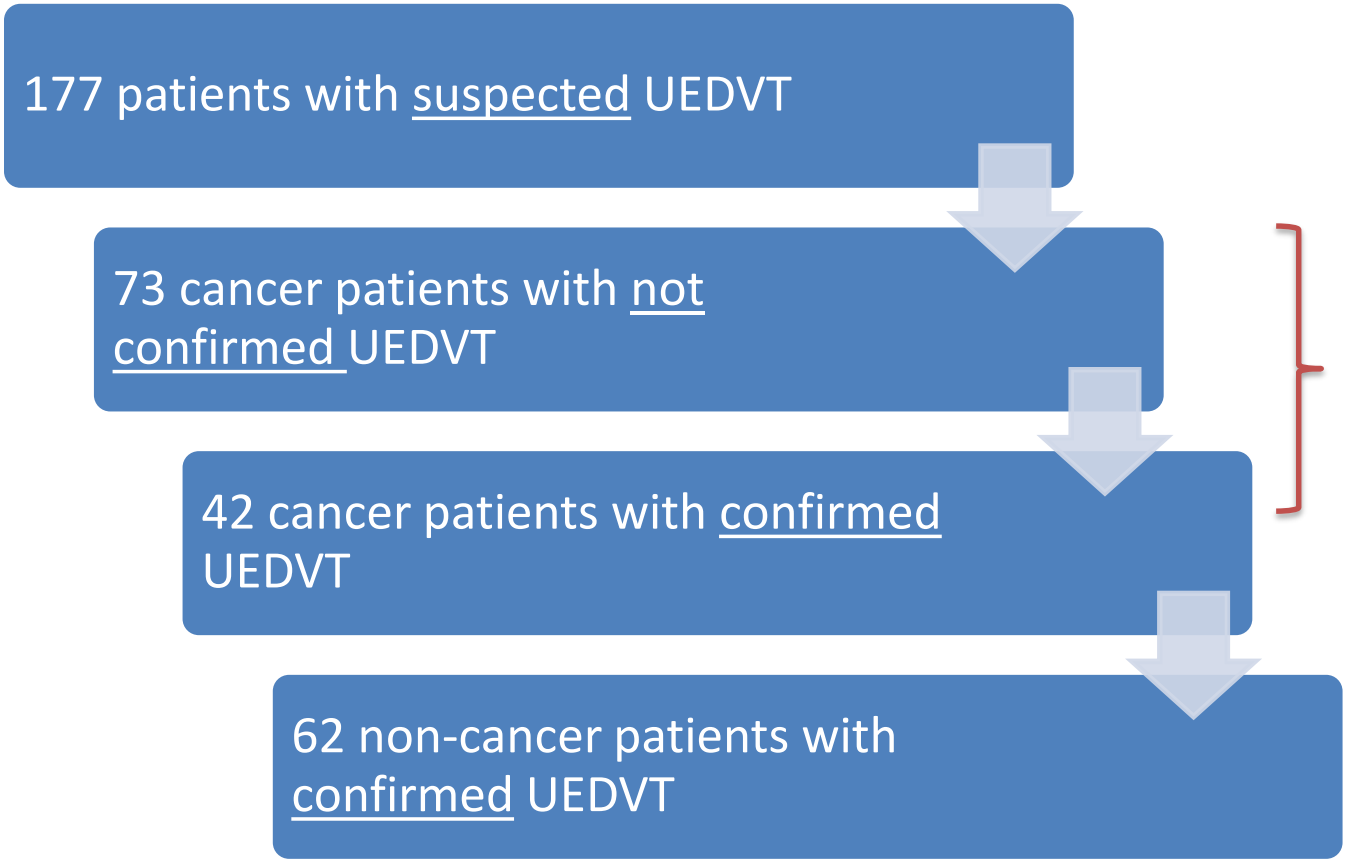


VTE in patients with active cancer is common and associated with high recurrence rates. Efforts are needed to prevent VTE and to reduce recurrences, especially in the first year following VTE diagnosis.

AS-084: *Cohen A et al*

Recurrent VTE and mortality in cancer patients with upper extremity deep vein thrombosis (UEDVT)

ISTH 2015-ABS-292: Bleker S et al



Mortality:
43.1 vs 51.2%

HR 1.47, 95% CI 0.84–2.58;

Recurrent VTE:
12.2 vs 6.5%

HR 1.68, 95% CI 0.51–5.55

Cancer patients with UEDVT **have a higher risk of recurrent VTE** than non-cancer patients. A diagnosis of UEDVT does **not appear to be associated with worse survival** in cancer patients, however, this may be due to the small number of patients in this study.

Safety of stopping anticoagulant treatment for cancer associated VTE after reaching complete remission from cancer (*PO651 Hulle TVD)*

358 consecutive cancer patients diagnosed with VTE between 2002 -2010.

196 patients survived the first 6 months after VTE

- 117 not cured → rVTE under anticoagulation: IR= 6.3/100 PY (95%CI 2.0–15)

  Anticoagulation-associated major bleeding : IR= 11/100 PY (95% CI 5.1–21).

  rVTE after cessation of anticoagulation: IR= 12/100 PY (95% CI 5.8–22)

- 79 complete remission of cancer → **rVTE after cessation of anticoagulation: IR = 3.2/100 PY (95%CI 1.5–5.9)**

  - 49 patients cancer-free → **rVTE after cessation of anticoagulation: IR = 1.2/100 PY (95%CI 0.2–3.5)**

Our data underline the recommendation to discontinue anticoagulant therapy for caVTE after patients have reached complete remission. A cancer relapse during follow-up however seems to be a strong risk factor for recurrent symptomatic VTE

VTE and OCCULT CANCER

- Unprovoked VTE may be the earliest sign of cancer
- Up to 10% of patients with unprovoked VTE receive a diagnosis of cancer in the year after their diagnosis of VTE
- More than 60% of occult cancers are diagnosed shortly after the diagnosis of unprovoked VTE
- Thereafter, the incidence rate of cancer diagnosis gradually declines and returns to the rate in the general population after 1 year.
- Currently, there is a great diversity in practices regarding screening for occult cancer in a person who has an unprovoked VTE.

Sørensen HT et al, N Engl J Med 1998; White RH et al, Arch Intern Med 2005; Van Doormaal FF et al, JTH 2011.

VTE and Occult cancer

Occult VTE: Do new trial results change practice?

SSC Education Session

Carrier M

Extensive screening based on 18F-FDG PET/CT for occult malignant disease in unprovoked VTE: a prospective randomized clinical trial

Abstract symposia-082

Robin P

Long-term cancer risk after VTE

Oral Presentation-226

Eischer L

Thrombotic burden and the risk of subsequent manifest cancer

Oral Presentation - 291

Prandoni P

Interrelation between cancer and myocardial infarction in the general population

Oral Presentation-293

Rinde RB

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 20, 2015 VOL. 373 NO. 8

Screening for Occult Cancer in Unprovoked Venous Thromboembolism

Marc Carrier, M.D., Alejandro Lazo-Langner, M.D., Sudeep Shivakumar, M.D., Vicky Tagalakis, M.D., Ryan Zarychanski, M.D., Susan Solymoss, M.D., Nathalie Routhier, M.D., James Douketis, M.D., Kim Danovitch, C.C.R.P., Agnes Y. Lee, M.D., Gregoire Le Gal, M.D., Philip S. Wells, M.D., Daniel J. Corsi, Ph.D., Timothy Ramsay, Ph.D., Doug Coyle, Ph.D., Isabelle Chagnon, M.D., Zahra Kassam, M.D., Hardy Tao, M.D., and Marc A. Rodger, M.D., for the SOME Investigators*

Multicenter, open-label, randomized, controlled trial in Canada, **854 patients with unprovoked VTE enrolled**.

1. **limited occult-cancer screening** (basic blood testing, chest radiography, and screening for breast, cervical, and prostate cancer)
2. **limited occult-cancer screening in combination with CT**.

Primary outcome: confirmed cancer that was missed by the screening strategy and detected by the end of the 1-year follow-up period.

ClinicalTrials.gov number, NCT00773448.

Carrier et al., NEJM 2015

33/854 (3.9 %) patients had a new diagnosis of occult cancer between randomization and the 1-year follow-up

- 14 /431 (**3.2%**) in the **limited-screening group**
- 19 /423 (**4.5%**) in the **limited-screening-plus-CT group**

In the primary outcome analysis, 4 occult cancers (29%) were missed by the limited screening strategy, whereas 5 (26%) were missed by the strategy of limited screening plus CT (P = 1.0).

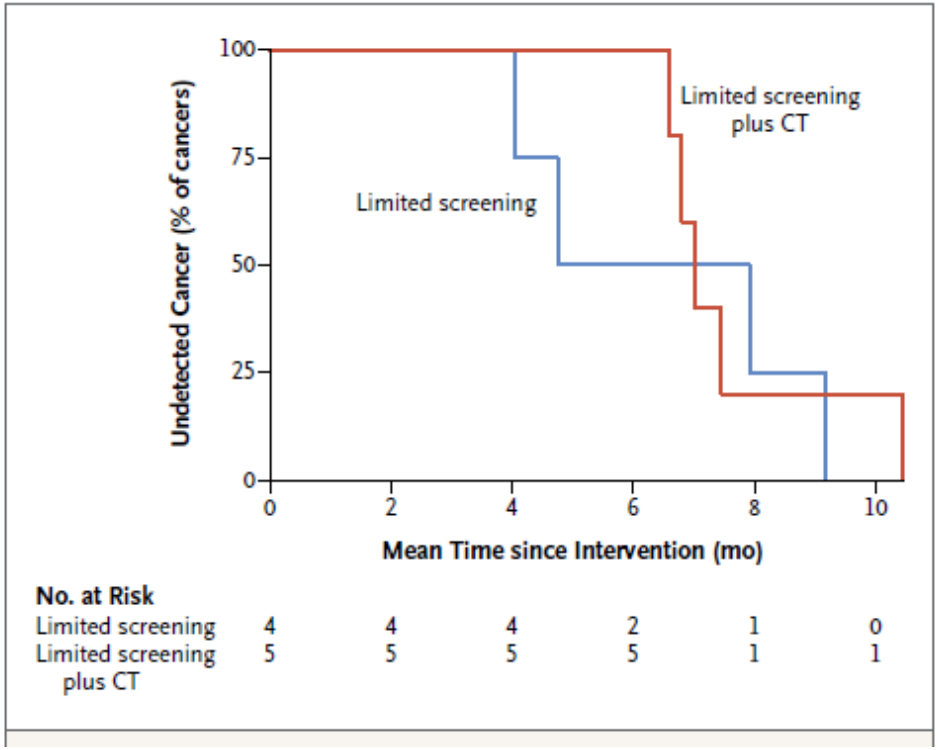
Table 2. Occult Cancer Tumor Types.

Tumor Type	Limited Occult-Cancer Screening (N=14)	Limited Occult-Cancer Screening plus CT (N=19)
	no. of tumors/total no. (%)	
During screening period		
Acute leukemia	0/10	0/14
Gynecologic	3/10 (30)	0/14
Skin: melanoma	1/10 (10)	0/14
Colorectal	0/10	3/14 (21)
Prostate	2/10 (20)	0/14
Pancreatic	2/10 (20)	0/14
Cholangiocarcinoma	1/10 (10)	2/14 (14)
Lymphoma	1/10 (10)	3/14 (21)
Breast	0/10	2/14 (14)
Urologic	0/10	3/14 (21)
Unknown primary	0/10	1/14 (7)
During follow-up period		
Acute leukemia	1/4 (25)	1/5 (20)
Gynecologic	1/4 (25)	1/5 (20)
Skin: melanoma	0/4	1/5 (20)
Colorectal	1/4 (25)	1/5 (20)
Prostate	0/4	1/5 (20)
Pancreatic	1/4 (25)	0/5

Carrier et al., NEJM 2015

The time to detection of a missed occult cancer over the 1 year FU period indicated no significant difference between the two groups

- 4.2 months in the limited-screening group (31% of missed occult cancer)
- 4.0 months in the limited-screening-plus-CT group (24% of missed occult cancer)



The prevalence of occult cancer is low among patients with a first unprovoked VTE. Routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit.

Carrier et al., NEJM 2015

Extensive screening based on 18F-FDG PET/CT for occult malignant disease in unprovoked VTE: a prospective randomized clinical trial

(***Symposium- AS082 - Robin P***)

- **394 patients with unprovoked VTE**
- Cancer was diagnosed in:
  - **11/197 (5.6%) patients** in the FDG PET/CT group
  - **4/197 (2%) patients** in standard strategy* group

  absolute risk difference: 3.6% (95% CI 0.4-7.9; P = 0.07)
- Risk of subsequent cancer diagnosis over the 2 years FU is of 2.6%:
  - **1/186 (0.5%)** in the FDG PET/CT group
  - **9/193 (4.7%)** in the standard strategy group

  absolute risk difference : 4.1% (95% CI 0.8–8.4; P = 0.01)

The use of FDG PET/CT is associated with a non-significant increase in the rate of cancer diagnosis at the time of unprovoked VTE.
The risk of subsequent cancer diagnosis was significantly lower in patients after a negative screening strategy that included a FDG PET/CT

*Physical examination, usual laboratory tests and basic X-Rays

Interrelation between cancer and myocardial infarction in the general population (***OR 293; Rinde MB***)

28 740 subjects without a history of MI and cancer. After a median follow-up of 15.7 years:
1858 incident MI + 2677 incident cancers

- Subjects with MI had increased risk of subsequent cancer *vs* subjects without MI (HR 1.60, 95% CI 1.15 – 2.21 in women and 1.28, 95% CI: 1.02 – 1.61 in men).
- Risk was highest the first 6 months after MI (HR 3.11, 95% CI 1.48 – 6.61 in women and 1.74, 95% CI: 0.90 – 3.36 in men)
- After 5 year the association was not longer significant.

- Cancer patients had increased risk of MI in the first 6 months after the cancer diagnosis (HR 2.11, 95% CI 1.05 – 4.25 in women and 1.79, 95% CI 1.07 – 3.00 in men), but declined rapidly thereafter and were no longer significant.

MI may be the first sign of occult cancer

8th ICTHIC

8th International Conference on

THROMBOSIS AND HEMOSTASIS ISSUES IN CANCER

April 8-10, 2016 • Bergamo, Italy

www.icthic.com