Extended-Duration Thromboprophylaxis in Acutely Ill Medical Patients: More Harm than Good?

https://www.dddmag.com/article/2017/06/vte-treatment-space-will-see-strong-growth-2026

Jenna Snoga, Pharm.D.
PGY-2 Pharmacotherapy Resident
University of the Incarnate Word Feik School of Pharmacy
San Antonio, TX
November 10, 2017

Learning Objectives:

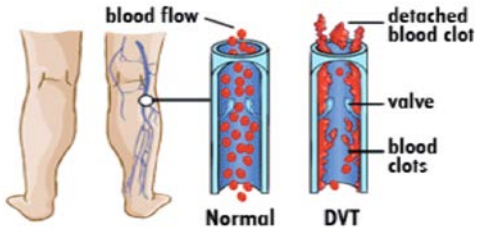
1. Identify risk factors for venous thromboembolism in hospitalized medically ill patients
2. List the anticoagulant therapy options recommended for venous thromboembolism prophylaxis in hospitalized medically ill patients
3. Evaluate primary literature comparing extended-duration versus short-term thromboprophylaxis in hospitalized medically ill patients

Venous Thromboembolism Definition and Epidemiology

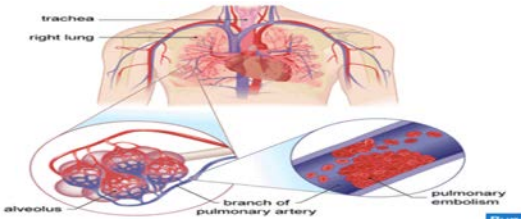
I. Definition[1]

Venous thromboembolism (VTE) results from clot formation within the venous circulation

Deep Vein Thrombosis (DVT)



Pulmonary Embolism (PE)



II. Epidemiology[2-4]

Incidence	•Precise number of people affected by VTE is unknown •1 to 2 per 1000 adults per year in the US •Estimated up to 900,000 cases per year in the US
Mortality	•60,000-100,000 die per year from DVT/PE •Majority of deaths occur among those with PE
Economic Burden	•Total annual health-care cost of VTE per patient: $7594 to $16,644
VTE related to hospitalization	•Approximately one-half of VTE events are related to current or recent hospitalization

VTE Risk Factors in Hospitalized Medical Patients

I. Padua Prediction Score[5,6]

Table 1: Padua Prediction Score Risk Assessment Model	
Risk Factor	Points
Active cancer	3
Previous VTE	3
Reduced mobility	3
Thrombophilic condition	3
Recent trauma and/or surgery (<1 month)	2
Elderly age (≥70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥30)	1
Ongoing hormonal treatment	1
High risk of VTE: cumulative score ≥ 4 points Low risk of VTE: cumulative score < 4 points	

Prevention of VTE in Hospitalized Medical Patients

I. 2012 CHEST Guideline: Prevention of VTE in Nonsurgical Patients[6]
   a. Prevention of VTE in acutely ill hospitalized medical patients
      i. Which patients need VTE prophylaxis?

Table 2: 2012 CHEST Guideline Recommendations		
Padua Score	Risk Level	Recommendation
< 4	Low VTE Risk	Prophylaxis not needed
≥ 4	High VTE Risk and Low Bleed Risk	Pharmacologic prophylaxis
	High VTE Risk and High Bleed Risk	Mechanical prophylaxis

   b. Duration of VTE prophylaxis
      a. Indicated only during hospitalization or until full mobility is restored
      b. Extending the duration of thromboprophylaxis beyond hospitalization not recommended

c. Anticoagulant thromboprophylaxis regimens[6-9]

Medical Patients	•enoxaparin 40 mg subQ every 24 hours •heparin 5000 units subQ every 8-12 hours •fondaparinux 2.5 mg subQ every 24 hours
Renal Impairment	•heparin 5000 units subQ every 8-12 hours
Obese Patients	•enoxaparin 40 mg subQ every 12-24 hours •heparin 5000 units subQ every 8-12 hours
Low-body Weight Patients	•enoxaparin 30 mg subQ every 24 hours •heparin 5000 units subQ every 8-12 hours

Clinical Controversy: How Long Should Thromboprophylaxis be Continued?

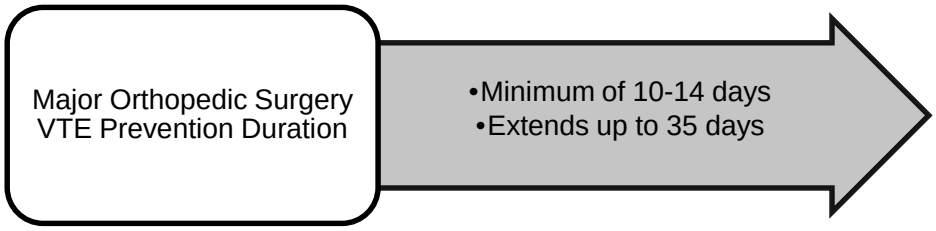
I. Evidence that the "at risk" period for VTE extends up to 3 months following hospital discharge

Table 3: Studies Assessing VTE-risk Post-discharge

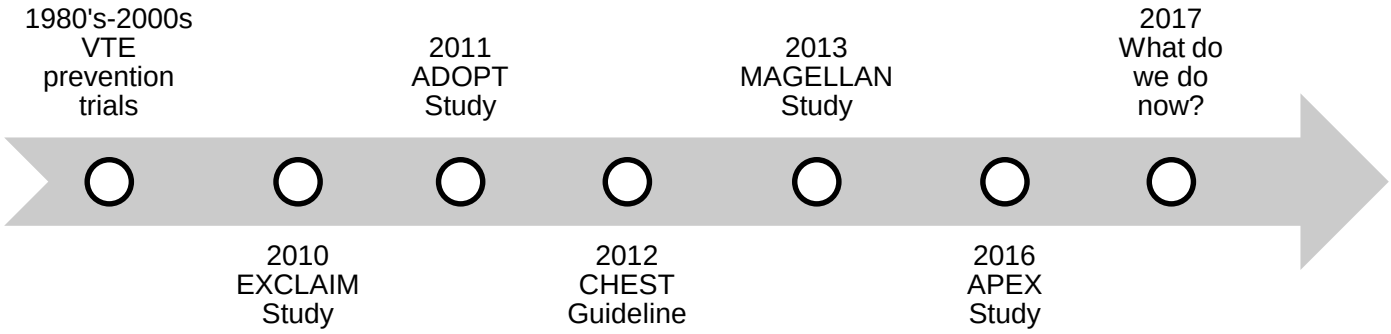
Study	Heit, et al[10]	Spencer, et al[11]	Spyropoulos, et al[12]	Hull, et al[13]	Amin, et al[14]
Study design	Population-based cohort	Observational	Observational	Observational	Observational
Patient population	Olmsted County Minnesota residents	Worcester metropolitan area residents	Medical patients	High-risk elderly, medical patients	Medical patients
Results	VTE events post D/C: 75% Median time to VTE: 19.5 days	VTE 1-month post-D/C: 67% VTE 1-2 months post-D/C: 20% VTE 2-3 months post-D/C: 13%	Cumulative VTE: 1% VTE post-D/C: 45%	Mean time to VTE: 33.5 days	VTE events post-D/C: 56% VTE risk highest: first 19 days after hospital admission

II. Thromboprophylaxis in orthopedic surgery patients

a. 2012 CHEST Guideline: Prevention of VTE in Orthopedic Surgery Patients[15-20]



III. History of VTE prophylaxis[20-29]



Extended-Duration Thromboprophylaxis: Literature Review

Table 4: EXCLAIM Study **Hull RD, Schellong SM, Tapson VF, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Ann Intern Med 2010;153(1):8-18.**		
Objective	To determine if the use of extended-duration enoxaparin for thromboprophylaxis in acutely ill medical patients is safe and effective.	
Methods		
Study Design	Multicenter, placebo-controlled, parallel, double-blind, randomized controlled trial	

Patient Selection	Inclusion Criteria:
	• Age ≥ 40 years
	• Acute medical illness (heart failure, respiratory failure, or infection)
	• Reduced mobility for up to 3 days
	  o Level 1
	  o Level 2 (one additional VTE risk factor)
		Exclusion Criteria:
		• Life expectancy < 6 months
		• Unevaluable ultrasonograms
		• Major surgery < 3 months
		• Severe anemia
		• Renal failure
		• Active bleeding disorder

Intervention	Treatment groups:
	• Open-label enoxaparin 40mg subQ once daily for 10 ± 4 days
	  o Randomly assigned in a 1:1 ratio to receive:
	  ▪ Enoxaparin 40mg subQ once daily ± 28 days
	  ▪ Placebo once daily for ± 28 days
	Follow-up:
	• During the study period:
	  o Bilateral compression ultrasonography or venography: suspected DVT
	  o Computed tomography or ventilation-perfusion lung scanning: suspected PE
	• End of study period: bilateral ultrasonography of lower extremities for asymptomatic proximal DVT	

Outcomes	Primary efficacy composite outcome: • VTE: Symptomatic or asymptomatic proximal DVT, symptomatic PE, or fatal PE during treatment period Primary safety outcome: • Incidence of major hemorrhagic complications[2]	Secondary efficacy outcomes: • VTE incidence through 3 months • Mortality at 1, 3, and 6 months Secondary safety outcomes: • Incidence of major and minor[3] hemorrhagic complications • Serious adverse events[4] • Thrombocytopenia
Statistical Analysis	• Power= 80% • Alpha= 4.2% for the primary efficacy outcome and 5% for all other outcomes • Incidence of VTE and bleeding: chi-square and Fisher exact tests • All-cause mortality: cox proportional hazards model • Formal tests of interaction	

Results

Baseline Characteristics

Characteristics	Preamendment		Postamendment		Total Population	
	Extended-duration (n=2159)	Placebo (n=2176)	Extended-duration (n= 816)	Placebo (n=812)	Extended-duration (n=2975)	Placebo (n=2988)
Mean Age, y (SD)	67.8 (12.2)	67.2 (12.4)	68.1 (12.0)	68.2 (12.7)	67.9 (12.1)	67.5 (12.5)
Men, n (%)	1081 (50.1)	1076 (49.4)	386 (47.3)	401 (49.4)	1467 (49.3)	1477 (49.4)
White race, n (%)	1678 (77.7)	1685 (77.4)	548 (67.2)	551 (67.9)	2226 (74.8)	2236 (74.8)
BMI, kg/m^2 (SD)	28.9 (8.6)	29.0 (8.6)	28.3 (7.2)	27.9 (7.3)	28.7 (8.3)	28.7 (8.2)
Primary enrollment diagnosis, n (%)						
Acute infection	760 (35.2)	794 (36.5)	217 (26.6)	211 (26.0)	977 (32.8)	1005 (33.6)
Acute respiratory insufficiency	692 (32.1)	666 (30.6)	213 (26.1)	234 (28.8)	905 (30.4)	900 (30.1)
Heart failure	329 (15.2)	350 (16.1)	217 (26.6)	214 (26.4)	546 (18.4)	564 (18.9)
Immobility level, n (%)						
Level 1 immobility	590 (27.3)	589 (27.1)	702 (86.0)	692 (85.2)	1292 (43.4)	1281 (42.9)
Level 2 immobility	1559 (72.2)	1576 (72.4)	113 (13.8)	120 (14.8)	1672 (56.2)	1696 (56.8)
Risk factors, n (%)						
Age >75 y	632 (29.3)	635 (29.2)	246 (30.1)	268 (33.0)	878 (29.5)	903 (30.2)
Cancer	296 (13.7)	329 (15.1)	99 (12.1)	93 (11.5)	395 (13.3)	422 (14.1)
History of VTE	143 (6.6)	154 (7.1)	57 (7.0)	48 (5.9)	200 (6.7)	202 (6.8)
Obesity ≥ 30 kg/m^2	743 (34.4)	764 (35.1)	275 (33.7)	244 (30.0)	1018 (34.2)	1008 (33.7)
Antiplatelet or anti-inflammatory drugs, n (%)	589 (27.3)	547 (25.1)	167 (20.5)	167 (20.6)	756 (25.4)	714 (23.9)
Antiplatelet drugs, n (%)	151 (7.0)	155 (7.1)	55 (4.7)	50 (6.2)	206 (6.9)	205 (6.9)

Study Outcomes	• Median treatment duration of open-label enoxaparin: 8.0 days [IQR 66-10 days] • Median treatment duration for enoxaparin: 27.0 days [IQR, 24-29 days] • Median treatment duration for placebo: 28.0 days [IQR, 24-29 days]

Study Outcomes

Incidence of Primary Efficacy and Safety Outcomes

Preamendment				
Endpoint	**Extended-duration enoxaparin (%)**	**Placebo (%)**	**Absolute Risk Difference (CI)**	**NNT/NNH**
VTE (All)	45 (2.5)	78 (4.2)	**-1.70 (-2.86 to -0.55)**	**NNT= 59**
VTE (Level 1)	12 (2.4)	30 (6.1)	**-3.73 (-6.25 to -1.20)**	**NNT= 27**
VTE (Level 2 High Risk)	18 (3.5)	31 (5.5)	-2.05 (-4.51 to 0.41)	---
Major Bleeding (All)	19 (0.9)	10 (0.5)	0.42 (-0.07 to 0.91)	---
Major Bleeding (Level 1)	5 (0.8)	2 (0.3)	0.51 (-0.37 to 1.38)	---

Postamendment				
Endpoint	**Extended-duration enoxaparin (%)**	**Placebo (%)**	**Absolute Risk Difference (CI)**	**NNT/NNH**
VTE (All)	16 (2.4)	22 (3.4)	-1.02 (-2.85 to 0.80)	---
VTE (Level 1)	13 (2.3)	17 (3.1)	-0.81 (-2.70 to 1.07)	---
VTE (Level 2 High Risk)	3 (3.9)	5 (6.3)	-2.35 (-9.20 to 4.49)	---
Major Bleeding (All)	6 (0.7)	0 (0.0)	**0.74 (0.15 to 1.32)**	**NNH= 142**
Major Bleeding (Level 1)	4 (0.6)	0 (0.0)	**0.57 (0.01 to 1.13)**	**NNH= 166**

Total Population				
Endpoint	**Extended-duration enoxaparin (%)**	**Placebo (%)**	**Absolute Risk Difference (CI)**	**NNT/NNH**
VTE (All)	61 (2.5)	100 (4.0)	**-1.53 (-2.54 to -0.52)**	**NNT= 67**
VTE (Level 1)	25 (2.3)	47 (4.5)	**-2.18 (-3.80 to -0.57)**	**NNT= 46**
VTE (Level 2 High Risk)	21 (3.5)	36 (5.6)	-2.09 (-4.50 to 0.31)	---
Major Bleeding (All)	25 (0.8)	10 (0.3)	**0.51 (0.12 to 0.89)**	**NNH= 200**
Major Bleeding (Level 1)	9 (0.7)	2 (0.2)	**0.54 (0.04 to 1.04)**	**NNH= 200**

Additional Outcomes:

Incidence of the Individual Components of the Composite Endpoint at Day 28 and 90			
Endpoint	**Preamendment**	**Postamendment**	**Total Population**
Symptomatic VTE at day 28 and 90	**SD**	NS	**SD**
Asymptomatic VTE at day 28 and 90	NS	NS	NS
PE at 90 days	NS	NS	NS
Fatal PE	NS	NS	NS
SD: significant difference, NS: not significant			

All-Cause Mortality	
Time Point	**Hazards Ratio (95% CI)**
Day 30	0.93 (0.65 to 1.32)
Day 90	1.04 (0.83 to 1.31)
Day 180	1.08 (0.89 to 1.31)

Tests of Interactions	
Variable	**P-Value**
Age	0.011
Female	0.016
Others: obesity, history of VTE, cancer, immobility level	

- Subgroup analysis:
  - VTE (women): AR difference, -2.71 (95.8% CI, -4.15 to -1.28)
  - VTE (men): AR difference, -0.36 (95.8% CI, -1.79 to 1.07)
  - Major bleeding (women): AR difference, 0.66 (95.8% CI, 0.11 to 1.21)
  - Major bleeding (men): AR difference, 0.34 (95.8% CI, -0.20 to 0.89)
  - VTE (>75 years): AR difference, -4.25 (95.8% CI, -6.45 to -2.04)
  - Major bleeding (>75 years): AR difference, 0.24 (95.8% CI, -0.46 to 0.94)
- Causes of major bleeding: gastrointestinal and intracranial were the most common
- Major hemorrhages similar across groups regardless of a 2 or 3 g/dL threshold
- Total bleeding events significantly increased in patients who received enoxaparin
- Serious adverse events were similar between groups

<table>
<tr><th colspan="3">Conclusion and Evaluation</th></tr>
<tr><td>Author's Conclusion</td><td colspan="2">Extended-duration enoxaparin prophylaxis was associated with a reduction in the combined incidence of VTE in acutely ill medical patients with level 1 immobility, those older than 75 years of age, and women. Extended-duration enoxaparin prophylaxis was also associated with increased rates of major bleeding. The findings of this study do not support the use of extended-duration enoxaparin in patients with level 2 immobility who do not have one of the three specified risk factors for VTE.</td></tr>
<tr><td>Critique</td><td><u>Strengths:</u>
Double-blind and placebo-controlled ↓ measurement bias
Randomization ↓ selection bias
Utilized ISTH's definition for major bleeding
Reduced mobility well defined
Adjudication of safety and efficacy endpoints
Population representative of traditional acutely ill medical patient (↑ external validity)
Follow-up duration: reasonable for study medication administered and clinical outcome studied
Intervention: appropriate since enoxaparin is standard of care and is recommended by current guidelines
Power of 80%: reasonable as it is commonly chosen as the accepted value
Alpha of 4.2%: reasonable as it is commonly chosen as the accepted value</td><td><u>Limitations:</u>
Clarity of the article
Medication adherence not addressed
Exclusion criteria not clearly stated
Funding bias potential
Most confirmed VTEs were asymptomatic DVTs diagnosed by ultrasonography
Routine ultrasonographic screening is not standard of care
Trial was underpowered for postamendment population
VTE-risk assessment score at the time of discharge would be useful
Bleeding-risk assessment score at the time of discharge would be useful</td></tr>
<tr><td>Take Away Summary</td><td colspan="2">In acutely ill medical patients, the use of extended-duration enoxaparin for VTE prophylaxis was associated with increased rates of major bleeding. Extended-duration enoxaparin reduced the combined incidence of VTE in the preamendment and total population analyses. It appears that certain groups of patients (women and those > 75 years of age) may benefit from extended-duration enoxaparin, however; further studies are needed to confirm that the benefits outweigh the risk of bleeding.</td></tr>
<tr><td>Footnotes</td><td colspan="2">1. Reduced mobility:
Level 1: bedrest without bathroom privileges
Level 2: bedrest with bathroom privileges (high risk: age > 75, previous DVT, active or previous cancer)
2. Major hemorrhage criteria: see appendix A for full criteria
Decrease in hemoglobin level of at least 3 g/dL
Requires surgical intervention
3. Minor bleeding criteria:
Overt and does not meet the following criteria for major hemorrhage
Epistaxis lasting more than 5 minutes or requiring intervention, ecchymosis or hematoma larger than 5 cm, hematuria, and subconjunctival or gastrointestinal hemorrhage
4. Serious adverse events:
Events that resulted in death or substantial disability, were life threatening or considered to be an important medical event, or required inpatient hospitalization</td></tr>
</table>

Table 5: ADOPT Study
Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med. 2011;365(23):2167-2177.

Objective	Evaluate the use of apixaban to prevent VTE in acutely ill medical patients during hospitalization and in the extended period after discharge from the hospital	
Methods		
Study Design	Multicenter, double-blind, double-dummy, randomized, placebo-controlled study	
Patient Selection	Inclusion Criteria: • Age ≥ 40 years • Hospitalized for heart failure, respiratory failure, infection, acute rheumatic disorder, or inflammatory bowel disease • Except for patients with heart failure or respiratory failure, patients had to have at least 1 additional risk factor (age ≥ 75, previous VTE, cancer, BMI ≥ 30, or receipt of estrogenic hormone therapy) • Expected hospital stay > 3 days • Moderately[1] or severely[2] restricted mobility	Exclusion Criteria: • Confirmed VTE on admission • Ongoing anticoagulation requirement • Active liver disease • Severe renal disease (CrCl < 30 ml/min) • Ongoing dual antiplatelet therapy • Aspirin dose > 165 mg • Scheduled surgical procedure planned during treatment period • Surgical procedure within the previous 30 days that might be associated with a risk of bleeding • Hemoglobin < 9 g/dL • Platelet count < 100 x 10^3 /µL
Intervention	Treatment groups: • Apixaban 2.5 mg PO twice daily for 30 days + enoxaparin placebo • Enoxaparin 40 mg subQ once daily for a minimum of 6 days + apixaban placebo Follow-up: • In-person follow-up visits: day 30 and 90 • Systematic compression ultrasound examination: time of discharge and at day 30	
Outcomes	Primary Composite Outcome: • Death related to VTE, fatal or nonfatal PE, symptomatic DVT, or asymptomatic proximal-leg DVT during 30-day treatment period Safety Outcomes: • Major bleeding[3] • Clinically relevant nonmajor bleeding[4] • All bleeding • Myocardial infarction, stroke, or thrombocytopenia	Secondary Efficacy Outcomes: • Composite of total VTE and VTE-related death o Time of randomization to enoxaparin discontinuation • Symptomatic DVT or nonfatal PE o 60-day follow-up period • Death from any cause during o 30-day treatment period o 90-day study period
Statistical Analysis	• Power = 90% and alpha = 5% (superiority analysis for primary outcome) o 6524 patients required • Mantel-Haenszel test (stratified according to history of VTE and cancer) • Significant superiority established for apixaban (primary outcome) ➔ noninferiority test would be performed (first secondary outcome)	
Results		

Baseline Characteristics

Characteristic	Apixaban (N=3255)	Enoxaparin (N=3273)
Mean age, years	66.8 ± 12.0	66.7 ± 12.0
Age distribution, n (%)		
< 65 yr	1401 (43.0)	1411 (43.1)
65-75 yr	890 (27.3)	884 (27.0)
≥ 75 yr	964 (29.6)	978 (29.9)
Male sex, n (%)	1626 (50.0)	1577 (48.2)
White race, n (%)	2474 (76.0)	2476 (75.6)

Characteristic	Apixaban (N=3255)	Enoxaparin (N=3273)
Mobility at randomization, n (%)		
Severely restricted	846 (26.0)	929 (28.4)
Moderately restricted	2388 (73.4)	2323 (71.0)
Reason for hospitalization, n (%)		
Congestive heart failure	1270 (39.0)	1246 (38.1)
Acute respiratory failure	1208 (37.1)	1213 (37.1)
Infection	701 (21.5)	746 (22.8)
Additional risk factors, n (%)		
Previous VTE	141 (4.3)	124 (3.8)
History of cancer	312 (9.6)	320 (9.8)
BMI ≥ 30 kg/m^2	1448 (44.5)	1451 (44.3)
Chronic heart failure	1531 (47.0)	1537 (47.0)

Study Outcomes

- Mean duration of apixaban: 24.9 ± 10 days
- Mean duration of enoxaparin: 7.3 ± 4 days

Efficacy Outcomes	Apixaban n (%)	Enoxaparin n (%)	Relative Risk with Apixaban (95% CI)	P-Value
Primary Outcome	60 (2.71)	70 (3.06)	0.87 (0.62 to 1.23)	0.44
Secondary Outcome	43 (1.73)	40 (1.61)	1.06 (0.69 to 1.63)	---

- Individual outcomes for prespecified subgroups: apixaban vs. enoxaparin
  - VTE-related death: 0.06% vs. 0.09%
  - Non-fatal PE: 0.22% vs. 0.24%
  - Symptomatic DVT: 0.15% vs. 0.49%
  - Asymptomatic proximal DVT: 2.36% vs. 2.12%

Safety Outcomes	Apixaban n (%)	Enoxaparin n (%)	Relative Risk with Apixaban (95% CI)	P-Value	NNH
Major bleeding	15 (0.47)	6 (0.19)	2.58 (1.02 to 7.24)	**0.04**	**358**
Major plus clinically relevant nonmajor bleeding	85 (2.67)	67 (2.08)	1.28 (0.93 to 1.76)	0.12	---
All bleeding	246 (7.73)	219 (6.81)	1.13 (0.95 to 1.34)	0.18	---

- Rate of death: 4.1% in both groups
- Adverse event rates (MI or stroke) did not differ significantly between groups

Conclusion and Evaluation

Author's Conclusion

Extended-duration thromboprophylaxis with apixaban was not superior to a shorter course of enoxaparin in medically ill patients and was associated with significantly more major bleeding events. Percise risk-stratification methods are needed to identify patients who may benefit from extended-duration thromboprophylaxis.

Critique

Strengths:

- Double-blind and placebo-controlled ↓ measurement bias
- Double-dummy design maintains blinding
- Randomization ↓ selection bias
- Adjudication of safety & efficacy endpoints
- Reduced mobility well defined
- Population representative of traditional acutely ill medical patient
- Utilized ISTH's definition for major bleeding
- Power of 90%: reasonable as it is ↑ than the commonly accepted value
- Alpha 5%: reasonable as it is commonly chosen as the accepted value

Limitations:

- Routine ultrasonographic screening is not standard of care
- Most confirmed VTEs were asymptomatic
- Trial was underpowered
- Medication adherence was not addressed
- Publication bias present
- Funding bias potential
- No mention of number of patients on ASA or use of other antiplatelet agents
- VTE-risk assessment score at the time of discharge would be useful
- Bleeding-risk assessment score at the time of discharge would be useful

Take Away Summary	In medically ill patients, extended-duration apixaban did not reduce the rate of the primary composite outcome when compared to a shorter course of enoxaparin. This study also demonstrated that patients receiving extended-duration apixaban had significantly more major bleeding events. The results of this trial do not justify the use of extend-duration apixaban in a broad population of medically ill patients after hospital discharge.
Footnotes	1. Moderate restricted mobility: • Allowed to walk within the hospital room or bathroom 2. Severely restricted mobility: • Confined to bed or to a chair at bedside 3. Major bleeding: • See appendix A • Bleeding that occurred in an operated joint that required intervention or intramuscular bleeding with compartment sydrome 4. Clinically relevant nonmajor bleeding: • Acute and overt that did not meet criteria for major bleeding o Epistaxis that required medical attention, gastrointestinal bleeding, endoscopically confirmed bleeding, spontaneous hematuria, unusual bruising, radiographically confirmed hematoma, or hemoptysis

Table 6: MAGELLAN Study **Cohen AT, Spiro TE, Büller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med. 2013;368(6):513-523.**		
Objective	To determine if the use of extended-duration rivaroxaban is safe and effective for VTE prophylaxis in acutely ill medical patients.	
Methods		
Study Design	Multicenter, placebo-controlled, double-blind, double-dummy, randomized controlled trial	
Patient Selection	Inclusion Criteria: • Age ≥ 40 years • Acute medical illness o Heart failure, respiratory failure, infection, active cancer, or acute rheumatic disease • Plus ≥ 1 risk factor for VTE[1] • Reduced mobility o Complete immobilization for ≥ 1 day o Decreased mobility for ≥ 4 days • Hospitalized < 72 hours before randomization	Exclusion Criteria: • Uncontrolled HTN • Drug or alcohol abuse • Indication for fibrinolysis • Severe renal insufficiency • Elevated bleeding risk o Clinically significant bleeding within 30 days of randomization o Major surgery within 6 weeks of randomization or anticipated surgery during study period o History of hemorrhagic stroke o Known intracranial neoplasm • CYP450 3A4 inhibitor use • HIV infection
Intervention	Treatment groups: • Enoxaparin 40mg subQ once daily for 10 ± 4 days and oral rivaroxaban placebo once daily for 35 ± 4 days • Rivaroxaban 10 mg PO once daily for 35 ± 4 days and subQ enoxaparin placebo for 10 ± 4 days Follow-up: • During the study period: o Bilateral compression ultrasonography or venography: suspected DVT o Computed tomography or ventilation-perfusion lung scanning: suspected PE • End of study period (day 10 and 35): bilateral ultrasonography of lower extremities for assessment of asymptomatic proximal DVT	

<table>
<tr><td>Outcomes</td><td><u>Primary efficacy outcome:</u>
• Composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death related to VTE at day 10 (noninferiority)
• Composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death related to VTE at day 35 (superiority)

<u>Safety outcome:</u>
• Clinically relevant bleeding[2]
o Composite of major bleeding or clinically relevant nonmajor bleeding</td><td><u>Secondary outcomes:</u>
• Composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from any cause at day 35
• Composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death related to VTE at day 10 (superiority)
• Incidence of symptomatic VTE
• Composite of cardiovascular death, acute myocardial infarction, or acute ischemic stroke
• Net clinical benefit or harm (day 10 and 35)
• Individual components of composite outcome</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">• Power= 90% (superiority analysis and noninferiority analysis)
o 2876 patients per group were needed
• Alpha= 5% (superiority analysis)
• Non-inferiority analysis: primary efficacy outcome at 10 days (per-protocol population)
• Superiority analysis: primary efficacy outcome at 35 days (modified intention-to-treat population)
• Utilized a modified intention-to-treat and per-protocol analysis
• Mantel-Haenszel model: relative risk ratio of the incidence rates</td></tr>
<tr><td colspan="3">Results</td></tr>
<tr><td>Baseline Characteristics</td><td colspan="2">
<table>
<tr><th>Characteristic</th><th>Rivaroxaban (n=4050)</th><th>Enoxaparin (n=4051)</th></tr>
<tr><td>Median age, years</td><td>71.0</td><td>71.0</td></tr>
<tr><td>Men, n (%)</td><td>2253 (55.6)</td><td>2136 (52.7)</td></tr>
<tr><td>White race, n (%)</td><td>2784 (68.7)</td><td>2744 (67.7)</td></tr>
<tr><td>Mean BMI, kg/m^2</td><td>28.2</td><td>28.2</td></tr>
<tr><td>Median duration of hospitalization, days</td><td>11.0</td><td>11.0</td></tr>
<tr><td colspan="3">Acute medical condition, n (%)</td></tr>
<tr><td>Acute infection</td><td>1854 (45.8)</td><td>1828 (45.1)</td></tr>
<tr><td>Respiratory insufficiency</td><td>1105 (27.3)</td><td>1163 (28.7)</td></tr>
<tr><td>Heart failure</td><td>1308 (32.3)</td><td>1312 (32.4)</td></tr>
<tr><td>Ischemic stroke</td><td>699 (17.3)</td><td>700 (17.3)</td></tr>
<tr><td>Active cancer</td><td>296 (7.3)</td><td>296 (7.3)</td></tr>
<tr><td>≥ 2 Medical conditions, n (%)</td><td>1240 (30.6)</td><td>1270 (31.4)</td></tr>
<tr><td>Median D-dimer, µg/mL</td><td>0.94</td><td>0.95</td></tr>
<tr><td colspan="3">Risk factor for VTE, n (%)</td></tr>
<tr><td>Age > 75 years</td><td>1551 (38.3)</td><td>1565 (38.6)</td></tr>
<tr><td>History of cancer</td><td>700 (17.3)</td><td>678 (16.7)</td></tr>
<tr><td>History of VTE</td><td>202 (5.0)</td><td>179 (4.4)</td></tr>
<tr><td>Obesity ≥ 35 kg/m^2</td><td>612 (15.1)</td><td>618 (15.3)</td></tr>
<tr><td>History of heart failure</td><td>1408 (34.8)</td><td>1382 (34.1)</td></tr>
<tr><td colspan="3">Creatinine clearance</td></tr>
<tr><td>> 80 ml/min</td><td>1582 (39.1)</td><td>1537 (37.9)</td></tr>
<tr><td>50-80 ml/min</td><td>1500 (37.0)</td><td>1546 (38.2)</td></tr>
<tr><td>30-50 ml/min</td><td>788 (19.5)</td><td>807 (19.9)</td></tr>
<tr><td><30 ml/min</td><td>82 (2.0)</td><td>64 (1.6)</td></tr>
</table>
</td></tr>
</table>

Outcomes

Primary Efficacy Outcomes	Rivaroxaban n (%)	Enoxaparin n (%)	Relative Risk, 95% CI	P-value	NNT
Primary outcome (10 days)	78 (2.7)	82 (2.7)	0.97 (0.71-1.13)	**P=0.003***	---
Primary outcome (35 days)	131 (4.4)	175 (5.7)	0.77 (0.62-0.96)	**P=0.02^**	**77**
* noninferiority and per-protocol population, ^ superiority and modified intention-to-treat population					

- Rates of the composite primary efficacy outcome and its components at 35 days
  - Asymptomatic DVT: 3.5% vs. 4.4%
  - Symptomatic DVT: 0.4% vs. 0.5%
  - Symptomatic non-fatal PE: 0.3% vs. 0.5%
  - VTE-related death: 0.6% vs. 1.0%

Efficacy Outcomes	Rivaroxaban n (%)	Enoxaparin n (%)	Relative Risk, 95% CI	P-value
Secondary outcome (day 35)*	266 (8.6)	293 (9.2)	0.93 (0.80-1.09)	0.38
Secondary outcome (day 10)^	98 (3.0)	100 (3.1)	0.99 (0.75-1.30)	0.95
Symptomatic nonfatal VTE (day 35)[#]	22 (0.6)	27 (0.7)	0.82 (0.47-1.43)	0.48
Symptomatic nonfatal VTE (day 10)[#]	18 (0.5)	12 (0.3)	1.5 (0.72-3.11)	0.28
Death from any cause (day 35)*	159 (5.1)	153 (4.8)	-----	---
CV death, MI, or stroke (day 35)[#]	71 (1.8)	64 (1.6)	1.11 (0.79-1.55)	0.55
Net clinical benefit or harm (day 35)*	286 (9.4)	240 (7.8)	1.21 (1.03-1.43)	**0.02**
Net clinical benefit or harm (day 10)*	216 (6.6)	151 (4.6)	1.44 (1.18-1.77)	**<0.001**

CV= cardiovascular, MI= myocardial infarction, stroke= acute ischemic stroke
* modified intention-to-treat population and patients that met criteria for safety population
^ modified intention-to-treat population
[#] safety population

Safety Outcomes	Rivaroxaban n (%)	Enoxaparin n (%)	Relative Risk, 95% CI	P-value	NNH
Clinically relevant bleeding (day 10)	111 (2.8)	49 (1.2)	2.3 (1.63-3.17)	**<0.001**	**62**
Clinically relevant bleeding (day 35)	164 (4.1)	67 (1.7)	2.5 (1.85-3.25)	**<0.001**	**41**
Any major bleeding (day 35)	43 (1.1)	15 (0.4)	2.9 (1.60-5.15)	**<0.001**	**142**
Fatal major bleeding	7 (0.2)	1 (<0.1)	----	**-----**	----

Conclusion and Evaluation

Author's Conclusions

Standard-duration thromboprophylaxis with rivaroxaban was noninferior to enoxaparin. The efficacy of extended-duration rivaroxaban was superior to that of standard-duration enoxaparin. However, the rate of clinically relevant bleeding was significantly higher in the extended-duration rivaroxaban group. The analysis of net clinical benefit or harm did not show a benefit with rivaroxaban at day 10 or 30.

Critique

Strengths:

- Double-blind and placebo-controlled ↓ measurement bias
- Double-dummy design maintains blinding
- Randomization ↓ selection bias
- Population representative of traditional acutely ill medical patients (↑ external validity)
- Utilized ISTH's definition for major bleeding
- Adjudication of safety and efficacy endpoints
- Power of 90%: reasonable as it is ↑ than the commonly accepted value
- Alpha ~5%: reasonable as it is commonly chosen as the accepted value

Limitations:

- Medication adherence not addressed
- Risk for funding bias
- Most confirmed VTEs were asymptomatic DVTs diagnosed by ultrasonography
- Routine ultrasonographic screening is not standard of care
- No mention of number of patients on ASA or other antiplatelet agents
- Complete and decreased mobility definition not well defined
- Renal insufficiency not defined
- Unable to determine what drove composite endpoint at 35 days (p-values)
- VTE-risk assessment score at the time of discharge would be useful

		• Bleeding-risk assessment score at the time of discharge would be useful • Modified intention-to-treat analysis included patients who had major protocol violations
Take Away Summary	Extended-duration rivaroxaban reduced the rate of the primary composite outcome in acutely ill medical patients; however, it was associated with an increased risk of bleeding. The prespecified analysis of net clinical benefit or harm showed that rivaroxaban was associated with more harm when compared to enoxaparin.	
Footnotes	1. VTE risk factors: • Severe varicosis, chronic venous insufficiency, history of cancer, history of VTE, history of HF, thrombophilia, recent surgery (8-12 weeks), hormone replacement therapy, advanced age ≥ 75 years, or morbid obesity (body mass index ≥ 35 kg/m^2) 2. Clinically relevant bleeding: composite of major bleeding or clinically relevant non-major bleeding • Major bleeding: See appendix A • Non-major clinically relevant bleeding: o Overt bleeding not meeting the criteria for major bleeding but associated with medical intervention or temporary cessation of study treatment o Any bleeding compromising hemodynamics or leading to hospitalization o Epistaxis lasting more than 5 minutes o Hematuria, rectal blood loss, or hemoptysis	

Table 7: APEX Study **Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely Ill medical patients. N Engl J Med. 2016;376(6):534-544.**		
Objective	To determine if the use of extended-duration betrixaban is a safe and effective treatment option for VTE prophylaxis in acutely ill medical patients.	
Methods		
Study Design	Multicenter, double-blind, double-dummy, active-controlled, randomized, superiority trial	
Patient Selection	Inclusion Criteria: • Age ≥ 40 years • Acute medical illness o Heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke • Elevated D-dimer level or age ≥ 75 years • Immobilization[1] ≥ 3 days o Severe ≥ 24 hours • Hemoglobin ≥ 10 g/dL • Expected total length of hospitalization ≥ 3 days • Enrollment occurs ≤ 96 hours after hospitalization	Exclusion Criteria: • Unable to receive nourishment by enteral administration • Anticipated need for prolonged anticoagulation • Life expectancy < 8 weeks • Unable to obtain an adequate bilateral compression ultrasound sonography • Low body weight < 45 kg • History of significant bleeding within 6 months of enrollment • Major surgery within 3 months of enrollment and throughout study • ESRD with CrCl < 15 mL/min or hemodialysis • Intracranial bleeding within three years prior to enrollment • Concomitant dual anti-platelet therapy • Uncontrolled HTN or HIV infection
Intervention	Treatment groups: • Enoxaparin 40mg subQ once daily for 10 ± 4 days plus oral betrixaban placebo once daily for 35-42 days • Enoxaparin placebo subQ once daily for 10 ± 4 days plus oral betrixaban once daily for 35-42 days o Betrixaban: 160mg loading dose ➔ 80mg once daily o Severe renal insufficiency: 50% of prespecified dose for each study medication	

	Cohorts:
	• Cohort 1: Patients with a D-dimer ≥ 2xULN
	• Cohort 2: Patients in cohort 1 plus those who were ≥ 75 years
	• Cohort 3: Patients who could be evaluated for the primary efficacy outcome (overall population)
	Follow-up:
	• During the study period:
	  o Bilateral compression ultrasonography or venography: suspected DVT
	  o Computed tomography or ventilation-perfusion lung scanning: suspected PE
	• End of study period: bilateral ultrasonography of lower extremities for asymptomatic DVT

Outcomes	Primary efficacy composite outcome: • Asymptomatic proximal DVT, symptomatic DVT (proximal or distal), symptomatic nonfatal PE, or VTE-related death Principal safety outcome: • Major bleeding[2] at any point until 7 days after discontinuation of study medication Secondary efficacy composite outcome: • VTE-related death, nonfatal PE, or symptomatic DVT through day 42 • Asymptomatic proximal DVT, symptomatic DVT (proximal or distal), non-fatal PE, or death from any cause through day 42 • Net clinical benefit: primary efficacy outcome plus primary safety outcome
Statistical Analysis	• Utilized a hierarchical sequence to adjust for type I error rate: primary outcome analysis • Alpha =5% and Power= 85% • Recalculated power after 80% enrollment using event rate data from study population • Cochran-Mantel-Haenszel model: risk ratio of incidence rates • Forest plots for subgroup risk ratios and confidence intervals
Results	
Baseline Characteristics	

Characteristic	Betrixaban (N=3759)	Enoxaparin (N=3754)
Mean age, years	76.6 ± 8.46	76.2 ± 8.31
Male sex, n (%)	1705 (45.4)	1720 (45.8)
White race, n (%)	3503 (93.2)	3518 (93.7)
Mean weight, kg	79.84	80.74
Mean BMI, kg/m^2	29.21 ± 6.60	29.54 ± 6.67
Median number of hospitalization days (IQR)	10 (7-4)	10 (8-14)
Creatinine clearance, n (%)		
15 to <30 ml/min	174 (4.6)	150 (4.0)
30 to <60 ml/min	1602 (42.6)	1531 (40.8)
60 to <90 ml/min	1299 (34.6)	1346 (35.9)
≥ 90 ml/min	672 (17.9)	716 (19.1)
Concomitant P-glycoprotein inhibitor, n (%)	677 (18.0)	649 (17.3)
Acute medical condition, n (%)		
Heart failure	1677 (44.6)	1672 (44.5)
Infection	1112 (29.6)	1058 (28.2)
Respiratory failure	448 (11.9)	474 (12.6)
Ischemic stroke	411 (10.9)	432 (11.5)
Rheumatic disorder	109 (2.9)	117 (3.1)
Risk factor for VTE, n (%)		
D-dimer ≥ 2xULN	2341 (62.3)	2332 (62.1)
Age ≥ 75 yr	2575 (68.5)	2517 (67.0)
History of cancer	466 (12.4)	443 (11.8)
History of DVT or PE	312 (8.3)	296 (7.9)
History of NYHA class III or IV heart failure	853 (22.7)	865 (23.0)
Concurrent acute infectious disease	602 (16.0)	620 (16.5)

Study Outcomes

- Median duration of betrixaban treatment: 36 days (34-49)
- Median duration of enoxaparin treatment: 9 days (7-13)

Efficacy Outcomes	Betrixaban (%)	Enoxaparin (%)	RR (95% CI)	p-value
Primary efficacy outcome				
Cohort 1	132 (6.9)	166 (8.5)	0.81 (0.65-1.00)	0.054
Cohort 2	160 (5.6)	204 (7.1)	0.80 (0.66-0.98)	**0.03**
Cohort 3	165 (5.3)	223 (7.0)	0.76 (0.63-0.92)	**0.006**
Symptomatic VTE				
Cohort 1	30 (1.3)	44 (1.9)	0.67 (0.42-1.07)	0.09
Cohort 2	35 (1.0)	49 (1.4)	0.71 (0.46-1.09)	0.11
Cohort 3	35 (0.9)	54 (1.5)	0.64 (0.42-0.98)	**0.04**
Primary outcome + any cause of death				
Cohort 1	232 (11.5)	264 (12.9)	0.89 (0.75-1.05)	0.16
Cohort 2	291 (9.8)	329 (10.9)	0.90 (0.77-1.04)	0.15
Cohort 3	298 (9.2)	359 (10.8)	0.85 (0.73-0.98)	**0.02**
Net clinical benefit				
Cohort 1	141 (7.4)	174 (8.9)	0.82 (0.66-1.01)	0.07
Cohort 2	174 (6.1)	214 (7.4)	0.82 (0.68-1.00)	0.05
Cohort 3	179 (5.8)	233 (7.3)	0.78 (0.65-0.95)	**0.01**

Safety Outcomes	Betrixaban (%)	Enoxaparin (%)	RR (95% CI)	p-value
Major bleeding				
Cohort 1	15 (0.6)	17 (0.7)	0.88 (0.44-1.76)	0.72
Cohort 2	25 (0.7)	21 (0.6)	1.19 (0.66-2.11)	0.56
Overall safety population	25 (0.7)	21 (0.6)	1.19 (0.67-2.12)	0.55
Major or clinically relevant nonmajor bleeding				
Cohort 1	72 (3.1)	44 (1.9)	1.64 (1.13-2.37)	**0.009**
Cohort 2	110 (3.2)	58 (1.7)	1.89 (1.38-2.59)	**<0.001**
Overall safety population	116 (3.1)	59 (1.6)	1.97 (1.44-2.68)	**<0.001**

Conclusion and Evaluation

Author's Conclusion

In acutely ill medical patients who have an elevated D-dimer level, there was no significant difference between standard-duration enoxaparin and extended-duration betrixaban in the prespecified primary efficacy outcome. However, prespecified exploratory analyses suggest that there may be a benefit for extended-duration betrixaban in the two larger cohorts. Extended-duration betrixaban was not associated with significantly more major bleeding compared to standard-duration enoxaparin.

Critique

Strengths:

- Double-blind and placebo-controlled ↓ measurement bias
- Randomization ↓ selection bias
- Double-dummy maintains double-blind set-up
- Population representative of traditional acutely ill medical patients (↑ external validity)
- Utilized ISTH's definition for major bleeding
- Adjudication of safety and efficacy endpoints

Limitations:

- Clarity lacking within study on their statistical analysis section
  - Claimed they met power, but did not specify sample size needed
- Medication adherence not addressed
- Most confirmed VTEs were asymptomatic DVTs diagnosed by ultrasonography
- Routine ultrasonographic screening is not standard of care
- Routine collection of D-dimer levels is not considered standard of care to assess DVT risk

	• Low risk of funding bias because use of DCRI, PERFUSE, and Pharmaceutical Product Development • Discussed drug interactions • Targeted higher risk population based on factors identified in previous trials • Power of 85%: reasonable as it is ↑ than the commonly accepted value • Alpha 5%: commonly chosen as the accepted value	• No mention of the number of patients on ASA or other antiplatelet agents in baseline characteristics section • VTE-risk assessment score at the time of discharge would be useful • Bleeding-risk assessment score at the time of discharge would be useful
Take Away Summary	Extended-duration betrixaban did not reduce the rate of the primary composite endpoint in acutely ill medical patients with an elevated D-dimer level. However, the prespecified exploratory analysis provides evidence that betrixaban may reduce the rate of the primary composite endpoint (cohorts 2 and 3). In addition, extended-duration betrixaban was not associated with an increase in major bleeding rates as seen in the previous trials. However, the combination of major or clinically relevant nonmajor bleeding was significantly increased with the use of extended-duration betrixaban. In addition, the net clinical benefit analysis favored the use of extended-duration betrixaban in the overall population.	
Footnotes	1. Immobilization • Severely immobilized o Confined to a bed or chair for the majority of the day and can only be independently mobile to the in-room toilet. In-bed/chair physical therapy is permitted. • Moderately immobilized o Patients can be independently mobile to the in-room or ward toilet; can be mobilized by physical therapy or nursing staff, and can be off-ward with assistance 2. Major bleeding • See appendix A 3. Nonmajor clinically relevant bleeding • Overt bleeding not meeting the criteria for major bleeding but associated with medical intervention or temporary cessation of study treatment • Any bleeding compromising hemodynamics or leading to hospitalization • Epistaxis lasting more than 5 minutes, hematuria, rectal blood loss, or hemoptysis	

Table 8: Systematic Review and Meta-Analysis **Liew AY, Piran S, Eikelboom JW, Douketis JD. Extended-duration versus short-duration pharmacological thromboprophylaxis in acutely Ill hospitalized medical patients: a systematic review and meta-analysis of randomized controlled trials. J Thromb Thrombolysis. 2017; 43:291–301.**	
Objective	Evaluate the risks and benefits of extended-duration pharmacologic thromboprophylaxis versus short duration pharmacologic thromboprophylaxis in medical patients.
Methods	
Study design	Meta-analysis and systematic review
Study Selection	• Studies identified by computerized search of PubMed, Medline, and EMBASE databases • Studies included if they satisfied all of the following characteristics: o Involved acutely ill hospitalized medical patients o Compared extended-duration with short-duration pharmacological thromboprophylaxis o Reported one or more of the following outcomes: ▪ Symptomatic DVT and symptomatic non-fatal PE ▪ Major or fatal bleeding ▪ VTE-related mortality and all-cause mortality
Data Extraction	• Two authors independently extracted data • Agreement was assessed using Cohen's unweighted kappa statistic • Quality of randomized trials was assessed using the Jadad score • Disagreements were resolved by joint review and consensus

Outcomes	• Symptomatic proximal or distal DVT • Symptomatic non-fatal PE • Major or fatal bleeding • VTE-related mortality and all-cause mortality
Statistical Analysis	• Intention-to-treat: safety outcomes • Modified intention-to-treat: efficacy outcomes • Mantel-Haenszel fixed effect model: pooled relative risks • I^2 index and Chi square test: heterogeneity assessment • Random effects model was used in the event of significant heterogeneity • Funnel plot: assess for publication bias • NNT and NNH calculations

Results

	APEX	MAGELLAN	ADOPT	EXCLAIM
Year of publication	2016	2013	2011	2010
Intervention	betrixaban	rivaroxaban	apixaban	enoxaparin
Patient population	Mean age 76, 45% male, hospitalized for heart failure or acute infection	Median age 71, 54% male, hospitalized for acute infection or heart failure	Mean age 67, 50% male, 73% moderately restricted in mobility, hospitalized for heart failure or acute respiratory failure	Mean age 68, 50% male, 43% level 1 immobility, hospitalized for acute infection or acute respiratory insufficiency

Outcomes	Risk ratio (95% CI)	p-value	Heterogeneity	ARR/ARI	NNT/NNH
Symptomatic DVT	**0.52 (0.35-0.77)**	**p= 0.001**	I^2= 45%, χ^2 =5.44	ARR= 0.32%	**NNT= 313**
Symptomatic non-fatal PE	**0.61 (0.38-0.99)**	**p=0.04**	I^2= 0%, χ^2 =2.27	ARR= 0.16%	**NNT= 625**
Major bleeding	**2.08 (1.50-2.90)**	**p<0.0001**	I^2= 42%, χ^2 =5.15	ARI= 0.41%	**NNH= 244**
Major bleeding (excluding APEX trial)	**2.69 (1.78-4.06)**	**p<0.00001**	I^2= 0%, χ^2 =0.10	ARI= 0.51%	**NNH= 196**
Fatal bleeding	2.01 (0.69-5.88)	p=0.20	I^2= 22%, χ^2 =3.87	---	---
VTE related mortality	0.69 (0.45-1.06)	p=0.09	I^2= 0%, χ^2 =0.34	---	---
All-cause mortality	1.00 (0.88-1.12)	p=0.95	I^2= 0%, χ^2 =0.78	---	---

Conclusion and Evaluation

Author's Conclusions	In acutely ill hospitalized medical patients, extended-duration thromboprophylaxis reduced the risk of symptomatic DVT and symptomatic non-fatal PE. Extended-duration thromboprophylaxis with rivaroxaban, apixaban, and enoxaparin increased the risk of major bleeding, whereas betrixaban did not.	
Critique	<u>Strengths:</u> • Two authors independently extracted data • Publication bias assessed using Funnel plots • Disagreements were resolved by joint review • Evaluated symptomatic DVT occurrence • Trials included had low risk of bias • Low heterogeneity reported • Meta-analysis performed according to PRISMA guidelines • NNT and NNH calculations provided	<u>Limitations:</u> • Average duration of prophylaxis in control arms is longer than in clinical practice • Publication errors within trial characteristic chart
Take Away Summary	In medically ill patients, extended-duration thromboprophylaxis reduces the risk of symptomatic DVT and symptomatic non-fatal PE when compared to standard-duration thromboprophylaxis. There was no difference in VTE-related mortality, fatal bleeding, and all-cause mortality. The use of extended-duration thromboprophylaxis was associated with higher rates of major bleeding when compared to standard-duration thromboprophylaxis.	

Extended-Duration Thromboprophylaxis: Conclusion

I. Summary of Primary Literature
   a. Randomized controlled trials and meta-analysis

EXCLAIM

- ↓ VTE risk (total population)
- ↑ bleed risk
- No mortality benefit

MAGELLAN

- ↓ VTE risk
- ↑ bleed risk
- No mortality benefit

ADOPT

- Similar VTE risk
- ↑ bleed risk
- No mortality benefit

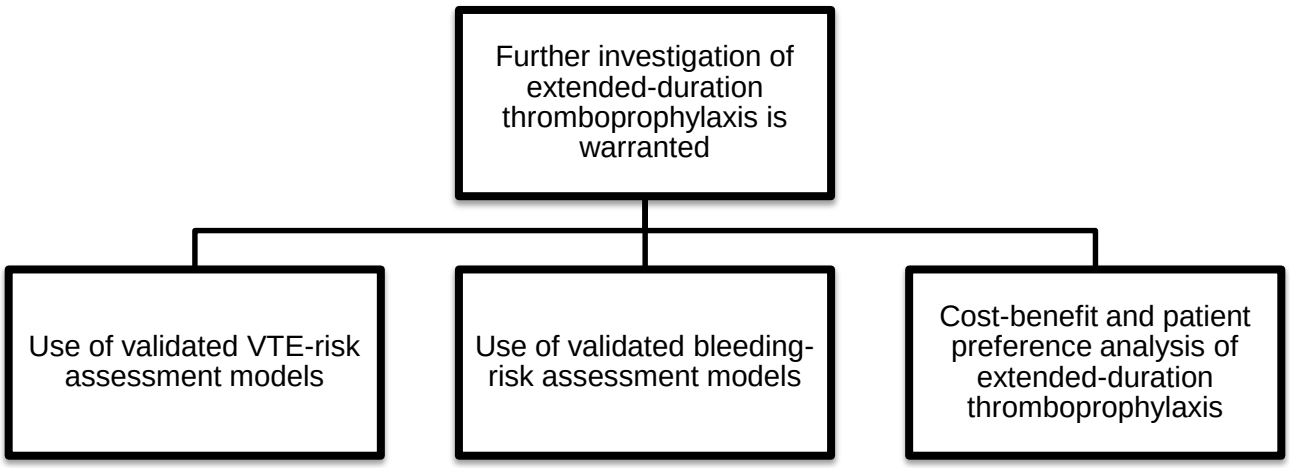
APEX

- Possible ↓ VTE risk
- Similar bleed risk
- No mortality benefit

Meta-analysis

- ↓ symptomatic DVT and non-fatal PE
- ↑ major bleeding
- No mortality benefit

II. Recommendation Based on Literature
   a. Evidence does not support the use of extended-duration thromboprophylaxis in medically ill patients
   b. Further studies are needed to evaluate the safety and efficacy of extended-duration thromboprophylaxis in medically ill patients



References

1. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012;379(9828):1835-46.
2. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med. 2010;38(4S):S495-501.
3. Centers for Disease Control and Prevention. Updated June 22, 2015. https://www.cdc.gov/ncbddd/dvt/data.html. Accessed October 1, 2017.
4. Spyropoulos AC, Lin J. Direct medical costs of venous thromboembolism and subsequent hospital readmission rates: an administrative claims analysis from 30 managed care organizations. J Manag Care Pharm. 2007;13(6):475-86.
5. Barbar S , Noventa F , Rossetto V , et al . A risk assessment model for the identify cation of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost, 2010; 8(11):2450–2457.
6. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in Nonsurgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e195S-226S.
7. Lovenox (enoxaparin) [package insert]. Bridgewater, NJ: Sanofi-Aventis; October 2013.
8. Heparin sodium injection [package insert]. Lake Forest, IL: Hospira; September 2016.
9. Fondaparinux sodium subcutaneous injection [package insert]. Rockford, IL: Mylan Institutional LLC; August 2017.
10. Heit JA, Crusan DJ, Ashrani AA, Petterson TM, Bailey KR. Effect of a near-universal hospitalization-based prophylaxis regimen on annual number of venous thromboembolism events in the US. Blood. 2017;130(2):109-114.
11. Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ. Venous thromboembolism in the outpatient setting. Arch Intern Med. 2007;167(14):1471-5.
12. Spyropoulos AC, Anderson FA, Fitzgerald G, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest. 2011;140(3):706-714.
13. Hull RD, Merali T, Mills A, Stevenson AL, Liang J. Venous thromboembolism in elderly high-risk medical patients: time course of events and influence of risk factors. Clin Appl Thromb Hemost. 2013;19(4):357-62.
14. Amin AN, Varker H, Princic N, Lin J, Thompson S, Johnston S. Duration of venous thromboembolism risk across a continuum in medically ill hospitalized patients. J Hosp Med. 2012;7(3):231-8.
15. Falck-ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in Orthopedic Surgery Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e278S-325S.
16. Eriksson BI, Borris LC, Friedman RJ, et al. Record1 Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008;358(26):2765-75.
17. Lassen MR, Ageno W, Borris LC, et al; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008;358(26):2776-2786.
18. Lassen MR, Raskob GE, Gallus A, et al; ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis afterknee replacement (ADVANCE-2): a randomised double-blind trial. Lancet. 2010;375(9717):807-815.
19. Lassen MR, Raskob GE, Gallus A, et al. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med. 2009;361(6):594-604.

20. Lassen MR, Gallus A, Raskob GE, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl JMed. 2010;363(26):2487-2498.
21. Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ. 2006;332:325-329.
22. Belch JJ, Lowe GD, Ward AG et al. Prevention of deep vein thrombosis in medical patients by low-dose heparin. Scott Med J 1981;26:115–117.
23. Samama MM, Cohen AT, Darmon JY et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999;341:793–800.
24. Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Ann Intern Med. 2007;146(4):278-288.
25. Hull RD, Schellong SM, Tapson VF, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Ann Intern Med. 2010;153(1):8-18.
26. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med. 2011;365(23):2167-77.
27. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. N Engl J Med. 2016;375(6):534-544.
28. Cohen AT, Spiro TE, Büller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med. 2013;368(6):513-23.
29. Liew AY, Piran S, Eikelboom JW, et al. Extended-duration versus short-duration pharmacological thromboprophylaxis in acutely Ill hospitalized medical patients: a systematic review and meta-analysis of randomized controlled trials. J Thromb Thrombolysis. 2017;43(3):291-301.
30. Mehran R, Rao SV, Bhatt DL, et al. Standardized Bleeding Definitions for Cardiovascular Clinical Trials. Circulation. 2011;123(23):2736-2747.
31. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015;13(11):2119-26.

Appendices

Appendix A: Criteria for ISTH Bleeding Definition[30, 31]	
Definition	**Criteria**
ISTH	<u>Major bleeding in non-surgical patients</u> • Fatal bleeding • Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome • Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells. <u>Clinically relevant nonmajor bleeding</u> • Any sign or symptom of hemorrhage that does not fit the criteria for major bleeding but does meet at least one of the following criteria: o Requiring medical intervention by a healthcare professional o Leading to hospitalization or increased level of care o Prompting face to face evaluation
ISTH: International Society on Thrombosis and Haemostasis	