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Clinical Meeting & Exhibition

Keep It Flowing: Controversies Surrounding Venous Thromboembolism Prophylaxis Strategies

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Disclosures

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Objectives

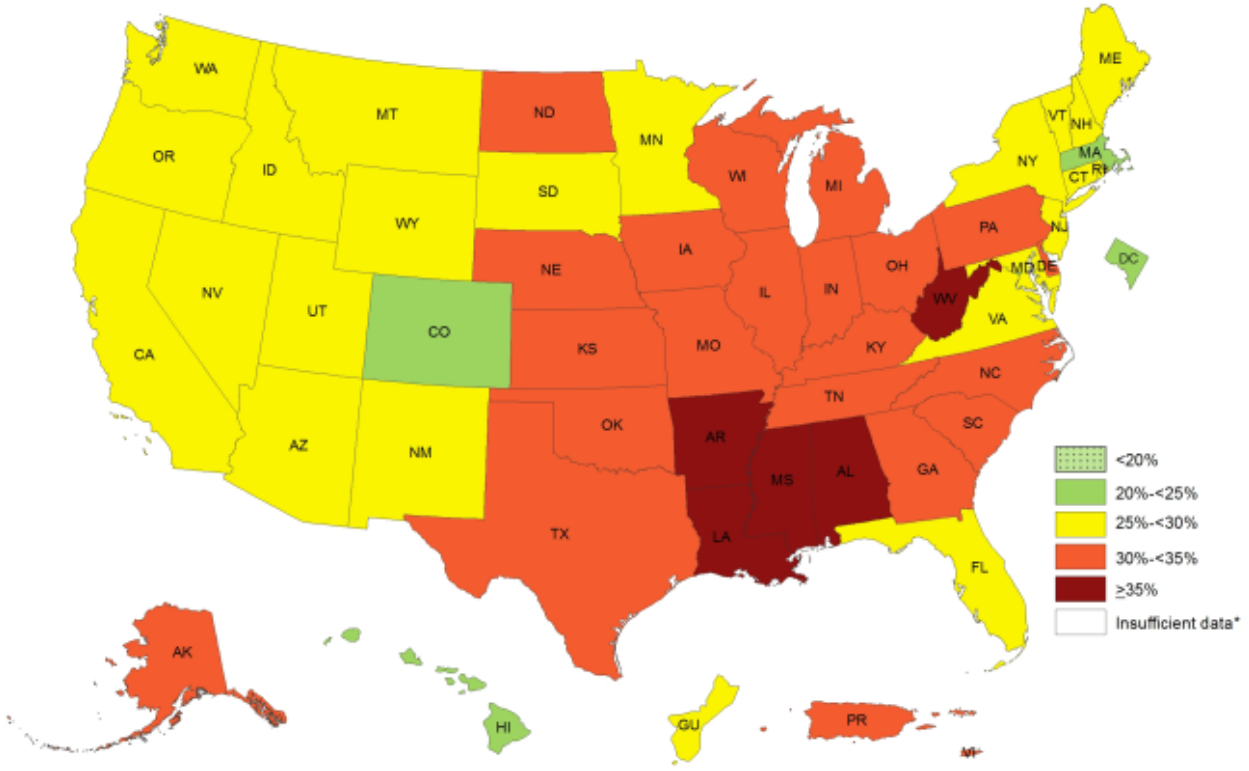
- Identify the challenges dosing venous thromboembolism (VTE) prophylaxis in the obese patient population.
- Evaluate dosing strategies with injectable agents for VTE prophylaxis in this population.
- Recognize the potential need for VTE prophylaxis beyond discharge in the medically ill .
- Interpret available literature and treatment options for extended VTE prophylaxis in the medically ill.

Background

- VTE prophylaxis is a mainstay of inpatient care
  - Standard, fixed doses may not be adequate in obese patients
- Obesity is both common and costly
  - 1 in 3 adults you take care of will be obese
  - Estimated annual medical cost of obesity was $147 billion in 2008
- Obesity is an independent risk factor for VTE

JAMA. 2014;311(8):806-814 | Chest. 2012;141(2_suppl):e24S-e43S
http://www.who.int/mediacentre/factsheets/fs311/en/ | http://www.cdc.gov/obesity/data/adult.html
https://www.cdc.gov/obesity/adult/causes.html

Prevalence of Self-Reported Obesity Among U.S. Adults



http://www.cdc.gov/obesity/data/prevalence-maps.html

Categories of Weight

Classification	Body Mass Index (BMI, kg/m^2)
Underweight	< 18.5
Normal	18.5-24.9
Overweight	25-29.9
Obese	≥ 30
Obese Class I	30-34.9
Obese Class II (Severely Obese)	35-39.9
Obese Class III (Morbidly Obese)	≥ 40

http://apps.who.int/bmi/index.jsp?introPage=intro_3.html
https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis.htm

Pharmacokinetic Differences

- Significant pharmacokinetic changes have been observed in obese patients
- FDA does not require evaluation of dosing in obesity
- Clinicians need to balance ensuring adequate exposure to medications while minimizing potential toxicities

J Clin Pharm Ther, 2014, 39, 584–608 | Clin Pharmacol Ther. 2011 Jul;90(1):77-89 |
Expert Opin Drug Metab Toxicol. 2011 Jun;7(6):697-706

Pharmacokinetic Differences

PK Parameter	Possible Alteration in Obese Population
Absorption	• Changes in gastric motility • Delayed or incomplete absorption of subcutaneous injections • Intramuscular injections inadvertently given as subcutaneous injections • Alterations in absorption of transdermal products

Clin Pharmacol Ther. 2011 Jul;90(1):77-89. | Expert Opin Drug Metab Toxicol. 2011 Jun;7(6):697-706
J Clin Pharm Ther, 2014, 39, 584–608 | Clin Infect Dis. 1997 Jul;25(1):112-8.

Pharmacokinetic Differences

PK Parameter	Possible Alteration in Obese Population

Distribution	• Changes in volume of distribution (Vd)
	  • Lipophilic vs. hydrophilic drugs
	• Alterations in protein binding
	  • Albumin not affected
	• Increase in cardiac output, blood volume, and tissue perfusion

Clin Pharmacol Ther. 2011 Jul;90(1):77-89. | Expert Opin Drug Metab Toxicol. 2011 Jun;7(6):697-706
J Clin Pharm Ther, 2014, 39, 584–608 | Clin Infect Dis. 1997 Jul;25(1):112-8.

Pharmacokinetic Differences

PK Parameter	Possible Alteration in Obese Population
Metabolism	• Altered liver blood flow due to increased fatty infiltration • Inconsistent changes in CYP450 enzymes • Increased glucoronidation and sulfation • Reduced drug clearance possible in patients with nonalcoholic steatohepatitis (NASH)

J Clin Pharm Ther, 2014, 39, 584–608 | Clin Pharmacol Ther. 2011 Jul;90(1):77-89. | BMJ Case Rep. 2012 Jul 12;2012.

Pharmacokinetic Differences

PK Parameter	Possible Alteration in Obese Population

Elimination/ Clearance (CL)	• Variable effects on renal function
	  • Increased GFR in healthy, obese patients, though not linear with TBW
	  • Increased risk of kidney dysfunction in obese patients with comorbidities

- Difficult to assess impact of obesity on renal clearance due to debate on which weight should be used in calculations

J Clin Pharm Ther, 2014, 39, 584–608 | Clin Pharmacol Ther. 2011 Jul;90(1):77-89.

Why does this matter?

Maximize efficacy

Minimize toxicity

Cost savings

J Clin Pharm Ther, 2014, 39, 584–608 | Clin Pharmacol Ther. 2011 Jul;90(1):77-89.

Patient Case

FJ is a 25 YOAAM with type 2 diabetes, obstructive sleep apnea, and depression. He is 69'' (175.3 cm) and weighs 173.8 kg. His BMI = 56.6 kg/m^2. Which of the following changes in pharmacokinetic parameters may be expected in FJ?

- A. Increased absorption of subcutaneous injections
- B. Significantly decreased albumin
- C. Decreased CYP enzymes
- D. Increased GFR

Enoxaparin

Mechanism of Action	Indications	PK	Dose
Low weight molecular heparin, inhibits factor Xa and factor IIa	VTE prophylaxis and treatment Acute coronary syndromes	**A**: 100% **D**: Vd 4.3 L **M**: Hepatic **E**: Urine	Prophylaxis: 40 mg once daily or 30 mg q12h Treatment: 1 mg/kg q12h or 1.5 mg/kg q24h

VTE = venothromboembolism

LexiComp | Enoxaparin Package Insert

Heparin

Mechanism of Action	Indications	PK	Dose
Potentiates antithrombin III, inactivates thrombin and clotting factors, inhibits formation of fibrin clots	VTE prophylaxis and treatment Acute coronary syndromes Atrial fibrillation	**A**: Well absorbed, subq and IV **D**: 0.07 L/kg **M**: Hepatic and reticulo-endothelial **E**: Nonrenal	Prophylaxis: 5000 units subq q8-12h Treatment: Various IV regimens, dosed in units/kg/hour ± a bolus

VTE = venothromboembolism

LexiComp | Heparin Package Insert

Enoxaparin: Prophylaxis

Author (year)	Borkgren-Okonek (2008)	Rondina (2010)
Design	Prospective, open-label, enoxaparin 40 or 60 mg subq q12h per BMI	Prospective study, enoxaparin 0.5 mg/kg subq once daily
Sample size	223 gastric bypass patents, stratified by BMI $\leq$ 50 or > 50 kg/m^2	28 patients, BMI $\geq$ 35 kg/m^2
Results	Target anti-Xa levels obtained in 79% of patients in 40 mg and 69% in 60 mg	Average anti-Xa level: 0.25 units/mL (SD $\pm$ 0.11)
Safety	4 patients in the 40 mg group and 1 patient in the 60 mg group developed bleeding	No bleeding events, VTE, or thrombocytopenia
Conclusions	BMI-stratified, high dose enoxaparin was well-tolerated and resulted in anti-Xa levels within target range	Enoxaparin 0.5 mg/kg once daily resulted in anti-Xa levels within or near recommended range

Surg Obes Relat Dis. 2008;4:625-631. | Ann Pharmacother 2011;45:1356-62.

Enoxaparin: Prophylaxis

Author (year)	Ludwig (2011)	Freeman (2012)
Design	Retrospective study, enoxaparin 0.5 mg/kg subq q12h	Prospective study, compared 3 enoxaparin regimens
Sample size	23 SICU patients, BMI $\geq$ 35 kg/m^2 or TBW $\geq$ 150 kg	31 patients, BMI $\geq$ 40 kg/m^2
Results	91% of patients achieved anti-Xa level of 0.2-0.5 units/mL	HD achieved target anti-Xa levels more frequently than LD or FD
Safety	One patient had a DVT, one patient had minor bleeding during suctioning, no HIT	No bleeding events, VTE, or thrombocytopenia
Conclusions	Enoxaparin 0.5 mg/kg q12h was effective in achieving target anti-Xa levels	Enoxaparin 0.5 mg/kg once daily is superior to FD or LD for achievement of target anti-Xa levels

Ann Pharmacother 2011;45:1356-62. | Am J Hematol. 2012 Jul;87(7):740-3.

Enoxaparin: Prophylaxis

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Design	Retrospective study, enoxaparin 0.5 mg/kg subq q12h	Prospective study, compared 3 enoxaparin regimens
Sample size	23 SICU patients, BMI $\geq$ 35 kg/m^2 or TBW $\geq$ 150 kg	Fixed-dose enoxaparin (FD): 40 mg q day Weight-based, low dose (LD): 0.4 mg/kg q day Weight-based, high dose (HD): 0.5 mg/kg q day
Results	91% of patients achieved anti-Xa level of 0.2-0.5 units/mL	
Safety	One patient had a DVT, one patient had minor bleeding during suctioning, no HIT	No bleeding events, VTE, or thrombocytopenia
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Ann Pharmacother 2011;45:1356-62. | Am J Hematol. 2012 Jul;87(7):740-3.

Enoxaparin, Heparin: Prophylaxis

Author (year)	Wang (2014)	Joy (2016)
Design	Retrospective cohort study	Retrospective cohort study, heparin alone
Sample size	3928 patients, weight > 100 kg and BMI ≥ 40 kg/m^2	1335 patients, > 100 kg
Results	High-dose prophylaxis halved the odds of VTE	No significant difference in incidence of VTE between groups
Safety	No difference in bleeding rates	Bleeding complications significantly higher in high-dose group
Conclusions	High-dose prophylaxis decreased the risk of in-hospital VTE without increasing bleeding	Higher doses of heparin not associated with a decrease in VTE, were associated with increased risk of bleeding and blood transfusion

Thromb Haemost. 2014 Jan; 111(1):88–93. | Pharmacotherapy. 2016 Jul;36(7):740-8.

Enoxaparin, Heparin: Prophylaxis

Author (year)	Wang (2014)	Joy (2016)
Design	Heparin 7500 units q8h Enoxaparin 40mg q12h	Retrospective cohort study, Heparin 7500 units q8h vs. 5000 units q8h
Sample size		
Results	of VTE	of VTE between groups
Safety	No difference in bleeding rates	Bleeding complications significantly higher in high-dose group
Conclusions	High-dose prophylaxis decreased the risk of in-hospital VTE without increasing bleeding	Higher doses of heparin not associated with a decrease in VTE, were associated with increased risk of bleeding and blood transfusion

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Enoxaparin, Heparin: Prophylaxis

Weighing in…which weight is it?

- CHEST Guidelines (2008):
  - "In obese patients given LMWH prophylaxis or treatment, we suggest weight-based dosing"
- CHEST Guidelines (2012):
  - "For thromboprophylaxis with fixed-dose enoxaparin and nadroparin, there is a strong negative correlation between total body weight and anti-Xa levels in obese patients"
  - "It may be prudent to consult with a pharmacist regarding dosing in bariatric surgery patients and other patients who are obese who may require higher doses of LDUH or LMWH"

CHEST 2008; 133:141S–159S | Chest. 2012;141(2_suppl):e24S-e43S. | Chest. 2012;141(2_suppl):e227S-e277S.

Enoxaparin, Heparin: Prophylaxis

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CHEST 2008; 133:141S–159S | Chest. 2012;141(2_suppl):e24S-e43S. | Chest. 2012;141(2_suppl):e227S-e277S.

Enoxaparin, Heparin: Prophylaxis

Weighing in…which weight is it?

- **No definitive answer**
- Expert opinion:
  - If BMI ≥ 40 kg/m^2:
    - Enoxaparin 40 mg subq q12h
    - Heparin 7500 units subq q8h (if CrCl < 30 mL/min)
  - If BMI ≥ 50 kg/m^2:
    - Consider enoxaparin 60 mg q12h or weight-based dosing

J Thromb Thrombolysis. 2016 Apr;41(3):475-81 | Hosp Pharm 2014;49:740–747 | Surg Obes Relat Dis. 2008;4:625-631.

Enoxaparin, Heparin: Prophylaxis

Monitoring parameters

- Renal function
- Hemoglobin/Hematocrit
- Platelets
- Signs/symptoms of bleeding
- Signs/symptoms of VTE

Anti-Xa Monitoring Limitations

- Lack of strong clinical correlation of Anti-Xa levels with patient outcomes
- Anti-Xa target levels are not well-defined
- Routine monitoring not warranted
  - If necessary to obtain, goal of 0.2-0.5 IU/mL suggested

Hosp Pharm. 2014;49:740-747. | Can J Hosp Pharm. 2015;68:33-47.
J Thromb Thrombolysis. 2016;41:475-481. | Ann Pharmacother. 2009;43:1064-1083.

Patient Case

ED is a 53 YOM with a PMH of HTN, CHF, T2DM, morbid obesity, and a history of prostate cancer. He presents to the ED with SOB and is admitted for a CHF exacerbation. The admitting service asks for a recommendation for VTE prophylaxis. Which of the following would you recommend?

Ht: 175 cm; Wt: 212 kg, BMI: 69 kg/m^2
SCr: 0.95 mg/dL; CrCl: > 120 mL/min

A. Enoxaparin 40 mg subq q24h
B. Enoxaparin 40 mg subq q12h
C. Enoxaparin 50 mg subq q12h
D. Enoxaparin 60 mg q12h

Patient Case

What therapeutic drug monitoring for ED's enoxaparin would you recommend?

Ht: 175 cm; Wt: 212 kg, BMI: 69 kg/m^2
SCr: 0.95 mg/dL; CrCl: > 120 mL/min

A. aPTT
B. INR
C. Anti-Xa
D. None

Anticoagulants Summary

Anticoagulant	Recommendation in Obesity
Enoxaparin	BMI $\geq$ 40 kg/m^2: enoxaparin 40 mg subq q12h BMI $\geq$ 50 kg/m^2: Consider enoxaparin 60 mg subq q12h or weight-based dosing
Heparin	BMI $\geq$ 40 kg/m^2: heparin 7500 units subq q8h

Anticoagulants Summary

Anticoagulant	Recommendation in Obesity
E	BMI ≥ 40 kg/m^2: enoxaparin 40 mg subq q12h g
Heparin	BMI ≥ 40 kg/m^2: heparin 7500 units subq q8h

Always consider patient's clinical picture

KEY TAKEAWAYS

1) Standard VTE prophylaxis dosing may not be adequate in patients with a BMI $\geq$ 40 kg/m^2

2) Though no definitive answer, higher doses of VTE prophylaxis have been safe and effective in cohort studies

3) Anti-Xa monitoring is not routinely recommended in VTE prophylaxis due to lack of correlation with clinical outcomes

Role of Extended Thromboprophylaxis in Medically Ill Post-Discharge

Thromboprophylaxis in Medically Ill

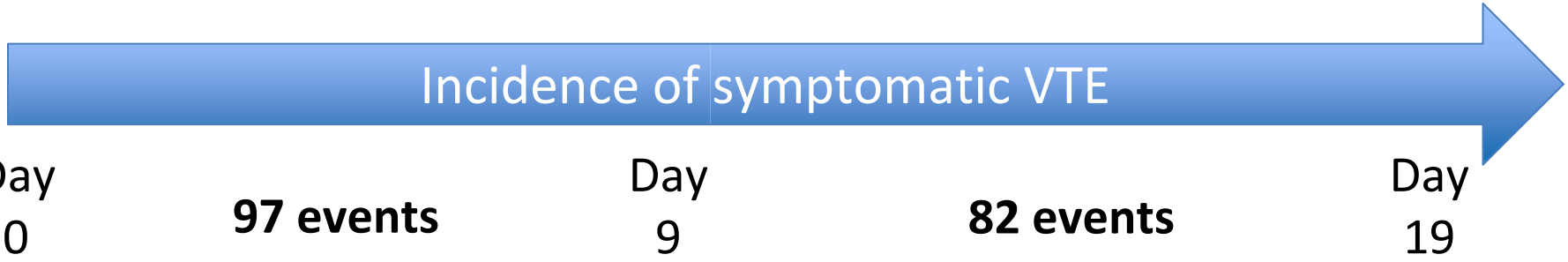
Trials	Study Design	VTE incidence	Median Days Received
MEDENOX (1999)	Enoxaparin x 6-14 days v. placebo	5.5% v. 14.9%	7
PREVENT (2004)	Dalteparin x 14 days v. placebo	2.8% v. 4.9%	14
ARTEMIS (2006)	Fondaparinux x 6-14 days v. placebo	5.6% v. 10.5%	7

N Engl J Med, 1999 Sept;341(11):793-800. | Circulation. 2004 Aug;110(7):874-9. | BMJ. 2006 Feb;332(7537):325-9.

Need for Extended Thromboprophylaxis

- 11,139 patients evaluated post-discharge
- Median length of stay: 5.0 +/- 4.7 days
- 366 (3.3%) symptomatic events across 180 days
- Nearly half of events occurred in first 19 days

Cancer
Heart failure
Severe lung disease/COPD
Infectious disease



J Hosp Med, 2012 Mar;7(3):231-238.

EXCLAIM (2010)

Enoxaparin 40 mg SQ Qday x 10 ± 4 days (n=2485)	Placebo x 28 ± 4 days (n=2510)

Primary outcome: Composite VTE post randomization x 28 ± 4 days

Event	Enoxaparin	Placebo
Composite VTE	65 (2.5)	100 (4.0)
Symptomatic DVT	5 (0.2)	20 (0.8)
Asymptomatic DVT	55 (2.2)	75 (3.0)
Symptomatic PE	0 (0.2)	4 (0.2)
Asymptomatic PE	1 (0.1)	1 (0.1)

Ann Intern Med, 2010 Jul;153(1):8-18.

Data reported as n(%)

EXCLAIM (2010)

- Secondary outcomes (enoxaparin v. placebo):

↓ Composite VTE at 90 days: 65 (2.6%) v. 105 (4.2%)
↑ Total bleeding: 186 (6.3%) v. 116 (3.9%)
↑ Major bleeding: 25 (0.8%) v. 10 (0.3%)
≈ Mortality: 39 (1.3%) v. 45 (1.5%)

Benefits of extended duration thromboprophylaxis with enoxaparin outweighed risk only in those with level 1 immobility, ≥ 75 years, and women

Ann Intern Med, 2010 Jul;153(1):8-18.

DOACs for Extended Thromboprophylaxis

	DOAC	Comparator	Inclusion Criteria
ADOPT (2011)	Apixaban 2.5mg BID x 30 days (n=2211)	Enoxaparin 40mg SQ Qday x ≥ 6 days (n=2284)	Hospitalized ≥ 3 days for specified acute illness Age ≥ 40 years Restricted mobility*
MAGELLAN (2013)	Rivaroxaban 10mg Qday x 35 ± 4 days (n=2938)	Enoxaparin 40mg SQ Qday x 10 ± 4 days (n=2993)	Hospitalized within 72 hours for specified acute illness Age ≥ 40 years Reduced mobility

*Moderately restricted or severely restricted mobility

N Engl J Med, 2011 Dec;365:2167-77. | N Engl J Med. 2013 Feb;368:513-23.

DOACs for Extended Thromboprophylaxis

	Efficacy	Safety	Results (DOAC v. enoxaparin)
ADOPT (2011)	Total VTE or VTE-related death at day 30	All bleeding	Efficacy: 60 (2.7%) v. 70 (3.1%); **NS** Safety: 15 (0.47%) v. 6 (0.19%); **p=0.04**
MAGELLAN (2013)	Composite VTE event at days 10 and 35	Clinically relevant bleeding	Day 10: 78 (2.7%) v. 82 (2.7%) **p=0.003 for non-inferiority** Day 35: 131 (4.4%) v. 175 (5.7%) **p=0.02 for superiority** Safety: 161 (4.1%) v. 67 (1.7%); **p<0.001**

N Engl J Med, 2011 Dec;365:2167-77. | N Engl J Med. 2013 Feb;368:513-23.

DOACs for Extended Thromboprophylaxis

	Conclusion
ADOPT (2011)	• Extended thromboprophylaxis with apixaban was **not superior** to shorter duration enoxaparin • **Significantly increased** bleeding with apixaban
MAGELLAN (2013)	• Rivaroxaban **noninferior** to enoxaparin for standard duration thromboprophylaxis • **Significantly reduced** VTE in extended duration thromboprophylaxis • **Significantly increased** clinically relevant bleeding

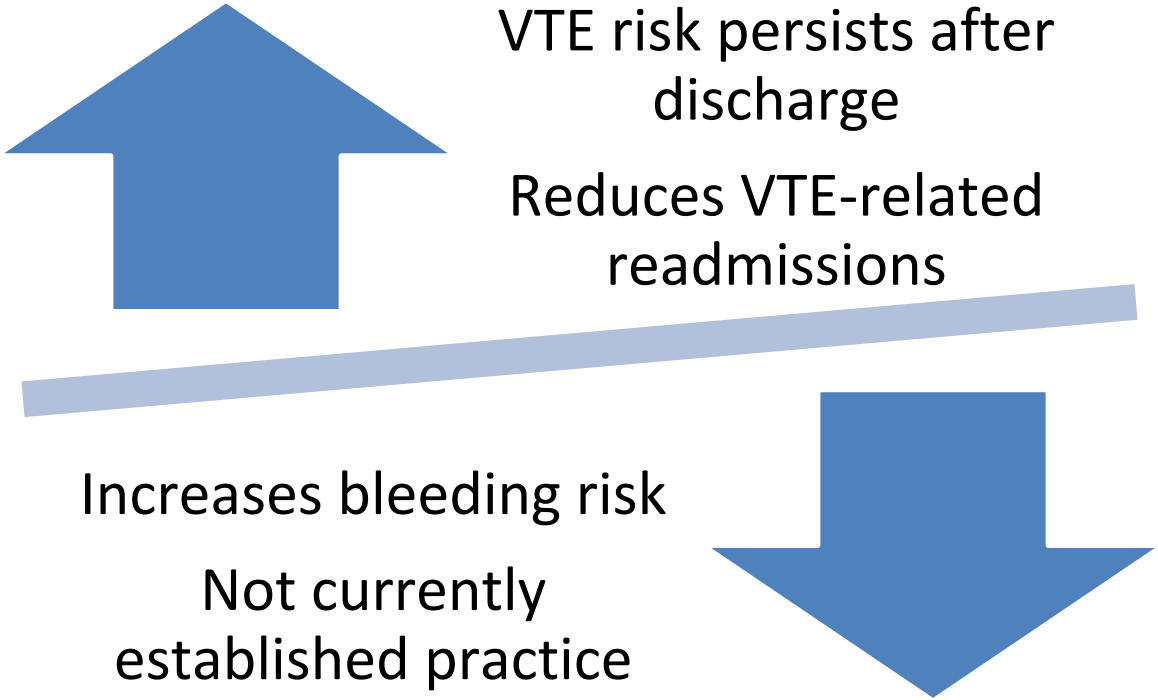
N Engl J Med, 2011 Dec;365:2167-77. | N Engl J Med. 2013 Feb;368:513-23.

Role of Extended Thromboprophylaxis

EXCLAIM (2010)	• Benefit of enoxaparin outweighs risk in select groups
ADOPT (2011)	• Apixaban less effective with increased bleeding
MAGELLAN (2013)	• Rivaroxaban proved effective, but with increased bleeding

Ann Intern Med, 2010 Jul;153(1):8-18. | N Engl J Med, 2011 Dec;365:2167-77. | N Engl J Med. 2013 Feb;368:513-23.

Role of Extended Thromboprophylaxis



CHEST Recommendations (2012)

Suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay

Chest, 2012 Feb;141(2 Suppl):e195S-e226S.

APEX (2016)

Betrixaban 160 mg x 1, 80 mg Qday x 35-42 days v.
Enoxaparin 40 mg SQ Qday x 10 ± 4 days

Betrixaban 40 mg given if CrCl <30 mL/min or concomitant p-glycoprotein inhibitors
Enoxaparin 20 mg SQ Qday if CrCl <30 mL/min

Cohort 1: Elevated d-dimer	Cohort 2: Elevated d-dimer or age>75	Cohort 3: Cohorts 1 and 2 combined
(n=3870)	(n=5735)	(n=6286)

Inclusion: age>40, hospitalized <96 hours for specified illness, reduced mobility, VTE risk factors

N Engl J Med, 2016 May;375:534-44.

APEX (2016)

	Cohort 1	Cohort 2	Cohort 3
Composite VTE	132 (6.9) v. 166 (8.5) **p=NS**	160 (5.6) v. 204 (7.1) **p=0.03**	165 (5.3) v. 223 (7.0) **p=0.006**
Asymptomatic	105 (5.5) v. 129 (6.6)	128 (4.5) v. 162 (5.6)	133 (4.3) v. 176 (5.5)
Symptomatic	19 (1.0) v. 36 (1.8)	23 (0.8) v. 39 (1.3)	23 (0.7) v. 40 (1.3)
Death from VTE	12 (0.6) v. 11 (0.6)	13 (0.5) v. 13 (0.4)	13 (0.4) v. 17 (0.5)
Major bleeding	15 (0.6) v. 17 (0.7) **p=NS**	25 (0.7) v. 21 (0.6) **p=NS**	25 (0.7) v. 21 (0.6) **p=NS**
+ Clinically relevant bleeding	72 (3.1) v. 44 (1.9) **p=0.009**	110 (3.2) v. 58 (1.7) **p<0.001**	116 (3.1) v. 59 (1.6) **p<0.001**

N Engl J Med, 2016 May;375:534-44.

Data reported for betrixaban v. enoxaparin; n(%)

APEX (2016)

- Extended duration betrixaban inferior to standard duration enoxaparin in acute medically ill with elevated d-dimer level
- Exploratory analyses suggest a benefit in other two larger cohorts (age >75 or elevated d-dimer, all cohorts enrolled)
- Similar major bleeding rates between betrixaban and enoxaparin

N Engl J Med, 2016 May;375:534-44.

APEX Substudy (2016)

Evaluated fatal or irreversible safety and efficacy events from APEX trial

Cohort 1 — Fatal bleed, ICH: 0 v. 4

- Composite events: 78 (3.5%) v. 96 (4.8%); **p=0.033**

Cohort 2 — Fatal bleed, ICH: 2 v. 6

- Composite events: 98 (3.1%) v. 124 (4.1%); **p=0.02**

Cohort 3 — Fatal bleed, ICH: 2 v. 6

- Composite events: 101 (2.9%) v. 136 (4.1%); **p=0.006**

Need to treat 65 patients with betrixaban to prevent 1 fatal or irreversible efficacy event

*Results from day 42 or visit 3

J Am Heart Assoc, 2017 Jul;6(7).

Data reported as betrixaban v. enoxaparin

Role of Betrixaban

June 23, 2017

FDA approved betrixaban (BEVYXXA, Portola) for the prophylaxis of venous thromboembolism (VTE) in adult patients

Considerations for use:

- Reduced betrixaban dose
- Major bleeding v. major + clinically relevant non-major bleeding
- Pharmacokinetics of betrixaban

N Engl J Med, 2016 May;375:534-44. | https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm564422.htm.

Comparing DOACs

Characteristic	Rivaroxaban	Apixaban	Betrixaban
Bioavailability (%)	80-100	50	34
Time to peak (hr)	2-4	3-4	3-4
Volume of Distribution (L/kg)	~50	~21	~32
Metabolism	CYP3A4/5, CYP2J2	CYP3A4/5, P-gp, BRCP	P-gp
$t_{1/2}$ (hr)	5-9; 11-13 (elderly)	~12	19-27

P-gp: P-glycoprotein; BRCP: breast cancer resistance protein

Lexicomp Online, Lexi-Comp, Inc.;2013; Sept 2018

Role of DOACs in Extended Thromboprophylaxis

	ADOPT	MAGELLAN	APEX
Primary Efficacy	Composite of symptomatic non-fatal PE, symptomatic/asymptomatic DVT, death related to VTE		
Primary Safety	All bleeding	Composite of major or clinically relevant non-major bleeding	Major bleeding
Outcome	Apixaban less effective, ↑ bleeding	Rivaroxaban proved effective, ↑ bleeding	Betrixaban effective in exploratory analyses, without ↑ major bleeding
NNT; NNH	NS; 357	77; 42	59; NS ***67**

NNT: number needed to treat; NNH: number needed to harm

N Engl J Med, 2011 Dec;365:2167-77.
N Engl J Med. 2013 Feb;368:513-23. I N Engl J Med, 2016 May;375:534-44.

Padua Prediction Score

- Stratified 1180 patients admitted to the hospital
- Observed patients for 3 months to assess VTE incidence
- 469 patients deemed high risk:
  - 35 VTE developed (7.5%)
- 711 patients deemed low risk
  - 2 VTE developed (0.3%)

High VTE risk ≥4

3 points each
Active cancer, prior VTE, reduced mobility, known thrombophilic condition
2 points each
Recent (<1 month) trauma or surgery
1 point each
Elderly age (>70 years), heart and/or respiratory failure, acute myocardial infarction, ischemic stroke, obesity (BMI≥30), hormonal treatment

J Thromb Haemost, 2010 Nov;8(11):2450-7.

IMPROVE Risk Assessment Model

- One of the largest, multicenter, externally validated VTE risk tools
- Evaluated 19,217 patients at two academic centers, age ≥18 years
- Incorporates 7 risk factors for VTE

Low risk (0-2): 0.49 event rate
High risk (≥3): 1.29 event rate

- IMPROVE risk score ≥3 equates to high risk for VTE

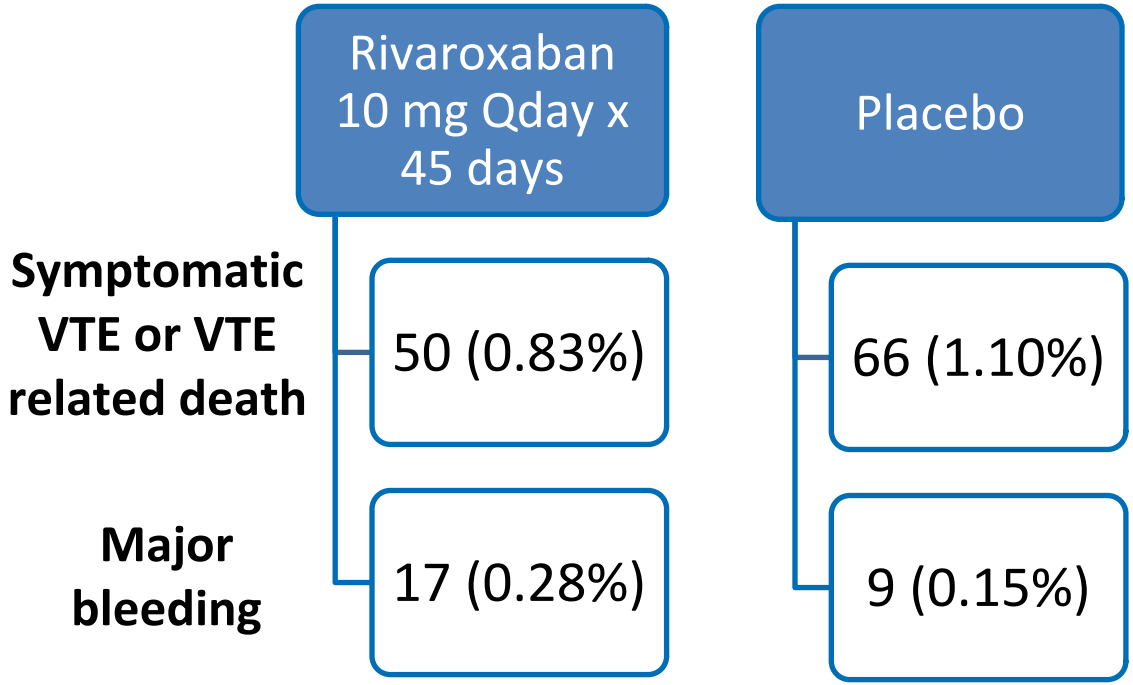
Prior VTE (3)
Prior cancer (2)
Lower limb paralysis (2)
Known thrombophilia (2)
Age >60 years (1)
ICU/CCU stay (1)
Immobility (1)

J Am Heart Assoc, 2014 Dec;3(6).

MARINER (2018)

Inclusion Criteria:

- Age ≥ 40 years
- Hospitalized for 3-10 days with specified acute illness
- IMPROVE score ≥ 4
- IMPROVE score ≥ 2 with elevated d-dimer
- Received VTE prophylaxis while admitted
- Randomized on day of discharge or day after



N Engl J Med, 2018 Sept;379:1118-1127.

MARINER (2018)

Rivaroxaban 10 mg Qday x 45 days after discharge was not associated with significantly lower symptomatic VTE or VTE related death.

Strengths

Utilized validated risk stratification tool
Did not evaluate asymptomatic VTE

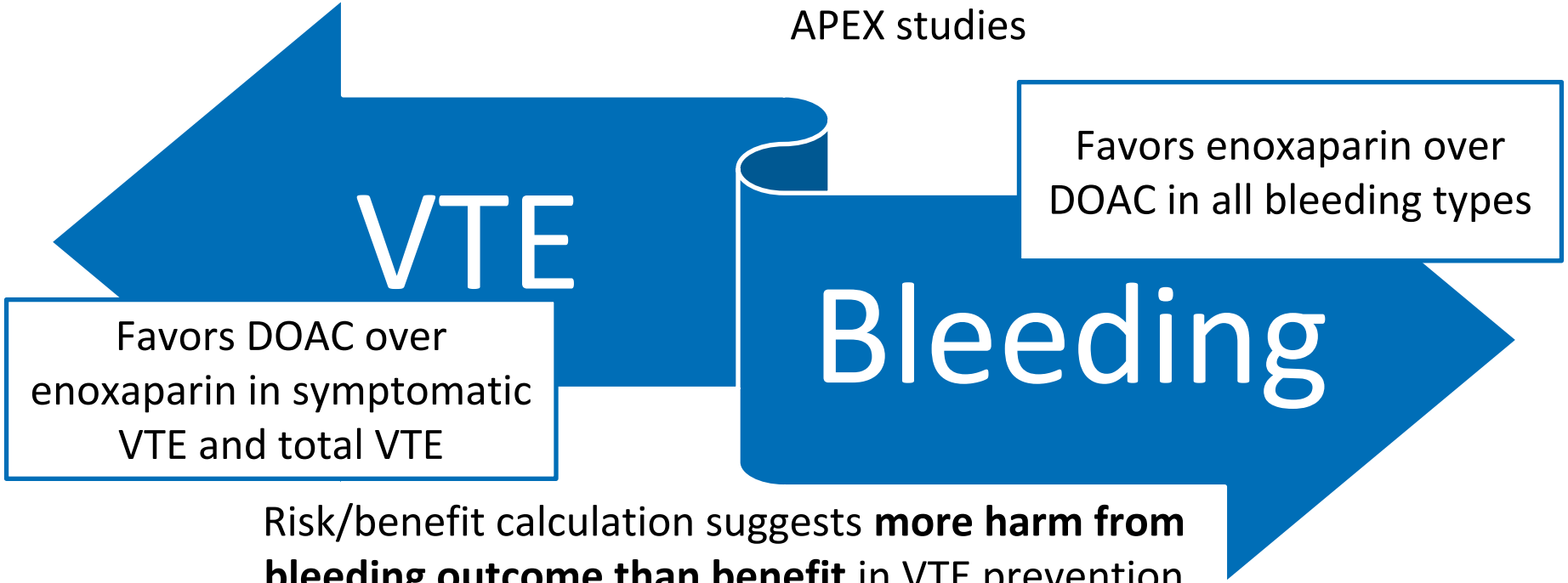
Weaknesses

Used modified form of tool
Excluded patients with active cancer

N Engl J Med, 2018 Sept;379:1118-1127.

Meta-Analysis – Al Yami, et al.

Included data from ADOPT, MAGELLAN, and APEX studies



Risk/benefit calculation suggests **more harm from bleeding outcome than benefit** in VTE prevention with extended DOAC thromboprophylaxis

J Blood Medicine, 2018 Feb;9:25-34.

Considerations for extended thromboprophylaxis

Is there a need for extended thromboprophylaxis?

- Impact of asymptomatic VTE, routine screening
- Risk v. benefit, heterogeneity of inclusion criteria in trials

Betrixaban only FDA-approved option for indication

- Cost analysis may be needed specific to each hospital
- Unanswered questions for utilization

Considerations for Betrixaban

- When to Initiate
- Affordability
- Managing Readmissions
- Patient Identification
- Bleeding Rates

Patient Case – Active Learning

JF is a 78 y/o WM admitted to the medical team for shortness of breath 2/2 possible HF exacerbation (EF 35%) and/or CAP. He is discharged home after three days with the following list of medications:

PMH: HTN, gout, CKD (CrCl 28 mL/min), Obesity (BMI: 32 kg/m^2)

Would this patient be a candidate for extended thromboprophylaxis with betrixaban?

Azithromycin 500 mg PO Qday
Cefdinir 300 mg PO Qday
Furosemide 40 mg PO BID
Losartan 25 mg PO Qday
Carvedilol 25 mg PO BID
Aspirin 81 mg PO Qday
Atorvastatin 40 mg PO QHS
Allopurinol 100 mg PO Qday

KEY TAKEAWAYS

1) Risk of VTE appears to persist after discharge with greatest incidence reported within first 19 days
2) Betrixaban is the only agent FDA-approved for extended thromboprophylaxis in medically ill
3) The need for extended thromboprophylaxis in medically ill and which patients will derive greatest benefit is still in question

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Keep It Flowing: Controversies Surrounding Venous Thromboembolism Prophylaxis Strategies

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