Prevention and management of venous thromboembolism

M. AAPRO
Thromboprophylaxis of DVT and PE in Ambulatory Cancer Patients

Zurich, February 2017

M. AAPRO

Based on a lesson in April 2016 by M. DICATO M.D., FRCP
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COI

Dr Aapro is/was a consultant for Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health, GSK, Helsinn, Hospira, JnJ, Novartis, Merck, Merck Serono, Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro, Teva, Vifor

and has received honoraria for lectures at symposia of Amgen, Bayer Schering, Biocon, Cephalon, Chugai, DRL, Eisai, Genomic Health, GSK, Helsinn, Hospira, Ipsen, JnJ OrthoBiotech, Kyowa Hakko Kirin, Merck, Merck Serono, Novartis, Ono Pharmaceuticals, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Tesaro, Taiho, Teva, Vifor

No responsibility accepted for involuntary errors or omissions.
The list may be incomplete, and does not reflect consultancy for NGOs, Universities, Governmental agencies, and others.
Relative Risk of VTE in Cancer Patients

Figure 4 Relative risk of venous thromboembolism (VTE) ranged from 1.02 to 4.34.

Incidence of VTE
Cancer patients with metastatic-stage disease

Chew HK. Arch Intern Med 2006; 166: 458
Risk Factors for VTE

- Previous venous thromboembolism
- Increased age
- Surgery
- Trauma - major, local leg
- Immobilization - bedrest, stroke, paralysis
- Malignancy and its treatment (CTX, hormonal..)
- Heart or respiratory failure
- Estrogen use, pregnancy, postpartum, SERMs
- Central venous lines
- Thrombophilic abnormalities
Risk Factors for VTE

- Previous venous thromboembolism
- Increased age
- Surgery
- Trauma - major, local leg
- Immobilization - bedrest, stroke, paralysis
- Malignancy and its treatment (CTX, hormonal..)
- Heart or respiratory failure
- Pregnancy, postpartum, SERMs
- Central venous lines
- Thrombophilic abnormalities

Most hospitalized patients have at least one risk factor for VTE
## V LEIDEN, OESTROGENS AND DVT

<table>
<thead>
<tr>
<th>$V_L$</th>
<th>OESTROGENS</th>
<th>DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>0.8</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>5.7</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>28.5</td>
</tr>
</tbody>
</table>

HOMOZYGOSITY: $> 100$

(BMJ 1996, 313 : 1127)
The Infernal Trio: Cancer- Inflammation- Thrombosis
Circulating microparticles (MPs)

- cell-to-cell communication
- small and heterogeneous membrane vesicles
  - size: 0.1 - 1.0 µm
  - negatively charged phosphatidylserine-rich surface
  - released from different cell types (including cancer cells)

Express membrane antigens characteristic of their cell of origin

Released in response to apoptosis and cell activation

Elevated levels of circulating MPs have been found in inflammatory, metabolic, malignant, and thrombotic diseases

Hugel et al. Physiology 2005
What is New?

**Research:**
- relations between cancer spread, hemostasis and inflammation

**Clinic:**
- VTE prevention in ambulatory Cancer Pts?
- Novel anticoagulants:
  - heparins
  - oral anticoagulants
Prophylactic Anticoagulation
Risk scoring models

Prediction of cancer-associated VTE

- Predictive Risk Scoring Model ("Khorana-Score") for chemotherapy-associated thrombosis
- Follow-up time: 2.4 months

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of cancer</td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynecologic, bladder, testicular)</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy platelet count $350 \times 10^9/L$ or more</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin level less than 100 g/L or use of red cell growth factors</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy leukocyte count more than $11 \times 10^9/L$</td>
<td>1</td>
</tr>
<tr>
<td>BMI 35 kg/m² or more</td>
<td>1</td>
</tr>
</tbody>
</table>

Khorana et al, Blood 2008
Vienna Cancer and Thrombosis Study (CATS)
Application of the predictive risk scoring model by Khorana et. al.

Ay C et al, Blood 2010; 116:5377-82
Novel Anticoagulants
Limitations of vitamin K antagonists (VKAs)

- Unpredictable pharmacology
- Narrow therapeutic window
  - Difficult to keep within therapeutic range
- Multiple drug–drug and food–drug interactions
- Dosing problems in the initial phase of therapy
- Increased risk of major and minor bleeding

Ansell *et al.*, *Chest* 2004; Hirsh *et al.*, *Chest* 2004
Percentage of Patients in therapeutic range (INR 2.3) with Coumarins

• Warfarin ~ 45% at 4 weeks (S.Kimmel NEJM 2013)
• Acenocoumarol & Phenprocoumon ~60% at 10 weeks (T Verhoef NEJM 2013)
Novel Anticoagulants

• FXI-ASO: FXI antisense oligonucleotide
• Semuloparin
• Oral: Dabigatran
  Rivaroxaban
  Apixaban
  Edoxaban
FXI-ASO (ISIS Pharmaceuticals) 2^e generation diminishes synthesis of FXI

N=300 pts. Knee replacement, Venography

FXI-ASO (200 vs 300mg) vs enoxaparine 40mg/j:

- Result similar for 200mg vs enoxaparine.
- For 300mg vs enoxaparine:
  - VTE 3/71pts (4%) vs 21/69 (30%), p<0.001.
  - Bleeding 3% vs 8%

➤ Antithrombotic with low risk of bleeding
Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute DVT Study</th>
<th>Continued Treatment Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban (N=1731)</td>
<td>Rivaroxaban (N=602)</td>
</tr>
<tr>
<td></td>
<td>Standard Therapy† (N=1718)</td>
<td>Placebo (N=594)</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>1055 (60.9)</td>
<td>440 (73.1)</td>
</tr>
<tr>
<td></td>
<td>1083 (63.0)</td>
<td>441 (74.2)</td>
</tr>
<tr>
<td>Recent surgery or trauma</td>
<td>338 (19.5)</td>
<td>21 (3.5)</td>
</tr>
<tr>
<td></td>
<td>335 (19.5)</td>
<td>28 (4.7)</td>
</tr>
<tr>
<td>Immobilization</td>
<td>265 (15.3)</td>
<td>89 (14.8)</td>
</tr>
<tr>
<td></td>
<td>260 (15.1)</td>
<td>77 (13.0)</td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td>140 (8.1)</td>
<td>23 (3.8)</td>
</tr>
<tr>
<td></td>
<td>115 (6.7)</td>
<td>22 (3.7)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>118 (6.8)</td>
<td>28 (4.7)</td>
</tr>
<tr>
<td></td>
<td>89 (5.2)</td>
<td>26 (4.4)</td>
</tr>
<tr>
<td>Puerperium</td>
<td>6 (0.3)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>11 (0.6)</td>
<td>0</td>
</tr>
</tbody>
</table>
Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism in patients with cancer

Martin H Prins
Maastricht University Medical Center, Maastricht, The Netherlands

ESMO Congress, 26–30 September 2014
## Outcomes

<table>
<thead>
<tr>
<th>History of cancer</th>
<th>Rivaroxaban</th>
<th>Enoxaparin/VKA</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE, n (%)</td>
<td>5/233 (2.1)</td>
<td>5/236 (2.1)</td>
<td>0.98 (0.28–3.43)</td>
</tr>
<tr>
<td>Major bleeding, n (%)</td>
<td>1/231 (0.4)</td>
<td>4/236 (1.7)</td>
<td>0.23 (0.03–2.06)</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>5/233 (2.1)</td>
<td>4/236 (1.7)</td>
<td>1.12 (0.30–4.22)</td>
</tr>
</tbody>
</table>
# Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Active cancer*</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>Enoxaparin/VKA</td>
<td>HR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE, n (%)</td>
<td>16/354 (4.5)</td>
<td>20/301 (6.6)</td>
<td>0.67 (0.35–1.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding, n (%)</td>
<td>8/353 (2.3)</td>
<td>15/298 (5.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>58/354 (16.4)</td>
<td>53/301 (17.6)</td>
<td>0.93 (0.64–1.35)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*At baseline or diagnosed during the study*
Major bleeding in patients with active cancer
Major bleeding in patients with active cancer

![Bar chart comparing major bleeding rates between Rivaroxaban and Enoxaparin/VKA based on creatinine clearance.](chart)

- Rivaroxaban:
  - >80 ml/min: 2.4%
  - 50–80 ml/min: 2.2%
  - <50 ml/min: 2.1%

- Enoxaparin/VKA:
  - >80 ml/min: 2.7%
  - 50–80 ml/min: 5.0%
  - <50 ml/min: 13.0%

Note: The trend p-value for Rivaroxaban is 0.92, while for Enoxaparin/VKA it is 0.01.
Novel oral anticoagulants

- Comparator non-inferiority studies on NOAC have been done with short initiation LMWH followed by AVK. No direct comparison.
- All studies done so far, life-threatening bleeding NOAC < AVK. Some dosage problems?
- New product. Lack of experience.
- Idarucizumab, antidote of dabigatran. In October 2015 FDA approval. CMP to EMA approval.
- Specific Ca patient studies on-going vs LMWH.
Ambulatory Prophylaxis of VTE in Cancer Patients
Ambulatory Chemotherapy and VTE prophylaxis

Patients: 311 with advanced (stage IV) breast cancer

Dosage: Warfarin 1 mg daily for the first 6 weeks followed by INR-adjusted doses (INR 1.3–1.9) (double-blind)

End-point: Objectively confirmed VTE

Results: RRR of 85% without increase of bleeding: 8 (5.3%) bleeding events in warfarin-treated patients compared with 5 (3.1%) in placebo recipients (p = 0.4)

• Open label unblinded randomized study
• No baseline screening at study entrance
• Pancreatic Ca: 43% of patients no other risk factor versus other with risk factors:
  - VTE: 2.6% if no other risk factor vs 6.3% if one or 10.5% >1 risk factor.
Enoxaparin in advanced pancreatic cancer

Symptomatic VTE

No. at risk
Enoxaparin 160 102 55 26 12 4
Observation 152 87 47 27 14 5

Incidence rate, %
Enoxaparin 0 1.3 3.8 5.1 5.7 6.4
Observation 0 10.2 14.4 14.4 15.1 15.1

Gray $P = .01$
HR, 0.40; 95% CI, 0.19 to 0.83
Competing risk regression

Enoxaparin in advanced pancreatic cancer

Major bleedings

Cumulative Incidence Rate (%)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Enoxaparin</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>4.5</td>
<td>3.4</td>
</tr>
<tr>
<td>6</td>
<td>7.6</td>
<td>5.5</td>
</tr>
<tr>
<td>9</td>
<td>7.6</td>
<td>5.5</td>
</tr>
<tr>
<td>12</td>
<td>8.3</td>
<td>6.9</td>
</tr>
<tr>
<td>18</td>
<td>8.3</td>
<td>6.9</td>
</tr>
</tbody>
</table>

No. at risk

- Enoxaparin: 160, 99, 52, 26, 14, 5
- Observation: 152, 94, 52, 26, 13, 4

Incidence rate, %

- Enoxaparin: 4.5, 7.6, 7.6, 8.3, 8.3
- Observation: 3.4, 5.5, 5.5, 6.9, 6.9

Gray $P = .63$

HR, 1.23; 95% CI, 0.54 to 2.79

Competing risk regression

Fig 4. Kaplan-Meier curve for (A) progression-free and (B) overall survival. HR, hazard ratio.
SAVE-ONCO: primary efficacy end-point
Composite of symptomatic DVT and any PE

Placebo: 3.4% (55/1,604)
Semuloparin 1.2% (20/1,608)
HR: 0.36 (0.21–0.60); p < 0.0001

Cumulative incidence (%)
Number at risk
Placebo 1,604 1,375 1,212 985 689 403 201 92
Semuloparin 1,608 1,410 1,227 986 681 384 197 77

RR 64%
Thromboprophylaxis of DVT and PE

SO WHAT DO GUIDELINES TELL US?
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Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines

M. Mandala¹, A. Falanga² & F. Roila³

On behalf of the ESMO Guidelines Working Group*

¹Unit of Medical Oncology; ²Division Immunotheamatology and Transfusion Medicine, Haemostasis and Thrombosis Center, Department of Oncology and Haematology, Ospedali Riuniti, Bergamo; ³Department of Medical Oncology, S. Maria Hospital, Terl, Italy
Chemotherapy: guideline recommendations for VTE prophylaxis in ambulatory cancer patients

<table>
<thead>
<tr>
<th>ASCO 2015¹</th>
<th>ACCP 2012²</th>
<th>ESMO 2012³</th>
<th>NCCN 2011⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambulatory cancer patients receiving outpatient chemotherapy</strong></td>
<td>1) Routine thromboprophylaxis during systemic chemotherapy is not recommended 2) But should be discussed in high risk population 3) Prophylaxis is recommended in myeloma patients receiving thalidomide or lenalidomide</td>
<td>Routine thromboprophylaxis is not recommended 2) But consider in high risk population</td>
<td>1) Routine thromboprophylaxis is recommended for: multiple myeloma patients receiving thalidomide or lenalidomide in combination with high dose dexamethasone or doxirubicin or multi-agent chemotherapy myeloma patients with 2 or more risk factors 2) Consider prophylaxis in other outpatients at risk</td>
</tr>
</tbody>
</table>

² Chest. 2012;133:381S-453S.  
Cancer patients should be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter.

Individual risk factors, including biomarkers or cancer site, do not reliably identify cancer patients at high risk of VTE.

In the outpatient setting, risk assessment can be conducted based on a validated risk assessment tool.
ASCO AND ESMO GUIDELINES: MULTIPLE MYELOMA

Patients with multiple myeloma receiving thalidomide- or lenalidomide- based regimens with chemotherapy and/or dexamethasone should receive pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients.
Table 1. Predictive model for chemotherapy-associated VTE in ambulatory cancer patients

<table>
<thead>
<tr>
<th>Cancer-related risk factors</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of cancer and tumour histotype</td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach adenocarcinoma, pancreas adenocarcinoma)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynaecological, bladder, testicular)</td>
<td>1</td>
</tr>
<tr>
<td>Haematological risk factors</td>
<td></td>
</tr>
<tr>
<td>Prechemotherapy platelet count $\geq 350$ 000 $/\mu l$</td>
<td>1</td>
</tr>
<tr>
<td>Haemoglobin $&lt;10$ g/dl or use of ESA growth factors</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy leukocyte count $&gt;11$ 000 $/\mu l$</td>
<td>1</td>
</tr>
<tr>
<td>Patient-related risk factor</td>
<td></td>
</tr>
<tr>
<td>Body mass index $\geq 35$ kg/m$^2$</td>
<td>1</td>
</tr>
</tbody>
</table>

The rates of VTE were as follows: low-risk category (score = 0), 0.5%; intermediate-risk category (score = 1–2), 2%; high-risk category (score $\geq 3$), 7%. ESA, erythropoiesis-stimulating agents VTE, venous thromboembolism.
International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer

Dominique Farge, Henri Bounamaux, Benjamin Brenner, Francis Caffinger, Philippe Debourdeau, Alok A Khorana, Ingrid Pabinger, Susan Solymoss, James Douketis, Ajay Kakkar

Venous thromboembolism (VTE) is the second leading cause of death in patients with cancer. These patients are at an increased risk of developing VTE and are more likely to have a recurrence of VTE and bleeding while taking anticoagulants. Management of VTE in patients with cancer is a major therapeutic challenge and remains suboptimal worldwide. In 2013, the International Initiative on Thrombosis and Cancer (ITAC-CME), established to reduce the global burden of VTE in patients with cancer, published international guidelines for the treatment and prophylaxis of VTE and central venous catheter-associated thrombosis. The rapid global adoption of direct oral anticoagulants for management of VTE in patients with cancer is an emerging treatment trend that needs to be addressed based on the current level of evidence. In this Review, we provide an update of the ITAC-CME consensus recommendations based on a systematic review of the literature ranked according to the Grading of Recommendations Assessment, Development, and Evaluation scale. These guidelines aim to address in-hospital and outpatient cancer-associated VTE in specific subgroups of patients with cancer.
Conclusion: ambulatory patients

• Does an absolute gain of 3-5% of VTE incidence justify the treatment of >90% of patients who shall not benefit but have to give themselves a daily injection for the rest of their life, without (?) improvement of OS?

• There is at present no final marker allowing to select out the high risk group within Ca patients.

• The clinician needs to discuss the situation with the high risk patient and may give prophylactic treatment
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MASCC/ISOO
ANNUAL MEETING ON
SUPPORTIVE CARE IN CANCER
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Thank you