Disclosures

A. Tafur

• I have the following relationships to disclose:
  Consultant for: VTE TAP.- The Joint Commission; Recovery Force
  Speaker’s Bureau for: None
  Grant/Research support from: Janssen, BMS, Daiichi Sankyo, Idorsia, Stago
  Stockholder in: None
  Honoraria from: None
  Employee of: NSUHS

• I will discuss the following off label use and/or investigational use in my presentation.
  Direct oral anticoagulants for primary prevention of medically ill patients
Prophylaxis in the Medically Ill Patient

Alfonso J. Tafur MD MS RPVI FSVM FIUA FACC
Medical Director: Cardiovascular Research, Vascular Medicine, and Anticoagulation Clinics
Cardiovascular Section - Department of Medicine
Northshore University HealthSystem
@ClotAwareSptGrp
VTE = More deaths and disability than Nosocomial pneumonia, Catheter related bloodstream infections, or adverse drug events in low-and-middle income countries.

In 2010, NHS England mandated reporting of risk of VTE with a target of 90% of adult admissions (increased later to 95%)

15.4% reduction in deaths within 90 days after discharge

NHS England. VTE risk assessment 2016/17
Inclusion Guidelines for Abstraction:
Explicit documentation that the patient does not need VTE prophylaxis

ALL INCLUSIVE VALIDATED RISK ASSESSMENTS:
- Caprini DVT Risk Assessment
- Padua Prediction Score
- International Medical Prevention Registry on Venous Thromboembolism (IMPROVE)

LOW RISK SCORES:
- Caprini score of 0 (zero) – no need for prophylaxis
- IMPROVE score of 0 (zero) or 1 (one), or a probability of less than 1.5%
- Padua score of less than 4 (0-3)

Refer to Appendix H, Table 2.7 Anticoagulation Therapy

Exclusion Guidelines for Abstraction:
Risk Assessment tools other than Caprini, Padua, and IMPROVE

Page 139 of the manual....
1. Compulsory Venous Thromboembolism risk assessment upon admission leveraging on EMR for facilitation.

2. Risk based prevention plan

<table>
<thead>
<tr>
<th>Caprini Risk</th>
<th>Action plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 5</td>
<td>Ambulation</td>
</tr>
<tr>
<td></td>
<td>Upgrade if change of status</td>
</tr>
<tr>
<td>5 to 8</td>
<td>Pharmacoprophylaxis during hospitalization</td>
</tr>
<tr>
<td></td>
<td>* Enoxaparin 40 mg subcutaneous once daily</td>
</tr>
<tr>
<td></td>
<td>* LDUH 5000 TID subcutaneous</td>
</tr>
<tr>
<td></td>
<td>IPC if high bleed risk or contraindication.</td>
</tr>
<tr>
<td></td>
<td>*entry needed for reason to avoid pharmacoprophylaxis</td>
</tr>
<tr>
<td>More than 8</td>
<td>IPC while hospitalized.</td>
</tr>
<tr>
<td></td>
<td>* Pharmacoprophylaxis during risk period</td>
</tr>
<tr>
<td></td>
<td>* Enoxaparin 40 mg subcutaneous once daily</td>
</tr>
<tr>
<td></td>
<td>* LDUH 5000 TID subcutaneous</td>
</tr>
<tr>
<td></td>
<td>- Extend prophylaxis to a minimum of 7 days</td>
</tr>
<tr>
<td></td>
<td>- Consider extended prophylaxis of 6 weeks in highest risk individuals (&gt;10 score) especially those with prior history of thrombosis.</td>
</tr>
<tr>
<td></td>
<td>IPC only if high bleed risk or contraindication.</td>
</tr>
<tr>
<td></td>
<td>*entry needed for reason to avoid chemoprevention</td>
</tr>
</tbody>
</table>

^Obesity and creatinine clearance alerts pre populated for pharmacoprophylaxis.

3. Design best practice alerts to integrate automatically via Electronic Medical Records and updated risk in the Discharge summary.

4. Internal coding to monitor 3 mo Thromboembolism rate and Thrombosis/Bleed related hospitalization to modify risk-based practice in specific populations.
WHY
   It is a Winnable battle

HOW
   Risk-Based Prevention

WHAT
   A historical review of pharmacoprophylaxis
   Mechanical prevention, data evolution
WHAT
A historical review of pharmacoprophylaxis

MEDENOX
Samama et al
N Engl J Med 1999

2000

2005

2010

2015

2020

ARTEMIS
Cohen et al
BMJ 2006
WHAT
A historical review of pharmacoprophylaxis

MEDENOX
Samama et al
N Engl J Med 1999
2000

EXCLAIM
Hull, et al
J Thromb Thrombolysis 2006
2005

MAGELLAN
Cohen et al.
N Engl J Med 2013
2010

APEX
Cohen et al.
2015

ARTEMIS
Cohen et al
BMJ 2006

ADOPT
Goldhaber et al.

MARINER
Spyropoulos et al.
N Engl J Med 2018
2020
EXCLAIM
Hull, et al
J Thromb Thrombolysis 2006
- Enoxaparin 40mg 7d
  VTE 2.5% vs 4% (Superior)
  Increased major bleeding (0.8% vs 0.3%)
- Enoxaparin 40mg 21d
  
MAGELLAN
Cohen et al.
N Engl J Med 2013
- Enoxaparin 40mg 7d
  VTE 4.4% vs 5.7% (Superior)
  Increased major bleeding (4.1% vs 1.7%)
- Rivaroxaban 10mg 35d
  
ADOPT
Goldhaber et al.
- Enoxaparin 40mg 7d
  VTE 2.7% vs 3% (NOT Superior)
  Increased major bleeding (0.5% vs 0.2%)
- Apixaban 2.5mg BID 35d
  
Discharge
WHAT
A historical review of pharmacoprophylaxis
WHO?

40 years of age or older

Hospitalized for less than 96 hours
  (heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke)

Reduced mobility

Risk factors for venous thromboembolism.

+ Elevated d-dimer level OR age 75

WHAT?

Enoxaparin 40 mg 10±4 days + oral betrixaban placebo

Enoxaparin placebo 10±4 days plus oral betrixaban
  (160 mg for the first dose
  80 mg once daily for 35 to 42 days).

Enoxaparin 40mg 10 ±4 d

Betrixaban 160/ 80mg 35 - 42d
Primary Outcome

Asymptomatic proximal DVT
Symptomatic DVT
Symptomatic PE
VTE Death

GLOBAL
Betrixaban 5.3% vs Enoxaparin 7.0%
RR 0.76 (0.63 – 0.92)
P 0.006
NNT 59

COHORT1
6.9% vs 8.5%

COHORT2
5.6% vs 7.1%
Primary Outcome

Asymptomatic proximal DVT
Symptomatic DVT
Symptomatic PE
VTE Death

GLOBAL
Betrixaban 5.3 % vs Enoxaparin 7.0%
RR 0.76 (0.63 – 0.92)
P 0.006
NNT 59

COHORT1
6.9% vs 8.5%

COHORT2
5.6% vs 7.1%

SYMPTOMATIC
0.9 vs 1.5 (RR 0.64; 0.42 – 0.98)
### APEX
Cohen et al.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Betrixaban</th>
<th>Enoxaparin</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principal safety outcome in cohort 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>15/2311 (0.6)</td>
<td>17/2310 (0.7)</td>
<td>0.88 (0.44–1.76)</td>
<td>0.72</td>
</tr>
<tr>
<td>Decrease in hemoglobin of ≥2 g/dl</td>
<td>9</td>
<td>6</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Transfusion of ≥2 units of blood</td>
<td>10</td>
<td>9</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Critical-site bleeding</td>
<td>1</td>
<td>7</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0</td>
<td>1</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Major or clinically relevant nonmajor bleeding</td>
<td>72/2311 (3.1)</td>
<td>44/2310 (1.9)</td>
<td>1.64 (1.13–2.37)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

- **Enoxaparin 40mg**: 10 ±4 d
- **Betrixaban 160/ 80mg**: 35 - 42d
**WHO?**

40 y-old or more

Hospitalized 3-10 d
- heart failure, acute respiratory insufficiency or exacerbation
- COPD, ischemic stroke, or acute infectious or inflammatory disease

Risk factors for venous thromboembolism

**IMPROVE** risk score of 4 or higher

OR

2 – 3 AND d-dimer x2 ULN

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior venous thromboembolism</td>
<td>3</td>
</tr>
<tr>
<td>Diagnosed thrombophilia</td>
<td>2</td>
</tr>
<tr>
<td>Current lower-limb paralysis</td>
<td>2</td>
</tr>
<tr>
<td>Current cancer</td>
<td>2</td>
</tr>
<tr>
<td>Immobilized for at least 7 days</td>
<td>1</td>
</tr>
<tr>
<td>Stay in the ICU or coronary care unit</td>
<td>1</td>
</tr>
<tr>
<td>More than 60 years old</td>
<td>1</td>
</tr>
</tbody>
</table>

**WHAT?**

- Enoxaparin 40 mg daily during hospitalizations
  - OR
  - Rivaroxaban 10 mg once daily (CrCl30-50=7.5mg) 45d

- Enoxaparin 40mg 7±4 d

- Xarelto 10mg 45d
Primary Outcome

Asymptomatic proximal DVT
Symptomatic DVT
Symptomatic PE
VTE Death

GLOBAL
Rivaroxaban 0.83% vs Enoxaparin 1.1%
HR 0.76 (0.52–1.09)

NNT

VTE ONLY
HR 0.44 (95% CI, 0.22–0.89)
Primary Outcome

Asymptomatic proximal DVT
Symptomatic DVT
Symptomatic PE
VTE Death

GLOBAL
Rivaroxaban 0.83 % vs Enoxaparin 1.1%
HR 0.76 (0.52–1.09)
NNT 370

VTE ONLY
HR 0.44 (95% CI, 0.22–0.89)
### Safety outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Enoxaparin 40mg (10 mg)</th>
<th>Xarelto 10mg (10 mg)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal safety outcome: major bleeding</td>
<td>17/5982 (0.28)</td>
<td>9/5980 (0.15)</td>
<td>1.88 (0.84–4.23)</td>
</tr>
<tr>
<td>Creatinine clearance ≥50 ml/min, 10-mg dose</td>
<td>13/4890 (0.27)</td>
<td>9/4890 (0.18)</td>
<td>1.44 (0.62–3.37)</td>
</tr>
<tr>
<td>Creatinine clearance 30 to &lt;50 ml/min, 7.5-mg dose</td>
<td>4/1092 (0.37)</td>
<td>0/1090</td>
<td>—</td>
</tr>
<tr>
<td>Criteria for major bleeding§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decrease ≥2 g/dl</td>
<td>14/5982 (0.23)</td>
<td>6/5980 (0.10)</td>
<td>2.33 (0.89–6.05)</td>
</tr>
<tr>
<td>Transfusion of ≥2 units of packed red cells</td>
<td>11/5982 (0.18)</td>
<td>3/5980 (0.05)</td>
<td>3.66 (1.02–13.10)</td>
</tr>
<tr>
<td>Critical site</td>
<td>3/5982 (0.05)</td>
<td>2/5980 (0.03)</td>
<td>1.50 (0.25–8.97)</td>
</tr>
<tr>
<td>Fatal</td>
<td>2/5982 (0.03)</td>
<td>0/5980</td>
<td>—</td>
</tr>
<tr>
<td>Nonmajor clinically relevant bleeding</td>
<td>85/5982 (1.42)</td>
<td>51/5980 (0.85)</td>
<td>1.66 (1.17–2.35)</td>
</tr>
<tr>
<td>Other bleeding</td>
<td>54/5982 (0.90)</td>
<td>34/5980 (0.57)</td>
<td>1.59 (1.03–2.44)</td>
</tr>
</tbody>
</table>

### Risk factor

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior venous thromboembolism</td>
<td>3</td>
</tr>
<tr>
<td>Diagnosed thrombophilia</td>
<td>2</td>
</tr>
<tr>
<td>Current lower-limb paralysis</td>
<td>2</td>
</tr>
<tr>
<td>Current cancer</td>
<td>2</td>
</tr>
<tr>
<td>Immobilized for at least 7 days</td>
<td>1</td>
</tr>
<tr>
<td>Stay in the ICU or coronary care unit</td>
<td>1</td>
</tr>
<tr>
<td>More than 60 years old</td>
<td>1</td>
</tr>
</tbody>
</table>

**NorthShore University Health System**
knowledge accumulation curve

waves of innovations

development

time
WHAT

Mechanical prevention, data evolution

American College of Physicians recommended “against the use of mechanical prophylaxis with graduated compression stockings for prevention of venous thromboembolism”

<table>
<thead>
<tr>
<th>CLOTS 1 TRIAL</th>
<th>CLOTS 2 TRIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lancet 2009</td>
<td>Ann Intern Med. 2010</td>
</tr>
<tr>
<td>Acute Stroke Patients</td>
<td>Acute Stroke Patients</td>
</tr>
<tr>
<td>2518 patients</td>
<td>1552 thigh-length stockings</td>
</tr>
<tr>
<td>Routine care + thigh-length GCS</td>
<td>1562 below-knee stockings</td>
</tr>
<tr>
<td>Routine care alone.</td>
<td>VTE</td>
</tr>
<tr>
<td>VTE:</td>
<td>98 patients (6.3%) thigh-length stockings</td>
</tr>
<tr>
<td>126 (10.0%) patients allocated to thigh-length GCS</td>
<td>138 patients (8.8%) below-knee stockings</td>
</tr>
<tr>
<td>133 (10.5%) allocated to avoid GCS</td>
<td>Diff 2.5% [95% CI, 0.7 to 4.4 percentage points]; P &lt; 0.01</td>
</tr>
<tr>
<td>ARR 0.5% (95% CI –1.9% to 2.9%).</td>
<td></td>
</tr>
</tbody>
</table>
WHAT
Mechanical prevention, data evolution

American College of Physicians recommended “against the use of mechanical prophylaxis with graduated compression stockings for prevention of venous thromboembolism”

CLOTS 3 TRIAL
Lancet 2013
IPC in immobile patients with acute stroke
2876 patients in 94 centers in UK.

VTE
122 (8.5%) of 1438 patients allocated IPC
174 (12.1%) of 1438 patients allocated no IPC

Absolute reduction in risk of 3.6% (95% CI 1.4–5.8).

Deaths
156 (11%) patients allocated IPC
189 (13%) patients allocated no IPC

(pre=0.057)

PREVENT
N Engl J Med 2019

Adults within 48 hours after ICU
IPC + Pharmacoprophylaxis vs Pharmacoprophylaxis alone

PROX DVT:
37 of 957 patients (3.9%) in IPC
41 of 985 patients (4.2%) in NO IPC
RR 0.93; 95% CI 0.60 to 1.44; P=0.74.

VTE any
103 of 991 patients (10.4%) in IPC
95 of 1012 patients (9.4%) in NO IPC
RR 1.11; 95% CI, 0.85 to 1.44
We are 2020 ready to implement VTE prevention.
Medically-ill patient VTE-prevention Plan

1.- Compulsory Venous Thromboembolism risk assessment upon admission leveraging on EMR for facilitation.

2.- Risk based prevention plan

<table>
<thead>
<tr>
<th>Caprini Risk</th>
<th>Action plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 5</td>
<td>Ambulation</td>
</tr>
<tr>
<td></td>
<td>Upgrade if change of status</td>
</tr>
<tr>
<td>5 to 8</td>
<td>Pharmacoprophylaxis during hospitalization</td>
</tr>
<tr>
<td></td>
<td>- Enoxaparin 40 mg subcutaneous once daily</td>
</tr>
<tr>
<td></td>
<td>- LDHU 5000 TID subcutaneous</td>
</tr>
<tr>
<td></td>
<td>IPC if high bleed risk or contraindication.</td>
</tr>
<tr>
<td></td>
<td>*entry needed for reason to avoid pharmacoprophylaxis</td>
</tr>
<tr>
<td>More than 8</td>
<td>Pharmacoprophylaxis during risk period</td>
</tr>
<tr>
<td></td>
<td>- Enoxaparin 40 mg subcutaneous once daily</td>
</tr>
<tr>
<td></td>
<td>- LDHU 5000 TID subcutaneous</td>
</tr>
<tr>
<td></td>
<td>*extend prophylaxis to a minimum of 7 days</td>
</tr>
<tr>
<td></td>
<td>*extend prophylaxis of 6 weeks in highest risk individuals (&gt;10 score) especially those with prior history of thrombosis.</td>
</tr>
<tr>
<td></td>
<td>IPC only if high bleed risk or contraindication.</td>
</tr>
<tr>
<td></td>
<td>*entry needed for reason to avoid chemoprevention</td>
</tr>
</tbody>
</table>

^Obesity and creatinine clearance alerts pre populated for pharmacoprophylaxis.

3.- Design best practice alerts to integrate automatically via Electronic Medical Records and updated risk in the Discharge summary.

4.- Internal coding to monitor 3 mo Thromboembolism rate and Thrombosis/Bleed related hospitalization to modify risk-based practice in specific populations.