Thrombosis in GI Cancer

ESMO World GI Cancer Congress
Barcelona 2014

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Centre Hospitalier
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Total VTE Mortality per Year. (Extrapolated to EU Countries)

<table>
<thead>
<tr>
<th></th>
<th>EU 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>684,019</td>
</tr>
<tr>
<td>PE</td>
<td>434,723</td>
</tr>
<tr>
<td>Mortality following VTE</td>
<td>543,454</td>
</tr>
</tbody>
</table>

- Deaths due to VTE: 543,454<sup>1</sup>

- More than double the combined deaths due to:
  - AIDS: 5,860<sup>2</sup>
  - breast cancer: 86,831<sup>2</sup>
  - prostate cancer: 63,636<sup>2</sup>
  - transport accidents: 53,599<sup>2</sup>

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<sup>1</sup>Cohen AT. Presented at the 5th Annual Congress of the European Federation of Internal Medicine; 2005.

Risk of DVT in Hospitalized Patients

- No prophylaxis + routine objective screening for DVT

<table>
<thead>
<tr>
<th>Patient group</th>
<th>DVT incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical patients</td>
<td>10 - 20 %</td>
</tr>
<tr>
<td>Major gyne/urol/gen surgery</td>
<td>15 - 40 %</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>15 - 40 %</td>
</tr>
<tr>
<td>Stroke</td>
<td>20 - 50 %</td>
</tr>
<tr>
<td>Hip/knee surgery</td>
<td>40 - 60 %</td>
</tr>
<tr>
<td>Major trauma</td>
<td>40 - 80 %</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>60 - 80 %</td>
</tr>
<tr>
<td>Critical care patients</td>
<td>15 - 80 %</td>
</tr>
</tbody>
</table>
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

Incidence of Venous Thromboembolism, %

Days After Diagnosis

Pancreas
Lung
Breast
Ovary
Prostate

Chew HK. Arch Intern Med 2006; 166: 458
Table 2. Risk Factors for VTE in Patients With Cancer

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td>Advanced age</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
</tr>
<tr>
<td></td>
<td>Ethnicity</td>
</tr>
<tr>
<td></td>
<td>- African American, higher</td>
</tr>
<tr>
<td></td>
<td>- Asian, lower</td>
</tr>
<tr>
<td>Cancer-related factors</td>
<td>Cancer site</td>
</tr>
<tr>
<td></td>
<td>- Brain</td>
</tr>
<tr>
<td></td>
<td>- Pancreas</td>
</tr>
<tr>
<td></td>
<td>- Kidney</td>
</tr>
<tr>
<td></td>
<td>- Stomach</td>
</tr>
<tr>
<td></td>
<td>- Bladder</td>
</tr>
<tr>
<td></td>
<td>- Gynecologic</td>
</tr>
<tr>
<td></td>
<td>- Lung</td>
</tr>
<tr>
<td></td>
<td>- Blood</td>
</tr>
<tr>
<td></td>
<td>Advanced stage</td>
</tr>
<tr>
<td></td>
<td>Initial period after diagnosis</td>
</tr>
</tbody>
</table>
Risk factors for VTE in patients with cancer (2)
G. Lyman, Cancer 2011, 117: 1334-49

Biomarkers
- Increased platelet count prior to chemotherapy
- D-dimer
- Tissue factor expression in tumor cells

Treatment-related factors
- Major surgery
- Hospitalization
- Cancer therapy
- Chemotherapy or hormonal therapy
- Antiangiogenic and immunomodulatory agents
  - Bevacizumab
  - Thalidomide and lenalidomide
- Erythropoiesis-stimulating agents
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
- Estrogen use, 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>
<tr>
<td></td>
<td></td>
<td>&gt; 100</td>
</tr>
</tbody>
</table>

HOMOZYGOSITY

(BMJ 1996, 313 : 1127)
Thrombophilia Mutations

In cancer patients with VTE, testing for mutations [VLeiden, PT, (MTHFR)] is only useful if there is a previous personal or family history of VTE.

(M. Dicato et al. : Blood 2001, S1: 3984)
FIG 1. Principal mechanisms by which tumor cells activate the coagulation system. Cancer cells can activate the hemostatic system by different pathways, including the production of procoagulant factors (i.e., tissue factor, cancer procoagulant); the release of inflammatory cytokines (interleukin-1); tumor necrosis factor-alpha; vascular endothelial growth factor; basic fibroblast growth factor; the expression of adhesion receptors by which they adhere to the endothelium, platelets, and leukocytes; and the release of microparticles.
Circulating microparticles (MPs)

- cell-to-cell communication
- small and heterogeneous membrane vesicles

Express membrane antigens characteristic of their cell of origin

Released in response to apoptosis and cell activation

Size: 0.1 - 1.0 μm

Negatively charged phosphatidylserine-rich surface

Released from different cell types (including cancer cells)

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

Hugel et al. Physiology 2005
• Subclinical hypercoagulable state due to: Prothrombin factor 1+2, fibrinopeptide A, thrombin-antithrombin and plasmin-antiplasmin complexes, d-dimer … all increased in Ca patients → in vivo thrombin generation and fibrinolysis.

• Circulating microparticles (MP) from platelets, WBC, endothelial cells → hypercoagulation and tumor growth, proportional to Ca burden
• Integral feature of neoplastic transformation is coagulation activation by HGFR (Hepatic growth factor receptor), loss of p53. EGFR mut → TF increase

• Malignant cells activate hemostatic system: TF, cancer procoagulant (CP) and inflammatory cytokines
Fig. 26-1 Molecular mechanism underlying venous thromboembolism (VTE) in cancer. Tissue factor expressed on the surface of cancer cells activates factor VII, thereby triggering coagulation. Fibrin enhances angiogenic interleukin (IL)-8 expression by endothelial cells. Endothelial cells further express tissue factor, which will help to maintain activated coagulation. Vascular endothelial growth factor (VEGF) expression by tumor cells (TCs) will favor angiogenesis. Activation of neutrophils by tumor cells will activate the procoagulant and adhesive properties of platelets and endothelial cells. Activation of monocytes by cancer cells induces coagulation through the expression of tissue factor.

L. Plawny, M. Dicato: Thrombosis in Cancer, in Mellar & Davis 2012, p275-283
Pathways of activation of coagulation in cancer: TF (tissue factor) and CP (cancer procoagulant) activate factors VIIa and Xa. TNF (tumour necrosis factor), IL-1 (interleukin-1) induce TF expression on monocytes and on endothelial cells.
Possible roles of TF activity in cancer

- initiation of a hypercoagulable state and thrombosis
- primary tumor growth – angiogenesis
- secondary tumor spread – metastasis

[KRAS-mut, EGFR, PTEN, p53 → ↑TF ; anti-EGFR → anticoagulant?]
(C.Milsom, Thromb Res. 2010)
Kaplan–Meier survival curve of patients with pancreatic carcinoma

P = 0.0004

TF act ≤ 273: 16 10 7 5 1
TF act > 273: 7 1 0

Tesselaar MET et al, JTH 2006
Table 1. Pancreatic cancer patients with thrombotic events (sample size: 6,870 patients) [15].

<table>
<thead>
<tr>
<th>Incidence of thrombotic events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Any thrombotic event</td>
<td>19% (n=1,322)</td>
</tr>
<tr>
<td>- Venous thrombotic events</td>
<td>17% (n=1,179)</td>
</tr>
<tr>
<td>- Pulmonary embolism</td>
<td>25% (n=290)</td>
</tr>
<tr>
<td>- Arterial thrombotic events</td>
<td>2% (n=143)</td>
</tr>
<tr>
<td>- Venous plus arterial thrombotic events</td>
<td>0.9% (n=64)</td>
</tr>
<tr>
<td>- Diagnosed after the diagnosis of pancreatic cancer</td>
<td>96%</td>
</tr>
<tr>
<td>- Diagnosed at, or before, the diagnosis of pancreatic cancer</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Treatment**

- Low-molecular weight heparins                                     | 95%   |
- Fondaparinux                                                      | 6%    |
- Warfarin                                                          | 0.4%  |
- Aspirin                                                           | 23%   |
- Inferior vena cava filter                                         | 19%   |

**Outcomes: median overall survival**

- Patients with thrombotic events                                  | 12.9 months |
- Patients without thrombotic events                               | 13.4 months |
- Occult thrombotic events, or diagnosed at the time of cancer diagnosis | 6.2 months |
- Patients with secondary thrombotic events                        | 13.7 months |
VTE Risk and Cancer

• Rate of growth and spread
• Sites: pancreas (rate 8.1%), kidneys & ovaries (5.6%), stomach (4.9%).
• Therapy: thalidomide, lenalidomide (?), bevacizumab (2 fold arterial thrombosis p=0.031, VTE none, posthoc analysis, Scapatacci; meta-analysis: VTE RR 1.33, p<0.001, Nalluri)
• ESA: RR 1.7
• RBC Transfusions vs none: 7.2 vs 3%
• Patient- disease- treatment related risk factors

Is there are Biomarker?

• ?Biomarkers: Recent risk factors
  - Platelet count $> 350.000$
  - WBC $>11.000$
  - CRP
  - TF expression
  - D-dimers

What is New?

Research:
• relations between cancer spread, hemostasis and inflammation
• GWAS?

Clinic:
• VTE Prevention in ambulatory Cancer Patients
• Novel anticoagulants:
  - heparins
  - oral anticoagulants
GWAS in VTE (www.genome.gov/gwastudies/)

- aPTT: decrease is risk of VTE: GWAS: Ile582Thr (in KNG1 gene encoding HMWK)
  KNG1 Knock out mice have a decrease of aPTT and arterial thrombosis
- PS: any SNP contributing to plasma variability, C’ and others; role of inflammation in VTE
- vWF increase
- Other GWAS data:
  Prot C level interference
  Plasminogen activator inhibitor-1 (PAI-1), MPV: SNPs variability on ABO: VTE, lipids, inflammatory markers, DM type 2 and CHD.
- Overall these risk are 1-1.5. Multiple SNPs with modest effect and rare variants with stronger impact; add DNA methylation modif, histone modifications...
Therapy of established VTE in cancer patients
## Risk Factors for Bleeding in Hospitalized Medical Patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active gastroduodenal ulcer</td>
<td>4.15 (2.21-7.77)</td>
</tr>
<tr>
<td>Bleeding in 3 mo before admission</td>
<td>3.64 (2.21-5.99)</td>
</tr>
<tr>
<td>Platelet count $&lt; 50 \times 10^9/L$</td>
<td>3.37 (1.84-6.18)</td>
</tr>
<tr>
<td>Age $\geq 85$ y (vs $&lt; 40$ y)</td>
<td>2.96 (1.43-6.15)</td>
</tr>
<tr>
<td>Hepatic failure (INR $&gt; 1.5$)</td>
<td>2.18 (1.10-4.33)</td>
</tr>
<tr>
<td>Severe renal failure (GFR $&lt; 30$ mL/m)</td>
<td>2.14 (1.44-3.20)</td>
</tr>
<tr>
<td>ICU or CCU admission</td>
<td>2.10 (1.42-3.10)</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>1.85 (1.18-2.90)</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>1.78 (1.09-2.89)</td>
</tr>
<tr>
<td><strong>Current cancer</strong></td>
<td><strong>1.78 (1.20-2.63)</strong></td>
</tr>
<tr>
<td>Male sex</td>
<td>1.48 (1.10-1.99)</td>
</tr>
</tbody>
</table>

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Khan SR. Chest 2012; 141 (Suppl): e195S
Standard Treatment of VTE

Initial treatment  (5 to 7 days)

LMWH or UFH

Bridging

Long-term therapy ≥ 3-6 months

Vitamin K antagonist (INR 2.0 - 3.0)
Clot trial: Recurrent VTE

- Risk reduction = 52%
- p-value = 0.0017

- OAC
  - N = 338

- LMWH 200 IU/Kg
  - N = 338

Lee et al. *NEJM*, 2003
Primary Prophylaxis of VTE

• Hospitalized
• Ambulatory
Reduction of Venous Thromboembolic Events in medical patients with Enoxaparin 40 mg/day

-63% reduction in All VTE

-65% reduction in Proximal DVT

NS for PE

Medenox Study: Blood Coag Fibrinolysis, 2003
# Clear benefit over placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>RRR</th>
<th>Thromboprophylaxis</th>
<th>Patients with VTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDENOX¹</td>
<td>63%</td>
<td>Placebo</td>
<td>14.9*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enoxaparin 40 mg</td>
<td>5.5</td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREVENT²</td>
<td>49%</td>
<td>Placebo</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dalteparin</td>
<td>2.8</td>
</tr>
<tr>
<td>p = 0.0015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARTEMIS³</td>
<td>47%</td>
<td>Placebo</td>
<td>10.5†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fondaparinux</td>
<td>5.6</td>
</tr>
<tr>
<td>p = 0.029</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*VTE at day 14; †VTE at day 15.

Three different placebo-controlled trials in general hospitalised medical patients

- 3 large, randomized, placebo-controlled, double blind trials in medical patients at high risk including cancer
  - the MEDENOX study\(^1\) \(\sim 15\%\)
    - enoxaparin 40 mg and 20 mg
    - evaluation criteria: venography
  - the PREVENT study\(^2\) \(\sim 5\%\)
    - dalteparin 5,000 IU/day
    - evaluation criteria: ultrasound proximal DVT
  - the ARTEMIS study\(^3\) \(\sim 15\%\)
    - fondaparinux 2.5 mg/day
    - evaluation criteria: venography

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Novel Anticoagulants
Conventional anticoagulant therapy is suboptimal

Vitamin K antagonists, e.g. warfarin (oral)
- Unpredictable
- Slow onset of action; bridging therapy is necessary
- Require frequent, costly, inconvenient monitoring
- Increased risk of major and minor bleeding

Heparin (injectable)
- Parenteral administration makes long-term and/or home use impractical
- Risk of heparin-induced thrombocytopenia (HIT)

LMWHs (injectable)
- Subcutaneous administration
- Risk of HIT
- Complicated dosing (mg/kg bid)

⇒ New, predictable, oral anticoagulants are needed

Ansell et al., Chest 2004; Hirsh et al., Chest 2004
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
Genotypes & haplotypes affecting AVK dose by >20%, different in Caucasians (Cau), Africans (Af) et Asians (As)

CYP2C9:
Genotype: « wild type » Cau 80%, Af & As >95%

VKORC1:
Haplotypes 1,2: Cau 37, Af 14, As 89%
Haplotypes 7,8,9: Cau 58, Af 49, As 10%

Novel Anticoagulants

- Semuloparin
- Oral: Dabigatran
  - Rivaroxaban
  - Apixaban
### Table 2
Properties of Rivaroxaban,\(^{35}\) Apixaban,\(^{36}\) and Dabigatran Etexilate\(^{37}\)

<table>
<thead>
<tr>
<th>Property</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran Etexilate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
</tr>
<tr>
<td>Administration</td>
<td>Oral, once or twice daily</td>
<td>Oral, twice daily</td>
<td>Oral, once or twice daily</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>&gt; 80</td>
<td>&gt; 50</td>
<td>6</td>
</tr>
<tr>
<td>Time to maximal concentration</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>7-11</td>
<td>9-14</td>
<td>14-17</td>
</tr>
<tr>
<td>Renal excretion (%)</td>
<td>33</td>
<td>25</td>
<td>80</td>
</tr>
</tbody>
</table>

Kenneth BAUER, 2010
Oral Anticoagulants:

• Coumarinics:
  Pharmacogenetics: CYP2C9
  VKORC1

• Antithrombins:
  Ximelagatran: hepatotoxicity, off market EMEA 2008
  Dabigatran

• Anti Xa:
  Rivaroxaban marketed 2008/2009; VTE med. 2011,
  Reimbursement 2012
  Dabigatran
  Apixaban
# Table 1. Novel Oral Anti-coagulant Drugs with Clinical Approval.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Typical Dose</th>
<th>Half-life</th>
<th>Stage of Clinical Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran Etexilate</td>
<td>Direct thrombin inhibitor</td>
<td>110mg or 150mg BID (AF) 150mg or 220mg QD (VTE)</td>
<td>12-17 hours</td>
<td>Approved for OAC in AF, for prophylaxis of VTE after hip/knee surgery (EU)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct factor Xa inhibitor</td>
<td>20mg or 15mg QD (AF) 10mg QD (VTE) 15mg BID (3 weeks) followed by 20mg QD (DVT, PE)</td>
<td>5-13 hours</td>
<td>Approved for OAC in AF, for prophylaxis of VTE after hip/knee surgery, for DVT, and for primary and secondary prevention of PE + one completed phase III ACS-trial</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Direct factor Xa inhibitor</td>
<td>2.5mg BID (VTE)</td>
<td>9-14 hours</td>
<td>Approved for prophylaxis of VTE after hip/knee surgery (EU only) + approval pending for OAC in AF (FDA)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Direct factor Xa inhibitor</td>
<td>30mg QD (for VTE prophylaxis in Japan) 15-60mg QD (in phase III AF trial) 60mg QD (in phase III DVT/PE trial)</td>
<td>9-10 hours</td>
<td>Approved (Japan only) for prophylaxis of VTE after hip/knee surgery + in phase III trial for OAC in AF + in phase III trial for prevention of DVT/PE</td>
</tr>
</tbody>
</table>

*Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; BID, bis in die (twice daily); DVT, deep vein thrombosis; OAC, oral anti-coagulation; PE, pulmonary embolism; QD, quotidie (once daily); VTE, venous thromboembolism.*
Apixaban versus Enoxaparin for Thromboprophylaxis in Medically Ill Patients

Samuel Z. Goldhaber, M.D., Alain Leizorovicz, M.D., Ajay K. Kakkar, M.D., Ph.D., Sylvia K. Haas, M.D., Ph.D., Geno Merli, M.D., Robert M. Knabb, Ph.D., and Jeffrey I. Weitz, M.D., for the ADOPT Trial Investigators*

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>3251</td>
<td>3098</td>
<td>2998</td>
<td>2935</td>
<td>2889</td>
<td>2850</td>
<td>2830</td>
<td>2810</td>
<td>2736</td>
<td>157</td>
<td>10</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>3266</td>
<td>3136</td>
<td>3049</td>
<td>2993</td>
<td>2946</td>
<td>2925</td>
<td>2892</td>
<td>2865</td>
<td>2783</td>
<td>195</td>
<td>12</td>
</tr>
</tbody>
</table>
# Apixaban versus Enoxaparin for Thromboprophylaxis in Medically Ill Patients

Samuel Z. Goldhaber, M.D., Alain Leizorovicz, M.D., Ajay K. Kakkar, M.D., Ph.D., Sylvia K. Haas, M.D., Ph.D., Geno Merli, M.D., Robert M. Knabb, Ph.D., and Jeffrey I. Weitz, M.D., for the ADOPT Trial Investigators

<table>
<thead>
<tr>
<th>Additional risk factors — no. (%)</th>
<th>Apixaban</th>
<th>Enoxaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous venous thromboembolism</td>
<td>141 (4.3)</td>
<td>124 (3.8)</td>
</tr>
<tr>
<td>History of cancer:‡</td>
<td>312 (9.6)</td>
<td>320 (9.8)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>113 (3.5)</td>
<td>98 (3.0)</td>
</tr>
<tr>
<td>Remote cancer</td>
<td>199 (6.1)</td>
<td>222 (6.8)</td>
</tr>
<tr>
<td>NYHA Class of chronic heart failure</td>
<td>1531 (47.0)</td>
<td>1537 (47.0)</td>
</tr>
<tr>
<td>I</td>
<td>60 (1.8)</td>
<td>47 (1.4)</td>
</tr>
<tr>
<td>II</td>
<td>228 (7.0)</td>
<td>240 (7.3)</td>
</tr>
<tr>
<td>III</td>
<td>854 (26.2)</td>
<td>833 (25.5)</td>
</tr>
<tr>
<td>IV</td>
<td>380 (11.7)</td>
<td>411 (12.5)</td>
</tr>
<tr>
<td>Not reported</td>
<td>9 (0.3)</td>
<td>6 (0.2)</td>
</tr>
<tr>
<td>Chronic respiratory failure</td>
<td>1683 (51.7)</td>
<td>1702 (52.0)</td>
</tr>
<tr>
<td>Body-mass index ≥30§</td>
<td>1448 (44.5)</td>
<td>1451 (44.3)</td>
</tr>
<tr>
<td>Estrogenic hormone therapy</td>
<td>49 (1.5)</td>
<td>27 (0.8)</td>
</tr>
</tbody>
</table>
### Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study

On behalf of the Botticelli Investigators, The Writing Committee, H. Buller,* D. Deitchman,† M. Prins‡ and A. Segers*§

### Table: Apixaban

<table>
<thead>
<tr>
<th></th>
<th>5 mg twice-daily</th>
<th>10 mg twice-daily</th>
<th>20 mg once-daily</th>
<th>Any</th>
<th>LMWH/VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 130)</td>
<td>(n = 134)</td>
<td>(n = 128)</td>
<td>(n = 392)</td>
<td>(n = 128)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>56 (14)</td>
<td>59 (17)</td>
<td>60 (15)</td>
<td>58 (15)</td>
<td>59 (16)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>83 (64)</td>
<td>76 (57)</td>
<td>83 (65)</td>
<td>242 (62)</td>
<td>81 (63)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>85.8 (16.7)</td>
<td>84.3 (18.0)</td>
<td>84.5 (18.3)</td>
<td>84.9 (17.7)</td>
<td>80.7 (17.6)</td>
</tr>
<tr>
<td>Range</td>
<td>50–129</td>
<td>49–137</td>
<td>45–143</td>
<td>45–143</td>
<td>38–140</td>
</tr>
<tr>
<td>History of VTE, n (%)</td>
<td>37 (28.5)</td>
<td>28 (20.9)</td>
<td>33 (25.8)</td>
<td>98 (25.0)</td>
<td>31 (24.2)</td>
</tr>
<tr>
<td>Documented active cancer, n (%)</td>
<td>11 (8.5)</td>
<td>6 (4.5)</td>
<td>9 (7.0)</td>
<td>26 (6.6)</td>
<td>11 (8.6)</td>
</tr>
<tr>
<td>Surgery/trauma in previous 3 months, n (%)</td>
<td>25 (19.2)</td>
<td>29 (21.0)</td>
<td>29 (18.0)</td>
<td>77 (19.6)</td>
<td>55 (27.3)</td>
</tr>
<tr>
<td>Treatment prerandomization, duration in hours, mean (SD)</td>
<td>6.9 (7.3)</td>
<td>6.4 (7.3)</td>
<td>9.3 (8.3)</td>
<td>7.5 (7.7)</td>
<td>7.1 (13.7)</td>
</tr>
</tbody>
</table>
Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators

Efficacy

Acute DVT Study

No. at Risk
Rivaroxaban 1731 1668 1648 1621 1424 1412 1220 400 369 363 345 309 266
Enoxaparin–VKA 1718 1616 1581 1553 1368 1358 1186 380 362 337 325 297 264

P<0.001 for noninferiority

Rivaroxaban (N=1731)
Enoxaparin–VKA (N=1718)
Oral Rivaroxaban for the Treatment of symptomatic Pulmonary Embolism. EINSTEIN Trial
NEJM 2012, 366: 1287

Non inferiority trial.
N = 4832 patients
Rp: Rivaroxaban 15mg bid 3w → 20mg qd 3, 6 or 9 mo
Vs
Enoxaparin → AVK 3, 6 or 9 mo

Exclusion: CrCl <30ml/′, bleeding tendancy...
# 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</td>
<td>Standard Therapy</td>
</tr>
<tr>
<td></td>
<td>(N = 1731)</td>
<td>(N = 1718)</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>1055 (60.9)</td>
<td>1083 (63.0)</td>
</tr>
<tr>
<td>Recent surgery or trauma</td>
<td>338 (19.5)</td>
<td>335 (19.5)</td>
</tr>
<tr>
<td>Immobilization</td>
<td>265 (15.3)</td>
<td>260 (15.1)</td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td>140 (8.1)</td>
<td>115 (6.7)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>118 (6.8)</td>
<td>89 (5.2)</td>
</tr>
<tr>
<td>Puerperium</td>
<td>6 (0.3)</td>
<td>11 (0.6)</td>
</tr>
</tbody>
</table>
## Subject characteristics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects in the safety population</td>
<td>7998</td>
</tr>
<tr>
<td>Primary diagnosis (%)^a&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Acute infectious and inflammatory disease</td>
<td>47.3</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>32.4</td>
</tr>
<tr>
<td>Acute respiratory insufficiency</td>
<td>28.0</td>
</tr>
<tr>
<td>Acute stroke</td>
<td>17.3</td>
</tr>
<tr>
<td>Active cancer</td>
<td>7.3</td>
</tr>
<tr>
<td>Other diseases</td>
<td>0.7</td>
</tr>
</tbody>
</table>

^a Patients could have more than one primary diagnosis
Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D.,

<table>
<thead>
<tr>
<th></th>
<th>N=21105</th>
<th>7036</th>
<th>7035</th>
<th>p</th>
<th>7034</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warfarin</td>
<td>High dose Edoxaban</td>
<td>W vs HD Edox</td>
<td>low dose Edoxaban</td>
<td>W vs LD Edox</td>
<td></td>
</tr>
<tr>
<td>Major Bleed</td>
<td>524(3.34)</td>
<td>418(2.75)</td>
<td>&lt;0.001</td>
<td>254((1.61)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>59(0.35)</td>
<td>32(021)</td>
<td>0.006</td>
<td>21(0.13)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Life threat</td>
<td>122(0.78)</td>
<td>62(0.4)</td>
<td>&lt;0.001</td>
<td>40(0.25)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Both edoxaban dose once qd non inferior in stroke or embolism prevention, significant lower rates of bleeding and cardiovascular death
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)
Rivaroxaban

- Indication: treatment for knee/hip surgery, and non valvuar atrial fibrillation.
- Since 12. 2011 EMA approval for DVT and PE. : 15mg bid for 3 weeks, thereafter 20mg qd. No data nor indicaion for acute treatment of PE
- Creatinine clearance: 30-49 ml 2x15mg/3 w, then 15mg qd.
- - CrCl 15-29ml: ?
- Age, sex and weight normally no adjustment
- Drug interference: CYP3A & PgP: clarithromycine, antifungal: keto-, itro- and voriconazole; fluconazole?; antivirals some ?
Novel oral anticoagulants

October 2013: 4 families went to court for involuntary homicide, supposedly 2nd NOAC. In each family a member died while on NOAC. Outcome?

All studies done so far, life-threatening bleeding

NOAC $\ll$ AVK

- New product. Lack of experience.
- Embolic disorder is being treated, bleeding is provoked by treatment.
- No anti-dote. Intracranial bleed while on AVK is not changed by vit.K.
Conclusions

- New anti-Xa drugs are attractive alternatives to heparins and warfarin
  - Fixed doses
  - No need of monitoring
  - Good efficacy and safety
  - Quality of life

- In cancer patients
  - Little specific experience in cancer patients
  - Potential drug interactions with chemotherapy
  - Contraindicated in renal insufficiency
  - No antidote
Prophylactic Anticoagulation
ACCP 2012
Cancer outpatients thromboprophylaxis

4.2.1. In outpatients with cancer who have no additional risk factors for VTE, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) and recommend against the prophylactic use of vitamin K antagonists (Grade 1B).

4.2.2. In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic dose LMWH or LDUH over no prophylaxis.

4.4. In outpatients with cancer and indwelling central venous catheters, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) and suggest against the prophylactic use of vitamin K antagonists (Grade 2C).

Additional risk factors include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.
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>

![Graph showing rate of VTE](image)

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
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><strong>Site of cancer and tumour histotype</strong></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><strong>Haematological risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Prechemotherapy platelet count ≥350 000/μl</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/μl</td>
<td>1</td>
</tr>
<tr>
<td><strong>Patient-related risk factor</strong></td>
<td></td>
</tr>
<tr>
<td>Body mass index ≥35 kg/m²</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 ≥3), 7%. ESA, erythropoiesis-stimulating agents VTE, venous thromboembolism.
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)

Recent RCTs of thromboprophylaxis in cancer patients on chemotherapy

- CONKO-004
- FRAGEM
- PROTECHT
- SAVE-ONCO

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

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

123 patients receiving chemotherapy for APC

Randomized to gemcitabine or gemcitabine + dalteparin

Dalteparin 200 IU/kg once daily x 4 weeks, then 150 IU/kg x 8 weeks

Primary outcome: all TE (arterial, venous, incidental) at 3 months

VTE
Fatal PE
Grade 3 bleed

p < 0.02
p = 0.03
NS
Incidence of VTE in recent interventional trials with low-molecular –weight –heparins for thromboprophylaxis during chemotherapy (in the ambulatory setting)

- PROTECHT study
  
  Rate of VTE (%)

  - Placebo: 3.9
  - Nadroparin 3800 IU: 2

- SAVE-ONCO study
  
  Rate of VTE (%)

  - Placebo: 3.4
  - Semuloparin 20 mg: 1.2

Agnelli et al, Lancet Oncol 2009
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 (%)

Time (months)

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

Components of the primary efficacy end-point

- **Symptomatic DVT**: OR 0.32 (95% CI: 0.15–0.62)
- **Any PE**: OR 0.41 (95% CI: 0.19–0.85)
- **Non-fatal PE**: OR 0.20 (95% CI: 0.05–0.63)
- **Any VTE-related death**: OR 0.77 (95% CI: 0.27–2.13)

SAVE-ONCO: bleeding

OR 1.41 (0.89–2.25)

OR 1.05 (0.55–2.04)

OR 1.86 (0.98–3.68)

**Includes 6 fatal bleedings (4 [0.3%] in placebo and 2 [0.1%] in semuloparin) and 5 (0.3%) non-fatal bleedings into critical area or organ in the semuloparin group.**

**6 events in placebo and 9 in semuloparin caused study drug discontinuation; 2 events in placebo and 3 in semuloparin were serious and caused study drug discontinuation; 13 events in placebo and 25 in semuloparin recovered.**

Conclusions

- LMWH are the standard for the acute and long term therapy of VTE in cancer patients
- LMWHs are effective and safe for the prevention of VTE in hospitalized medical cancer patients
- Recent studies have demonstrated the benefit of VTE prevention in cancer patients receiving chemotherapy
- There is no evidence that LMWHs improve long term survival in cancer patients

Varia

- Incidental finding compatible with PE on CT
- Thalidomide, lenalidomide
- Bevacizumab
- Idiopathic VTE
- Superficial vein Thrombosis
- Recurrent VTE under adequate treatment
Distal Deep Vein Thrombosis: What to do?

• No controlled trial
• ?Proximal extension: 0- 25%
  serial US: 0- 5.7%
• Distal calf US, center dependent: risk of overtreatment
• ?Treatment:
  Lagerstedt, : 3 mo anticoag., Lancet 1985
  M. Righini: 0- 6w; J Thromb Haemost 2007
Economy Class Syndrome → Traveler’s VTE

• Does it exist? Immobilization effect?
• If no risk factor, no Rp
• If risk factor and long distance (>4h), consider Rp
• No ASA

• (NEJM: T. Brighton 2012, Nov 4, 2012: Low dose aspirin to prevent recurrent Venous thromboembolism)
Take Home Message (1)

- Inter-relations between Hemostasis and Cancer patients: studies on-going
- LMWH is the preferred therapy for treatment and prevention of VTE in the onco patient.
- LMWH and/or the novel anticoagulants may supplant AVK usage in future? Cost is an issue.
- Usage of novel oral anticoagulants has doubled in a year (~30%)
- Novel anticoagulants not recommended in recent ESMO or ASCO guidelines
Take Home Message (2)

• Novel oral anticoagulants are available for VTE treatment and prevention of VTE in knee/hip surgery and non-valvular AF. There is no large RCT in cancer patients. Rivaroxaban is approved and marketed for VTE treatment and to prevent relapse. Not endorsed by 2013 guidelines in Ca.

• Their use is contraindicated in patients with a CrCl <30ml/min.

• As of now there is no antidote available for these new drugs.
Take Home Message (3)

• Ultralow molecular heparins have been extensively studied recently. Their marketing in the near future is not defined.
• As of now they do not seem to induce thrombocytopenia (HIT).
• Unfractionated heparin (UFH) remains the preferred drug in renal insufficiency (follow Xa)
Take Home Message (4)

• There is no recommendation for treatment of superficial venous thrombosis, though EMA approval for fondaparinux.
• There is no indication to use anticoagulants as anticancer agents except in a clinical trial.
• Prophylaxis of VTE in the ambulatory setting should be evaluated according to known risk factors.
• Guidelines (ESMO, ASCO, NCCN, ACCP...) are very similar. The physician should use common sense when the patient does not fit the guidelines.
ASCO Guidelines 2013

- Most hospitalized patients with cancer require thromboprophylaxis throughout hospitalization.
- Thromboprophylaxis is not routinely recommended for ambulatory patients with cancer; it may be considered for very select high-risk pts.
- Patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone should receive prophylaxis with either low molecular–weight heparin (LMWH) or low-dose aspirin to prevent venous thromboembolism (VTE).
- Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days.
- Extending postoperative prophylaxis up to 4 weeks should be considered in those with high-risk features.
- LMWH is recommended for the initial 5 to 10 days of treatment for patients with established deep vein thrombosis and pulmonary embolism, as well as for long-term (6 months) secondary prophylaxis.
- Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE.
Thank you

If you wish a set of these slides: Dicato.mario@chl.lu
Hemostasis: Case Study
Barcelona 2014
62 y old Caucasian male with atrial fibrillation is on rivaroxaban since 2010 and doing fine.

2012: Colorectal cancer with liver metastases is diagnosed. The patient is given chemotherapy (FOLFOX) and after 4 cycles is on partial remission but not resectable.

Before his 5th cycle (to be switched to FOLFIRI), a diagnosis of left leg DVT is made.

What to do?
1. Increase dosage of rivaroxaban?
2. Switch to AVK
3. Switch to LMWH followed by AVK?
4. Only LMWH?
• The patient was treated with LMWH only
• He continued his chemotherapy and while for 2 months on LMWH, he had again a DVT.
• What next?
1. Increase dose of LMWH?
2. LMWH 2x/day?
3. Inferior Vena Cava filter?
4. 1 & 3
• The patient had an IVC (retrievable) filter and LMWH once daily.
• 10 weeks after insertion of filter, the patient is doing fine with LMWH, on chemotherapy.
• Cancer regressed and patient has become operable. After surgery the patient is still on LMWH.
• LMWH is given now for 6 months postoperatively.
• To be given for how long?
1. Indefinitely?

2. If patient remains in complete remission, to be stopped after 6 more months and switched to rivaroxaban?
• It was decided, following also the patient’s request, to stop LMWH after 6 months and go back to rivaroxaban. The patient is fine.
• The patient, now February 2014, wants to visit his nephew in Canada.
• His wife had a DVT after hip replacement 2 years ago. Does she need anticoagulation for the journey?
1. Does not exist?
2. It is a reality
3. May exist sometime.
If it exists. What to do?

1. LMWH
2. Rivaroxaban
3. ASA
4. 1 & 3 are correct
5. 1, 2 & 3 are correct
6. If it does not exist, no therapy is necessary.
Economy Class Syndrome → Traveler’s VTE

• Does it exist? Immobilization effect?
• If no risk factor, no Rp
• If risk factor and long distance (>4h), consider Rp
• No ASA
• *(NEJM: T. Brighton 2012, Nov 4, 2012: Low dose aspirin to prevent recurrent Venous thromboembolism)*
• We gave aspirin.
• This is a real patient’s history.
• I thought at some point making up the patient’s spouse as a female patient with breast cancer and bringing in a hormone story, but as you have a full day program, we leave it at that and

Thank you