PRIMARY THROMBOPROPHYLAXIS IN AMBULATORY CANCER PATIENTS: CURRENT GUIDELINES

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Venous thromboembolic disease in cancer

- Thromboembolism is the second leading cause of death in cancer patients\textsuperscript{1,2}
- VTE occurs in over 20% of cancer patients through their lifetime\textsuperscript{3}
- VTE may be present in as much a 50% of patients at the time of death\textsuperscript{4}

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Treatment</th>
<th>Patient</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary site</td>
<td>Chemotherapy</td>
<td>Older age</td>
<td>Platelet count &gt; 350,000/mcL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>Antiangiogenic drugs</td>
<td>Medical comorbidities</td>
<td>Leukocyte count &gt; 11000 /mcL</td>
</tr>
<tr>
<td>Histology</td>
<td>ESAS Transfusion</td>
<td>Obesity</td>
<td>Hemoglobin &lt; 10gr/dl</td>
</tr>
<tr>
<td></td>
<td>Hormonal therapy</td>
<td>History of VTE</td>
<td></td>
</tr>
<tr>
<td>Time from Diagnosis</td>
<td>CVC</td>
<td>PS</td>
<td>Inherited mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MY AGENDA

- PRIMARY THROMBOPROPHYLAXIS: WHAT KIND OF EVIDENCE?
- ESMO, ASCO, NCCN, ACCP GUIDELINES: STRENGTHS AND LIMITATIONS
- RISK ASSESSMENT TOOL
SOLID TUMORS
PROTECHT: RESULTS

Thromboembolic events by treatment group and cancer site

<table>
<thead>
<tr>
<th></th>
<th>Nadroparin (n = 769)</th>
<th>Placebo (n = 381)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall thromboembolic events, N (%)</td>
<td>15 (2.0)*</td>
<td>15 (3.9)</td>
</tr>
<tr>
<td>deep-vein thrombosis</td>
<td>8 (1.0)</td>
<td>8 (2.1)</td>
</tr>
<tr>
<td>pulmonary embolism</td>
<td>3 (0.4)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>visceral venous thrombosis</td>
<td>1 (0.1)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>stroke and peripheral thrombosis</td>
<td>3 (0.4)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Lung</td>
<td>7/199 (3.5)</td>
<td>7/80 (8.8)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4/272 (1.5)</td>
<td>4/148 (2.7)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3/36 (8.3)</td>
<td>1/17 (5.9)</td>
</tr>
<tr>
<td>Other</td>
<td>1/262 (0.4)</td>
<td>3/136 (2.2)</td>
</tr>
</tbody>
</table>

*p = 0.02 one-sided

- 5 (0.7%) patients in the nadroparin group and 0 (0%) in the control group had a major bleeding event (p = 0.18) NNT: 53

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
NNT 45

PROSPECT-CONKO 004

Study design
- RCT, 312 patients
- Pancreatic cancer
- GFFC vs Gem chemo
- Enoxaparin 1 mg/kg/day* vs none

Results
- 12 week incidence of VTE: 14.5% (control) vs 5% (enoxaparin)
- RR: 65% reduction
- No difference in PFS, OS

*R 1 mg/kg once daily s.c. for the first 12 weeks, thereafter 40 mg once daily.
GFFC = gemcitabine, cisplatin, 5-fluorouracil, folinic acid.

UK – FRAGEM Study

- 123 patients receiving chemotherapy for APC
- Randomized to gemcitabine or gemcitabine + dalteparin
- Dalteparin 200 IU/kg once daily × 4 weeks, then 150 IU/kg × 8 weeks
- Primary outcome: all TE (arterial, venous, incidental) at 3 months

APC = metastatic pancreatic cancer.

# Prophylaxis in medical outpatients: efficacy (VTE)

<table>
<thead>
<tr>
<th>Study</th>
<th>MH risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Control</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAMOUS</td>
<td>0.77</td>
<td>0.21</td>
<td>2.84</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>TOPIC-1</td>
<td>1.01</td>
<td>0.36</td>
<td>2.81</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>TOPIC-2</td>
<td>0.53</td>
<td>0.25</td>
<td>1.11</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>PRODIGE</td>
<td>0.66</td>
<td>0.29</td>
<td>1.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROTECHT</td>
<td>0.50</td>
<td>0.22</td>
<td>1.13</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>SIDERAS</td>
<td>0.82</td>
<td>0.23</td>
<td>2.94</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Other cancers</td>
<td>0.64</td>
<td>0.44</td>
<td>0.94</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>CONKO004</td>
<td>0.35</td>
<td>0.16</td>
<td>0.75</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>FRAGEM</td>
<td>0.37</td>
<td>0.17</td>
<td>0.81</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.36</td>
<td>0.20</td>
<td>0.62</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

# Chemotherapy: guideline recommendations for VTE prophylaxis in ambulatory cancer patients

<table>
<thead>
<tr>
<th>ASCO 2015&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ACCP 2012&lt;sup&gt;2&lt;/sup&gt;</th>
<th>ESMO 2012&lt;sup&gt;3&lt;/sup&gt;</th>
<th>NCCN 2011&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambulatory cancer patients receiving outpatient chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Routine thromboprophylaxis during systemic chemotherapy is not recommended</td>
<td>Routine thromboprophylaxis is not recommended</td>
<td>Routine thromboprophylaxis is not recommended, But consider in high risk population</td>
<td>1) Routine thromboprophylaxis is recommended for:</td>
</tr>
<tr>
<td>2) But should be discussed in high risk population</td>
<td>But consider in high risk population</td>
<td>But may be considered in high risk patients</td>
<td>• multiple myeloma patients receiving thalidomide or lenalidomide in combination with high dose dexamethasone or doxirubicin or multi-agent chemotherapy</td>
</tr>
<tr>
<td>3) Prophylaxis is recommended in myeloma patients receiving thalidomide or lenalidomide</td>
<td></td>
<td></td>
<td>• myeloma patients with 2 or more risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) Consider prophylaxis in other outpatients at risk</td>
</tr>
</tbody>
</table>

1. Routine pharmacologic thromboprophylaxis is not recommended in cancer outpatients.

2. Clinicians may consider LMWH prophylaxis on a case-by-case basis in highly selected outpatients with solid tumors receiving chemotherapy.

3. Discussion with the patient about the uncertainty concerning benefits and harms, as well as dose and duration of prophylaxis in this setting.
ACCP GUIDELINES

- Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angio-genesis inhibitors, thalidomide, and lenalidomide.

Guyatt et al. Chest 2012
In patients receiving chemotherapy, prophylaxis is not recommended routinely [Grade 1B].

Primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic pancreatic cancer treated with chemotherapy and having a low bleeding risk [Grade 1B].
Pharmacological prophylaxis is not routinely recommended in patients undergoing chemotherapy or radiotherapy or hormonal therapy (grade C) except in the following cases:

- Patients with lung or gastrointestinal cancer should receive nadroparin (3,800 U anti-FXa daily) for no more than 4 months (grade A)
- Multiple Myeloma at high risk

Siragusa Thrombosis Res 2012
VTE RISK ASSESSMENT: ASCO AND ESMO GUIDELINES

- 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.
## TEV CLINICAL SCORE
Khorana Blood 2008

### Table 2. Predictors of venous thromboembolism in the derivation cohort by multivariate logistic regression analysis

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>β</th>
<th>Odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>1.46</td>
<td>4.3 (1.2-15.6)</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate)</td>
<td>0.43</td>
<td>1.5 (0.9-2.7)</td>
</tr>
<tr>
<td>Low risk (breast, colorectal, head and neck)</td>
<td>0.0</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Prechemotherapy platelet count $350 \times 10^9$/L or more</td>
<td>0.60</td>
<td>1.8 (1.1-3.2)</td>
</tr>
<tr>
<td>Hemoglobin level less than 100 g/L or use of red cell growth factors</td>
<td>0.89</td>
<td>2.4 (1.4-4.2)</td>
</tr>
<tr>
<td>Prechemotherapy leukocyte count more than $11 \times 10^9$/L</td>
<td>0.77</td>
<td>2.2 (1.2-4)</td>
</tr>
<tr>
<td>BMI 35 kg/m² or more</td>
<td>0.90</td>
<td>2.5 (1.3-4.7)</td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for stage.

RATE OF VTE: CLINICAL SCORE

RATE OF VTE: CLINICAL SCORE

More than 4000 pts
7% SYMPTOMATIC VTE = VTE IN HOSPITALISED PATIENTS

IMPROVING RISK-BENEFIT THROUGH RISK ASSESSMENT TOOLS
## RISK ASSESSMENT IN MYELOMA

<table>
<thead>
<tr>
<th>Individual risk factors:</th>
<th>Body mass index $\geq 30$ kg/m²</th>
<th>Previous VTE</th>
<th>Central venous catheter or pacemaker</th>
<th>Associated disease (cardiac disease, chronic renal disease, diabetes, acute infection, immobilisation)</th>
<th>Surgery (general surgery, any anesthesia, trauma)</th>
<th>Medications (erythropoietin)</th>
<th>Blood clotting disorders</th>
<th>≤ 1 risk factor: Aspirin 81–325 mg once daily</th>
<th>≥ 2 risk factors: LMWH (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin (target INR 2–3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma-related risk factors:</td>
<td>Diagnosis</td>
<td>Hyperviscosity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloma therapy:</td>
<td>High dose dexamethasone (480 mg/month), doxorubicin, multiagent chemotherapy</td>
<td>LMWH (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin (target INR 2–3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
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.
Medical ambulatory cancer patients and prophylaxis of VTE

- VTE prevention in ambulatory cancer patients
  - prevention of CVC-associated VTE
  - prevention of chemotherapy-associated VTE
# Prophylaxis for CVC-related DVT: randomized trials

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>N</th>
<th>Regimen</th>
<th>Duration</th>
<th>Endpoint assessment</th>
<th>DVT, %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bern, 1990¹</td>
<td>P, open</td>
<td>82</td>
<td>Warfarin 1 mg</td>
<td>90 days</td>
<td>Mandatory venography</td>
<td>9.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No treatment</td>
<td></td>
<td></td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>Monreal, 1996²</td>
<td>P, open</td>
<td>29</td>
<td>Dalteparin 2,500 U</td>
<td>90 days</td>
<td>Mandatory venography</td>
<td>6</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No treatment</td>
<td></td>
<td></td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Couban, 2005³</td>
<td>R, DB</td>
<td>255</td>
<td>Warfarin 1 mg</td>
<td>Variable</td>
<td>Symptomatic events</td>
<td>4.6</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Verso, 2005⁴</td>
<td>R, DB</td>
<td>385</td>
<td>Enoxaparin 40 mg</td>
<td>42 days</td>
<td>Mandatory venography</td>
<td>14.1</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>Karthaus, 2006⁵</td>
<td>R, DB</td>
<td>439</td>
<td>Dalteparin 5,000 U</td>
<td>16 weeks</td>
<td>Symptomatic events</td>
<td>3.7</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td>3.4</td>
<td></td>
</tr>
</tbody>
</table>

Patients with central venous catheter (CVC)

VTE Incidence 8-10%

Tip of CVC not positioned at the junction between atrium and vena cava

Factor V Leiden Mutation Or Previous VTE

Mediastinal Syndrome

Consider Primary Prophylaxis

Consider Primary Prophylaxis

Consider Primary Prophylaxis

Consider Primary Prophylaxis
CONCLUSION 1

- Patient education increases the likelihood of early intervention
- Patient education by the oncology team should include VTE warning signs and symptoms
- Ongoing communication, including H&P, can facilitate awareness of VTE
- Targeted prophylaxis, based on appropriate risk assessment, is clearly the way forward.
CONCLUSION 2

- Additional research is needed to clarify which cancer patients sufficiently benefit from prophylactic anticoagulation
- Patients receiving hospice/home palliative care
...Waiting for randomised trials in high risk
...Waiting for randomised trials in high risk
...Waiting for randomised trials in high risk