BETRIXABAN

Pulling out New (Trix):
Extended Thromboprophylaxis For Venous Thromboembolism

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OBJECTIVES

<table>
<thead>
<tr>
<th>Define</th>
<th>Define venous thromboembolism and extended thromboprophylaxis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyze</td>
<td>Analyze current guideline recommendations and literature for extended thromboprophylaxis.</td>
</tr>
<tr>
<td>Review</td>
<td>Review the trial behind the FDA approval for betrixaban.</td>
</tr>
<tr>
<td>Anticipate</td>
<td>Anticipate the place in therapy for betrixaban and extended thromboprophylaxis.</td>
</tr>
</tbody>
</table>
Objective 1

Define venous thromboembolism and extended thromboprophylaxis.

BACKGROUND

DVT + PE = VTE

Pain, erythema, tenderness, swelling of the lower extremity

Dyspnea, tachyypnea, chest pain, tachycardia

**BACKGROUND**

- VTE is the *third most common* cardiovascular illness
- PE is the *third most common* cause of hospital-related death
- Infection, age > 75, cancer, and a history of VTE are factors most associated with an *increased VTE risk*
- Only 1/3 of all hospitalized patients at risk receive adequate **prophylaxis**

http://www.clevelandclinicmeded.com/medpubs/diseasemanagement/cardiology/venous-thromboembolism/

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**BACKGROUND**

![Virchow's Triad Diagram]

- **Circulatory Stasis**
  - Bed rest
  - Travel
  - Immobilization
  - Obesity
  - Limb paralysis

- **Virchow’s Triad**
  - **Endothelial injury**
  - **Hyper-coagulable state**

- **Trauma**
  - Surgery
  - Catheters
  - Smoking

- **Malignancy**
  - Trauma
  - Pregnancy
  - Factor V Leiden
  - Estrogen

PADUA SCORE

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>3</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>3</td>
</tr>
<tr>
<td>Reduced mobility</td>
<td>3</td>
</tr>
<tr>
<td>Already known thrombophilic condition</td>
<td>3</td>
</tr>
<tr>
<td>Recent trauma and/or surgery</td>
<td>2</td>
</tr>
<tr>
<td>Elderly age</td>
<td>1</td>
</tr>
<tr>
<td>Heart and/or respiratory failure</td>
<td>1</td>
</tr>
<tr>
<td>Acute MI or ischemic stroke</td>
<td>1</td>
</tr>
<tr>
<td>Acute infection and/or rheumatologic disorder</td>
<td>1</td>
</tr>
<tr>
<td>Obesity</td>
<td>1</td>
</tr>
<tr>
<td>Ongoing hormonal treatment</td>
<td>1</td>
</tr>
</tbody>
</table>

< 4: Low risk of VTE

> 4: High risk of VTE
Thromboprophylaxis recommended


CURRENT PROPHYLACTIC THERAPIES
HOSPITALIZED MEDICAL PATIENTS

<table>
<thead>
<tr>
<th>Dosing</th>
<th>LMWH</th>
<th>UFH</th>
<th>Factor Xa Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acutely ill hospitalized medical patients</td>
<td>Enoxaparin</td>
<td>Heparin</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>40 mg subcutaneously daily</td>
<td>5000 units subcutaneously Q 8-12H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &lt; 30: 30 mg daily</td>
<td>≥ 50 kg: 2.5 mg PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50 kg: contraindicated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anticoagulants and their targets

**VKA**: inhibit synthesis of Factors II, VII, IX, X

**Heparins**: Inhibit Factor Xa and thrombin indirectly through antithrombin

**Rivaroxaban, apixaban, and edoxaban**: directly inhibit Factor Xa

**Dabigatran**: directly inhibits thrombin

BACKGROUND

- Hospitalized medical patients may have risk factors for VTE that persist for months after discharge
- Studies show that incidence of VTE is highest during days 0-19 and extended up to at least 30 days
- Peak VTE at day 8

More than half of VTE events occur after discharge.

PE is a 68 year old female who has been hospitalized for a heart failure exacerbation 4 days ago. She has been unable to get around very much due to feeling very weak and out of breath. She has no previous history of VTE.

- **Vitals**
  - Height: 5'4"
  - Weight: 194 lbs
  - BP: 164/130
  - HR: 88
  - Temp: 98.7F

- **PMH**
  - Cancer (2014, in remission since 2016)
  - Heart Failure (2003)

- **Medications**
  - Estradiol 1 mg by mouth once daily
  - Metoprolol succinate 100 mg by mouth once daily

**BMI** = 33.3

**Padua Score** = 6

Recommend VTE Prophylaxis

**Extended Thromboprophylaxis**
Extended-duration thromboprophylaxis refers to prophylaxis that is continued beyond the initial (e.g. 5-14 days) course, for up to approximately 35 days total.


Objective 2

Analyze current guideline recommendations and literature for extended thromboprophylaxis.
In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of immobilization or acute hospital stay. (Grade 2B)

**EXCLAIM Trial**

Extended Prophylaxis for Venous Thromboembolism in Acutely Ill Medical Patients with Prolonged Immobilization


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**EXCLAIM TRIAL**

- **Background**
  - Studies have not assessed the efficacy and safety of extended duration prophylaxis in acutely ill medical patients

- **Hypothesis**
  - An extended duration enoxaparin regimen similar to that evaluated in patients undergoing elective hip arthroplasty would be beneficial for acutely ill medical patients at high risk for VTE

**EXCLAIM - METHODS**

**Inclusion Criteria**
- > 40 years old
- Acute medical illness
- Life expectancy at least 6 months
- Recently reduced mobility for up to 3 days
- Reduced mobility for at least 3 days after enrollment

**Exclusion Criteria**
- Evidence of bleeding disorder
- Major surgery within previous 3 months
- Lumbar puncture within preceding 24 hours
- Previous episode of HIT
- Persistent renal failure


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**EXCLAIM - METHODS**

**Level 1**
- Reduced mobility requiring total bed rest or sedentary **WITHOUT** bathroom privileges

**Level 2**
- Reduced mobility requiring total bed rest or sedentary **WITH** bathroom privileges

EXCLAIM - METHODS

Enoxaparin group
- Enoxaparin 40 mg/day 10 days
- Enoxaparin 40 mg/day Additional 28 days

Placebo group
- Enoxaparin 40 mg/day 10 days
- Placebo Additional 28 days

EXCLAIM - EFFICACY OUTCOMES

Primary
- VTE Composite
  - Symptomatic or asymptomatic proximal DVT
- Symptomatic PE
- Fatal PE

Secondary
- VTE through 3 months
- Mortality
  - 1 month
  - 3 months
  - 6 months

EXCLAIM - SAFETY OUTCOMES

Primary
- Incidence of major hemorrhagic complications
- Up to 48 hours after treatment period

Secondary
- Incidence of major and minor hemorrhagic complications
- Serious adverse events
- Thrombocytopenia

EXCLAIM - RESULTS

- Lower than assumed VTE rates with no statistically significant difference between treatment groups
- Statistically significant increase in major hemorrhages in the enoxaparin versus placebo group

Recommendation for study as designed to be terminated

**EXCLAIM - RESULTS**

- Event rates in patients with level 1 immobility and other risk factors *consistent with study design assumptions*
- Protocol amendment changed eligibility criteria to require patients with level 2 immobility to also have 1 or more risk factors

- **Age > 75**
- **Previous VTE**
- **Active or previous cancer**


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**EXCLAIM - METHODS**

**Level 1**
- Reduced mobility requiring total bed rest or sedentary **WITHOUT** bathroom privileges

**Level 2**
- Reduced mobility requiring total bed rest or sedentary **WITH** bathroom privileges
  - **Age > 75** and/or
  - **Previous VTE** and/or
  - **Active or previous cancer**

**EXCLAIM - RESULTS**

<table>
<thead>
<tr>
<th>Percentage of events (%)</th>
<th>Enoxaparin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE at 28 days</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-1.53 (-2.54 to -0.52)</td>
<td>0.51 (0.12 to 0.89)</td>
</tr>
<tr>
<td>Major bleeding at 30 days</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>


**EXCLAIM - AUTHOR CONCLUSIONS**

- **Extended-duration enoxaparin prophylaxis was associated with a reduction in VTE**

- **Major bleeding events were similar** to those seen in previous studies of short-term VTE prophylaxis in medical patients
EXCLAIM - PRESENTER CONCLUSIONS

Strengths

- Identified population to benefit from extended prophylaxis
- First RCT to study extended prophylaxis in acutely medical ill population

Limitations

- Few data available on population that would benefit the most
- Shift in eligibility during trial
- Not generalizable to entire population


QUESTION

At what point in time after hospitalization for a medical illness is a DVT most likely to occur?

A. A DVT is most likely to occur in the first 3 days
B. A DVT is most likely to occur in the first 7 days
C. A DVT is most likely to occur in the first 30 days
D. A DVT is most likely to occur in the first 60 days
Extended Thromboprophylaxis in Oral Agents

ADOPT Trial

Apixaban versus Enoxaparin for Thromboprophylaxis in Medically Ill Patients

ADOPT TRIAL

- **Background**
  - Efficacy and safety of prolonging prophylaxis for VTE in medically ill patients beyond hospital discharge remains uncertain

- **Hypothesis**
  - Extended prophylaxis with apixaban would be safe and more effective than short-term prophylaxis with enoxaparin

ADOPT - METHODS

- **Enoxaparin group**
  - Enoxaparin 40 mg/day
    - 6-14 days
  - Placebo
    - 30 days

- **Apixaban group**
  - Placebo
    - 6-14 days
  - Apixaban 2.5 mg BID
    - 30 days

ADOPT - RESULTS

VTE at 30 days

Percentage of events (%)

0 0.5 1 1.5 2 2.5 3 3.5

2.71 3.06

95% CI: 0.87 (0.62 to 1.23)
P = 0.44

Major bleeding

Percentage of events (%)

0 0.05 0.1 0.15 0.2 0.25 0.3 0.35 0.4 0.45 0.5

0.47

95% CI: 2.58 (1.02 to 7.24)
P = 0.04


ADOPT - AUTHOR CONCLUSIONS

- **Author**
  - In medically ill patients, an extended course of thromboprophylaxis with apixaban was not superior to a shorter course with enoxaparin
  - Apixaban was associated with significantly more major bleeding events than enoxaparin
  - More studies needed to identify a narrow spectrum of medically ill patients who may benefit from extended thromboprophylaxis

ADOPT - PRESENTER CONCLUSIONS

Strengths
- Large, broad population
- Demonstrated promise for use of extended thromboprophylaxis
- Overall low rates of major bleeding

Limitations
- Underpowered study
- Screening not applicable to typical population
- Comparator not typical to standard care


MAGELLAN Trial

Rivaroxaban for Thromboprophylaxis in Acutely Ill Medical Patients

Background

The clinically appropriate duration of thromboprophylaxis in hospitalized patients with acute medical illness is unknown.

Goal

Assess efficacy and safety of rivaroxaban administered for 35 days, as compared with enoxaparin administered for 10 days and followed by placebo.


MAGELLAN - METHODS

Enoxaparin group

- Enoxaparin 40 mg/day 6-14 days
- Placebo 35 days

Rivaroxaban group

- Placebo 6-14 days
- Rivaroxaban 10 mg 35 days

MAGELLAN - RESULTS

![Graph showing VTE and major bleeding rates for rivaroxaban and enoxaparin.]


MAGELLAN - AUTHOR CONCLUSIONS

- In acutely ill medical patients, rivaroxaban was superior to enoxaparin for extended duration thromboprophylaxis.
- Frequency of VTE was 3.5 times greater in patients with high D-dimer concentrations.
- Rivaroxaban was associated with an increased risk of clinically relevant bleeding.

MAGELLAN - PRESENTER CONCLUSIONS

Strengths
- Superiority trial
- Demonstrated promise for the use of extended thromboprophylaxis
- Identified high-risk patient populations

Limitations
- Screening not applicable to typical population
- Comparator not typical to standard care


QUESTION

Which of the below statement(s) is/are true about the ADOPT and MAGELLAN trials? (select all)

A. Both apixaban and rivaroxaban demonstrated superiority against enoxaparin in regards to percentage of VTE events
B. Both apixaban and rivaroxaban demonstrated an increased risk of bleeding when compared to enoxaparin
C. Both apixaban and rivaroxaban demonstrated a numerical reduction in VTE events when compared to enoxaparin
D. Neither apixaban or rivaroxaban demonstrated promise in the use of extended thromboprophylaxis
## TRIAL CONCLUSIONS

<table>
<thead>
<tr>
<th>Population</th>
<th>EXCLAIM Trial</th>
<th>ADOPT Trial</th>
<th>MAGELLAN Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin versus placebo</td>
<td>Apixaban versus enoxaparin</td>
<td>Rivaroxaban versus enoxaparin</td>
<td></td>
</tr>
<tr>
<td>VTE Outcome</td>
<td>Enoxaparin demonstrated less VTE in high risk patient groups</td>
<td>Apixaban did not meet superiority</td>
<td>Rivaroxaban met superiority</td>
</tr>
<tr>
<td>Bleeding Outcome</td>
<td>Enoxaparin demonstrated increased bleeding</td>
<td>Apixaban demonstrated increased bleeding</td>
<td>Rivaroxaban demonstrated increased bleeding</td>
</tr>
</tbody>
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**Betrixaban’s Place in Therapy**

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Objective 3

Review the trial behind the FDA approval for betrixaban.

BETRIXABAN

- **Indication**
  - Extended thromboprophylaxis in acute medically ill patients

- **Mechanism of Action**
  - Factor Xa inhibitor

- **Cost**
  - 100 40 mg capsules: $1,800
  - 100 80 mg capsules: $1,800

http://www.bevyxxa.com/
BETRIXABAN

■ Dosing
  ■ 160 mg x 1, then 80 mg daily x 35-42 days

■ Dose Adjustments
  ■ CrCl 15-30 ml/min OR P-gp inhibitor use
    ■ 80 mg x 1, then 40 mg x 35-42 days
  ■ Not recommended in renal impairment AND P-gp inhibitor use
  ■ Not recommended in hepatic impairment
  ■ Not recommended if CrCl < 15 ml/min


QUESTION

PE is a 68 year old female who is indicated to receive thromboprophylaxis following hospitalization for her acute medical illness and her doctor opts for extended thromboprophylaxis after hearing about a new drug, Bevyxxa®. Her renal function is normal and she is not on any medications that may interfere with Bevyxxa® such as a P-gp inhibitor or a blood thinner. Which of the following doses is appropriate for PE?

A. 180 mg as a single dose on day 1, followed by 90 mg once daily for 35 to 42 days

B. 160 mg as a single dose on day 1, followed by 80 mg once daily for 35 to 42 days

C. 80 mg as a single dose on day 1, followed by 40 mg once daily for 35 to 42 days

D. 60 mg as a single dose on day 1, followed by 30 mg once daily for 35 to 42 days
APEX Trial

Acute Medically Ill Venous Thromboembolism Prevention with Extended Duration Betrixaban


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APEX TRIAL

- **Background**
  - EXCLAIM, ADOPT, and MAGELLAN did not identify an effective AND safe treatment option for extended thromboprophylaxis
  - Randomized, double-blind, double-dummy, active-controlled, multinational clinical trial
  - Sponsored by Portola Pharmaceuticals

APEX - METHODS

Enoxaparin group
- Enoxaparin 40 mg/day
- 6-14 days
- Placebo 35-42 days

Betrixaban group
- Placebo 6-14 days
- Betrixaban 35-42 days

APEX - STUDY POPULATION

Inclusion
- > 40 years old
- Hospitalized < 96 hours
- Acute medical illness
- Reduced mobility
- Specific risk factors for VTE

Exclusion
- Increased bleeding risk
- Anticipated need for prolonged anticoagulation
- Pregnancy or breastfeeding
- Severe renal insufficiency AND P-gp inhibitor use

APEX – STUDY POPULATION

Cohort 1
D-dimer ≥ 2x ULN

Cohort 2
D-dimer ≥ 2x ULN
and/or
age ≥ 75 years

Overall Population
Initial 35% + Cohort 1 + Cohort 2


APEX – STUDY POPULATION

8,589 patients screened
(460 sites + 35 countries)

7,513 patients eligible

3,759 patients randomized to betrixaban
1,914 patients in cohort 1
2,842 patients in cohort 2

3,754 patients randomized to enoxaparin
1,956 patients in cohort 1
2,893 patients in cohort 2

APEX - BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Betrixaban (n=3759)</th>
<th>Enoxaparin (n=3754)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>76.6</td>
<td>76.2</td>
</tr>
<tr>
<td>Male sex</td>
<td>45.4</td>
<td>45.8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79.84</td>
<td>80.74</td>
</tr>
<tr>
<td>Median no. of days of hospitalization</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Concomitant P-gp use, %</td>
<td>18.0</td>
<td>17.3</td>
</tr>
<tr>
<td>Level of D-dimer &gt; 2x ULN, %</td>
<td>62.3</td>
<td>62.1</td>
</tr>
<tr>
<td>History of cancer, %</td>
<td>12.4</td>
<td>11.8</td>
</tr>
<tr>
<td>History of VTE, %</td>
<td>8.3</td>
<td>7.9</td>
</tr>
<tr>
<td>Age &gt; 75, %</td>
<td>68.5</td>
<td>67.0</td>
</tr>
</tbody>
</table>


APEX - EFFICACY OUTCOMES

Primary
- Composite
  - Asymptomatic proximal DVT day 32-47
  - Symptomatic proximal or distal DVT
  - Symptomatic nonfatal PE
  - Death from VTE day 1-42

Secondary
- Composite
  - Symptomatic VTE through day 42
- Composite
  - Asymptomatic proximal DVT day 32-47
  - Symptomatic DVT
  - Nonfatal PE
  - Death from any cause day 1-42

APEX - SAFETY OUTCOMES

**Primary**

- Occurrence of major bleeding at any point until 7 days after discontinuation
- Bleeding events classified according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH)


APEX - RESULTS

APEX – AUTHOR CONCLUSIONS

- No significant difference between extended-duration betrixaban and a standard regimen of enoxaparin in the prespecified primary efficacy outcome among patients with elevated D-dimer

- Prespecified exploratory analyses provided evidence suggesting a benefit for betrixaban in the two larger cohorts


APEX – PRESENTER CONCLUSIONS

Strengths

- Superiority trial
- Lower frequency of bleeding compared to other trials
- Numerical reduction in VTE across all cohorts
- Large population size

Limitations

- No statistical significance
- 15% of patients underwent either no or inadequate imaging
- Comparator not typical to standard care

Objective 4

Anticipate the place in therapy for betrixaban and extended thromboprophylaxis.

2012 CHEST GUIDELINES

In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of immobilization or acute hospital stay. (Grade 2B)

LOOKING TO THE FUTURE

Recommendation
- ACCP will be forced to reevaluate prior guideline statements for extended thromboprophylaxis
- Patient populations at an increased risk for VTE will benefit the most from extended therapy
- Future studies needed to demonstrate statistically significant results

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  - Kathleen Lusk, Pharm.D., BCPS
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- CTVHCS Co-Residents
QUESTIONS?
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