MSHP Annual Meeting 2016

Controversies & Conundrums in Obesity

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Objectives

- Describe pharmacokinetic and pharmacodynamic changes in obesity
- Identify the appropriate dosing and monitoring of anticoagulants in obese patients
- Integrate concepts of dosing strategies for anticoagulants in obese patients

Controversy #1

- MG is a 51 yo male initially admitted to an outside hospital with ADHF. After 5 days, he is transferred to your facility with recurrent VT.
  - PMH: HFrEF (25%), Afib, T2DM
  - PTA: dabigatran
  - Weight: 158kg, BMI:54, CrCl >100ml/min
- Upon arrival to the CCU he is cardioverted due to hemodynamic instability, now in NSR.

What is the optimal anticoagulant for MG at presentation?

Definitions

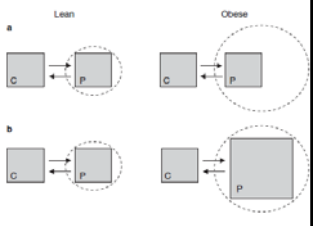
WHO Classifications – BMI

Normal Weight	Overweight	Obese Class I	Obese Class II	Obese Class III
18.5 – 24.9	25 – 29.9	30 – 34.9	35 – 39.9	≥ 40

- Body fat percentage, waist-circumference, waist-hip ratio
- LBW, IBW, ABW, adjusted BW
- *Lean muscle vs adipose?*

Pharmacokinetic Changes: Volume of Distribution

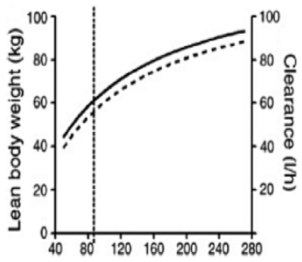
- Extent of distribution into extravascular tissues
- Lipophilicity
- Molecular size
- Tissue perfusion
- Plasma protein binding



Hanely et al. *Clin Pharmacokinet* 2010;4971-87.

Pharmacokinetic Changes: Drug Clearance

- ↑ GFR
- ↑ renal plasma flow
- CYP 450??
- Non-linear changes



Patel et al. *British Journal of Haematology* 2011;155:137-49.

Parenteral Agents

Parenteral Agents

Agent	Vd (L/kg)	Protein Binding	Clearance	Elimination $t_{1/2}$
UFH	0.07 – 0.37	+++	Endothelial cells & macrophages*	Dose-dependent
Fondaparinux	0.1 – 0.12	+++	↑↑ Renal	17 – 21 hrs
Enoxaparin	0.06 – 0.08	++	↑↑ Renal	5 – 7 hrs

- Adipose tissue less vascularized than lean muscle
- Altered levels of AT in obesity

Unfractionated Heparin

Table 3. Infusion Rates to First and Two Consecutive Therapeutic aPTTs Separated by Indication[a]

Parameter	Weight Classification (BMI range, kg/m²) ≥40	25–39.9	<25	p Value
Infusion rate at first therapeutic aPTT				
VTE	12.5 ± 2.8 (n = 37)	13.2 ± 3.4 (n = 17)	15.6 ± 4.4 (n = 23)	0.005
Non–VTE-related indications	10.8 ± 3.1 (n = 50)	12.3 ± 3.0 (n = 63)	12.6 ± 2.7 (n = 57)	0.004
ACS	12.7 ± 2.5 (n = 19)	13.1 ± 3.2 (n = 21)	12.4 ± 2.8 (n = 27)	0.703
atrial fibrillation	9.2 ± 2.9 (n = 26)	11.7 ± 2.8 (n = 34)	13.4 ± 2.9 (n = 21)	<0.001
valve replacement	11.8 ± 1.3 (n = 5)	14.0 ± 2.3 (n = 8)	11.7 ± 2.0 (n = 9)	0.059
Other indications	NA (n = 0)	10.0 ± 2.6 (n = 3)	12.0 ± 2.6 (n = 3)	0.407
Infusion rate at 2 consecutive therapeutic aPTTs				
VTE	11.9 ± 3.3 (n = 29)	13.2 ± 3.3 (n = 13)	15 ± 4.7 (n = 17)	0.034
Non–VTE-related indications	11.2 ± 3.3 (n = 44)	12.6 ± 3.1 (n = 46)	12.3 ± 2.8 (n = 44)	0.073
acute coronary syndrome	13.2 ± 2.7 (n = 16)	13.5 ± 3.3 (n = 15)	11.8 ± 2.5 (n = 19)	0.145
atrial fibrillation	9.6 ± 3.1 (n = 23)	11.5 ± 2.9 (n = 24)	13.4 ± 3.2 (n = 18)	0.001
valve replacement	11.2 ± 2.2 (n = 5)	14.4 ± 2.3 (n = 7)	11.1 ± 2.0 (n = 7)	0.019
Other indications	NA (n = 0)	11.5 ± 0.7 (n = 2)	11.0 ± 0.0 (n = 1)	0.667

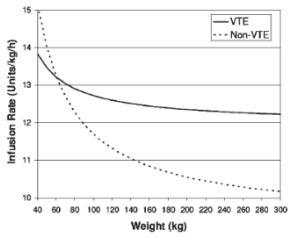
ACS = acute coronary syndrome; aPTT = activated partial thromboplastin time; BMI = body mass index; NA = not applicable; VTE = venous thromboembolism.
[a]Mean ± SD units/kg/h.

Riney et al. *Ann Pharmacother* 2010;44:1141-51.

Unfractionated Heparin

Table 5. Percentage of aPTTs in Therapeutic Ranges[a]

aPTT Status	Weight Classification (BMI range, kg/m²) ≥40 (n = 94)	25–39.9 (n = 92)	<25 (n = 87)	p Value
Therapeutic (60–94 sec)	50.1	45.7	48.7	0.463
Subtherapeutic (<60 sec)	17.9	24.5	29.5	0.001
Supratherapeutic (>94 sec)	32.0	29.8	21.9	0.008
first aPTT >150 sec	25.5	21.7	17.2	0.400
% of all aPTTs >150 sec	10.1	10.4	5.3	0.040



Patients with BMI >40 require LOWER un/kg/hr infusion to attain goal aPTT.

Riney et al. *Ann Pharmacother* 2010;44:1141-51.

Unfractionated Heparin

- Weight based dosing standard of care
- Use total body weight
  - As weight increased, Vd decreases, leading to lower weight-based doses
- Dose capping should generally not occur
- Weight likely one factor affecting UFH dose requirements

Fondaparinux – MATISSE Trials

Table 1 Baseline characteristics and enoxaparin/unfractionated heparin dose according to body weight and body mass index (BMI)

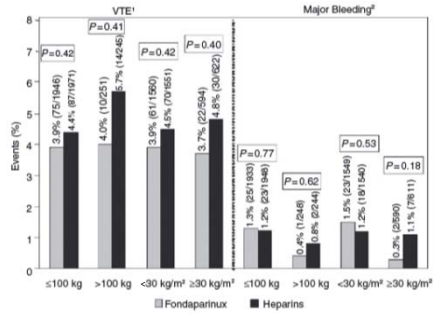
	Fondaparinux (n = 2201)				Heparin (n = 2217)			
	Body weight		BMI		Body weight		BMI	
	≤100 kg	>100 kg	<30 kg/m²	≥30 kg/m²	≤100 kg	>100 kg	<30 kg/m²	≥30 kg/m²
n (%)	1946 (88.4)	251 (11.4)	1560 (70.9)	594 (27.0)	1971 (88.9)	245 (11.1)	1551 (70.0)	622 (28.1%)
Median (range)	76.0 (33.2–100.0)	110.0 (100.5–175.5)	25.5 (12.8–29.9)	33.0 (30.0–80.3)	76.0 (33.0–100.0)	111.0 (100.5–216.7)	25.6 (12.6–29.9)	33.2 (30.0–78.1)
Age (years), mean ± SD	62.8 ± 16.5	54.0 ± 14.0	62.7 ± 16.8	59.6 ± 15.2	62.8 ± 16.7	54.0 ± 13.5	62.2 ± 17.3	60.8 ± 15.0
Women, n (%)	1207 (52.8)	89 (35.5)	739 (47.4)	356 (59.9)	1062 (53.9)	100 (40.8)	757 (48.8)	384 (61.7)
≥Two risk factors of VTE*, n (%)	748 (38.4)	80 (31.9)	595 (38.1)	217 (36.5)	747 (37.9)	87 (35.5)	592 (38.2)	220 (35.4)
Anticoagulant total dose, day 3, median (range)								
Enoxaparin (mg)	–	–	–	–	152 (60–200)	220 (106–344)	148 (60–220)	190 (95–344)
Unfractionated heparin, units	–	–	–	–	24,500 (1940–72 000)	33,460 (6000–82 184)	24,282 (1940–53 825)	28,080 (6000–82 184)

*Risk factors for venous thromboembolism (VTE) include estrogen use, immobilization, recent surgery or trauma, neoplastic disease, previous episodes of VTE and prothrombotic states.

- Standard dosing 5 – 10mg by weight
- Weight range inclued: 39 – 176kg

Davidson et al. *J Thromb Haemost 2007*;5:1191-4.

Fondaparinux – MATISSE Trials



Davidson et al. *J Thromb Haemost 2007;5*:1191-4.

Low Molecular Weight Heparins

- Variability within anti-Xa assays
- TBW provides best correlation to Vd & Cl
- Limited data suggests low level may correlate to poor outcome, inconsistent data regarding elevated levels
- Retrospective cohort 99 patients (BMI ≥ 40 or wt >150kg) had anti-Xa levels assessed after 3rd dose
  - 50% above goal, 35% within goal, 14% below goal
  - No data provided on clinical outcomes

Lee et al. *Pharmacotherapy 2015;35*:1007-15.

Low Molecular Weight Heparins

Trial	LMWH	Obese Definition	Outcome	Obese	Non-Obese
FRISC	Dalteparin	BMI ≥ 26	Death, MI	2.5%	0.8%
	UFH			4%	5.5%
Spinler	Enox	BMI ≥ 30	MACE/MB	14.3/0.4%	16.1/1.6%
	UFH			18/1.2%	19.2/1%
Merli	Enox	BMI > 26.9 M BMI > 27.2 F	Recurrent VTE	3.4%	2.9%
	UFH			2.5%	4.1%
Barba	LMWH	> 100kg	Recurrent VTE	0.7%	1%
			Major bleeding	1%	1.3%

FRISC Study Group. *Lancet* 1996;347:561-8., Spinler et al. *Am Heart J* 2003;146:33-41., Merli et al. Ann Intern Med 2001;134:191-202., Barba et al. *J Thromb Haemost* 2005;3:856-62.

Low Molecular Weight Heparins

- Dose should be based on total body weight
- Dose capping is not recommended*
- Twice daily dosing *may* be preferred
- Anti-Xa monitoring may be considered in those with BMI > 40 & is not routinely needed in those <190kg.

Nutescu et al. *Ann Pharmacother 2009;43*:1064-83.

Controversy #1

- MG is a 51 yo male initially admitted to an outside hospital with ADHF. After 5 days, he is transferred to your facility with recurrent VT.
  - PMH: HFrEF (25%), Afib, T2DM
  - PTA: dabigatran
  - Weight: 158kg, BMI:54, CrCl >100ml/min
- Upon arrival to the CCU he is cardioverted due to hemodynamic instability, now NSR.

What is the optimal anticoagulant for MG at presentation?

Oral Agents

Controversy #2

- MG is a 51 yo male initially admitted to an outside hospital with ADHF. After 5 days, he is transferred to your facility with recurrent VT. He was cardioverted & is now in normal sinus.
- After optimization of HF, VT & Afib have been suppressed with amiodarone.

What is the optimal anticoagulant for MG at discharge for stroke prevention?

Warfarin

- Numerous challenges with warfarin dosing
  - Genetic polymorphisms
  - Disease state and drug interactions
  - Age related metabolic changes
- Increased weight is correlated to higher dose requirement, not consistent predominant factor in dose determination

Target Specific Oral Agents

Characteristic	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	IIa	Xa	Xa	Xa
Bioavailability	7%	60-80%	80%	60%
$t_{1/2}$	12 – 17 hrs	7 – 11 hrs	8 – 13 hrs	10 – 14 hrs
Protein binding	35%	95%	87%	55%
Clearance	80% renal	60% renal 33% biliary	25% renal 75% biliary	50% renal 50% biliary
Vd (L)	60 – 70	50	21	3 – 4

All manufactures state no dose adjustment necessary in obesity

Galanis T et al. Thromb Thrombolysis 2011;31:310-320. Weitz et al. Circ 2010; 121:1523-32 Patel et al. British Journal of Haematology 2011;155:137-49.

Dabigatran

	RELY	RECOVER I + II
Population	Afib	DVT/PE
Primary outcome	2.2% vs 3.3%[#]	2.3% vs 2.2%*
Bleeding	6.5% vs 6.9%[+]	1.2% vs 1.7[+]
Weight (kg)	85.5 ± 19.4	83.2 ± 19.7 (36 – 184)
BMI	Not reported	28.4 ± 5.8

*[#]p<0.001, *non-inferior to comparator group, [+]NS difference between groups*

- Weight > 100kg
  - Trough concentrations 20% lower than those 50 – 100kg
- Attribute changes in concentration due to reliance upon renal elimination

Connolly et al. NEJM 2009;361:1139-51 Connolly et al. NEJM 2010;363:1875-6. DOI: 10.1161/CIRCULATIONAHA.113.004450. Personal communication from Boehringer Ingelheim Pharmaceuticals, Inc

Dabigatran – Clinical Outcomes

Weight (kg)	Dabigatran		Warfarin	
	Event/Total	Annual Event	Event/Total	Annual Event
40 – 50	4/119	1.9%	10/111	5.16%
50 – 100	111/4931	1.41%	170/4845	1.8%
≥ 100	18/1017	0.87%	20/1044	0.94

- Stroke
  - Higher rate of events seen in patients <50kg
  - No difference in bleeding event rates
  - Case report: 48yo M, BMI 45, weight 153kg after change from warfarin
- Orthopedic surgery
  - No difference in class I-III obesity

Personal communication from Boehringer Ingelheim Pharmaceuticals, Inc; Eriksson et al. Thromb Res 2012;130:818-20. Breurer et al. NEJM 2013;368:2440-2.

Dabigatran – VTE Outcomes

	Dabigatran	Warfarin	p value
Weight			
<50kg	0/26	1/31	0.99
50 – 100kg	42/2084	40/2127	
> 100kg	18/438	14/394	
BMI			
<25	10/655	16/704	0.48
25 – < 30	24/1035	18/1043	
30 – ≤ 35	16/544	15/527	
> 35	10/302	6/277	

- CI for weight >100kg & BMI > 35 shower higher incidence of VTE, favoring warfarin therapy

DOI: 10.1161/CIRCULATIONAHA.113.004450

Rivaroxaban

	ROCKET-AF	EINSTEIN-DVT	EINSTEIN-PE
Primary outcome	2.2% vs 3.3%*	2.1% vs 3%*	2.1% vs 1.8%*
Bleeding	6.5% vs 6.9%+	0.8 vs 1.2+	1.1 vs 2.2#
Weight (kg)	Not reported	82.2 (33 – 192.8)	82.9 (37.4 – 187)
BMI	28.3 (25.2 – 32.1)	Not reported	Not reported

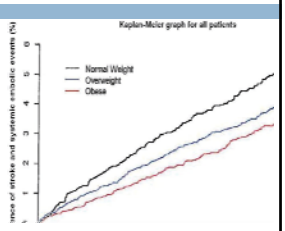
#p<0.001, *non-inferior to comparator group, +NS difference between groups

- PK/PD Metrics
  - Age & renal function predicted clearance
  - Weight impacted Vd, Cmax unchanged
- *Low* body weight may increase exposure

DOI:10.1056/NEJMoa1009638. DOI:10.1056/NEJMoa1113572. DOI:10.1056/NEJMoa1007903. Personal communication from Janssen Pharmaceuticals

Rivaroxaban – Afib Outcomes

BMI	Rivaroxaban	Event Rate
≤ 25	72/1695	4.25
25 – ≤ 35	169/4409	3.83
> 35	28/972	2.9

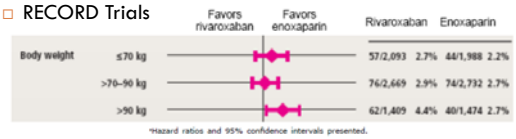


- No difference by weight compared to warfarin
- Higher rates of stroke & SEE noted in *lower* weight patients

J Am Coll Cardiol. 2014;63:12S. Personal communication from Janssen Pharmaceuticals, Inc;

Rivaroxaban – VTE Outcomes

- RECORD Trials



- EINSTEIN Pooled Analysis
  - < 50kg: *Higher* VTE with rivaroxaban compared to warfarin (7.1% vs 3.1%) but lower bleeding (0 vs 4.6%)
- EINSTEIN Extended
  - ↑ VTE in those ≤ 70kg (2.2%) compared to > 90kg (0.5%)

Prins et al. Thrombosis J 2013;11:21. Personal communication from Janssen Pharmaceuticals, Inc;

Apixaban

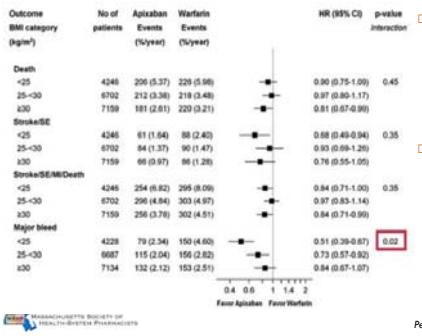
	ARISTOLE	AMPLIFY	AMPLIFY-EXT¥
Primary outcome	1.27% vs 1.6%#	2.1% vs 3%*	3.8% vs 11.6%#
Bleeding	2.13% vs 3.09#	0.8 vs 1.2+	0.2% vs 0.5%+
Weight (kg)	82 (29.4 – 205)	84.6 ± 19.8	85.7 ± 19.8
	NA	≥ 100kg: 19.4%	> 60kg: 92.9%

#p<0.001, *non-inferior to comparator group, +NS difference between groups ¥2.5mg data.

- PK/PD Metrics – Health subjects ≥120kg & BMI ≥ 30
  - Cmax 31% lower, AUC 23% lower
  - $t_{1/2}$ 3hrs shorter, Vd 24% higher, similar anti-Xa activity
- Minimal effects from obesity

DOI:10.1056/NEJMoa1107039. DOI:10.1056/NEJMoa1302507. DOI:10.1056/NEJMoa1207541. Upreti et al. BJCP 2013;76:908-16. Personal communication from BMS.

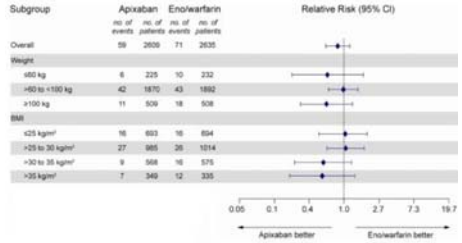
Apixaban – Afib Outcomes



- Efficacy favors BMI >30 compared to warfarin
- BMI >30 no reduction in bleeding compared to lower weight patients

Personal communication from BMS.

Apixaban – VTE Outcomes



- Trend for improved efficacy as BMI increases, but low n
- Bleeding metrics favored apixaban for all weight groups

DOI:10.1056/NEJMoa1302507. Personal communication from BMS.

Edoxaban

	ENGAGE AF[¥]	Hokusai-VTE
Primary outcome	1.2% vs 1.5%*	3.2% vs 3.5%*
Bleeding	2.8% vs 3.4%#	8.5% vs 10.3#
Weight (kg)	84	> 100kg: 14.8%
BMI	Not reported	Not reported

*#p<0.001, *non-inferior to comparator group, ⁺NS difference between groups ¥Data for 60mg group.*

- PK/PD Concerns
  - Contraindicated in CrCl >95ml/min due to ↑ elimination
  - Given ↑ GFR in obesity, may see higher failure rate
- No information on clinical outcomes

DOI: 10.1056/NEJMoa1310907. DO: 10.1056/NEJMoa11306638. Savaysa PI, Daiichi Sankyo Co. 2015.

Controversy #2

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What is the optimal anticoagulant for MG at discharge for stroke prevention?

Key Takeaways

- Managing anticoagulation in obese patients requires consideration of alterations in PK parameters and clinical endpoints
- Actual body weight should be used in dose determinations for parenteral agents
- While data remains limited in the morbidly obese population, apixaban appears to confer the most consist reduction in primary events with no change in bleeding metrics