Venous Thromboembolism Case Disussions

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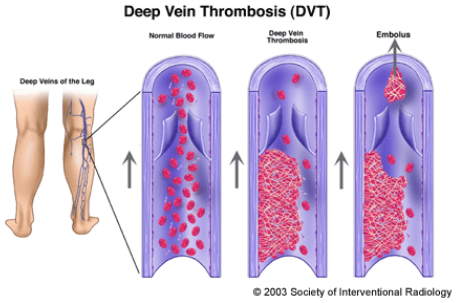
Deep Vein Thrombosis (DVT)



Presenter Disclosure

- Presenter's Name: Artemis Diamantouros
- I have the following relationships with commercial interests:
  - Advisory Board/Speakers Bureau – Sanofi, Leo Pharma
  - Funding (Grants/Honoraria) : Sanofi

Deep Vein Thrombosis - DVT

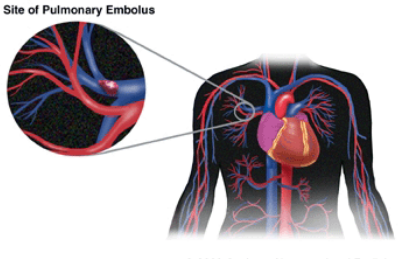
- Thrombus or blood clot in the deep vein system
  - Lower limbs (80-90%) & upper limbs
  - Renal, mesenteric, portal, splenic, cerebral
- Proximal DVT
  - Popliteal → iliac vein
  - 90% + of pulmonary emboli
- Distal or calf DVT (below popliteal)
  - Peroneal, post-tibial veins
  - < 5% of pulmonary emboli

Learning Objectives

By the end of this session, participants will be able to:

- Explain the concerns with the use of Low Molecular Weight Heparins (LMWH) in patients with increased body weight
- Summarize the evidence regarding the use of LMWHs as thromboprophylaxis and treatment in obese patients
- Make decisions about adjusting doses of LMWH when appropriate for patient management

Pulmonary Embolism



Pulmonary Embolism - PE

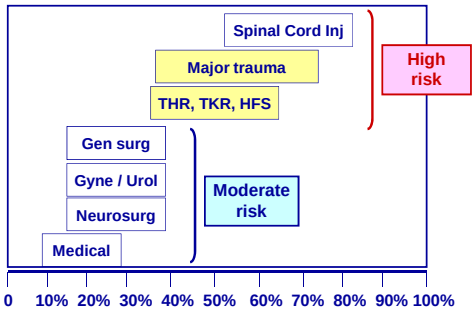
- Thrombus migrates / embolizes from deep veins to pulmonary arteries
- Massive PE:
  - Hemodynamic compromise
  - Shock, cardiac arrest – 5% of cases
- Submassive PE:
  - Right Heart Strain, normal BP (30%)
- Nonmassive PE
  - No heart strain, normal BP (65%)

Patient Case

- **66 year old male**
- **Diagnosed with colon cancer a month ago**
- **Scheduled for hemicolectomy**
- **Post-op day 1:**
  - **Started on enoxaparin 40mg SC daily**
- **Post-op day 2:**
  - **He becomes febrile and is started on antibiotics**
- **Post-op day 6:**
  - **Develops a swollen right leg**
  - **Doppler U/S shows a clot in his common femoral vein**

Risk of DVT in Hospitalized Patients

- **If no prophylaxis used + routine screening for DVT**



8th ACCP Guidelines on Antithrombotic Therapy (Geerts 2008)

Patient Case

- **Past Medical History:**
  - Hypertension x 7 years (well-controlled)
  - Colon Cancer – diagnosed one month ago
  - Some arthritis pain in the knees (osteoarthritis; mild, does not limit mobility) x 10 years
- **No known drug allergies**
- **Insurance coverage –** ODB plus private insurance

Risk Factors for VTE

- **Stasis**
  - **Age > 40**
  - **Immobility**
  - **CHF**
  - **Stroke**
  - **Paralysis**
  - **Spinal Cord Injury**
  - **Hyperviscosity**
  - **Polycythemia**
  - **Severe COPD**
  - **Anesthesia**
  - **Obesity**
  - **Varicose Veins**
- **Hypercoagulability**
  - **Cancer**
  - **High estrogen states**
  - **Inflammatory Bowel**
  - **Nephrotic Syndrome**
  - **Sepsis**
  - **Smoking**
  - **Pregnancy**
  - **Thrombophilia**
- **Endothelial Damage**
  - **Surgery**
  - **Prior VTE**
  - **Central Lines**
  - **Trauma**

Patient Case

- **Bloodwork**
  - **Hemoglobin is now 109**
  - **Platelets = 66**
  - **Weight = 160 kg**

Is this a case of hospital-acquired VTE?

Outline

- Review of the literature
  - VTE Prophylaxis
    - Obesity
  - Treatment of VTE
    - Obesity

Did the patient receive appropriate VTE prophylaxis?

Enoxaparin 40mg daily?

VTE Prophylaxis in Obesity

Patient Management

A look at the literature

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Comparative Effectiveness Review of Thromboprophylaxis in Special Populations

- Comparative effectiveness review
- Patients with renal insufficiency, **obesity**, or on Antiplatelet Agents
- 9 controlled studies – 5 trials, 4 observational studies

Kebede S, et al. J Hosp Med. 2013;8(7):394-401

VTE Prophylaxis and Obesity

- Two studies included in the comparative effectiveness review
- 1 subgroup analysis (Kucher, PREVENT)
  - Dalteparin 5000 IU/day vs placebo
- Freeman et al, 31 medical ill patients with extreme obesity (BMI > 40)
  - Enoxaparin 40mg
  - Enoxaparin 0.4mg/kg
  - Enoxaparin 0.5mg/kg

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Obese patients and VTE prophylaxis

Obese patients				
Kucher et al., 2005[11]	Arm 1 (dalteparin), 558	2.8% (95% CI: 1.3–4.3)	0%	Mortality at 21 days: 4.6%
	Arm 2 (placebo), 560	4.3% (95% CI: 2.5–6.2)	0.7%	Mortality at 21 days: 2.7%
Freeman et al., 2012[12]	Arm 1 (fixed-dose enoxaparin), 11	NR	NR	Peak anti-factor Xa level ~1.9 %
	Arm 2 (lower-dose enoxaparin), 9	NR	NR	Peak anti-factor Xa level ~.32 %
	Arm 3 (higher-dose enoxaparin), 11	NR	NR	Peak anti-factor Xa level ~.86 %

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Kebede et al, J Hosp Med 2013; 8(7):394

Obesity and VTE Prophylaxis

Intervention	Outcome	Risk of Bias	Evidence Statement and Magnitude of Effect
Obese patients			
Dalteparin vs placebo	VTE	Moderate	Insufficient evidence for effectiveness of dalteparin vs placebo in reducing total VTE in obese patients; 2.8% vs 4.3%, RR: 0.64, 95% CI: 0.32-1.28
Dalteparin vs placebo	Mortality	Moderate	Insufficient evidence for effectiveness of dalteparin vs placebo in reducing mortality in obese patients; 9.9% vs 8.6%, $P = 0.36$
Dalteparin vs placebo	Major bleeding	Moderate	Insufficient evidence for safety of dalteparin vs placebo in reducing major bleeding in obese patients; 0% vs 0.7%, $P > 0.99$
Enoxaparin 40 mg daily vs 0.4 mg/kg	Percentage of patients achieving target anti-factor Xa level	Moderate	Insufficient evidence for effectiveness of enoxaparin 40 mg daily versus 0.4 mg/kg in achieving peak anti-factor Xa level in obese patients; 19% vs 32%, $P = NR$
Enoxaparin 40 mg daily vs 0.5 mg/kg	Percentage of patients achieving target anti-factor Xa level	Moderate	Insufficient evidence for effectiveness of enoxaparin 40 mg daily versus 0.5 mg/kg in achieving peak anti-factor Xa level in obese patients; 19% vs 86%, $P < 0.001$
Enoxaparin 0.4 mg/kg vs 0.5 mg/kg	Percentage of patients achieving target anti-factor Xa level	Moderate	Insufficient evidence for effectiveness of enoxaparin 0.4 mg/kg versus 0.5 mg/kg in achieving peak anti-factor Xa level in obese patients; 32% vs 86%, $P = NR$

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Kebede et al, J Hosp Med 2013; 8(7):394

Obesity and VTE Prophylaxis

- BJC Healthcare system
- 3928 patients (> 100 kg and BMI ≥ 40 kg/m^2)
- Modified standard orders to:
  - Heparin 7500 units TID (instead of 5000 units BID to TID) OR
  - Enoxaparin 40 mg BID (instead of 40mg daily)
- Primary safety outcome: bleeding events (ICD-9 codes)
  - Bleeding in high dose vs. standard = OR 0.84, 95% CI 0.66-1.07 (p=0.15)
- Rates of VTE:
  - Standard dose: 1.48%
  - Higher dose: 0.77%
  - OR = 0.52, 95% CI 0.27-1.00, p=0.050
- NNT = 140

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Wang TF, et al. Thromb Haemost 2014; 111:88

Obesity and VTE Prophylaxis

Riskof Bias – moderate

Obese patients			
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Insufficient evidence for safety…..effectiveness…..

Obesity and VTE Prophylaxis

Table 1: Demographics of the cohort, stratified by development of venous thromboembolism (VTE).

	VTE (N=132) Mean (SD)	No VTE (N=9,109) Mean (SD)	P-value
Age (years)	57.1 (15.2)	54.3 (13.8)	0.02
Weight (kg)*	119.8 (13.4)	118.6 (13.6)	0.32
BMI (kg/m^2)*	38.7 (5.2)	39.6 (6.5)	0.11
Female gender (%)	25.8 (n=34)	42.5 (n=3870)	<0.001
Non-Caucasian Race (%)**	14.4 (n=19)	26.1 (n=2378)	0.002
Median length of stay (days)	13.4	4.3	<0.001

*Based on 95% Winsorised values. **Non-White Race: includes 2298 African Americans, 8 Asian, 12 American Indian, and 79 Other Race patients.
Kg, kilogram; SD, standard deviation; BMI, body mass index.

Wang TF, et al. Thromb Haemost 2014; 111:88

Obese Patients and Prophylaxis

- Risk of underdosing especially in high-risk patients
- No current guidelines
- Consider dose increase
  - *Double usual prophylactic dose*
  - E.g. enoxaparin 40mg SC BID
  - (or 30mg SC BID if also renal insufficiency)
  - > 120 kg, enoxaparin 0.4mg/kg BID (dalteparin 40U/kg BID)

VTE Prophylaxis in morbid obesity

- Vandiver et al (2016)
  - Literature review and dosing recommendations
- Main recommendations
  - Anti-factor Xa
    - No clear clinical correlation
    - Questionable clinical utility

Vandiver, et al. J Thromb Thrombolys 2016; 41:475

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  - > 120 kg, enoxaparin 0.4 to 0.5 mg/kg BID (dalteparin 40U/kg BID)

VTE Prophylaxis in morbid obesity

- Specific recommendations largely based on expert opinion

Medication	Recommended dosing regimen
Enoxaparin	Enoxaparin 40mg SC BID
Unfractionated heparin	7500 units SC TID
Fondaparinux	Consider using enoxaparin if not contraindicated. If unable to substitute, use standard fondaparinux 2.5 mg SC DAILY
Other LMWHs (dalteparin, tinzaparin, nadroparin)	Consider using enoxaparin. If unable to subsitute, consider increasing the daily dose by 25-30%

Vandiver, et al. J Thromb Thrombolys 2016; 41:475

Obese Patients and Prophylaxis

Weight (kg)	Enoxaparin 0.4mg/kg BID	Dalteparin 40 units/kg BID
< 50	30 mg once daily	2,500 U once daily
50-100	40 mg once daily	5,000 U once daily
100-125	40 mg BID	5,000 U BID
125-150	60 mg BID	7,500 U BID
150-200	80 mg BID	10,000 U BID

What would be the most appropriate VTE prophylaxis in this patient?

- ❑ Rivaroxaban 20mg DAILY
- ❑ Enoxaparin 40 mg DAILY
- ❑ Enoxaparin 40 mg BID
- ❑ Dalteparin 5000 units DAILY

Outline

- Review of the literature
  - VTE Prophylaxis
    - Obesity
  - Treatment of VTE
    - Obesity

What would be the most appropriate VTE prophylaxis in this patient?

- ❑ Rivaroxaban 15 mg BID
- ❑ Enoxaparin 250 mg DAILY
- ❑ Enoxaparin 150 mg BID
- ❑ Dalteparin 18,000 units DAILY

Treatment of VTE

Obesity

Obese Patients and VTE treatment

- LMWH subcutaneously has almost 100% bioavailability
- Distribution – mainly plasma and vascular tissues (not fat)
- Small cohort studies suggest dosing for treatment should be based on actual body weight not ideal body weight (Lim et al, J Thromb Thrombolysis 2010)

Treatment of VTE

Drug	Initial	Transition	Precautions
Warfarin	LMWH or UFH or Fondaparinux	Start warfarin at same time, target INR 2-3	5-10 days of bridging with LMWH
LMWH	LMWH	Stay with LMWH Continue with warfarin	Caution with LMWH in CrCl< 30mL/min
Dabigatran	LMWH x 5-10 days	Dabigatran 150mg BID (or 110mg BID)	Caution in CrCl< 30ml/min
Rivaroxaban	15mg BID x 21 days	20mg daily	Caution in CrCl<30mL/min
Apixaban	10mg BID x 7 days	5mg BID	Caution in CrCl<25mL/min

Obese patients and VTE treatment

- RIETE registry:
  - 50-100kg same bleeding and thrombotic outcomes as those > 100 kg
- SYNGERGY trial
  - Subpopulation of obese patients (n=3137)
  - Underdosing observed in 15% of patients randomized to enox (more likely in the obese vs. non-obese)

Obese patients and VTE treatment

- LMWH
  - Dose based on actual body weight
  - Do not dose cap
    - Based on limited data (small numbers)
    - And clinical experience
- Warfarin – INR
- DOACs
  - Limited number of patients with obesity in treatment trials
  - Outcomes did not seem different

DOACs for VTE prophylaxis

- Not an option as VTE prophylaxis for renal insufficiency
  - Not recommended in CrCl < 30mL/min
  - Apixaban cut off 25mL/min
- Insufficient evidence in extremes of weight

Where would the Direct Oral AntiCoagulants (DOACs) play a role?

Summary

- For patients with increased body weight or BMI
  - Consider dose increases in VTE prophylaxis
    - e.g. Enoxaparin 40mg SC BID
  - For VTE treatment, dose according to body weight
    - DO NOT dose cap

Comparing the new agents

	Dabigatran	Rivaroxaban	Apixaban
Target of action	Thrombin	Factor Xa	Factor Xa
Biovailability	6.5%	80%	66%
Dosing	OD or BID	OD or BID	BID
Pro-drug	Yes	No	No
Half-life	12-14	7-13	8-13
Renal clearance	80%	66% (30%)	25%
Drug Interactions	P-gp inhibitors Rifampicin, quinidine, amiodarone	Potent inhibitors of CYP 3A4 and P-gp	Potent CYP 3A4 inhibitors
Studied indications	•VTE prophylaxis •Stroke prophylaxis in afib (SPAF) •Treatment of VTE	•VTE prophylaxis •SPAF •Treatment of VTE	•VTE prophylaxis •SPAF •Treatment of VTE