The 'WHITH - Women's Health in Thrombosis and Haemostasis and ITAC-CME' (or) 'Thrombosis and Cancer in Women' is accredited by the European Accreditation Council for Continuing Medical Education (EACCME) to provide the following CME activity for medical specialists. The EACCME is an institution of the European Union of Medical Specialists (UEMS), www.uems.net.

The 'Thrombosis and Cancer in Women' program is designated for a maximum of (or 'for up to') 2 hours of European external CME credits. Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity.

Through an agreement between the European Union of Medical Specialists and the American Medical Association, physicians may convert EACCME credits to an equivalent number of AMA PRA Category 1 Credits.™ Information on the process to convert EACCME credit to AMA credit can be found at www.ama-assn.org/go/internationalcme.

Live educational activities, occurring outside of Canada, recognized by the UEMS-EACCME for ECMEC credits are deemed to be Accredited Group Learning Activities (Section 1) as defined by the Maintenance of Certification Program of The Royal College of Physicians and Surgeons of Canada.
Agenda

Opening remarks
*Pr. Dominique Farge-Bancel, MD*

Myeloproliferative disorders in women
*Dr. Martin H. Ellis, MD*

Thrombosis and cancer in special female populations
*Pr. Benjamin Brenner, MD*

Central venous catheters and thrombosis in patients with breast cancer
*Dr. Philippe Deboureau, MD*

Specific guidelines for cancer-associated thrombosis in women?
Pro-Con Debate
- **Moderator:** Pr. Benjamin Brenner, MD
- **Debaters:** Pr. Rupert Bauersachs, MD
  Pr. Dominique Farge-Bancel, MD

Concluding remarks
*Pr. Benjamin Brenner, MD*
Opening Remarks

Pr. Dominique Farge-Bancel, MD
St Louis Hospital and Paris Diderot University
FRANCE
Pr. Farge-Bancel’s Disclosures

Receipt of grants/research supports:
• Leo Pharma
• Pfizer
• Sanofi
Learning Objectives

At the end of the presentation, participants will be able to:

- Review diagnostic and treatment duration considerations of venous thromboembolism in myeloproliferative disorders
- Identify the risks and consequences of thrombosis and cancer in special female populations
- Assess factors associated with central venous catheters that may influence the occurrence of venous thromboembolism and its management in breast cancer
- Discuss the clinical utility of a mobile app for implementing the international guidelines, including pro and con perspectives
Polling Question 1

- In which of the following patients would you most likely recommend VTE prophylaxis?
  a. Breast cancer patient treated with chemotherapy
  b. Female patient undergoing surgery for gynecologic cancer
  c. Ovarian cancer patient with a central venous catheter
  d. All of the above
  e. None of the above
Women’s Cancers Potentially Have Greater Burden on Society

• 17.2 million women living with cancer worldwide in 2012¹
  o 6.7 million new cancer cases and 3.6 million cancer deaths
• The growing aging population is disproportionately female²
• Women are the main providers for their children’s health and education; often manage their partner’s health needs³
  o More than 1 in 10 women take care of an aging or chronically ill relative³
• Women comprise a significant proportion of the workforce in many countries⁴,⁵
• Women worldwide are taking on high profile leadership roles in government and business⁵

⁵. The Economist. 2009.
Top Cancers Affecting Women

Estimated age-standardised incidence and mortality rates
Women Worldwide

- Breast
- Colorectum
- Cervix uteri
- Lung
- Stomach
- Ovary

ASR, age standardised rate.
Thrombosis and Cancer Incidence

- VTE is a frequent and serious complication in cancer patients
  - 2nd cause of death in cancer patients (after metastasis)\(^1\)

Cancer
- VTE (= DVT, PE, or CRT) in 4% to 20% cancer patients\(^2\)
  - VTE at autopsy in 50% of cancer patients\(^3\)

VTE
- 20% of VTE patients have active cancer\(^4\)
- 4% to 12% of patients with idiopathic VTE have an underlying cancer\(^3\)

VTE: venous thromboembolism
DVT: deep vein thrombosis
PE: pulmonary embolism
CRT: catheter-related thrombosis

Mechanisms of Thrombosis in Cancer

PROCOAGULANT ACTIVITIES

Clotting activation induced by tumour cells

ADHESION MOLECULES

Clotting activation induced by tumour-stimulated host normal cells (endothelial cells, leukocytes, platelets)

CYTOKINES, GROWTH FACTORS, PROTEASES

INCREASED RISK OF THROMBOSIS

Mechanisms of Thrombosis in Cancer

Tumor Cells

Inflammatory Cytokines (TNF-α, IL-1) and VEGF

Procoagulant Molecules (Tissue Factor and Others)

Thrombosis

Platelets

Extrinsic Factors
- Chemotherapy
- Anti-angiogenic therapy
- Hormonal Therapy

Central Venous Catheters

IL, interleukin; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.
Mechanisms of Thrombosis in Cancer

Risk Factors for VTE in Cancer

- Cancer site
  - Especially gastrointestinal, neurological, pulmonary, gynecological, renal, and hematological
- Disease stage
- Surgery
- Chemotherapy
- Hospitalization
- Hormone therapies (HT)
  - Including contraceptive preparations, postmenopausal HT, and selected estrogen receptor modulators
- Pregnancy
Rate of VTE by Site of Cancer

Pooled incidence rates (per 1000 person-years) of VTE per type of cancer

- breast (n=4 studies)
- prostate (n=6)
- bone (n=2)
- colorectal (n=5)
- haematologic (n=9)
- lung (n=7)
- brain (n=5)
- pancreas (n=7)

Rate of VTE by Stage of Cancer

- Higher rates of VTE in metastatic disease
VTE in Cancer Patients Undergoing Surgery

• Cancer patients undergoing surgery have twice the risk of postoperative VTE compared with noncancer patients undergoing the same surgery\(^1\)

• The following were found to be independent risk factors for VTE in female mastectomy patients\(^2\)
  o Obesity
  o Venous catheterization
  o Prolonged operative time >3 hours
  o Immediate reconstruction

VTE in Cancer Patients Undergoing Surgery

Rates of VTE and Mortality with VTE in Patients Undergoing Major Cancer Surgery (MCS) in the United States (1999-2009)

- 2,508,916 patients
- Overall VTE rate was 1.3%
- ↑VTE incidence 4.0%/year
- Decreased mortality from VTE

VTE Secondary to Use of Central Venous Catheter (CVC) Is Common

- Incidence of symptomatic VTE is 0.3% to 28.3% in patients with cancer with a CVC
- Pulmonary embolism is the manifestation of VTE in 15.9% to 25.0% of CVC-related VTEs

Chemotherapy in Cancer and Thrombosis

• Chemotherapy is strongly associated with VTE\(^1\)
  o Cancer alone is associated with a 4.1-fold risk
  o Chemotherapy increased the risk 6.5-fold

• Antiangiogenic agents such as bevacizumab, which are being used or investigated to treat breast and ovarian cancers, are associated with very high rates of VTE\(^2\)

• IMiDs (thalidomide in particular) used to treat myeloma are also associated with very high rates of VTE\(^2,3\)

IMiDs, immunomodulatory drugs; VTE, venous thromboembolism.
Prothrombotic Effects of Chemotherapy

Prothrombotic Effects of Chemotherapy

AT, antithrombin; IL, interleukin; PAI, plasminogen activator inhibitor; TF, tissue factor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

Haddad TC, Greeno EW. Thromb Res. 2006;118:555-68.
Prothrombotic Mechanisms of Thalidomide in Myeloma

Hormone Therapy in Cancer and Thrombosis

• About 70% of breast cancers are estrogen receptor (ER)-positive
  o It has been postulated that ER-mediated alteration of hepatic synthesis of hemostatic proteins may increase risk of VTE

• Chemotherapy plus tamoxifen increased the risk for VTE over chemotherapy alone by about 4-fold

VTE, venous thromboembolism/
Benefits of VTE Prophylaxis

• VTE prophylaxis is underused in women undergoing surgery for gynecologic cancer\(^1\)
  - Incidence of VTE within 30 days of surgery decreased from 2.7% to 0.6% following implementation of VTE prevention guidelines

• 12% reduction in VTE and higher 5-year survival rate in high-risk surgical patients with ovarian cancer who received prolonged prophylaxis\(^2\)
  - 95% of the initial investment cost of prolonged anticoagulation was recovered within 1 year

---

VTE, venous thromboembolism.

Improving Women’s Health

• With an increase in female participation in social, educational, economic, and political spheres, addressing women’s health is a necessary and effective approach to strengthening health systems overall.

• Unfortunately, few clinicians appear to be aware of the higher risk of thrombosis in cancer patients.

• Prevention and treatment of VTE in women with cancer are essential to patient survival.

VTE, venous thromboembolism.
Myeloproliferative Neoplasms & Thrombosis: Emerging Issues and Relevance for Women

Dr. Martin H. Ellis, MD
Meir Medical Center and Tel Aviv University
ISRAEL
Dr. Ellis’ Disclosures

- Receipt of honoraria: Novartis
A 45-year-old woman is found to have an isolated superior mesenteric vein thrombosis at laparotomy for acute severe abdominal pain. A segment of small bowel required resection. At diagnosis she had polycythemia, thrombocytosis, and leukocytosis all of which persisted after her surgery and a diagnosis of P vera was confirmed. Anticoagulation had been initiated already, and phlebotomies and hydroxyurea resulted in normalization of the CBC within 8 weeks.

• After 8 months of anti coagulation what would you do?
  a. Continue vitamin K antagonist (VKA) therapy for another 6-12 months and then switch to low dose aspirin
  b. Continue VKA therapy indefinitely without aspirin
  c. Continue VKA therapy indefinitely together with low dose aspirin
  d. Stop VKA therapy now and start low dose aspirin
  e. Other
Objectives

• Define and classify the MPNs
• Advances in molecular pathophysiology
• Thrombosis in MPNs
• Focus on polycythemia vera
  o Thrombosis risk
  o “Female” phenotype
  o Treatment: current and emerging
The Myeloproliferative Neoplasms

- Chronic myeloid leukaemia
- Essential thrombocythaemia
- Polycythaemia vera
- Idiopathic myelofibrosis

- BCR-ABL
- JAK2 V617F mutation

Acute myeloid leukaemia
Acquired Abnormalities in MPNs
The Calreticulin Protein (CALR)

**CALR** located on 19p13.2
9 exons

Exon 9 indel mutations-1bp reading frameshift
Mutational frequencies 20-30% in ET or PMF
Specific to JAK2-unmutated ET and PMF
Mutually exclusive of JAK2 and MPL mutations

ER, estrogen receptor; ET, essential thrombocythemia; PMF, primary myelofibrosis.
MPNs Confer a Thrombotic Phenotype

(JAK2 V617F in portal & splanchnic vessel endothelium)

TF, tissue factor.

TF, tissue factor.
Causal Role for JAK2 V617F in Thrombosis

Enhanced Platelet Activation in Polycythemia Vera (PV) and Essential Thrombocythemia (ET)

Urinary excretion rates of 11-dehydro-TXB\(_2\) in untreated PV and ET patients are at least comparable to unstable angina and higher than a variety of clinical settings at increased cardiovascular risk.

Clinical Studies of the Annual and/or Cumulative Incidence of Thrombosis in MPN

<table>
<thead>
<tr>
<th>References</th>
<th>No. of patients</th>
<th>Median follow-up (years)</th>
<th>Events at diagnosis</th>
<th>Events during FU</th>
<th>Annual incidence rate of thrombosis, 100 patient-years</th>
<th>Cumulative incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gruppo Italiano Studio</td>
<td>1213</td>
<td>6.1</td>
<td>34</td>
<td>33</td>
<td>66</td>
<td>19</td>
</tr>
<tr>
<td>Policitemia [7]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marchioli et al.</td>
<td>1638</td>
<td>2.7</td>
<td>38.6</td>
<td>25</td>
<td>75</td>
<td>13.8</td>
</tr>
<tr>
<td>(ECLAP study) [8]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passamonti et al. [15]</td>
<td>396</td>
<td>9.6</td>
<td>29</td>
<td>NA</td>
<td>NA</td>
<td>9.3</td>
</tr>
<tr>
<td>Vannucchi et al. [18]</td>
<td>323</td>
<td>5</td>
<td>19.2</td>
<td>21</td>
<td>79</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ET</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruggeri et al. [12]</td>
<td>65†</td>
<td>4.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7.6</td>
</tr>
<tr>
<td>Besses et al. [13]</td>
<td>148</td>
<td>4.8</td>
<td>25</td>
<td>NA</td>
<td>NA</td>
<td>22.3</td>
</tr>
<tr>
<td>Jensen et al. [14]</td>
<td>96</td>
<td>5.8</td>
<td>14</td>
<td>15.4</td>
<td>84.6</td>
<td>16</td>
</tr>
<tr>
<td>Passamonti et al. [15]</td>
<td>435</td>
<td>9.3</td>
<td>19</td>
<td>NA</td>
<td>NA</td>
<td>15.3</td>
</tr>
<tr>
<td>Wolansky et al. [16]</td>
<td>322</td>
<td>13.6</td>
<td>26.3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Alavarez et al. [17]</td>
<td>126</td>
<td>10</td>
<td>7.14</td>
<td>NA</td>
<td>NA</td>
<td>14.2</td>
</tr>
<tr>
<td>Vannucchi et al. [18]</td>
<td>639</td>
<td>5</td>
<td>17.8</td>
<td>41</td>
<td>59</td>
<td>11.6</td>
</tr>
<tr>
<td>Passamonti et al. [19]</td>
<td>605</td>
<td>5.6</td>
<td>14.8</td>
<td>NA</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td>Palandri et al. [20]</td>
<td>386</td>
<td>9.5</td>
<td>17</td>
<td>NA</td>
<td>NA</td>
<td>12</td>
</tr>
<tr>
<td>Alvarez et al. [21]</td>
<td>300†</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10.6</td>
</tr>
<tr>
<td>Girodon et al. [22]</td>
<td>311</td>
<td>9.5</td>
<td>21.5</td>
<td>37.3</td>
<td>62.7</td>
<td>17</td>
</tr>
<tr>
<td>Carobbio et al. [22]</td>
<td>891</td>
<td>6.2</td>
<td>20</td>
<td>27.7</td>
<td>72.3</td>
<td>12</td>
</tr>
<tr>
<td>Barbui et al. [25]</td>
<td>178§</td>
<td>7.6</td>
<td>13</td>
<td>62</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>MF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervantes et al. [10]</td>
<td>155</td>
<td>4.2</td>
<td>7</td>
<td>50</td>
<td>50</td>
<td>9</td>
</tr>
<tr>
<td>Barbui et al. [11]</td>
<td>707</td>
<td>2.92</td>
<td>9.5</td>
<td>53.8</td>
<td>46.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Barbui et al. [23]</td>
<td>180†</td>
<td>6.2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>15</td>
</tr>
<tr>
<td>Buxhofer-Ausch et al. [24]</td>
<td>264†</td>
<td>6.28</td>
<td>22</td>
<td>29.4</td>
<td>70.6</td>
<td>20.8</td>
</tr>
</tbody>
</table>

Risk Factors for Thrombosis in P vera by Multivariable Analysis

• Arterial
  o Previous arterial thrombosis
  o Hypertension

• Venous
  o Previous venous or arterial thrombosis
  o Age >65 years

CALR Mutations and Outcome in ET

717 patients with ET

Thrombotic events

Leukemic transformation

Abdominal Vein Thrombosis – A Unique Entity in MPNs

• Prevalence (meta-analysis)\(^1\)
  o Budd Chiari syndrome: 41%
  o Portal vein thrombosis: 32%
  o Splanchnic vein thrombosis, no MPN features: JAK2 pos-17%

• Pathophysiology
  o CALR-positive patients, no MPN features: no splanchnic thrombosis\(^2\)

• Presentation
  o Variable: benign, chronic → fulminant

CALR, calreticulin; MPN, myeloproliferative neoplasm.
2. JTH 2014
MPN-related Abdominal Vein Thrombosis: A Gender-related Phenomenon?

- Retrospective, multicentre analysis of MPN-related abdominal vein thrombosis
- 519 patients (75% SpVT+PVT; 25% BCS), 1686 MPN controls

<table>
<thead>
<tr>
<th></th>
<th>P vera</th>
<th>ET</th>
<th>Myelofibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall incidence (%)</td>
<td>36.8</td>
<td>37.8</td>
<td>15.4</td>
</tr>
<tr>
<td>Females (with thrombosis, vs. controls)</td>
<td>54.5 vs. 44.5*</td>
<td>68.4 vs. 63.5</td>
<td>63.7 vs. 29.1*</td>
</tr>
</tbody>
</table>

BCS, Budd Chiari syndrome; MPN, myeloproliferative neoplasm; PVT, portal vein thrombosis; SpVT, splanchnic vein thrombosis.
Treatment of Thromboembolic Events Coincident with the Diagnosis of MPNs: A Physician Survey

- Web-based survey of physicians
  - Israel, UK, Italy
- 5 clinical scenarios in untreated MPN
  - PE, CVT, splenic infarcts, SpVT, CVA
- Supplementary questions
  - Professional profiles
  - (JAK2 positive, normal CBC, and thrombosis)

6 months VKA then:

VKA → ASA
VKA →
VKA+ASA →
ASA →

ASA, acetylsalicylic acid; CBC, complete blood count; CVA, cerebrovascular accident; CVT, cerebral vein thrombosis; MPN, myeloproliferative neoplasm; PE, pulmonary embolus; SpVT, splanchnic vein thrombosis; VKA, vitamin K antagonist.

Physicians' Treatment Decisions for Different Clinical Case Scenarios

PE: pulmonary embolus, CVT: cerebral vein thrombosis, CVA: cerebrovascular accident, SpVT: splanchnic vein thrombosis

Conclusions

• Little data to inform long-term anticoagulant management strategies
• Practice varies widely
  – Independent of expertise, experience
• Potential for clinical studies
A New Standard of Treatment in P Vera

Cardiovascular Events and Intensity of Treatment in Polycythemia Vera

CYTO-PV Collaborative Group

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Primary End Point & Total Cardiovascular Events Among Patients with a High or Low Hematocrit (HCT) Target

Conclusions: In patients with polycythemia vera, those with a hematocrit target of <45% had a significantly lower rate of cardiovascular death and major thrombosis than did those with a hematocrit target of 45% to 50%.

"I don't believe it. It's 97% octane gasolene!"

Denis meets interesting patients at Dr. Ellis's bloodletting sessions at the Maccabi clinic in Netanya, 28.1.2004
Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera

Alessandro M. Vannucchi, M.D., Jean Jacques Kiladjian, M.D., Ph.D., Martin Griesshammer, M.D., Tamas Masszi, M.D., Ph.D., Simon Durrant, M.D., Francesco Passamonti, M.D., Claire N. Harrison, D.M., Fabrizio Pane, M.D., Pierre Zachee, M.D., Ph.D., Ruben Mesa, M.D., Shui He, Ph.D., Mark M. Jones, M.D., William Garrett, M.B.A., Jingjin Li, Ph.D., Ulrich Pirron, Ph.D., Dany Habr, M.D., and Srdan Verstovsek, M.D., Ph.D.
Patients and Study Design

- Randomized, open-label
- PV diagnosis according to WHO criteria
- Refractory or intolerant to hydroxyurea (HU) or HU contraindicated

110 pts on Ruxolitinib; 110 patients on standard therapy

Part 1:
- 10 mg BID (n=7)
- 25 mg BID (n=8)
- 50 mg QD (n=7)

Part 2:
- 10 mg BID (n=12)

PV, Polycythemia Vera.

Primary Response and Duration of Response

Thromboembolic Events (All Grades) up to Week 32

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Ruxolitinib (n = 110)</th>
<th>BAT (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grade All thromboembolic events</td>
<td>1 (0.9)</td>
<td>6 (5.4)</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Splenic infarction</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>
Conclusions

- Ruxolitinib treatment resulted in clinical benefit in patients with PV resistant or intolerant to hydroxyurea by providing:
  - Durable response rates
  - Rapid and sustained improvements in PV-associated symptoms
- Ongoing studies will help further define the safety and efficacy of ruxolitinib in PV patients
Two Clinical Phenotypes in Polycythemia Vera

Jerry L. Spivak, M.D., Michael Considine, M.S., Donna M. Williams, Ph.D., Conover C. Talbot, Jr., B.A., Ophelia Rogers, A.A., Alison R. Moliterno, M.D., Chunfa Jie, Ph.D., and Michael F. Ochs, Ph.D.
P Vera in Women

- Earlier age of onset
- Higher platelet count
- Increased incidence of splanchnic vein thrombosis
- Splenomegaly more common

Clinical Features & Gene Expression of the 19 Patients

Clinical Features:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (N = 8)</th>
<th>Women (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) — yr</td>
<td>71 (57–82)</td>
<td>60 (46–79)</td>
</tr>
<tr>
<td>Median disease duration (range) — yr</td>
<td>12 (1–25)</td>
<td>9 (1–14)</td>
</tr>
<tr>
<td>Median JAK2 V617F neutrophil allele burden (range) — %</td>
<td>94 (55–100)</td>
<td>100 (60–100)</td>
</tr>
<tr>
<td>Median hemoglobin level (range) — g/dl</td>
<td>13.2 (8.3–15.9)</td>
<td>11.7 (10.4–14.7)</td>
</tr>
<tr>
<td>Median white-cell count per mm$^3$ (range)</td>
<td>16,690 (4430–177,190)</td>
<td>19,970 (5080–50,070)</td>
</tr>
<tr>
<td>Median platelet count per mm$^2$ (range)</td>
<td>421,000 (151,000–810,000)</td>
<td>948,000 (191,100–1,480,000)</td>
</tr>
<tr>
<td>Median spleen size (range) — cm below costal margin</td>
<td>10 (0–32)</td>
<td>5 (0–20)</td>
</tr>
</tbody>
</table>

* Characteristics did not differ significantly between the sexes, with the exception of platelet count (P=0.02).

Gene expression:

- 235 genes deregulated in women:
  - Increased:126; decreased:109
- 571 genes deregulated in men:
  - Increased:486; decreased:85
- 3 times more molecular pathways activated in women
- 102 genes deregulated concordantly

Deregulated Genes by “Cluster”

- Stem cell maintenance genes
- “Master” transcription factor
- Antiapoptotic genes
- Proapoptotic genes
- Stromal genes
- Cytokine and inflammatory mediator genes

# Clinical Features Segregated with the Use of Unsupervised Hierarchical Clustering


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with Aggressive Disease (N=7)</th>
<th>Patients with Indolent Disease (N=12)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex — no.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Median age (range) — yr</td>
<td>66 (48–74)</td>
<td>68 (46–82)</td>
<td>NS</td>
</tr>
<tr>
<td>Median disease duration (range) — yr</td>
<td>14 (7–24)</td>
<td>6 (1–25)</td>
<td>0.05†</td>
</tr>
<tr>
<td>Median JAK2 V617F neutrophil allele burden (range) — %</td>
<td>100 (64–100)</td>
<td>85 (55–100)</td>
<td>NS</td>
</tr>
<tr>
<td>Median hemoglobin level (range) — g/dl</td>
<td>11.1 (8.3–12.9)</td>
<td>13.3 (10.7–15.9)</td>
<td>0.007†</td>
</tr>
<tr>
<td>Median white-cell count per mm³ (range)</td>
<td>17,620 (10,020–171,190)</td>
<td>17,870 (4430–27,270)</td>
<td>NS</td>
</tr>
<tr>
<td>Median platelet count per mm³ (range)</td>
<td>454,000 (171,000–1,017,000)</td>
<td>837,000 (151,000–1,480,000)</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombosis — no. of patients</td>
<td>4</td>
<td>1</td>
<td>0.04‡</td>
</tr>
<tr>
<td>Palpable splenomegaly — no. of patients</td>
<td>7</td>
<td>6</td>
<td>0.03‡</td>
</tr>
<tr>
<td>Median spleen size (range) — cm below costal margin</td>
<td>20 (5–32)</td>
<td>2 (0–14)</td>
<td>0.005‡</td>
</tr>
<tr>
<td>Splenectomy — no. of patients</td>
<td>4</td>
<td>0</td>
<td>0.007‡</td>
</tr>
<tr>
<td>Chemotherapy — no. of patients</td>
<td>5</td>
<td>2</td>
<td>0.03‡</td>
</tr>
<tr>
<td>Transformation to acute leukemia — no. of patients</td>
<td>4</td>
<td>1</td>
<td>0.04‡</td>
</tr>
<tr>
<td>Surviving — no. of patients</td>
<td>1</td>
<td>11</td>
<td>0.001‡</td>
</tr>
</tbody>
</table>

* NS denotes not significant.
† The P value was calculated with the use of Student’s t-test.
‡ The P value was calculated with the use of Fisher’s exact probability test (two-sided).
Summary

- Molecular pathogenesis allowing more accurate diagnosis of clonal disease
- Thrombosis is an important cause of morbidity and mortality, particularly in P vera
- Thrombosis can effectively be prevented by appropriate treatment
- Duration of anticoagulant therapy for established thrombosis is uncertain
- Women with P vera may have particular disease phenotype and thrombotic risk
Thrombosis and Cancer in Special Female Populations

Pr. Benjamin Brenner, MD
Rambam Health Care Campus
Haifa, ISRAEL
Benjamin Brenner’s Disclosures

Receipt of honoraria or consultation fees:

• Sanofi
• Pfizer
• ROVI Laboratories
• Daiichi Sankyo
• Bayer Pharmaceuticals
A 36-year-old woman known to have essential thrombocythemia for the last 4 years has a platelet count range is between 700,000 to 900,000/µL. She is asymptomatic. Two previous pregnancies ended with miscarriages at 10 and 14 weeks of gestation. She also failed 3 IVF procedures during the last year. She is currently planning another pregnancy.

- How would you manage her during IVF procedures & in pregnancy?
  
a. Use of anagrelide/hydroxycarbamide; no antiplatelet therapy
b. Use of anagrelide/hydroxycarbamide with low dose aspirin
c. Use of interferon-alpha; no antiplatelet therapy
d. Use of interferon-alpha with low dose aspirin
e. Use of interferon-alpha with LMWH in combination with lose dose aspirin
f. Other
TOPICS

- Epidemiology
- Cancer and Pregnancy
- Travel and Thrombosis
- Diagnostic Innovations
Risk of VTE Varies Over Cancer Evolution

- Hospitalization
- Diagnosis
- Chemotherapy
- Remission
- Metastasis
- End of life

Risk (odds ratio)

Risk of VTE Varies Over Cancer Evolution

Effect of VTE on Survival in Cancer Patients

Atypical Localization of VTE in Cancer Compared to Major Surgery Setting

Natural history following major surgery¹

Incidental VTE in cancer with chemotherapy²

- Retrospective, single institution cohort study
- N=1921 medical records of cancer patients (solid T + chemotherapy)

DVT, deep vein thrombosis; SVT, superficial vein thrombosis; PE, pulmonary embolism.

Risk Factors for VTE in Patients with Malignant Disease

• **Patient-related factors**
  - Older age (esp. >65)
  - Race (Black/Asian > Hispanic/Caucasian)
  - Comorbid conditions (obesity, infection, renal disease, pulmonary disease, arterial thrombosis)
  - Prior history of VTE
  - Heritable prothrombotic mutations
  - **Pregnancy**

• **Treatment-related factors**
  - Recent major surgery
  - Current hospitalization
  - Active chemotherapy
  - Active hormonal therapy
  - Current or recent antiangiogenic therapy (thalidomide, lenalidomide, bevacizumab)
  - Current erythropoiesis-stimulating agents
  - Presence of central venous catheters

• **Cancer-related factors**
  - Primary site of cancer (pancreatic, GI, brain, lung, gynecological, renal, hematological)
  - Initial 3 to 6 months after diagnosis
  - Current metastatic disease

TOPICS

- Epidemiology and Mechanisms
- Cancer in Pregnancy
- Travel and Thrombosis
- Diagnostic Innovations
Cancer in Pregnancy

• The diagnosis of cancer during pregnancy or in the postpartum period poses a major burden on the woman and her family.

• Issues of fetal and neonatal well-being are intricate, while mother's health is of primary concern.
Epidemiology

- With an estimated prevalence of one per thousand pregnancies, cancer is considered to be the second leading cause of maternal mortality behind pregnancy-associated vascular complications.

- The epidemiology of cancer in pregnancy is mediated in part by maternal age and by specific factors of gestation.
Epidemiology (cont...) 

- Solid tumours constitute the majority of cancers diagnosed at gestation, while hematological malignancies are less commonly reported.

- Breast and cervix cancers account for about 50% of pregnancy-related malignancies, followed by lymphoma and leukemia, the latter comprising around one-quarter of cases.
Pathogenesis

- Current limited data fail to suggest a causative association between pregnancy and malignancy development.

- Estrogens, though reported to increase proliferation of various tumour cell subtypes in vitro (breast, some rare subtypes of NHL, etc.) have not been shown to directly increase the risk of primary occurrence of gestation-related malignancies.

NHL, non-Hodgkin lymphoma.
NHL Diagnosed During Pregnancy

• 121 cases were reported between 1967 to 2011:
  – 4.6% indolent lymphoma
  – 48% aggressive lymphoma
  – 47% highly aggressive lymphoma
  – unspecified histology – 13 cases

• Reproductive organ involvement in 44.3% of the series:
  – 84.6% in Burkitt lymphoma
  – 46.2% in T cell lymphoma
  – 40% in immunoblastic lymphoma
  – 23.1% in DLBCL
  – 40% in low grade lymphoma
  – 22.2% in unclassifiable high grade lymphoma

Virchow's Triad in Cancer Patients

- **Endothelial damage**
  - Shift to procoagulant endothelium
  - Invasion of cancer cells into vessel wall

- **Stasis of blood**
  - Frequent immobilization, surgery
  - Compression of blood vessels by tumour

- **Changes in the blood constituents**
  - Activation of clotting proteins and blood cells

These mechanisms are further escalated in pregnancy
Tissue Factor in Hemostasis and Angiogenesis

IL, interleukin; TF, tissue factor; VEGF, vascular endothelial growth factor.
### Acquired APC-resistance Is Common in Cancer Patients without Thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Cancer Patients</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>99</td>
<td>79</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (Y)</td>
<td>49 ± 11</td>
<td>41 ± 10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APC-SR</td>
<td>2.37 ± 0.5</td>
<td>2.96 ± 0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APC-SR &lt;2.0 (%)</td>
<td>23 (23)</td>
<td>1 (1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

APC Resistance Deepens with Pregnancy Progression

Thrombotic Manifestations

- The hypercoagulability state in pregnant women with cancer may lead to:
  - Placental thrombosis, fetal growth restriction or loss
  - Venous thromboembolism: DVT, pulmonary embolism, and thrombosis at unusual sites (cerebral and splanchnic veins)
VTE Presentation in Pregnancy

MPN Management

• Pregnant women with essential thrombocythemia, polycythemia vera, and myelofibrosis are known to be at an increased risk for miscarriages and preterm deliveries.

• While anagrelide and hydroxycarbamide cannot be recommended during the first trimester, alpha-interferon may be safely used in this patient population.
Antithrombotic Agents

- The role of antiplatelets in preventing arterial thrombosis has been well-established and LDA is therefore recommended in MPN.
- LMWH are often used in combination with LDA.
- However, the benefit of the combination remains to be determined.

LDA, low-dose aspirin; LMWH, low molecular weight heparin; MPN, myeloproliferative neoplasm.
Reproduction Counselling

- Acetylsalicylic acid prophylaxis is often required to reduce thrombotic burden in MPN.
- Combined hormonal contraceptives increase the risk of thrombosis and therefore are not recommended in patients with active cancer.
- Progesterone-only preparations, taken either orally or as an intrauterine device, are probably safe in terms of thrombotic risk.

MPN, myeloproliferative neoplasm.
Cancer & Pregnancy – Conclusions

- Cancer in pregnancy presents major diagnostic and therapeutic challenges
- Maternal survival is considered the main concern, while reduction in treatment-related fetal toxicity should be attempted
- Prevention and management of thrombotic and hemorrhagic complications may affect outcome
TOPICS

- Epidemiology and Mechanisms
- Cancer and Pregnancy
- Travel and Thrombosis
- Diagnostic Innovations
Case Presentation

• 48-year-old woman with advanced breast cancer on hormonal therapy asked your advice before travelling from LA to Berlin to visit her sister

• The sister is paraplegic following an accident 2 years ago

• There is a possibility that the sister will visit her

Who is at greater risk on a long haul flight?
How would you consult this case?
PE on Arrival According to Travel Distance

Frequency of PE increased 150-fold in long haul travelers >5000 km compared to <5000 km

Incidence of pulmonary embolism (per million passenger arrivals)

Gender and Travel-related PE

- Travelers who experienced PE after landing in CDG - 90/116 (78%) were females
- **Risk: 3.5-fold higher in females**

Coagulation Factors and Travel-related VTE

334 travelers (200 patients, 134 controls)

- High factor II 2.2 (1.3-3.7)
- High factor VIII 6.2 (3.6-10.5)
- High factor IX 3.2 (0.9-11.0)
- High fibrinogen 2.0 (0.7-5.5)
- OC + high FVIII 52 (5.4-498)

Prospective Randomized Study

300 Patients Randomized

- ASA 400 mg 12 hours before flight for 3 days
- S.C. enoxaparin 1 mg/kg 2-4 hours before flight
- No prophylaxis
### LONFLIT 3 – Results

52/300 failed to complete study (equally distributed)

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>ASA</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>82</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>DVT</td>
<td>0</td>
<td>3 (3.6%)</td>
<td>4 (4.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.002</td>
</tr>
<tr>
<td>SVT</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Medical Guidelines for Airline Travel

Moderate Risk:
- Varicose veins
- Heart failure
- Recent myocardial infarction
- Hormonal therapy
- Polycythemia
- Pregnancy
- Lower limb paralysis
- Recent lower limb trauma

High Risk:
- Previous VTE
- Known thrombophilia
- Recent major surgery
- Previous CVA
- Malignancy
- Family history of VTE
# Medical Guidelines for Airline Travel

Aerospace Medical Association (AsMA) – May 2003.

## Prophylaxis

<table>
<thead>
<tr>
<th>Level</th>
<th>Behavioral</th>
<th>Mechanical</th>
<th>Antithrombotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>+</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>Moderate</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>High</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
TOPICS

- Epidemiology and Mechanisms
- Cancer and Pregnancy
- Travel and Thrombosis
- Diagnostic Innovations
An Assay to Evaluate Heparanase Procoagulant Activity

- Heparanase procoagulant activity is significantly elevated in hypercoagulable clinical set-ups:
  - Oral contraceptive use¹
  - Patients with lung cancer²
  - End of pregnancy³
  - Following orthopedic surgery⁴

Conclusions

- Cancer and thrombosis are closely related
- Unusual clinical presentations are common
- Diagnostic and therapeutic innovations are essential to improve outcome
- Multicentre collaborations are warranted to advance basic and clinical research in this complicated clinical setting
Central Venous Catheters and Thrombosis: Emerging Issues and Relevance for Women

Dr. Philippe Debourdeau, MD
Institut Sainte-Catherine
Avignon, FRANCE
Dr. Debourdeau’s Disclosures

• Receipt of grants/research supports: Sanofi, Leo Pharma
• Receipt of honoraria or consultation fees: Merck Serono
• Participation in a company sponsored speaker's bureau: Daïtchi Sankyo, Pfizer
• Grants for CAVECCAS: Sanofi, GFTC, AP-HP (National Health Research Program PHRC AOM 97)
A 66-year-old woman with ovarian cancer develops central venous catheter (CVC) related thrombosis. The CVC is well-positioned, functional and is not infected.

- How would you manage this patient?
  a. Remove CVC
  b. Remove CVC and treat with LMWH
  c. Remove CVC and treat with oral VKA
  d. Leave CVC in place; treat with LMWH
  e. Leave CVC in place; treat with oral VKA
  f. Other
Definition

• Mural thrombus extending from catheter into the lumen

• CRT catheter dysfunction without mural thrombus
  o Pinch off
  o Fibrin sheath
  o Distal tip thrombus

CRT, catheter-related thrombosis.
False CRT

Pinch-off syndrome occurs when the catheter is compressed between the first rib and the clavicle, causing an intermittent mechanical occlusion for both infusion and withdrawal.

The evolving risk is a breaking of the catheter leading to its migration to the pulmonary arteries.
False CRT

- Distal tip thrombus without any mural component
- Fibrin sheath occurs in about 70% of cases within the first month after catheter insertion

Treatment ≠ anticoagulant
Treatment = fibrinolytics

CRT, catheter-related thrombosis.
Physiopathology of CRT

Catheter insertion → Vascular wall injury → Thrombus formation

Thrombus lysis in 3 out of 4 cases
Thrombogenic factor local or systemic → Thrombus growth

In some cases, thrombus occurs in a delayed manner away from the catheter insertion point

CRT, catheter-related thrombosis.
Various Catheters Used in Oncology

Long-term CVC

Without implanted port

Nontunneled

PICC Lines

Broviac catheter

With a sleeve

Hickman catheter

Without a sleeve

Open-ended

With implanted port

With Groshong system
Catheter Types

Hickman catheter

Broviac catheter inducing a fibrin sleeve at the subcutaneous route

PICC Line
Catheter Types

- Close-ended
  Three-way Groshong® valve
  Negative pressure opens valve inward
  Positive pressure opens valve outward
  At neutral pressure, valve remains closed

- With implanted port
Epidemiology of CVC and CRT

• 5 million CVCs inserted / year (USA)

• Number of CVCs is growing
  o ‣ inserted catheters
  o ‣ treated patients
  o More thrombogenic treatments

CRT, catheter-related thrombosis; CVC, central venous catheter.
Epidemiology of CRT

- **Incidence**
  - 27% to 66% of CRT with phlebography
  - 12% to 18% of CRT with US Doppler
  - 3% to 5% of symptomatic CRT

- **Time to onset**
  - 30% to 60% 1\textsuperscript{st} week
  - 60% to 90% 1\textsuperscript{st} month
  - \approx 100% within 6 to 8 weeks

CRT, catheter-related thrombosis; US, ultrasound.
Medical Consequences of CRT

- Delay in receiving chemotherapy
- Decreased quality of life
- Catheter dysfunction = 70% of CRT
- PE in 10% to 15% of cases

CRT, catheter-related thrombosis; PE, pulmonary embolism.
Economic Burden of CRT

• Cost (France) = 1242 € / CRT

• duration of hospitalisation
  o DVT lower limbs = 3 days
  o DVT upper limbs = 5 days
  o CRT = 9 days

• Catheter removal (10%) (USA) = 4500 €

CRT, catheter-related thrombosis; DVT, deep vein thrombosis.
Diagnostic of Symptomatic CRT

- **Phlebography**
  - Gold standard
  - Unfeasible in 5% to 7% of patients
  - Nephrotoxicity +/- potentially thrombogenic
  - Too heavy to be used in clinical practice

- **US Doppler**
  - Axillary and jugular veins = ++
  - Superior vena cava and brachiocephalic veins = +/-
  - Easy and reproducible exam

CRT, catheter-related thrombosis; US, ultrasound.
US Doppler in Symptomatic CRT

- Sensitivity
  - Overall = 56 to 100%
  - Subclavian = 95%, jugular = 100%
  - Brachiocephalic, SVC ≈ 10%

- Specificity
  - 95 to 100%

- Diagnostic thrombus visualization
  - vein incompressibility
  - slow blood flow
  - collateral circulation
  - variation with respiration, heart beats = 0

- Consistency with phlebography = 85% to 95%

CRT, catheter-related thrombosis; SVC, superior vena cava.
US Doppler in Asymptomatic Patients

- Sensitivity 30% to 40% (n=66 and 32) 70%
- Specificity 82% (n=105)
- PNV 95%
- The only exam to be performed for VTE screening

PNV, predictive negative value; VTE, venous thromboembolism
CRT Risk Factors

- **Insertion-related**
  - PICC lines > CVC with implanted port
  - Subclavian CVC > jugular CVC
  - D-Dimer levels after insertion (fibrin lysis)

- **Patient-related**
  - Factor V and prothrombin mutation

- **Cancer-related**
  - Not very well-documented

CRT, catheter-related thrombosis; CVC, central venous catheter; PICC, peripherally inserted central catheter.
Treatment of CRT

- Anticoagulation is recommended for a minimum of 3 months
  - LMWHs are suggested
  - Oral VKA can also be used, in the absence of direct comparisons of these two types of anticoagulants in this setting

- CVC can be kept in place if it is functional, well-positioned, and noninfected with good resolution of symptoms under close surveillance

CRT, catheter-related thrombosis; CVC, central venous catheter; LMWH, low molecular weight heparin; VKA, vitamin K antagonist.
Prevention of CRT

• Use of anticoagulation for routine prophylaxis of CRT is not recommended

• Catheters should be inserted on the right side, in the jugular vein, and the distal extremity of the central catheter should be located at the junction of the superior vena cava and the right atrium

CRT, catheter-related thrombosis.
Relevant Data for Women

• Influence of cancer\(^1\)
  o 444 consecutive patients with cancer
  o Ovarian cancer = risk factor for CRT (OR = 4.8; 95% CI, 1.5-15.1; \(P = 0.01\))

• Influence of prothrombotic state\(^2\)
  o Case control study 300 patients with locally advanced or metastatic breast cancer \(\rightarrow\) 25 CRT
  o FVL mutation CRT = 25%, control = 4%

CRT, catheter-related thrombosis; FVL, Factor V Leiden.
CAVECCAS Study (under review)

- 539 pts with BC + (neo)adjuvant CT
- Same rate of CRT as previous studies
- Onset of CRT within 2 months
- Risk factors = patient + cancer + catheter
- Value of Doppler US in asymptomatic patients for CRT

BC, breast cancer; CRT, catheter-related thrombosis; CT, chemotherapy; US, ultrasound.
Specific Guidelines for Cancer-Associated Thrombosis in Women?

Moderator: Benjamin Brenner, MD
Debaters: Dominique Farge-Bancel, MD
Rupert Bauersachs, MD
Polling Question 5

• Would you routinely prescribe anticoagulant-based VTE prophylaxis for women with stage 4 breast cancer treated with chemotherapy + tamoxifen?
  a. Yes
  b. No
VTE Prophylaxis in Metastatic Breast Cancer: Yes or No?

- **Two clinical trials with conflicting results**
  - Women receiving chemotherapy for metastatic breast cancer assigned to very low-dose warfarin (n=152) or placebo (n=159)\(^1\)
    - Incidence of VTE: 0.6% (warfarin) vs 4.4% (placebo)
    - Relative risk reduction of about 85% (p = 0.031)
    - No difference in survival
  - TOPIC-1 study: 353 patients with metastatic breast cancer\(^2\)
    - Primary VTE prophylaxis with certoparin 3000 IU daily compared to no anticoagulation had no effect on VTE incidence (4% vs 4%)
    - No difference in survival

---

Debate Question 1

Should prophylaxis of VTE with anticoagulation be routinely prescribed for women with locally advanced breast cancer treated with chemotherapy + tamoxifen?

<table>
<thead>
<tr>
<th></th>
<th>Pr. Bauersachs</th>
<th>Pr. Farge-Bancel</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRO</td>
<td></td>
<td>CON</td>
</tr>
</tbody>
</table>
Disclosures for Pr. Bauersachs

- Receipt of grants/research supports: Pfizer
- Receipt of honoraria or consultation fees: Bayer, Boehringer, BMS, Daiichi-Sankyo, LEO
- Participation in a company sponsored speaker's bureau: Bayer, Boehringer, Daiichi-Sankyo, BMS, LEO
### Tamoxifen Increases Risk of VTE

A case-control study of women with breast cancer

<table>
<thead>
<tr>
<th>Tamoxifen exposure</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure timing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never or past</td>
<td>2</td>
<td>62</td>
<td>1.0†</td>
</tr>
<tr>
<td>Current</td>
<td>23</td>
<td>110</td>
<td>7.1 (1.5–33)</td>
</tr>
<tr>
<td><strong>Exposure duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never or past</td>
<td>2</td>
<td>62</td>
<td>1.0†</td>
</tr>
<tr>
<td>Current, 1–11 months</td>
<td>7</td>
<td>28</td>
<td>9.0 (1.0–83)</td>
</tr>
<tr>
<td>Current, 12 + months</td>
<td>16</td>
<td>82</td>
<td>6.8 (1.4–33)</td>
</tr>
<tr>
<td><strong>Exposure dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never or past</td>
<td>2</td>
<td>62</td>
<td>1.0†</td>
</tr>
<tr>
<td>Current, short, &lt; 40 mg day(^{-1})</td>
<td>5</td>
<td>22</td>
<td>8.3 (0.8–83)</td>
</tr>
<tr>
<td>Current, long, &lt; 40 mg day(^{-1})</td>
<td>14</td>
<td>71</td>
<td>7.9 (1.5–41)</td>
</tr>
<tr>
<td>Current, short, 40 + mg day(^{-1})</td>
<td>2</td>
<td>6</td>
<td>14.1 (0.8–245)</td>
</tr>
<tr>
<td>Current, long, 40 + mg day(^{-1})</td>
<td>2</td>
<td>11</td>
<td>4.3 (0.5–35)</td>
</tr>
</tbody>
</table>

Adjusted for body mass index, smoking status, and hysterectomy status.

Chemotherapy + Tamoxifen Increases Risk for VTE in Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th># of Patients</th>
<th>% of Patients with VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher et al.</td>
<td>Tamoxifen</td>
<td>1318</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>1326</td>
<td>0.15</td>
</tr>
<tr>
<td>Fisher et al.</td>
<td>CMF + Tamoxifen</td>
<td>768</td>
<td>4.2</td>
</tr>
<tr>
<td>(NSABP)</td>
<td>Tamoxifen</td>
<td>771</td>
<td>0.8</td>
</tr>
<tr>
<td>Node Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levine et al.</td>
<td>CMFVP</td>
<td>102</td>
<td>8.8</td>
</tr>
<tr>
<td></td>
<td>CMFVP + AT</td>
<td>103</td>
<td>4.9</td>
</tr>
<tr>
<td>Pritchard et al.</td>
<td>CMF + Tamoxifen</td>
<td>353</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td>352</td>
<td>1.4</td>
</tr>
<tr>
<td>Rivkin et al.</td>
<td>CMFVP + Tamoxifen</td>
<td>303</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>CMFVP</td>
<td>300</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td>295</td>
<td>0</td>
</tr>
<tr>
<td>Fisher et al.</td>
<td>AC + Tamoxifen</td>
<td>383</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td>367</td>
<td>1.6</td>
</tr>
</tbody>
</table>

A, Adriamycin; C, cyclophosphamide; F, fluorouracil; M, methotrexate; P, prednisone; T, tamoxifen; V, vincristine.

### Danish Breast Cancer Cooperative Group; n=16289

#### Tamoxifen Treatment in Breast Cancer and Risk of VTE: Age

<table>
<thead>
<tr>
<th>Years 1-2</th>
<th>Tamoxifen</th>
<th>No Tamoxifen</th>
<th>Tamoxifen</th>
<th>No Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>7071</td>
<td>5825</td>
<td>1161</td>
<td>2232</td>
</tr>
<tr>
<td>Risk</td>
<td>8.8</td>
<td>2.7</td>
<td>2.6</td>
<td>0.90</td>
</tr>
<tr>
<td>Risk difference</td>
<td>6.0</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction contrast</td>
<td>4.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years 3-5</th>
<th>Tamoxifen</th>
<th>No Tamoxifen</th>
<th>Tamoxifen</th>
<th>No Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>5783</td>
<td>5340</td>
<td>994</td>
<td>2112</td>
</tr>
<tr>
<td>Risk</td>
<td>5.4</td>
<td>3.6</td>
<td>4.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Risk difference</td>
<td>1.8</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction contrast</td>
<td>-0.33</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DVT/PE: deep venous thrombosis and pulmonary embolism.
Breast Cancer and Tamoxifen: Risk Factors for VTE

A case-control study, n=124 women who experienced a VTE while taking tamoxifen for breast cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs no</td>
<td>4.73 (2.10 to 10.68)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior history of clot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs no</td>
<td>3.05 (1.18 to 7.87)</td>
<td>.021</td>
</tr>
<tr>
<td>Family history of clot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs no</td>
<td>2.06 (1.04 to 4.11)</td>
<td>.040</td>
</tr>
<tr>
<td>Unknown vs no</td>
<td>1.34 (0.67 to 2.66)</td>
<td>.411</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs no</td>
<td>2.97 (1.34 to 6.56)</td>
<td>.007</td>
</tr>
<tr>
<td>Unknown vs no</td>
<td>0.37 (0.07 to 1.87)</td>
<td>.230</td>
</tr>
</tbody>
</table>

CI = confidence ratio; OR = odds ratio.
Breast Cancer and Tamoxifen: Risk Factors for VTE

A case-control study, n=150 women with breast cancer (50 developed VTE while treated with tamoxifen; 100 did not as control)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonsignificant</strong></td>
<td></td>
</tr>
<tr>
<td>BMI &gt; 25 kg/m²</td>
<td>P = 0.327</td>
</tr>
<tr>
<td>Stage of disease</td>
<td>P = 0.428</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>P = 0.609</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>P = 0.409</td>
</tr>
</tbody>
</table>

| **Significant**                 | Z-test          | OR (95% CI)                    |
| group.log group log = 1:group.log = 0) | P = 0.009       | 3.528 (1.354–9.191)            |
| FVIII > 1.5 IU/ml               | P = 0.016       | 3.764 (1.276–11.096)           |

Group log = 1 (tamoxifen users without VTE), group.log = 0 tamoxifen users with VTE.

CI = confidence ratio; OR = odds ratio.

VTE Prophylaxis in Metastatic Breast Cancer: No

- Should we continue tamoxifen treatment in women at risk of VTE or stop?

Tamoxifen Treatment in Breast Cancer and Risk of VTE: Over Time

Danish Breast Cancer Cooperative Group; n=16 289

|            | Tamoxifen No. (Risk) | No Tamoxifen No. (Risk) | Risk Ratio (95% CI) | No. Needed to Treat 1/|RD| |
|------------|----------------------|-------------------------|---------------------|-----------------------|
| **DVT/PE** |                      |                         |                     |                       |
| Year 1     | 34 (0.41)            | 8 (0.10)                | 4.2 (1.9-9.0)       | 319                   |
| Year 2     | 37 (0.45)            | 10 (0.12)               | 3.6 (1.8-7.3)       | 307                   |
| Year 3     | 18 (0.22)            | 9 (0.11)                | 2.0 (0.88-4.4)      | 935                   |
| Year 4     | 15 (0.18)            | 12 (0.15)               | 1.2 (0.57-2.6)      | 3005                  |
| Year 5     | 6 (0.07)             | 4 (0.05)                | 1.5 (0.41-5.2)      | 4303                  |
| Years 1-5  | 97 (1.2)             | 40 (0.50)               | 2.4 (1.6-3.4)       | 147                   |

DVT/PE: deep venous thrombosis and pulmonary embolism; 95% CI, 95% confidence interval; RD, risk difference.
VTE Prophylaxis in Metastatic Breast Cancer: No

- Are anti-aromatase inhibitors an alternative to tamoxifen?

Polling Question 6

- What do you think would improve the outcomes of women with cancer at risk of VTE?
  a. Further research specific to VTE in women with cancer
  b. VTE guidance document specific to women with cancer
  c. Mobile app with treatment decision-tree algorithms
  d. Patient education for women with cancer
  e. All of the above
  f. Nothing at this time (continue current clinical practice)
Need for Best Treatment and Effective Prevention of VTE in Cancer Patients

- Several scientific societies have issued guidelines:
  - 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 (SOR-INCa)
  - International Myeloma Working Group (IMWG)
  - Italian Association of Medical Oncology (AIOM)
  - International Guidelines

Various methodologies ...different questions

Low level of implementation\(^1-3\)

# Clinical Issues and Quality/Validation of Various VTE Guidelines

<table>
<thead>
<tr>
<th></th>
<th>AIOM</th>
<th>SOR</th>
<th>NCCN</th>
<th>ACCP</th>
<th>ASCO</th>
<th>International Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT/PE prophylaxis</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>DVT/PE treatment</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CRT prophylaxis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CRT treatment</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Methods of CVC insertion</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Target patient population</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Grading of recommendations</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>External reviewers</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ACCP, American College of Chest Physicians; AIOM, Italian Association of Medical Oncology; ASCO, American Society of Clinical Oncology; CRT, catheter-related thrombosis; CVC, central venous catheter; DVT, deep vein thrombosis; NCCN, National Comprehensive Cancer Network; SOR, Standards, Options & Recommendations (French national guidelines); VTE, venous thromboembolism.

International Guidelines: Clinical Issues

1. Initial treatment (first 10 days) of established VTE
2. Early maintenance (10 days – 3 months) & long term treatment (>3 months) of established VTE
3. Treatment of VTE recurrence with VKA, LMWH, and vena cava filter
4. Prophylaxis of VTE in surgical cancer patients
5. Prophylaxis in medical cancer patients (special focus on lung, pancreatic, and myeloma patients)
6. Treatment of established Catheter Related Thrombosis (CRT)
7. Prophylaxis of CRT
8. Specific cases: brain tumors, neurosurgery, renal failure, thrombocytopenia, and pregnant women with cancer

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

Treatment & Management of Established VTE in Patients with Cancer

• **Q1**: Initial treatment of established VTE in patients with cancer
  - LMWH is recommended, although fondaparinux and UFH can be also used
  - Vena cava filters may be considered, and thrombolysis may be considered only on a case-by-case basis

• **Q2**: Early maintenance and long-term treatment
  - LMWH for a minimum of 3 months is preferred over VKAs
  - After 3-6 months, LMWH or VKA continuation should be based on individual evaluation of the benefit–risk ratio, tolerability, patient preference, & cancer activity

• **Q3**: Treatment of VTE recurrence under anticoagulation
  - Three options are recommended:
    - A switch from VKA to LMWH when treated with VKA
    - An increase in LMWH dose when treated with LMWH
    - In some patients, vena cava filter insertion

Prevention of VTE in Patients with Cancer

• **Q4: Surgical cancer patients**
  - Use of LMWH or low doses of UFH is recommended; it should be started 12 to 2 hours preoperatively and continued for at least 7 to 10 days
  - Extended prophylaxis (4 weeks) after major laparotomy may be indicated in patients with cancer who have a high risk of VTE and low risk of bleeding
  - Mechanical methods are not recommended as monotherapy except when pharmacological methods are contraindicated

• **Q5: Medical cancer patients**
  - Prophylaxis with LMWH, UFH, or fondaparinux is recommended in hospitalized medical cancer patients with reduced mobility
  - In patients receiving chemotherapy, prophylaxis cannot be recommended routinely
  - For patients treated with thalidomide or lenalidomide combined with steroids and/or chemotherapy, VTE prophylaxis is recommended

Treatment & Prevention of Thrombosis Associated with CVC in Patients with Cancer

• Q6. Treatment of Established CRT
  - Anticoagulant treatment is recommended for a minimum of 3 months
  - LMWHs are suggested; VKAs can also be used in the absence of direct comparisons of these two types of anticoagulants
  - The CVC can be kept in place if it is functional, well positioned and non-infected, and there is good resolution under close surveillance
  - Whether the CVC is kept or removed, no standard approach in terms of anticoagulant treatment duration has been established

• Q7: Prevention of CRT
  - Use of anticoagulant treatment for routine prophylaxis of CRT is not recommended
  - Central venous catheters should be inserted on the right side, in the jugular vein, and the distal extremity of the CVC should be located at the junction of the superior vena cava and the right atrium

Future Considerations?

- Role of new oral anticoagulant agents for the treatment of VTE in cancer patients
- Aside from pregnancy, in which standard treatment for established VTE and prophylaxis is recommended, specific clinical scenarios related to women with cancer are not addressed in current VTE guidelines
Do we need a guidance document specific to women?

<table>
<thead>
<tr>
<th>Pr. Bauersachs</th>
<th>Pr. Farge-Bancel</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES or NO</td>
<td>YES or NO</td>
</tr>
</tbody>
</table>
Concluding Remarks

Benjamin Brenner, MD
The WHITH planning committee, ITAC-CME and symposium faculty acknowledge the contribution of Aspen Pharmacare.

This launch symposium marks the beginning of an accredited educational continuum designed to gather data and clinical insights globally.

Look forward to further initiatives in your country!

Made possible through an Aspen Pharmacare unrestricted educational grant
Thank you!

*Please leave your touchpad units on the table!*

*Don’t forget to complete your evaluation form!*