TREATMENT OF VENOUS THROMBOEMBOLISM IN CANCER PATIENTS

D. Farge and Ph Debourdeau
for the GFTC (Groupe Francophone Thrombose et Cancer)

www.thrombose-cancer.com
<table>
<thead>
<tr>
<th>Disclosures of FARGE Dominique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employment</td>
</tr>
<tr>
<td>Research support</td>
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<tr>
<td>Scientific advisory board</td>
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<tr>
<td>Consultancy</td>
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<td>Speakers bureau</td>
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<td>Major stockholder</td>
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<td>Patents</td>
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<td>Honoraria</td>
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<td>Travel support</td>
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<td>Other</td>
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</tbody>
</table>
The association between VTE and cancer

First description by Trousseau in 1865 (Hôtel-Dieu, Paris)

Cancer
- Venous Thromboembolism (VTE = VT, PE or CAT) in 4 - 20% cancer pts
  - VTE at autopsy in 50% of cancer pts

VTE
- 20% of VTE pts have active cancer
- 4-12% of pts with idiopathic VTE have an underlying cancer

Cancer increases the risk of VTE: \( \times 4 - 6 \)

- Case-control study – Olmsted County (1976-1990)
- 625 patients with 1\textsuperscript{st} episode of VTE/PE
- Matched (age, sex) with 625 pts without VTE/PE

Odds ratio (IC 95%)

- Cancer with chemotherapy: 6.53 (2.11-20.23)
- Cancer without chemotherapy: 4.05 (1.93-8.52)

- Surgery
- Trauma
- Hospitalisation
- Cancer with chemotherapy
- Cancer without chemotherapy
- Central venous catheter or pacemaker
- Neurological Disease
- Superficial venous Thrombosis
- Varicose veins (aged 45 yrs)
- Varicose veins (aged 60 yrs)
- Varicose veins (aged 70 yrs)
- CCF/VTE (post-mortem finding)
- CCF/VTE (ante-mortem or VTE cause of death)
- Severe liver failure


- CCF: congestive cardiac failure
- VTE: Venous thromboembolism
Various factors increase the risk of VTE in cancer patients: RISK SCORING MODELS?

**Patient related**
- Older age
- Gender
- Ethnic origin (afro-american > asian)
- Obesity
- Co-morbidities
- Previous VTE
- Thrombophilia
- Biomarkers: D dimers, platelets, TF, P selectin....

**Cancer related**
- Cancer site
  - Especially gastro-intestinal, neurological, pulmonary, gynecological, renal and hematological
- Histological type
- Metastatic status
- Early treatment after cancer diagnosis

**Treatment related**
- Recent surgery
- Hospitalisation
- Chemotherapy
- Hormonotherapy
- Anti-angiogenic agents
- EPO
- Central Venous Catheter

PREDICTION OF VTE in cancer patient?
Which is the best score for a single patient?

VTE risk and need for adequate treatments will vary during cancer evolution

Hospitalisation: in patient
Biopsy, Surgery, CVC insertion

Metastases

Palliative care

Diagnosis

Chemotherapy

Rémission

VTE risk in cancer patients

VTE risk in the general population

Risk of VTE (VT, PE, CAT) is underestimated in cancer pts, who necessitate adequate TT.

- VTE or PE is present in 50% of deceased cancer patients by autopsy\(^1\)
- Significant number of asymptomatic PE discovered during routine evaluation of cancer patients \(\textit{(repeated multislice CT scan for cancer staging)}\)
  - Retrospective study 581 patients: 3.4% VTE incidental \(^2\)
    (higher prevalence of cancer if asymptomatic PE: 64.7% vs. 35.3%, p<0.05)
  - Prospective study of 385 cancer patients: 2.6% PE incidental \(^3\)
    => Asymptomatic PE? 75% of cases: symptoms found retrospectively \(^4\)
- Increasing number of incidental VTE in cancer patients
  - In 135 pancreatic cancer pts: 33.3% of PE, 21.4% of VT and 100% of visceral veins events were incidental VTE

VTE is an independent risk factor of death in cancer patients.\(^1\)

- VTE is the 2\textsuperscript{nd} cause of death in cancer patients.\(^1\)
- When cancer is diagnosed at the same time or within a year after VTE, the risk of death is enhanced by 3 at one year compared to cancer patients without VTE.\(^2\)
- VTE enhances the risk of death by 2 in cancer patients hospitalized with neutropenia.\(^3\)
- Cancer enhances by 3.7 the risk of postoperative death related to PE in general surgery as compared to non-cancer patients undergoing the same surgery.\(^4\)
- Cancer enhances by 1.8 the risk of death related to PE in hospitalized patients.\(^5\)
- In 578 patients with fatal and non-fatal PE, one of every 7 hospitalized cancer patients died of PE and 60% who died from PE had localized or limited cancer, strongly underlying need for adequate VTE prophylaxis in hospitalized patients.\(^5\)

VTE increases the costs (x3) and the needs for healthcare in cancer pts 1,2

Retrospective study of 2 paired cohorts of cancer patients starting chemotherapy with solid tumor between 2004 and 2009 and matched controls (duration of FU: 1 year).2

<table>
<thead>
<tr>
<th>Costs and need for health care access (any cause)</th>
<th>Patients with VTE* (n=912)</th>
<th>Patients without MTEV* (n=2736)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (mean) of hospitalisations / patient</td>
<td>1.38</td>
<td>0.55*</td>
</tr>
<tr>
<td>Number (mean) of days of hospitalisation / patient</td>
<td>10.19</td>
<td>3.37*</td>
</tr>
<tr>
<td>Hospitalisation Costs (mean) / patient (US$)</td>
<td>21 299</td>
<td>74 959*</td>
</tr>
<tr>
<td>Total costs (mean) / patient (US$)</td>
<td>74 959</td>
<td>41 691*</td>
</tr>
</tbody>
</table>

*p<0.0001 vs. patients with VTE

VTE cost can be partly due to difference in diseases and required adjusted treatment (propensity matching)
VTE increases the costs and the needs for health cares in cancer patients 1,2

Retrospective study of 2 paired cohorts of cancer patients starting chemotherapy with solid tumor between 2004 and 2009 (duration of FU : 1 year).2

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*p<0.0001 vs. patients with VTE

VTE incidence, specific morbidity and mortality, costs

Need for best curative treatment effective prevention and for VTE in cancer patients

Several scientific societies issued GCP

- American College of Chest Physicians (ACCP), American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN)
- European Society of Medical Oncology (ESMO)
- Institut National du Cancer” (INCa)
- International Myeloma Working Group (IMWG)
- Italian Association of Medical Oncology (AIOM)
Many national Guidelines published for the treatment of VTE in cancer patients¹,²


• Various methodologies ...different questions

• Low level of implementation¹-³

To foster physicians awareness + Improve cancer pts care = >Pool data of existing GCP to reach consensus = >Study unanswered clinical questions

**Independent institutional support**

<table>
<thead>
<tr>
<th>Topic</th>
<th>NCCN</th>
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<th>AIOM</th>
<th>ACCP</th>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Curative treatment of DVT and PE</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
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<td>No</td>
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<td>Yes</td>
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<td>Methods of catheter insertion</td>
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<td>Target population of patients of CPG</td>
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<tr>
<td>Professionals to whom the CPG is targeted</td>
<td>Oncologists</td>
<td>Oncologists</td>
<td>Oncologists</td>
<td>Internist Vascular pathology</td>
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<td>Expected outcomes Amelioration of clinical practice</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Preference of patients</td>
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<td>No</td>
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<td>Economic evaluation and appicability of CPG</td>
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<td>Assessment of acceptability and applicability of CPG</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

An international working group:
24 multidisciplinary experts, 2 methodologists
1 nurse, 3 patients, 42 independent reviewers

Coordination: **D. Farge – H. Buller**
Methodological experts: **Ph Debourdeau, M Beckers**

Oncology Hematology: **M Marty, M Mandala, R Lecumberri, C Zervas, D Brilhante, N Haim, M Qari, M Streiff, A Khorana**

Vascular disease Internal medicine: **A Kakkar, S Noble, P Prandoni, M Monréal, H Buller, R Bauersachs, H Bounameaux, B Brenner**

Biology, Epidemiology, Others: **M Prins, I Pabinger, G Gerotzafias, S Mousa, A Falanga**

Nurses representatives: **C Baglin, Chair ISTH SSC:** A Falanga


- **Initiated by the Groupe Francophone Thrombose et Cancer with the collaboration of Académic Medical Center and University Medical Center Groningen,** **INCa (Institut National du Cancer)** methodological support

- Institutional fundings

- Consensus of the WG, Project duration: November 2009 – June 2012
### Literature review:

**all published studies January 1996-June 2011**

**MEDLINE:** cancer, VTE, anticoagulant drugs. National GCP + EBM sites, English / French.

**Inclusion:** meta-analyses, systematic reviews, RCT/non-RT prospective/retrospective studies if no RCT

**Exclusion:** editorials, letters, cases, publications without abstract, abstract without full paper

If no specific study on cancer pts => general population VTE pts also including pts with cancer.

Pts with tumor-associated thrombosis, or history of cancer remission for more than 5 yrs: not analyzed.

**Study outcomes:** VTE rates (recurrence, de novo VTE), major bleeding, thrombocytopenia, death.
METHODS: CLINICAL QUESTIONS FOR INTERNATIONAL GCP on TREATMENT and PROPHYLAXIS of VTE in cancer pts

• Q1.  Initial treatment (0 up to 10 days) of established VTE
• Q2.  Early maintenance (10 D-3 mths) and long term treatment (>3 mths) of established VTE
• Q3.  Treatment of VTE recurrence: VKA or LMWH, Vena cava filter
• Q4.  Prophylaxis of VTE in surgical cancer patients :
• Q5.  Prophylaxis in medical cancer patients:
• Q6.  Tt of established Catheter Related Thrombosis (CRT):
• Q7.  Prophylaxis of CRT
• Q8.  Specific cases: brain tumors, neurosurgery, renal failure, thrombocytopenia, in pregnant women with cancer

# GRADE: going from evidence to recommendations

≈ 40 organisations WHO, CHEST, NHS....ACCP 2012

pts, clinicians, health policy makers to harmonize international collaboration

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Study design</th>
<th>Lower if *</th>
<th>Higher if *</th>
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<tbody>
<tr>
<td>High (4)</td>
<td>Randomized trial</td>
<td>Study limitations</td>
<td>Large effect</td>
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<td></td>
<td></td>
<td>-1 Serious</td>
<td>+ 1 Large</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>+ 2 Very large</td>
</tr>
<tr>
<td>Moderate (3)</td>
<td>Observational study</td>
<td>Inconsistency</td>
<td>Dose response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td>+ 1 Evidence of a gradient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td></td>
</tr>
<tr>
<td>Low (2)</td>
<td>Observational study</td>
<td>Indirectness</td>
<td>All plausible confounding</td>
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<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td>+ 1 Would reduce a demonstrated effect, or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>+ 1 Would suggest a spurious effect when results show no effect</td>
</tr>
<tr>
<td>Very low (1)</td>
<td>Observational study</td>
<td>Imprecision</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td></td>
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<td></td>
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<td>Publication bias</td>
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<td>-1 Likely</td>
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<tr>
<td></td>
<td></td>
<td>-2 Very likely</td>
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</table>

### Table 1

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
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<tbody>
<tr>
<td>High (A)</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect</td>
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<tr>
<td>Moderate (B)</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Low (C)</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate</td>
</tr>
<tr>
<td>Very low (D)</td>
<td>Any estimate of effect is very uncertain</td>
</tr>
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</table>

### Recommendation

<table>
<thead>
<tr>
<th>Strong (Grade 1)</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Weak (Grade 2)</td>
<td>The panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects</td>
</tr>
<tr>
<td>Best clinical practice (Guidance)</td>
<td>The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident</td>
</tr>
</tbody>
</table>

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OUR GOALS ..for France

The cost of VTE in cancer patients in France

- 365,000 new cancer cases / year in France
- ~10% VTE, => 36,000 patients in F
- Extra costs: 839,500,000 €/year
  = 4,2 milliards € over 5 years

Potential cost benefits if adequate VTE prevention in cancer patients

- Prophylaxis: 2% decrease in VTE risk
- 730 cases prevented / year in F
- Benefits: 1,679,000 € / year

Estimated benefits in survival

- 147,500 deaths related to cancer in France in 2011
- Estimated benefits: 5 to 7000 lifes per year
VTE prophylaxis as recommended by ACCP 20004 is not implemented: Endorse study (358 hospitals in 32 countries)

*Cohen A et al Lancet 2008*

VTE prophylaxis in hospitalised patients for surgical (n=19 842) or medical

<table>
<thead>
<tr>
<th>Type of Prophylaxis</th>
<th>Medical patients (N=15 487)</th>
<th>Surgical patients (N=19 842)</th>
<th>Overall (N=35 329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any anticoagulant</td>
<td>6596 (43%)</td>
<td>10 901 (55%)</td>
<td>17 497 (50%)</td>
</tr>
<tr>
<td>Intermittent pneumatic compression without anticoagulant</td>
<td>318 (2%)</td>
<td>880 (4%)</td>
<td>1198 (3%)</td>
</tr>
<tr>
<td>Graduated compression stockings without anticoagulant</td>
<td>291 (2%)</td>
<td>745 (4%)</td>
<td>1036 (3%)</td>
</tr>
<tr>
<td>Aspirin for prophylaxis without anticoagulant/intermittent pneumatic compression/elastic stockings</td>
<td>214 (1%)</td>
<td>83 (0.4%)</td>
<td>297 (0.8%)</td>
</tr>
<tr>
<td>None</td>
<td>8068 (52%)</td>
<td>7233 (36%)</td>
<td>15 301 (43%)</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>4667 (30%)</td>
<td>9204 (46%)</td>
<td>13 871 (39%)</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>1454 (9%)</td>
<td>1564 (8%)</td>
<td>3018 (9%)</td>
</tr>
<tr>
<td>Vitamin K antagonist</td>
<td>694 (4%)</td>
<td>483 (2%)</td>
<td>1177 (3%)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>9 (0.1%)</td>
<td>39 (0.2%)</td>
<td>48 (0.1%)</td>
</tr>
<tr>
<td>Other anticoagulants</td>
<td>308 (2%)</td>
<td>252 (1%)</td>
<td>560 (2%)</td>
</tr>
<tr>
<td>Intermittent pneumatic compression</td>
<td>564 (4%)</td>
<td>1949 (10%)</td>
<td>2513 (7%)</td>
</tr>
<tr>
<td>Foot pump</td>
<td>41 (0.3%)</td>
<td>338 (2%)</td>
<td>379 (1%)</td>
</tr>
<tr>
<td>Graduated compression stockings</td>
<td>777 (5%)</td>
<td>3677 (19%)</td>
<td>4454 (13%)</td>
</tr>
</tbody>
</table>

Data are n (%).

*Table 4: Type of prophylaxis used in at-risk patients*
GCP for VTE treatment in cancer patients is not implemented as recommended

One day practice study CARMEN french study (500 cancer patients in 47 centers) to evaluate 2008 Inca national GCP guidelines between May and October 2010

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% patients under adequate VTE treatment *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial VTE treatment (0-10 days)</td>
<td>98%</td>
</tr>
<tr>
<td>Treatment of VTE after 10 days (without severe renal failure)</td>
<td>62%</td>
</tr>
<tr>
<td>Treatment of VTE after 10 days (with severe renal failure)</td>
<td>25%</td>
</tr>
<tr>
<td>Treatment of VTE (with severe renal failure)</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Tel que recommandé par l'INCa (SOR 2008)

WHY GCP for TT of VTE in cancer pts are not implemented? insufficient EDUCATION

- **Fear of secondary effects?** Benefits on thrombosis > risk of hemorrhage

- **Benefits from VTE treatment in cancer lower than expected?**
  + 10% VTE treatment + 3-4% VTE prophylaxis > most chemotherapies

- **Special cases?** Multidisciplinary approach for adequate medical decision

- **VTE diagnosis in oncology?** VTE symptoms well known, US and CT scan

- **Underestimation of the mortality risk?** *VTE the 2nd cause of death in cancer*

- **Underestimation of the economic consequences**
  - VTE cost if cancer ~20 000 $\text{^1}$
  - Extra cost if VTE + cancer ~30 000$/\text{an}\text{^2}$

- **Too many Guidelines** => adapt INTERNATIONAL GUIDELINES to local practices
To facilitate dissemination and implementation of international GCP for prophylaxis and treatment of VTE in cancer patients.

Public health priority
To reduce morbidity and mortality related to VTE, 2ème cause of death in cancer patients.

International level

National (French) level
1. To update Good Clinical Practices Guidelines in cancer patients

2. To homogenize existing GCP on VTE and cancer

3. To implement Good Clinical Practices Guidelines using specific organisation and NTI tools for multidisciplinary medical decision and cases registration.

4. To develop specific education on VTE in cancer (medical and paramedical staff, health policy makers,)

5. To set up a common national registry with individual access in each site

6. To develop clinical and translational research programs on VTE in cancer

7. To foster collaboration with national and international existing working groups (RIETE, ISTH, ASCO, AIOM, NCCN)
Application Mobile

ITAC-CME lance l’application mobile dont le but est la mise en application des recommandations internationales dans la prise en charge de la Maladie Thrombo-embolique Veineuse et le cancer.

[Images of app store icons for Apple and Google Play]

The International VTE Clinical Guidelines
Mobile App
L’Application Mobile des recommandations internationales sur la MTEV
Download it now ! Télécharger

[QR code]

ADHÉRER AU GFTC
Cliquez ici pour adhérer au GFTC

ÉVÉNEMENTS À VENIR

[Event details]

3rd July 2013
Initial treatment (first 10 days) of established VTE in cancer patients (1)

Unfractionated Heparin (HNF) followed by Vitamin K agonists (VKA)

Tt of VTE in cancer pts with UFH and VKA is associated with a high rate of relapse (7-10 %) and major bleeding (4-7 %).

Low Molecular Weight Heparin (LMWH) followed by VKA

The rate of major bleeding and VTE relapse is increased in the cancer pts.

LMWH + VKA vs UFH + AVK

**General population**

- **Efficacy:** LMWH ≥ UFH
- **Bleeding risk:** LMWH < UFH
- **Mortality:** LMWH < UFH

**Cancer Patients**

- **Relapses:** LMWH = UFH
- **Mortality:** LMWH < UFH

Initial treatment (first 10 days) of established VTE in cancer pts (2)

**Fondaparinux***

<table>
<thead>
<tr>
<th></th>
<th>vs. UFH + VKA</th>
<th>vs. LMWH + + VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapses</td>
<td>Fondaparinux &lt; UFH</td>
<td>Fondaparinux &gt; LMWH</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Fondaparinux = UFH</td>
<td>Fondaparinux = LMWH</td>
</tr>
<tr>
<td>Mortality</td>
<td>Fondaparinux = UFH</td>
<td>Fondaparinux = LMWH</td>
</tr>
</tbody>
</table>

**Thrombolytics**

- Only 1 *a posteriori* analysis of 5 randomized trials (57 pts with PE)
  - Relapse rate: 6%
  - Major Bleeding: 12%

**Vena Cava Filter**

- Few data in cancer patients
- Evidence is lacking to recommend their use in case of VTE recurrence.
- Cancer is neither a specific indication nor a special contra indication to vena cava filter.

Recommandations for initial tt (0-10 days) of established VTE in cancer pts

- **[Grade 1B]**
  - LMWH is recommended in the initial tt of established VTE in cancer pts

- **[Grade 2D]**
  - Fondaparinux and UFH can be used equally for initial tt of established VTE in cancer pt (fondaparinux is easier to use than UFH).

- **[Best practice or Guidances]**
  - Thrombolysis may only be based on a case by case basis, with specific attention to contra indication, especially bleeding risk (brain metastasis). An expert opinion is recommended before using thrombolytics.
  - VCF may be considered in case of CI to AC or of recurrence under optimal AC. Periodic reassessment of CI to AC is recommended and AC should be resumed when safe. VCF is not recommended for primary VTE prophylaxis in cancer pts.
All metanalyses have shown that long-term treatment by LMWH significantly reduce the risk of VTE recurrence by 50% with no increased risk of bleeding or any effect on the mortality rate.

No study compares 3 vs. 6 mths of LMWH.
In patients with DVT, after 6 mths of anticoagulation, the use of:
- US Doppler is not reliable and remains debated at this stage
- D-Dimer is not well documented to determine the need for further anticoagulation

Recommandations in cancer pts with established VTE for early maintenance (10 D-3 mths) + long term (>3 mths) tt of established VTE

[Grade 1A]

- LMWH are preferred over VKA for the early maintenance (10 D-3 mth) and long term tt ( > 3 mths) of VTE in cancer pts
- LMWH should be used for a minimum of 3 mths to treat established VTE in cancer pts. However, in this setting the largest study treated pts for 6 mths.

[Best Practice or Guidances]

- After 3-6 mths, termination or continuation of AC (LMWH or VKA) should be based on individual evaluation of risk/benefit, tolerability, patients’ preference and cancer activity

[Best Practice or Guidances]

- In case of recurrence, 3 options:
  - switch from VKA to LMWH in pts treated with VKA,
  - ↑LMWH in pts treated with LMWH,
  - VCF insertion

LMWH or UFH vs. placebo / no treatment

- LMWH or UFH > placebo or no prophylaxis in postoperative VTE prophylaxis in cancer pts
- Rate of any bleeding with LMWH > placebo or no treatment (one study)

LMWH vs. UFH

- Same efficacy for LMWH vs UFH (3/D) (but LMWH (1/D) > UFH (2/D), same bleeding rate)
- With a trend towards less bleeding with LMWH.

LMWH doses

- High dose of dalteparine (5000 UI) are superior than low doses (2500 UI)
- With no significant difference for bleeding risk (4.6% vs. 3.6%)

Extended duration prophylaxis

- One meta analysis: 4 wks LMWH ↓ postoperative risk of VTE after major laparotomy in cancer pts
- The superiority of extended duration of LMWH (4 wks) cannot be generalized to all cancer pts with major abdominal surgery, but may be considered in selected pts without high risk of bleeding.

Recommendations for VTE prophylaxis in surgical cancer patients

- **[Grade 1A]**
  - LMWH 1/D or low dose UFH x3/D are recommended to prevent postoperative VTE in cancer pts. Pharmacological prophylaxis should be started 12 to 24 H preoperatively and continued at least 7 to 10 D.
  - No data allow conclusion on the superiority of one type of LMWH.
  - Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in cancer pts.

- **[Grade 2B]**
  - Extended prophylaxis (4 wks) to prevent postoperative VTE after major laparotomy in cancer pts may be indicated in patients with a high VTE risk and low bleeding risk.

- **[Grade 2C]**
  - There is no evidence to support fondaparinux as an alternative to LMWH for the prophylaxis of postoperative VTE in cancer pts.

**Best practices**

- The use of LMWH for the prevention of VTE in cancer pts undergoing laparoscopic surgery may be recommended in the same way as for laparotomy.
- Mechanical methods are not recommended as monotherapy, except when pharmacological methods CI

Patients Hospitalized for acute medical disease with reduced mobility

- LMWH and UFH have a similar efficacy and safety
- LMWH and fondaparinux > placebo with a non-significant trend towards increased bleeding

Acute Lymphoblastic leukemia (ALL) in children

- Une étude randomisé chez des enfants présentant une LAL et traités par L-asparginase a comparé un traitement par antithrombine vs. pas de traitement, et a conclu à une absence de différence en termes de survenue d'ETEV ou de saignement

Ambulatory patients treated with chemotherapy

- 5 randomised studies compared LMWH vs. placebo (or no treatment) for primary prophylaxis in pts treated with chemotherapy:
  - ↓ the rate VTE without an excess of bleeding in pts with locally advanced or metastatic pancreatic (at subtherapeutic dosages) or locally advanced or metastatic lung cancers
  - no effect on VTE in pts with metastatic breast cancer

Recommendations for VTE primary prophylaxis in medical cancer patients

- **[Grade 1B]**
  - Prophylaxis with LMWH, UFH or fondaparinux is recommended in hospitalized medical cancer pts with reduced mobility.
  - In patients receiving chemotherapy, prophylaxis cannot be recommended routinely.
  - VTE primary pharmacological prophylaxis may be indicated in pts with locally advanced or metastatic pancreatic cancer with chemotherapy and having a low bleeding risk.

- **[Grade 2B]**
  - VTE primary pharmacological prophylaxis of VTE may be indicated in pts with locally advanced or metastatic pulmonary cancer treated with chemotherapy and having a low bleeding risk.

- **[Grade 2C]**
  - In pts treated with IMiDs combined with steroids and/or chemotherapy (doxorubicin), VTE prophylaxis is recommended: VKA at low or therapeutic doses, LMWH at prophylactic dose and low-dose aspirin have shown similar effects with regard to preventing VTE.

- **[Best practices or Guidances]**
  - In children and adults treated with L-asparaginase, depending on local policy and individual characteristics (platelet count, kidney function, fibrinogen and AT III levels, etc.), prophylaxis may be considered in some pts.

Recommendations for specific cases in cancer patients with venous thromboembolism (VTE)

1/ Brain Tumor-Neurosurgery -

- [Grade 1A]
  • We recommend the use of LMWH or UFH commenced postoperatively for the prevention VTE in cancer pts undergoing neurosurgery

- [Grade 2C]
  • A brain tumor per se is not a contraindication to anticoagulation.

- [Best practices or Guidances]
  • For the treatment of established VTE in pts with brain tumors, we prefer LMWH

2/ Severe Renal Failure (ClCr <30 ml/min)

- [Best practices or Guidances]
  • For treatment of established VTE, we suggest using UFH followed by early VKA (from D 1) or LMWH adjusted to anti-Xa level
  • ECD may be applied and pharmacological prophylaxis considered on a case-by-case basis; in such cases UFH may be used.

3/ Thrombocytopenia

- [Best practices or Guidances]

- In cancer pts with thrombocytopenia, full doses of anticoagulant can be used for tt of established VTE if platelets > 50 GL⁻¹ and no evidence of bleeding.
- For pts with platelets < 5 < 50 GL⁻¹, decisions on tt and dosage should be made on a case per case basis with extreme caution.
- Pharmacological prophylaxis may be used in pts with mild thrombocytopenia and platelets > 50 GL⁻¹, If platelets < 80 G/L, pharmacological prophylaxis may only be considered on a case-by-case basis and careful monitoring is recommended.

4/ In pregnant cancer patients,

- [Best practices or Guidances]

  - Standard tt for established VTE and prophylaxis should be implemented.
At time of elaborating these recommendations,

- In the absence of specific data, concerning the use of NOAC in cancer patients for VTE

  ➡️ impossible to draw any conclusion

  ➡️ Need for prospective studies

VENOUS THROMBOEMBOLISM AND CANCER

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Zeidan Streiff 2013 Am J Hematol

VTE prophylaxis smart order set: improved compliance, fewer events

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**Major VTE Risk**
- Yes
  - Contraindications
    - Yes
      - Use mechanical prophylaxis until contraindication no longer present. Review patient status daily
    - No
      - Heparin 5000 units subcutaneously q8 hours
  - No
    - Use mechanical prophylaxis until contraindication no longer present. Review patient status daily

**Contraindications**
- Yes
  - Heparin 5000 units subcutaneously q12 hours
- No

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**Major Risk Factors**
- Age older than 60 years
- Cancer (active or on chemotherapy)
- Previous VTE
- Acute Cerebrovascular event with paresis (within last 3 months)
- Thrombophilia
- Decompensated New York Heart Association (NYHA) Class III/IV congestive heart failure
- Respiratory failure (ventilator-dependent)
- Clinically-significant infection/sepsis

**Contraindications**
- High risk of bleeding
- Active bleeding
- Systemic anticoagulation
- INR ≥ 1.5 or aPTT ratio ≥ 1.3

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<th>Pre-implementation N=1,000</th>
<th>Post-implementation N=942</th>
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<tr>
<td>Total VTE Episodes</td>
<td>25 (2.5%)</td>
<td>7 (0.7%)</td>
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<td>Preventable Harm from VTE</td>
<td>11 (1.1%)</td>
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<td>Total In-House VTE</td>
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<td>5 (0.5%)</td>
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<td>Total 30-Day Post-Discharge VTE</td>
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<td>Total 90-Day Post-Discharge VTE</td>
<td>20 (2.7%)</td>
<td>2 (0.3%)</td>
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<tr>
<td>Fatal PE</td>
<td>2 (0.2%)</td>
<td>1 (0.1%)</td>
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**Anatomic Location of VTE Episodes**
- Lower extremity DVT: 14 (1.4%) vs. 3 (0.3%) (P=0.0130)
- Upper extremity DVT: 6 (0.6%) vs. 1 (0.1%) (P=0.1255)
- PE (= DVT): 5 (0.5%) vs. 3 (0.3%) (P=0.7270)
- Major Bleeding Episodes: 3 (0.3%) vs. 1 (0.1%) (P=0.6253)
- In-Hospital All-Cause Mortality: 13 (1.3%) vs. 19 (2.0%) (P=0.2845)