Cardiovascular pharmacotherapy in special population: Morbid obesity

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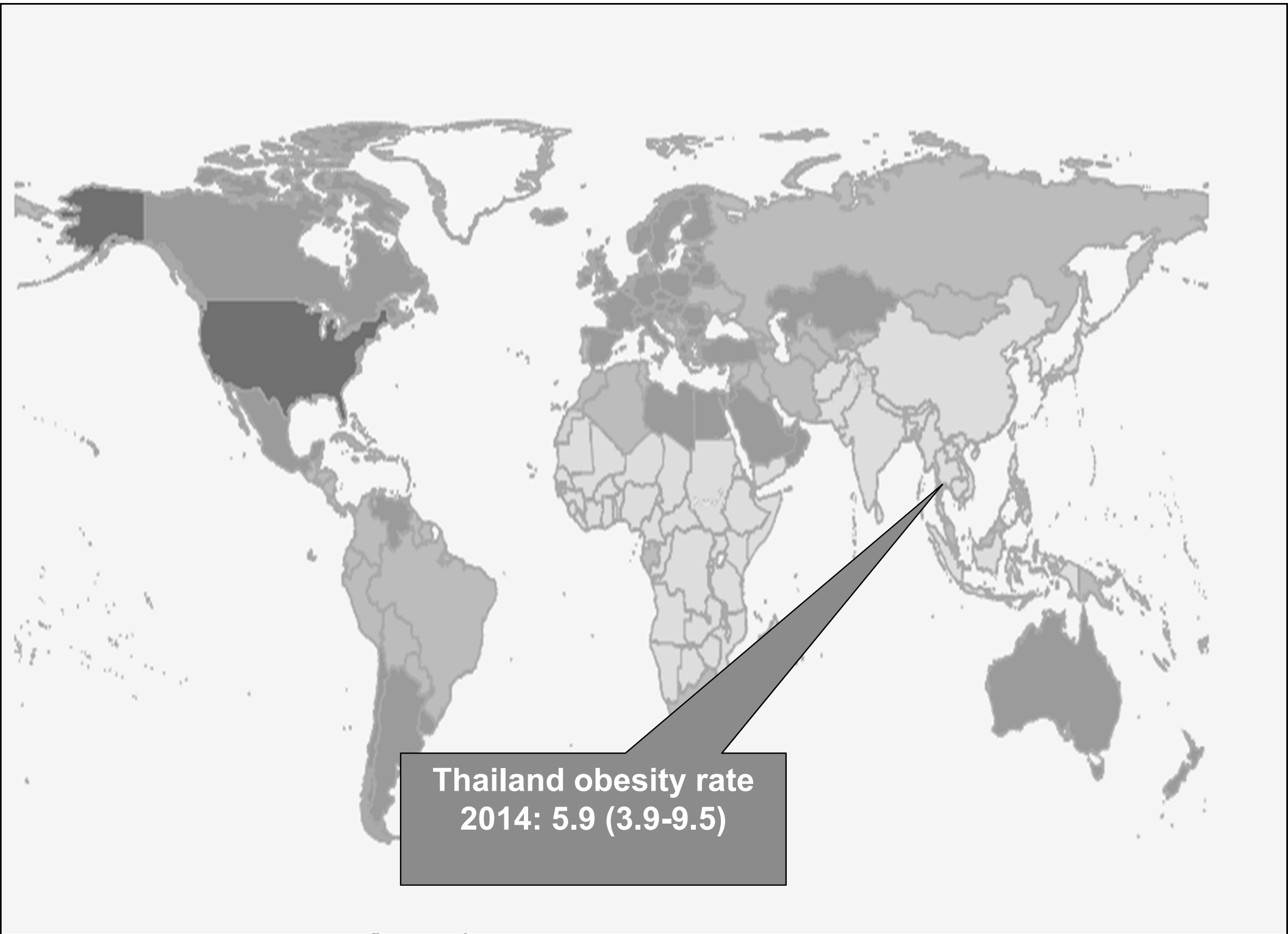
Case

- ชายไทยอายุ **61** ปี น้ำหนัก **150 kg** สูง **170** ซม.

  (BMI 48.7 kg/m^2)
- **CC: Shortness of breath and chest pain**
- **Spiral CT scan: Confirmed pulmonary embolism**
- **Which anticoagulant should we use and which dose?**



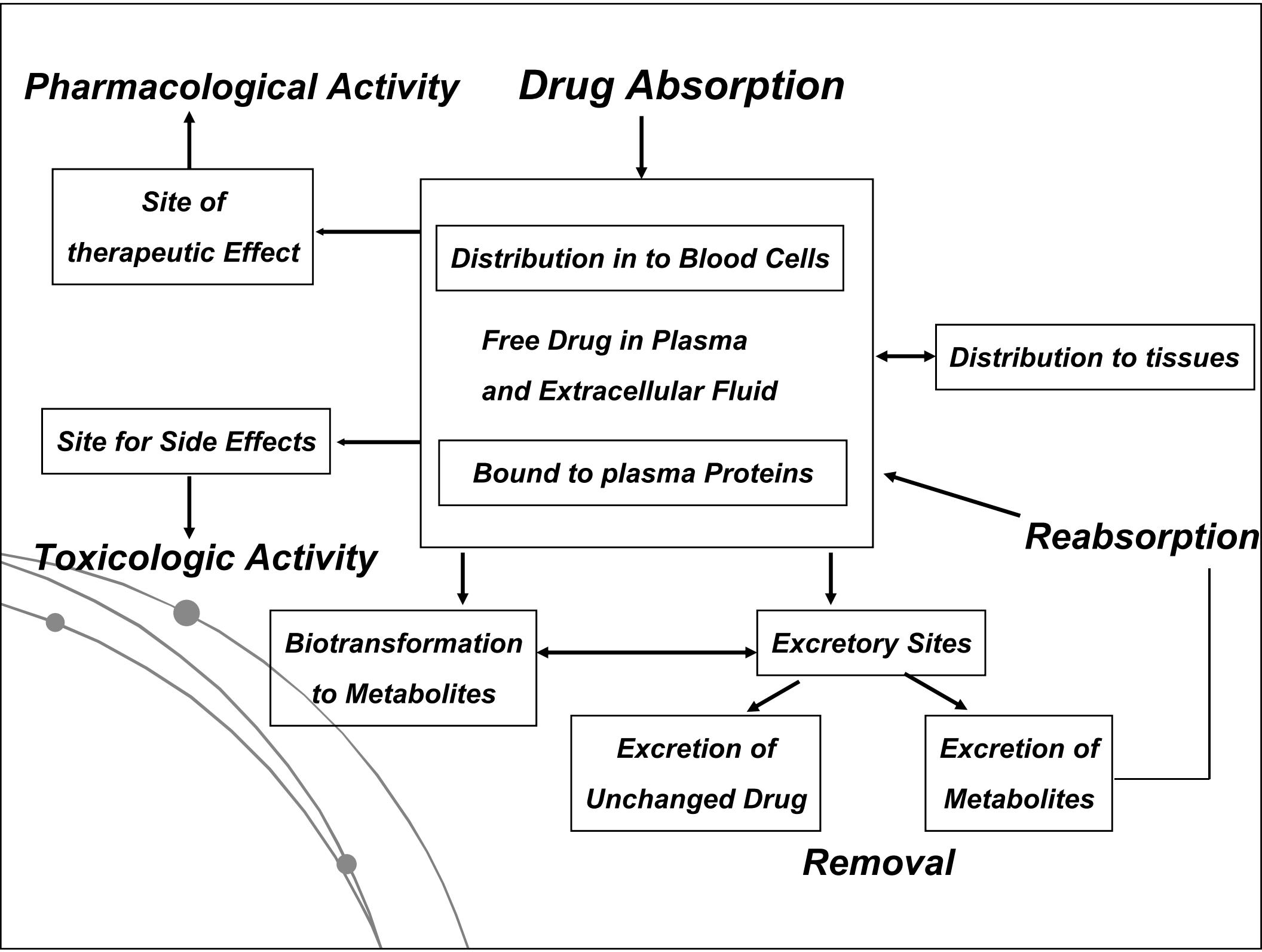
http://www.who.int/gho/ncd/risk_factors/overweight/en/

Cardiovascular pharmacotherapy in special population: Morbid obesity

- Obesity is not only associated with an increase in fat but also in lean body weight (LBW) which is the weight devoid of all adipose tissue.
- The percentage of fat mass per kg of total body weight increase more than LBW in obese patient.

Cardiovascular pharmacotherapy in special population: Morbid obesity

- Dosages of many medications are determined using patient weight, clinicians may have reservations about weight based dosing in obese patients due to the increased possibility of toxicities with larger doses.
- The practice of “capping” doses for obese patients may increase the risk that suboptimal dosing regimens may lead to treatment failure.


Pharmacological Activity
Drug Absorption
Site of therapeutic Effect
Distribution in to Blood Cells
Free Drug in Plasma and Extracellular Fluid
Distribution to tissues
Site for Side Effects
Bound to plasma Proteins
Reabsorption
Toxicologic Activity
Biotransformation to Metabolites
Excretory Sites
Excretion of Unchanged Drug
Excretion of Metabolites
Removal

Physiologic change in obesity

- ↑ Cardiac output, blood volume
- No change in serum albumin but ↑ alpha-1 acid glycoprotein
- ↑ Liver size
- Fatty infiltrate may effect drug metabolism
- ↑ LBM, adipose tissue
- ↓ Peripheral blood flow
- ↑ Kidney size, glomerular filtration

Measure of body size

- BMI: descriptor of body shape
- IBW: rarely use for drug dosing and dose not consider BW
- ABW: very little evidence for guide dosing
- BSA: use mostly in cancer
- LBW: fat-free mass less evidence

Size descriptor	Formula
BSA	Du Bois and Du Bois: $TBW\ (kg)^{0.425} \times HT\ (cm)^{0.725} \times 0.007184$ Mosteller: $\sqrt{(HT\ (cm) \times TBW\ (kg))/3600}$ Schlich: Men: $0.000579479 \times W^{0.38} \times HT^{1.24}$ Women: $0.000975482 \times W^{0.46} \times HT^{1.08}$
BMI	$TBW\ (kg)/HT\ (m^2)$
IBW	Men: $45.4\ kg + 0.89 \times (HT\ [cm] - 152.4)$ Women: $49.9\ kg + 0.89 \times (HT\ [cm] - 152.4)$
LBW	Men: $1.10 \times TBW - 0.0128 \times BMI \times TBW$ Women: $1.07 \times TBW - 0.0148 \times BMI \times TBW$ Based on BIA: $(9270 \times TBW)/(A + B \times BMI)$ Men: $A = 6680;\ B = 216$ Women: $A = 8780;\ B = 244$
ABW	Calculate IBW and then increase final estimate by a certain proportion (usually 40%)

Sankaralingam S, et al. Can J Cardiol. 2015 Feb;31(2):167-76.

PK of drug in obese

- Drug absorption and oral bioavailability are not change, except SC route.
- CL and Vd often change in obesity but the magnitude and direction are vary.
- Increase phase II metabolism while phase I is depend on type of CYP used.
- Renal clearance is higher.
- ClCr is very biased in obese when use TBW.

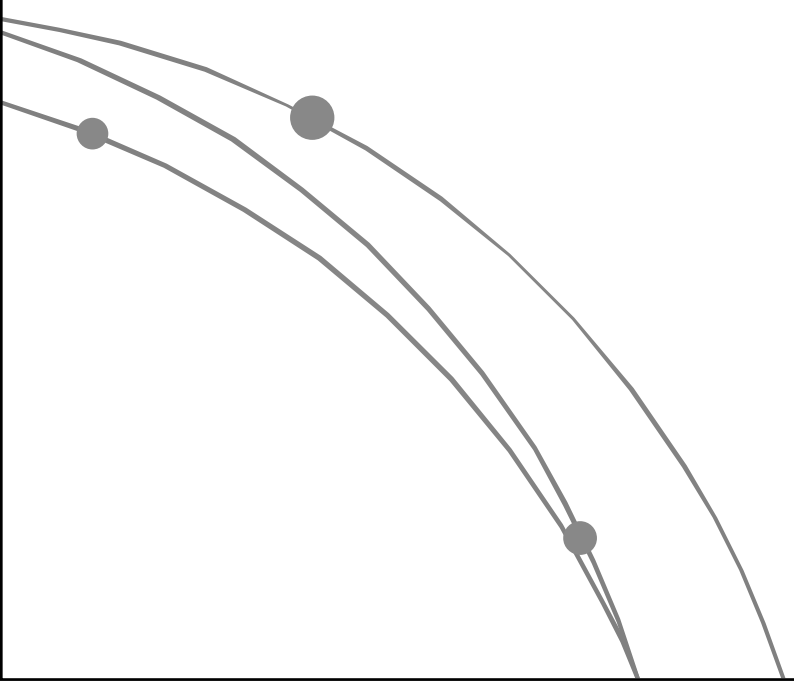
PK of drug in obese

- **Highly lipophilic drugs have increased Vd in patients with excess adipose tissue, and therefore may require higher bolus doses to rapidly achieve therapeutic plasma concentrations.**

- **Higher blood volume in obese patients may increase bolus dose requirements even for hydrophilic medications, while maintenance dosing of lipophilic medications must account for the potential for prolonged elimination half-life given the depot effect of adipose.**

UFH

- **The American College of Chest Physicians (ACCP) practice guidelines recommend weight-based dosing of UFH over fixed dosing in obese patients.**



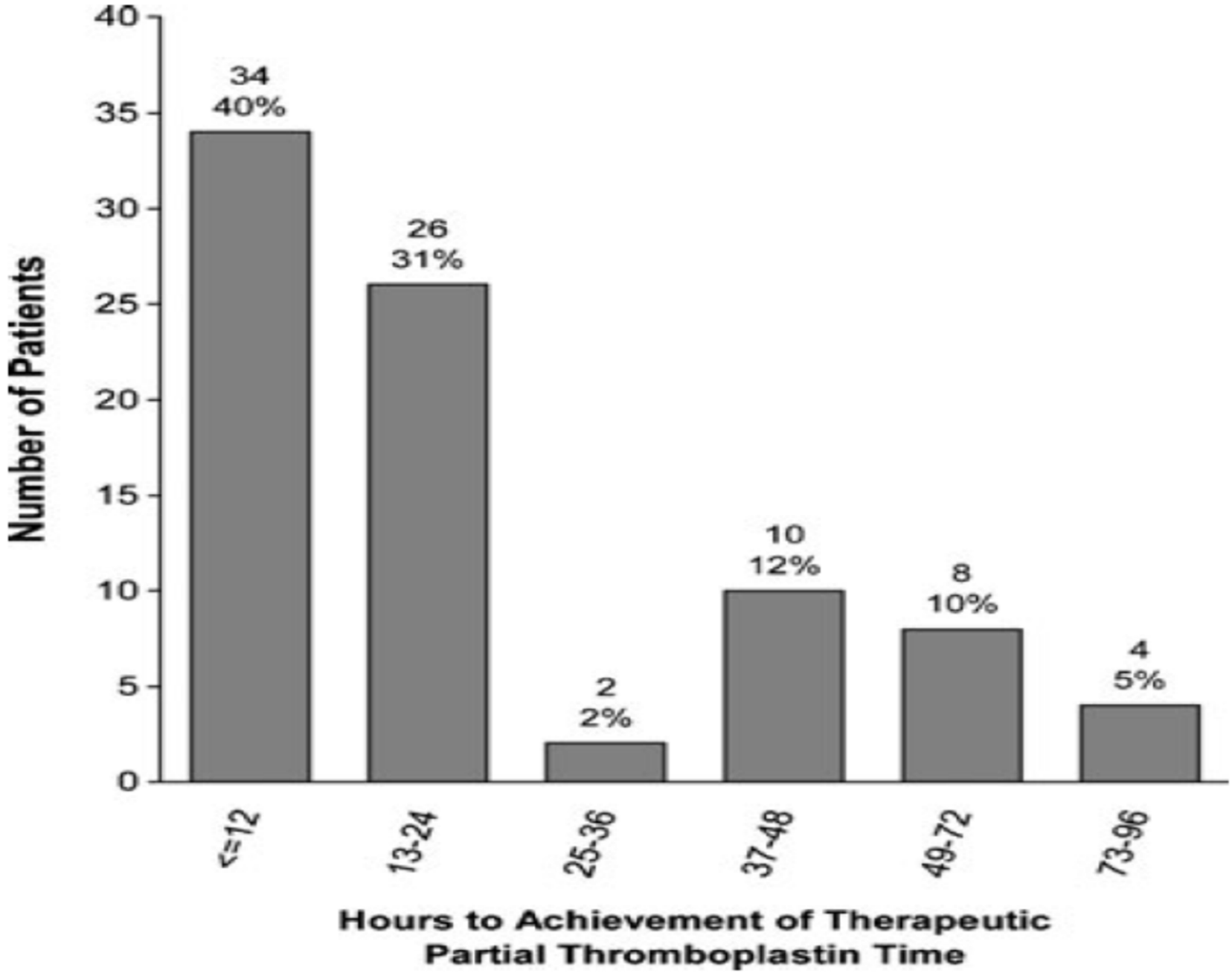


Figure 1. Hours required to achieve therapeutic anticoagulation (partial thromboplastin time >60 s). N=84.

Hurewitz AN, et al. J Gen Intern Med. 2011 May;26(5):487-91.

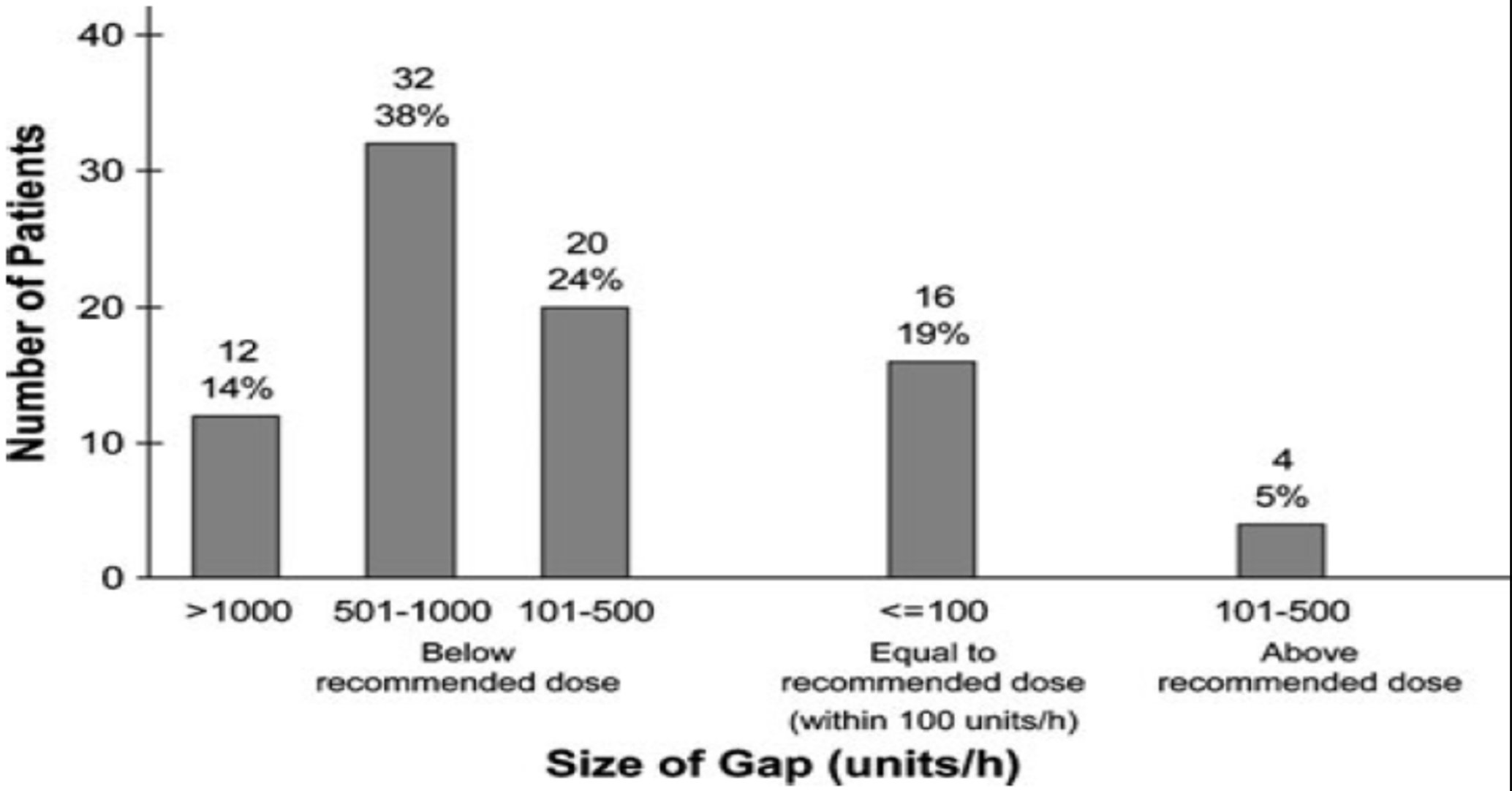


Figure 3. Gap between recommended and actual initial continuous heparin doses. Histogram shows number of patients receiving initial continuous heparin doses that fell below or above the recommended dose (18 units/kg/h) by the indicated amounts (units/h). N=84.

Hurewitz AN, et al. J Gen Intern Med. 2011 May;26(5):487-91.

Enoxaparin

- **Because obese patients have a lower proportion of lean body mass compared to their TBW, there are concerns about potential overdosing with the weight-adjusted therapeutic dose of LMWH and underdosing with the standard prophylactic dose of LMWH.**

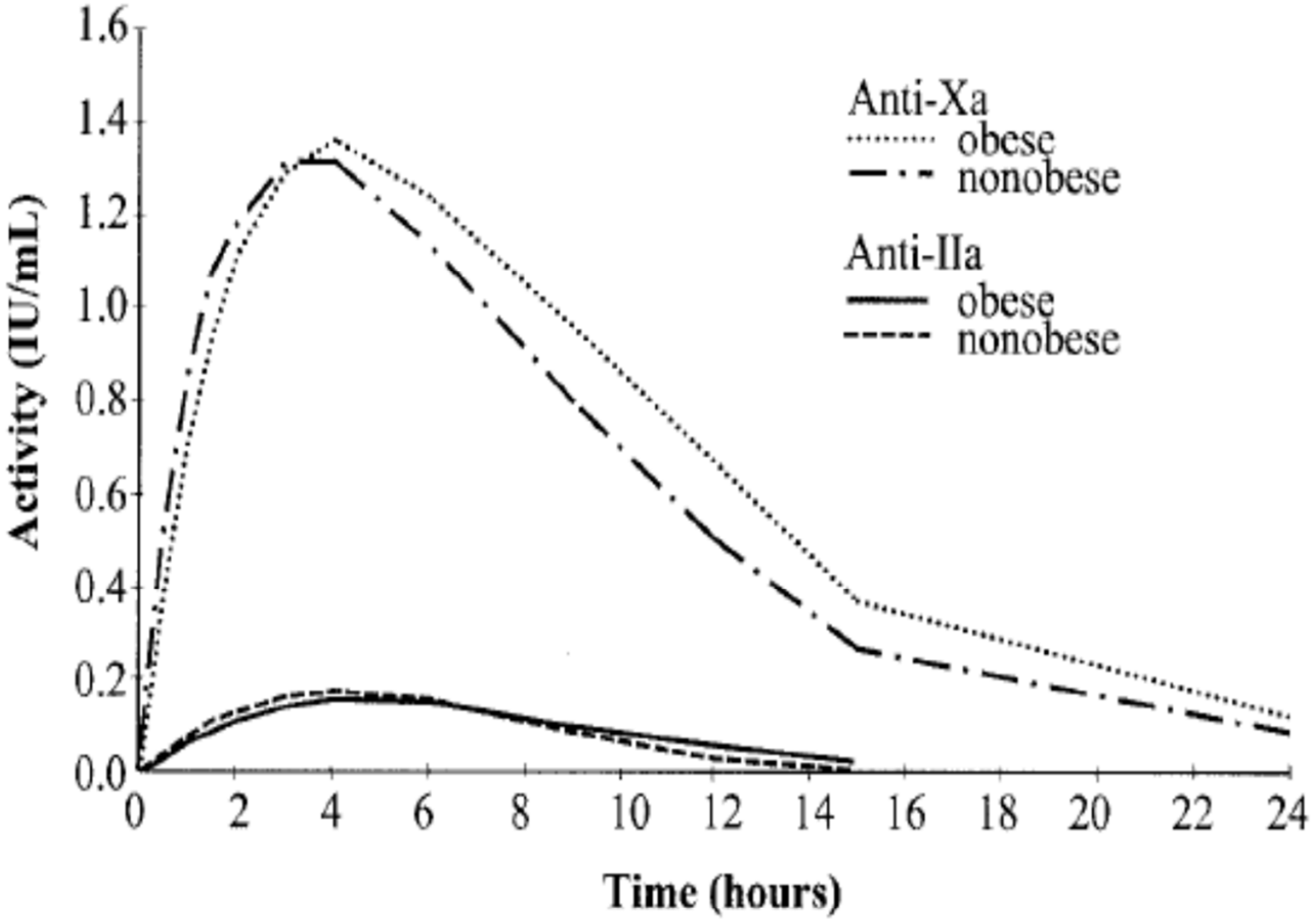


Fig 1. Mean anti-Xa and anti-IIa activity–versus–time profile in 24 obese volunteers and 24 nonobese volunteers after subcutaneous enoxaparin injection, 1.5 mg/kg, on day 1. IU, International units.

Sanderink GJ, et al. Clin Pharmacol Ther. 2002 Sep;72(3):308-18.

Table 3. Recurrence of Venous Thromboembolism and Attendant Risk Factors for All Treated Patients and Evaluable Patients

Clinical Outcome	Unfractionated Heparin Group	Once-Daily Enoxaparin Group	Twice-Daily Enoxaparin Group	Total
All treated patients, *n*	290	298	312	900
Recurrent venous thromboembolic event, *n* (%)*	12 (4.1)	13 (4.4)	9 (2.9)	34 (3.8)
Deep venous thrombosis (lower extremity), *n*	7	11	6	24
Deep venous thrombosis (upper extremity), *n*	1	0	1	2
Pulmonary embolism, *n*	1	1	2	4
Deep venous thrombosis and pulmonary embolism, *n*	3	1	0	4
Evaluable patients, *n*	235	247	258	740
Recurrent venous thromboembolic event, *n* (%)†	10 (4.3)	11 (4.5)	8 (3.1)	29 (3.9)
Risk factors for recurrent thromboembolism for all treated patients (occurrences/patients at baseline), *n*/*n* (%)				
Obesity	3/122 (2.5)	10/137 (7.3)	5/146 (3.4)	18/405 (4.4)
Pulmonary embolism at baseline	4/88 (4.5)	5/94 (5.3)	5/105 (4.8)	14/287 (4.9)
Asymptomatic	0/44 (0.0)	1/54 (1.9)	2/59 (3.4)	3/157 (1.9)
Symptomatic	4/44 (9.1)	4/40 (10.0)	3/46 (6.5)	11/130 (8.5)
Cancer	3/45 (6.7)	6/49 (12.2)	3/47 (6.4)	12/141 (8.5)

* Treatment difference was 0.2% (95% CI, −3.04% to 3.49%) for once-daily enoxaparin compared with heparin and −1.2% (CI, −4.2% to 1.7%) for twice-daily enoxaparin compared with heparin.
† Treatment difference was −0.2% (CI, −3.45% to 3.84%) for once-daily enoxaparin compared with heparin and −0.6% (CI, −4.49% to 2.18%) for twice-daily enoxaparin compared with heparin.

Merli G, et al. Ann Intern Med. 2001;134:191-202.

Table 2.
Recommended Weight-Based Anticoagulant Dosing at Saint Vincent Hospital[a]

Medication	Usual Dosage[35]	BMI (kg/m²) Required for Dosage Adjustment	Weight (kg) Required for Dosage Adjustment[b]	Dosage Adjustment Based on CL_{cr} (mL/min)			
				Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
Enoxaparin							
Prophylaxis[12,13,36,39-41,c]	30 mg subcutaneously every 12 hr or 40 mg subcutaneously daily	≥35	>150	CL_{cr} >50: 0.5 mg/kg subcutaneously daily	CL_{cr} = 30–50: 0.5 mg/kg subcutaneously daily	CL_{cr} <30: 30 mg subcutaneously daily	Same as for moderate impairment
Treatment[12,13,36,d]	1 mg/kg subcutaneously every 12 hr or 1.5 mg/kg subcutaneously daily	≥35	>150	CL_{cr} ≥30: 1 mg/kg subcutaneously every12 hr or 1.5 mg/kg subcutaneously daily (as written on original order); *do not cap dose*	Same as for normal function	CL_{cr} <30: 1 mg/kg subcutaneously daily; *do not cap dose*	Same as for moderate impairment
Heparin							
Prophylaxis[12,14,43-45,e]	5000 units subcutaneously every 8 or 12 hr	30–50	>100	5000 units subcutaneously every 8 hr	Same	Same	Same
		>50	>150	7500 units subcutaneously every 8 hr	Same	Same	Same
Treatment[12,14,30,46-48,50,51]	For DVT/PE: 80 units/kg by i.v. bolus, then 18 units/kg/hr by i.v. infusion For ACS: 60 units/kg by i.v. bolus, then 12 units/kg/hr by i.v. infusion	>30	>100	Use ABW for dosing[f]; *do not cap dose*	Same	Same	Same

ABW = IBW + 0.4(TBW – IBW)

IBW male = 50 + (2.3 x ส่วนสูงเป็นนิ้วที่เกินจาก **150** ซม.**)**
IBW female = 45.5 + (2.3 x ส่วนสูงเป็นนิ้วที่เกินจาก **150** ซม.**)**

Russell JM, et al. Am J Health Syst Pharm. 2015 Oct 1;72(19):1656-63.

Other medications

- Lipophilic BBs: may need higher dose to achieve steady state.
- Verapamil: may prolong elimination and the effect may slightly reduce.
- Amiodarone, digoxin, propranolol: may need more supplemental dose.
- Warfarin: may require higher dose of warfarin to maintain a therapeutic INR.
- NOACs: Cmax and AUC may lower

Thank you