Venous Thromboembolism Update: 2016

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Disclosures

Sanofi Poland - Visiting Professor
Janssen R&D - Steering Committee
Pfizer - Bleeding Advisory Board
BMS - Advisory Board
CHEST Enterprises - Lecturer
Venous thromboembolism (VTE) is a leading cause of death worldwide. In the western world, someone develops a VTE every 16 seconds.
VTE Incidence

Incidence:¹

- 900,000 PEs and DVTs in the U.S. in 2002
- Estimated 296,000 PE deaths
  - 7% treated unsuccessfully, 34% sudden and fatal and 59% undetected

Annual number at risk for VTE: U.S. hospitals:²

- 7.7 million medical service inpatients
- 4.3 million surgical service inpatients
- Based upon ACCP guidelines for VTE prophylaxis
- 2/3 of VTE cases and deaths are hospital-acquired¹

Venous Thromboembolism estimated to occur in 900,000 U.S. patients/year.

University Of Michigan stadium
113,000 Capacity
Fatal Pulmonary Emboli estimated to occur in 296,000 patients/year

University Of Michigan stadium
113,000 Capacity
The Many Faces of Venous Thromboembolism

• Fatal pulmonary emboli.
  — 1-5% incidence in patients with >4 risk factors
  — 16.7% mortality at three months
  — 34% of those with Pulmonary emboli present as sudden death

• Chronic pulmonary hypertension
  — 4% of patients suffering PE

• Clinical venous thromboembolism.
  — Morbidity, drugs, tests, hose, changes in life style
  — Phlegmasia Cerula & alba Dolens
  — Venous Gangrene with limb loss
The Many Faces of Venous Thromboembolism

- Silent venous thromboembolism.
  - Risk of subsequent event double that of control population

- Embolic stroke (20-30% PFO rate).
  - 50% disabled; 20% die; 30% recover

- The Post Thrombotic Syndrome and Venous Insufficiency-induced Lymphedema
  - 25-40% incidence following DVT and 7% severe
  - May not be evident for 2-5 -10 YEARS.
Pulmonary Embolism

• The patient presented to ER with non-productive cough, mild wheezing, dyspnea and moderate back pain for five days

• The patient developed a massive PE and died three days after admission to intensive care unit

The patient did not receive prophylaxis!

Photo courtesy of Victor F. Tapson, MD: Duke University Hospital
Patient developed acute DVT with major venous obstruction limiting arterial inflow.

Thrombosis extended above the inguinal ligament obstructing the venous circulation of the leg producing venous gangrene.
Thrombus Lodged in a Patent Foramen Ovale

Clot in a PFO as seen in surgery

Paradoxical embolism
Patent foramen ovale

Picture taken from Color Atlas of the CV System, Thomas et al.
Post-Thrombotic Syndrome

- A common event
- Caused by both symptomatic and asymptomatic deep venous thrombosis (DVT)
- Characterized by leg aching, pain, swelling in the early stages
- Late manifestations include skin changes, a variety of skin rashes and, sometimes, eczema
- Brawny edema, bronze discoloration, varicose and spider veins can be seen
- Venous ulceration is the end result, along with venous insufficiency-induced lymphedema
Venous Insufficiency-Induced Lymphedema
Post Thrombotic Syndrome

Thirty-eight year-old male suffered a leg fracture and developed a major DVT while in a cast. This is his leg 10 years later. The ulcer first appeared 2 years previously and failed to respond to treatment due in part to the poor compliance of the patient once the ulcer appeared.
Risk Assessment as a Guide to Thrombosis Prophylaxis
# VTE Risk Factors

**1231 Patients Treated for VTE**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Patients %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 40 yrs</td>
<td>88.5</td>
</tr>
<tr>
<td>Obesity</td>
<td>37.8</td>
</tr>
<tr>
<td>History of VTE</td>
<td>26.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>22.3</td>
</tr>
<tr>
<td>Immobility</td>
<td>12.0</td>
</tr>
<tr>
<td>Major surgery</td>
<td>11.2</td>
</tr>
<tr>
<td>CHF</td>
<td>8.2</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>5.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.8</td>
</tr>
<tr>
<td>1 or more risks</td>
<td>96.3</td>
</tr>
<tr>
<td>2 or more risks</td>
<td>76.0</td>
</tr>
<tr>
<td>3 or more risks</td>
<td>39.0</td>
</tr>
</tbody>
</table>

**Evidence of VTE, %**

<table>
<thead>
<tr>
<th>Number of Risk Factors</th>
<th>Evidence of VTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
</tr>
</tbody>
</table>

Incidence of VTE Increases With Age

Risk Factors Associated With Venous Thromboembolism (VTE): Basic Assumptions

1. The more risk factors present, the greater the likelihood of developing a VTE

2. Strength of each risk factor – for example

   *Abdominal operations*
   - Benign disease (20% VTE incidence)
     » [Caprini score = 2]
   - Malignant disease (36% VTE incidence)
     » [Caprini score = 4]
Caprini Thrombosis Risk Scoring

• Assign a point value to each risk factor according to the relative risk of VTE, based on the literature and validation studies
  – Total the points to obtain a score
  – Compare the scores to 30- and 60-day incidence of clinically relevant VTE
  – Balance the risks and benefits of anticoagulation according to the relative probability of bleeding vs. thrombosis
  – Account for ALL risk factors that could affect the outcome of a procedure or illness

The person performing the history and physical should complete the Caprini Risk Assessment.

The Risk Assessment should be recalculated if additional events occur during hospitalization.

The Assessment should be updated at hospital discharge.

The patient should fill out the intake risk assessment form.
## VTE Risk Factor Assessment

### Each Risk Factor Represents 1 Point
- Age 40-59 years
- Minor surgery planned
- History of prior major surgery
- Varicose veins
- History of inflammatory bowel disease
- Swollen legs (current)
- Obesity (BMI >30)
- Acute myocardial infarction (< 1 month)
- Congestive heart failure (< 1 month)
- Sepsis (< 1 month)
- Serious lung disease incl. pneumonia (< 1 month)
- Abnormal pulmonary function (COPD)
- Medical patient currently at bed rest
- Leg plaster cast or brace
- Central venous access
- Other risk factor _______________
- Blood transfusion (<1 month)

### Each Risk Factor Represents 2 Points
- Age 60-74 years
- Major surgery (> 60 minutes)*
- Arthroscopic surgery (> 60 minutes)*
- Laparoscopic surgery (> 60 minutes)*
- Previous malignancy
- Morbid obesity (BMI >40)

### Each Risk Factor Represents 3 Points
- Age 75 years or more
- Major surgery lasting 2-3 hours*
- BMI > 50 (venous stasis syndrome)
- History of SVT, DVT/PE
- **Family history of DVT/PE**
- Present cancer or chemotherapy
- Positive Factor V Leiden
- Positive Prothrombin 20210A
- Elevated serum homocysteine
- Positive Lupus anticoagulant
- Elevated anticardiolipin antibodies
- Heparin-induced thrombocytopenia (HIT)
- Other thrombophilia
- Type__

*Select only one from the surgery category

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## VTE Risk Factor Assessment

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- Elevated anticardiolipin antibodies
- Heparin-induced thrombocytopenia (HIT)
- Other thrombophilia
- Type

### For Women Only (Each Represents 1 Point)
- Oral contraceptives or hormone replacement therapy
- Pregnancy or postpartum (<1 month)
- History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant

### Each Risk Factor Represents 5 Points
- Elective major lower extremity arthroplasty
- Hip, pelvis or leg fracture (< 1 month)
- Stroke (< 1 month)
- Multiple trauma (< 1 month)
- Acute spinal cord injury (paralysis)(< 1 month)
- Major surgery lasting over 3 hours*

**Total Risk Factor Score**

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### Prophylaxis Safety Considerations: Check box if answer is ‘YES’

#### Anticoagulants: Factors Associated with Increased Bleeding

- Is patient experiencing any active bleeding?
- Does patient have (or has had history of) heparin-induced thrombocytopenia?
- Is patient’s platelet count <100,000/mm³?
- Is patient taking oral anticoagulants, platelet inhibitors (e.g., NSAIDS, Clopidogrel, Salicylates)?
- Is patient’s creatinine clearance abnormal? If yes, please indicate value __________

If any of the above boxes are checked, the patient may not be a candidate for anticoagulant therapy and you should consider alternative prophylactic measures such as IPC or FP.

#### Intermittent Pneumatic Compression (IPC)

- Does patient have severe peripheral arterial disease?
- Does patient have congestive heart failure?
- Does patient have an acute superficial/deep vein thrombosis?

If any of the above boxes are checked, then patient may not be a candidate for intermittent compression therapy and you should consider alternative prophylactic measures. (IVC filter?)

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**REVISED NOVEMBER 5, 2009**

**THIS DOCUMENT IS FOR EDUCATIONAL PURPOSES ONLY AND THE OPINIONS EXPRESSED ARE SOLELY THOSE OF THE AUTHOR.**

**CHEST Guidelines 2012**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Caprini Score</th>
<th>*VTE incidence</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>0</td>
<td>0.5%</td>
<td>Early ambulation</td>
</tr>
<tr>
<td>Low</td>
<td>1-2</td>
<td>1.5%</td>
<td>IPC</td>
</tr>
<tr>
<td>Moderate</td>
<td>3-4</td>
<td>3.0%</td>
<td>LMWH, UFH,IPC</td>
</tr>
<tr>
<td>High</td>
<td>5+</td>
<td>6.0%</td>
<td>LMWH, UFH + IPC or GS</td>
</tr>
</tbody>
</table>

*Estimated baseline risk in the absence of pharmacologic or mechanical prophylaxis*

*Gould, MK et al; CHEST 2012; 141(2) (Suppl):e327S-e227S*
A Validation Study of a Retrospective Venous Thromboembolism Risk Scoring Method

Clinically evident-imaging proven VTE rates at 30 days

“The incidence of VTE increases with Caprini risk assessment model score, and a score of >8 predicts a high risk (>13%) of VTE in postoperative otolaryngology inpatients, despite chemoprophylaxis”

Venous Thromboembolism Risk Assessment Scoring in the Critically Ill: A Validation Study

VTE Incidence Rate by Risk Level

CIDSS Risk Level

VTE Incidence Rate with 95% Confidence Intervals

0 %
3.45 %
5.4 %
8.28 %

Low
Moderate
High
Highest

4,856 patients U. of Michigan ICU (submitted for publication, 2012)
The Correlation between Caprini Score and DVT Rate

All patients had from five to 15 Caprini scores and were divided in three tertiles 5-8 (n=54), 9-11 (n=46) and 12-15 (n=40)

P<0,0001 for trend, chi-squared test
Validation of a Venous Thromboembolism Risk Assessment Model in Gynecologic Oncology

This study included 1,123 gynecologic oncology patients

- The overall incidence of VTE was 3.3%, including 17 DVTs and 20 pulmonary emboli.
- 92% of patients had a score of five or more.

The Caprini RAM accurately predicted all 37 VTEs, all of which scored in the “Highest Risk” category

The percentage of patients that received double prophylaxis increased with time from 12% in 2004 to 63% in 2010. Importantly, 25 of the 37 VTEs (68%) did not receive double prophylaxis.

Of importance, all patients with VTE were within the highest group, and there was a statistically significant difference in the raw Caprini score (8.82 vs. 6.39; p < 0.001).

W. Stroud et al. / Gynecologic Oncology 134 (2014) 160–163
The best U.S. application so far uses the Caprini Score to reduce the incidence of postoperative venous thromboembolism
While the Caprini scoring system has been well validated in terms of its predictive value for VTE, to our knowledge, this is the first study to demonstrate a reduction of VTE events based upon its standardized and required use, in conjunction with a formal mobilization program.
Mandatory Electronic Risk Assessment System and Prophylaxis

- Check box format
- Score automatically calculated
- Mandatory for every patient
- Score must be calculated before completing preop and postop orders
- e-Reminder at discharge
<table>
<thead>
<tr>
<th>Caprini Score</th>
<th>Risk Category</th>
<th>Recommended Prophylaxis</th>
<th>Recommended Duration of Chemoprophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lowest</td>
<td>Early frequent ambulation only, OR At discretion of surgery team: Compression boots OR Low dose heparin OR Low molecular weight heparin</td>
<td>During hospitalization</td>
</tr>
<tr>
<td>1-2</td>
<td>Low</td>
<td>Compression boots OR Low dose heparin OR Low molecular weight heparin (Choose one item)</td>
<td>During hospitalization</td>
</tr>
<tr>
<td>3-4</td>
<td>Moderate</td>
<td>Compression boots AND Low dose heparin OR Low molecular weight heparin (Choose one medication)</td>
<td>During hospitalization</td>
</tr>
<tr>
<td>5-8</td>
<td>High</td>
<td>Compression boots AND Low dose heparin OR Low molecular weight heparin (Choose one medication)</td>
<td>7 – 10 days total</td>
</tr>
<tr>
<td>≥9</td>
<td>Highest</td>
<td>Compression boots AND Low dose heparin OR Low molecular weight heparin (Choose one medication)</td>
<td>30 days total</td>
</tr>
</tbody>
</table>
VTE Prophylaxis Compliance

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Compliance with Recommended Prophylaxis</th>
<th>Contraindication</th>
<th>Surgeon Discretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low - Moderate</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>High</td>
<td>89%</td>
<td>1%</td>
<td>10%</td>
</tr>
<tr>
<td>Highest</td>
<td>77%</td>
<td>23%</td>
<td>0%</td>
</tr>
</tbody>
</table>

No patient received inappropriate or inadequate prophylaxis without electronic documentation. We cannot confirm compliance at home.
The 2005 Caprini Score Predicts Both Baseline VTE Risk and Effectiveness of Chemoprophylaxis: a Meta-Analysis of 13,605 Surgical Patients

1. The 2005 Caprini score predicts post-operative VTE events in surgical patients who do not receive chemoprophylaxis
2. The 2005 Caprini score identifies patients who will and will not benefit from chemoprophylaxis in the peri-operative period
3. There is no association between 2005 Caprini score and risk for peri-operative bleeding when chemoprophylaxis is provided

Christopher Pannucci, MD, Lukasz Swistun, MD, John MacDonal, MA, Ben Brooke, MD, PhD, Peter Henke, MD. Presented at the 28th annual meeting of the American Venous Forum, Orlando, FL; February 26, 2015
Process Measure vs. Outcome Measure
Current VTE Metrics

• Process Measure:
  – SCIP-VTE-2: VTE prophylaxis administration
  – **Problem:** Only measures the 24 hours before and after surgery
    **FLAWED MEASURE**

• Outcome Measure:
  – PSI 12: Risk-adjusted VTE rate after surgery
  – **Problem:** Surveillance bias significantly affects VTE outcome measurement and thus comparison between hospitals is impossible
  – *Venous duplex scanning documents the VTE incidence postoperatively*
  – *The incidence of VTE associated with the process measure is revealed*
  – *If it is high, one can assume the process measure is flawed*
Association between Surgical Care Improvement Program VTE Measures And Postoperative Events

• Study evaluated SCIP-VTE adherence for 30,531 operations from 2006 to 2009 linked with VA Surgical Quality Improvement Program data
• It was noted that 89.9% of the patients adhered to the SCIP-VTE measure and 1.4% suffered a VTE event
• The incidence of VTE events in those not complying with the SCIP-VTE mandate was 1.3%
• The authors concluded that there was no association between SCIP-VTE adherence and the incidence of postoperative VTE

Process Measures vs. Outcome Measures

Process measures should remain central in efforts to measure and improve care

*(THE CURRENT PROCESS MEASURE IS FLAWED)*

- It is known that protecting the patient for the period of time that they are “at risk” lowers the VTE rate
- Making sure that patients receive appropriate anticoagulation *during their entire hospitalization* is a CRITICAL factor in reducing the VTE incidence *(IMPORTANT ISQIC INITIATIVE)*

*Bilimoria, JAMA 2013, 2015*
Anticoagulants need to be given for the entire period of time that the patients are at risk for VTE. That should include the ENTIRE hospitalization at the very least.

The SCIP Measure was envisioned as a first step and did not imply that one dose of anticoagulation was sufficient to prevent VTE during the entire hospitalization.

THIS POINT WAS NEVER MADE CLEAR BY THE AUTHORITIES.
Thrombosis Prophylaxis Following Hospital Discharge
Time Course and Clinical Presentation of Postoperative VTE in RIE TE


55% of VTEs were diagnosed after prophylaxis was discontinued.

<table>
<thead>
<tr>
<th>Days</th>
<th>Clinically overt PE</th>
<th>Distal DVT</th>
<th>Proximal DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>22 (2.8%)</td>
<td>2 (1.1%)</td>
<td>9 (1.4%)</td>
</tr>
<tr>
<td>48 hours</td>
<td>41 (5.2%)</td>
<td>5 (2.78%)</td>
<td>21 (3.3%)</td>
</tr>
<tr>
<td>7 days</td>
<td>149 (19%)</td>
<td>34 (19%)</td>
<td>91 (14%)</td>
</tr>
<tr>
<td>15 days</td>
<td>376 (48%)</td>
<td>98 (54%)</td>
<td>248 (39%)</td>
</tr>
<tr>
<td>30 days</td>
<td>608 (77%)</td>
<td>145 (80%)</td>
<td>432 (68%)</td>
</tr>
<tr>
<td>60 days</td>
<td>787</td>
<td>182</td>
<td>633</td>
</tr>
</tbody>
</table>
**Validated Risk Assessment Studies: Very High-Risk Patients**

<table>
<thead>
<tr>
<th>Population</th>
<th>Caprini Score</th>
<th>VTE incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>General &amp; Vascular Surgery</td>
<td>&gt;8</td>
<td>6.3%*</td>
</tr>
<tr>
<td>Plastic Surgery</td>
<td>&gt;8</td>
<td>11.3%**</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>&gt;8</td>
<td>18.3%*</td>
</tr>
<tr>
<td>ICU Population</td>
<td>&gt;8</td>
<td>8.28%*</td>
</tr>
</tbody>
</table>

* Clinically-Relevant Venous Thromboembolism Rate  * 30 Days  **60 Days

**Extended Prophylaxis Suggested**

Shuman, AG et al. Otolaryngology -- Head and Neck Surgery 2012 146: 719  
4,856 patients U. of Michigan ICU (submitted for publication, 2012)
Risk Assessment for Bleeding
Hemostasis is a *balance* between multiple pro-coagulant and anti-coagulant components.
Rate of Bleeding Complications after Pharmacological DVT Prophylaxis

* Bleeding incidence not trivial

33 RCTs in 33,000 patients

Death From PE but not Death From Bleeding

Evenly randomized trials of perioperative s.c. heparin in general, orthopaedic and urological surgery

<table>
<thead>
<tr>
<th></th>
<th>PE</th>
<th>Fatal bleeds</th>
<th>“Other” deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>109 (1.7)</td>
<td>19 (0.3)</td>
<td>210 (3.3)</td>
</tr>
<tr>
<td>C</td>
<td>191 (3)</td>
<td>55 (0.9)</td>
<td>223 (3.5)</td>
</tr>
</tbody>
</table>

Number of subjects affected, n (%)

Heparin (H), n = 6,386
Control (C), n = 6,246

# Fatal Pulmonary Embolism in Surgical Patients

Randomized double-blind comparison of LMWH with UFH, involving 23,078 surgical patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LMWH (N = 11,542)</th>
<th>UFH (N = 11,536)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>PE (at autopsy)</td>
<td>22 (0.191)</td>
<td>22 (0.191)</td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>17 (0.147)</td>
<td>18 (0.156)</td>
<td>0.87</td>
</tr>
<tr>
<td>Non-fatal</td>
<td>5 (0.043)</td>
<td>4 (0.035)</td>
<td>1</td>
</tr>
</tbody>
</table>

Anticoagulant prophylaxis reduces the risk of death to 0.15%

No deaths from anticoagulant bleeding occurred in this large series

The New Oral Anticoagulants
To Do

• Greater physician education regarding the nuances of each compound
• To bridge or not to bridge; when?
• Appropriate testing for clinical scenarios as outlined by ISTH and suggested by the FDA using specific assays
• Proper use of antidotes under development; how to prevent rebound thrombosis is a must!
• How to maintain patient compliance; quarterly visits?
• Understand when not to prescribe one of these drugs
Conclusions

• There are many faces of VTE
• VTE is associated with 300,000 deaths yearly in the U.S.
• Postoperative anticoagulant prophylaxis saves lives from fatal PE while fatal bleeding events are rare
• The Boston program of Caprini Score-driven mandated prophylaxis is a method to reduce the VTE incidence at 30 days to an absolute minimum
Conclusions

• The new anticoagulants are a great step forward in the prophylaxis and treatment of VTE

• Widespread use of these amazing new drugs await:
  – Further clinical experience and results with the newly approved antidotes
  – Availability of appropriate tests to monitor these drugs in special situations
  – Establishing clinics for periodic monitoring of the patients, at least quarterly, to evaluate compliance and adjust care according to changing medical issues
Yellowstone Park
Questions