Anticoagulation Management in the Obese Patient

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Disclosures

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Objectives

1) Increase awareness of the potential implications of obesity on anticoagulation management.

2) Summarize key findings from the literature on use of commonly prescribed anticoagulants in the obese population.

3) Follow recommended guidelines and evidence to appropriately use anticoagulation in the obese patient.

Outline

- Epidemiology of obesity, impact on disease, and medications
- Specific anticoagulants:
  - Warfarin
  - Direct oral anticoagulants (DOACs)
  - Low-molecular-weight heparin (LMWH), i.e., enoxaparin
  - Unfractionated heparin (UFH)
- Pharmacokinetics, Dosing, and Evidence
- Clinical recommendations

Disclaimer – Anticoagulation in Obesity

- Evidence is limited and often of low quality
- Prospective, RCT's had limited inclusion of obese patients
- Limited guidelines/expert opinion
- Optimal dosing for anticoagulants is unknown

Epidemiology

- U.S. obesity prevalence in 2015-16:
  - 40%
- Projected prevalence by 2030:
  - 50% obese
  - 25% severely obese

NCHS;2017. N Engl J Med 2019;381:2440-50.

Impact of Obesity on Disease

- Obesity is a known risk factor for VTE, Afib, and CVD
- ↑ procoagulant factors (factor VIII, fibrinogen, tissue factor)
- Platelet and endothelial dysfunction
- Hypofibrinolysis, venous stasis, ↑ inflammation

Br J Haematol 2007;139:289-96. Throm Haemost 2004;91:683-89. Thromb Haemost 2013;110:669-80. J Thromb Haemost 2021;19:1874-82.

Impact of Obesity on Medications

- Pharmacokinetic effects:
  - ↑ volume of distribution
  - ↑ drug clearance

- Relative lipophilicity of medications

Am J Med 2017;130:517-24.

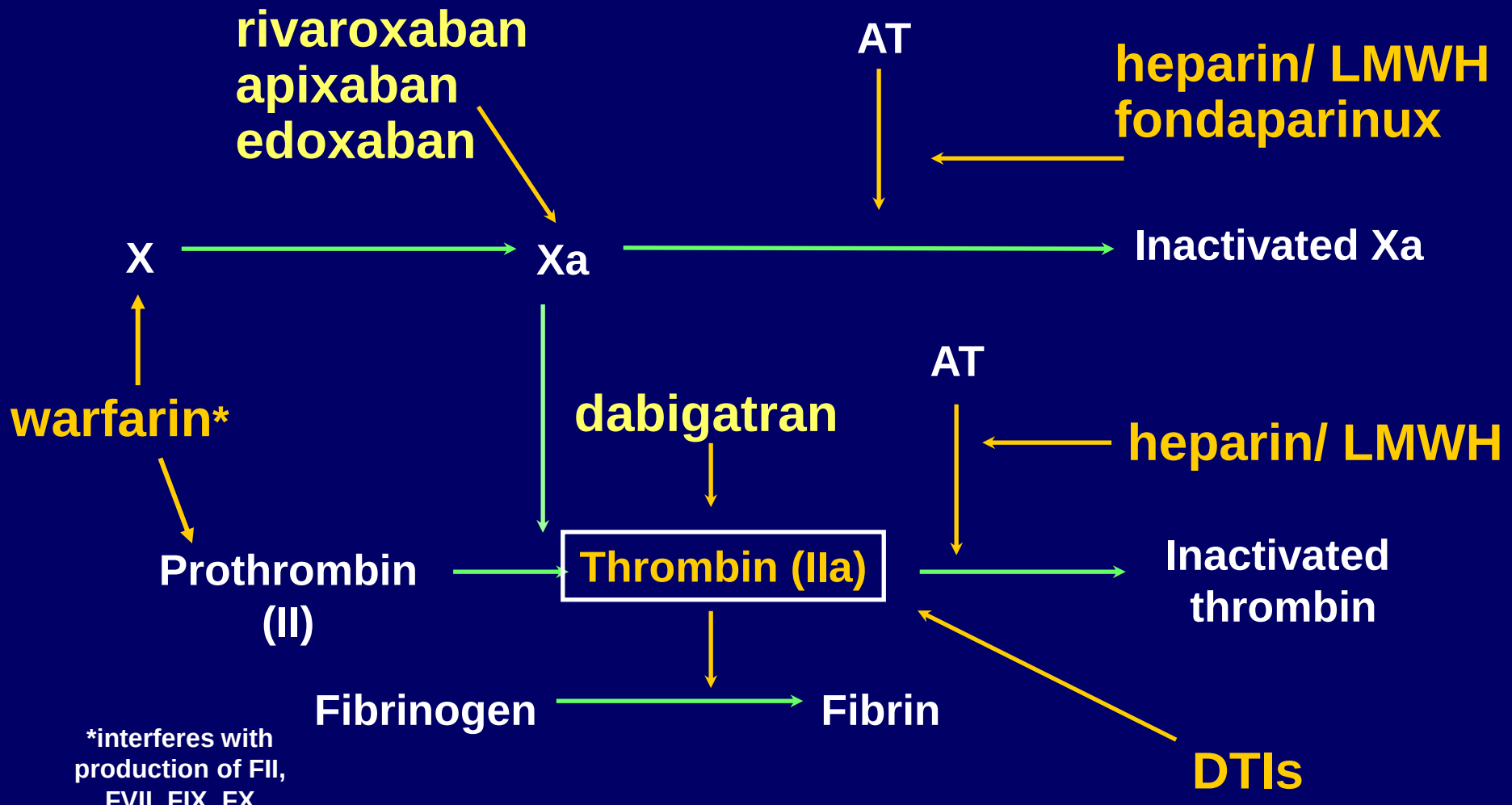
Case #1

- 35 y/o Caucasian male with history of type 2 diabetes mellitus, obstructive sleep apnea, and hypertension admitted with new-onset atrial fibrillation with rapid ventricular response (HR 130's) complicated by acute on chronic heart failure (non-ischemic cardiomyopathy)
- BP 136/84
- Weight – 186 kg
- Serum creatinine 1.0 mg/dL

Case #1

- Patient initially had no insurance, but then was able to get financial assistance for medications
- Which anticoagulant would you recommend for this patient?
- What dose would you prescribe?

Therapeutic Targets of Anticoagulation



*interferes with production of FII, FVII, FIX, FX

WARFARIN AND OBESITY

Warfarin and Obesity

- Body weight is positively correlated with dose requirements
- Weight was found to affect dose in most studies
- Obese and morbidly obese patients have longer time to achieve therapeutic INR
- Bleeding risk is higher in obese (BMI > 30) vs. normal weight (BMI < 30) patients on warfarin

Clin Pharmacol Ther 2004;75:204-12.
Pharmacogenet Genomics 2006;16:101-10.
J Thromb Thrombolysis 2015;40:494-98.

Select Study of Warfarin

Study	Patient Population and Design	Aims	Results
Wallace et al.	n = 211 hospitalized patients stratified by BMI category; new warfarin initiation; retrospective study	Assess effect of obesity on initial response to warfarin	Obese & morbidly obese patients required significantly higher average daily dose (6.6 ± 0.3 and 7.6 ± 0.5 vs. 5 ± 0.3 mg) and mean discharge dose (6.7 ± 0.5 and 6.7 ± 0.7 vs. 4.4 ± 0.5 mg).
			Longer median time to achieve therapeutic INR (8 and 10 d vs. 6 d) & % of patients with therapeutic INR before discharge were significantly different (42% vs. 38% vs. 71% for obese, morbidly obese vs. normal weight (p=0.0004)

J Thromb Thrombolysis 2013;36:96-101.

Warfarin Recommendations

- Higher initial doses needed to maintain therapeutic INR
- An initial dose increase of ˜ 30% in obese patients and ˜ 50% in morbidly obese patients is suggested

South Med J 2015;108:637-43. J Thromb Thrombolysis 2013;36:96-101. Eur J Clin Pharmacol 2006;62:713-20.

DOACS AND OBESITY

DOAC Comparison

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Savaysa®)
Target	IIa (thrombin)	Xa	Xa	Xa
Hrs to Cmax	2	2-4	1-3	1-2
Vd (L)	50-70 (0.7-1 L/kg)	50 (0.7 L/kg)	21 (0.3 L/kg)	107 (1.5 L/kg)
Protein binding (%)	35	93.5	87	49.5
CYP3A4 Metabolism	None (hydrolysis)	32%	15%	Minimal
Half-Life	12-17 hrs	5-9 hrs	12 hrs	10-14 hrs
Renal Elimination	80%	33%	40%	50%

Clin Pharmacokinet 2009; 48: 1-22
Am Heart J 2010; 160:635-41

DOACs and Obesity

- Studies have indicated shorter half-lives, lower peak concentrations, and modest lowering of drug exposure
- Majority of prospective, randomized trials enrolled patients < 100 kg

Br J Clin Pharmacol 2013;76:908-16. J Clin Pharmacol 2007;47:218-26. N Engl J Med 2009;361:1139-51. N Engl J Med 2009;361:2342-52. N Engl J Med 2010;363:2499-2510. N Engl J Med 2011;365:883-91. N Engl J Med 2011;365:981-92. J Thromb Haemost 2013;11:444-51.

DOACs and Obesity

- Minor impact of body weight on PK/PD of *rivaroxaban*
- Levels of *apixaban* within expected range in obesity
- Limited data for *dabigatran*, but considerable proportion of levels below expected range in obesity
- Little impact of body weight on PK of *edoxaban*

J Thromb Haemost 2021;19:1874-82.

DOAC vs. Warfarin in Obese Patients with VTE

Medication	Phase 3 Studies		Phase 4 Studies	
	BMI > 35 or BW > 120 kg	BMI > 40	BMI > 35 or BW > 120 kg	BMI > 40
Apixaban	No data	No data	Similar outcomes	Similar outcomes
Dabigatran	No data	No data	No data	No data
Edoxaban	No data	No data	No data	No data
Rivaroxaban	Similar outcomes	Similar outcomes	Similar outcomes	Similar outcomes
Pooled DOAC	Similar outcomes	Similar outcomes	Similar outcomes	Similar outcomes

J Thromb Haemost 2021;19:1874-82.

Select Study of DOACs in Acute VTE

- Retrospective evaluation of DOAC vs. warfarin for acute VTE in patients with weight 100-300 kg
- DOAC (n = 632) vs. warfarin (1,208)
- VTE recurrence at 12 months:
  - DOAC vs. warfarin (6.5% vs. 6.4%, p = 0.93)
- No difference in bleeding (1.7% vs. 1.2%, p = 0.31)

Pharmacotherapy 2020;40:204-210.

Select Study of DOACs in Afib

- n = 36,094 patients with NVAF across BMI categories (≥ 40 and < 18.5 kg/m^2)
- DOAC vs. warfarin
- DOACs associated with better safety and effectiveness (ischemic stroke, bleed, mortality) across all BMI categories

J Am Coll Cardiol EP 2021;7:649-58.

DOAC Recommendations

- VTE treatment
  - Use of any DOAC is appropriate for patients ≤ 120 kg or BMI ≤ 40 kg/m^2
  - For patients > 120 kg or > 40 kg/m^2, standard doses of rivaroxaban or apixaban may be used
  - Other DOACs are not recommended

J Thromb Haemost 2021;19:1874-82.

DOAC Recommendations

- Bariatric surgery
  - DOACs not recommended in acute setting due to absorption concerns
  - Parenteral anticoagulation is advised in early post-surgical phase
  - VKA or DOAC could be considered after 4 weeks of parenteral treatment
  - DOAC trough level could be considered

J Thromb Haemost 2021;19:1874-82.

DOACs and Therapeutic Drug Monitoring

- Therapeutic targets are unknown
  - Not widely reported from clinical studies
  - Not correlated with clinical outcomes
- Current reference ranges represent “expected” or “on-therapy ranges”
- Peak or trough DOAC specific levels should not be routinely monitored

J Thromb Haemost 2021;19:1874-82.

Limitations of DOACs in Obesity

- Paucity of data at extremes of weight
  - BMI ≥ 50 kg/m^2
  - Weight > 150 kg
- Comparisons between individual DOACs and warfarin are limited
- Lack of prospective trials with long-term follow-up

J Thromb Haemost 2021;19:1874-82.

HEPARINS AND OBESITY

LMWH in Obesity

- LMWHs mainly reside in intravascular compartment (Vd ˜ 5-7 L)
- Saturable metabolism via non-renal mechanisms, similar to UFH
- Potential concerns about standard doses being insufficient to prevent/treat VTE vs. higher doses leading to bleeding risk

Haemostasis 1996;26(suppl 2):24-38. J Clin Pharmacol 1995;3:1194-99. Ann Pharmacother 2009;43:1064-83. Chest 2008;133:381S-453S. Pharmacotherapy 2001;21:218-34.

Select Studies of Enoxaparin

- Retrospective (n = 194)
- Obese (1 mg/kg vs. < 1 mg/kg) vs. non-obese
- Median weight of obese cohort (130 kg; 105-222 kg)
- Anti-Xa concentrations within range similar:
  - 56% (obese, 1 mg/kg) vs. 46% (obese, < 1 mg/kg)
- No difference in bleeding or recurrence

Semin Thromb Hemost 2019;45:94-99.

Select Studies of Enoxaparin

- Prospective, RCT (n = 62)
- 0.8 mg/kg vs. 1 mg/kg q12 hrs
- BMI 47 kg/m^2; 46% were > 150 kg
- Initial anti-Xa concentrations similar:
  - (89% vs. 77%; p = 0.29)
- No bleeding or thrombotic events

Ann Pharmacother 2019;53:567-73.

LMWH Recommendations

- VTE prophylaxis
  - 0.5 mg/kg SC q12 hrs or a 25% increase in standard dose
- VTE prophylaxis – Bariatric surgery
  - BMI ≤ 50 kg/m^2: 40 mg SC q12 hrs
  - BMI > 50 kg/m^2: 60 mg SC q12 hrs

Chest 2008;133:381S-453S. Surg Obes Relat Dis 2008;4:625-31. Obes Surg 2002;12:19-24. Semin Thromb Hemost 2020;46:932-69.

LMWH Recommendations

- VTE treatment
  - Use actual body weight (without dose capping)
  - 1 mg/kg SC q12 hrs
    - For BMI ≥ 40 kg/m^2, consider 0.8 mg/kg SC q12 hrs
  - Consider anti-Xa monitoring if weight > 190 kg
    - Check peak level 4 hours post-dose
    - Goal range: 0.5-1 IU/mL

Ann Pharmacother 2009;43:1064-83. Chest 2008;133:381S-453S. Pharmacotherapy 2001;21:218-34. Semin Thromb Hemost 2020;46:936-69.

UFH in Obesity

- Vd of UFH ~ blood volume (40-70 mL/kg)
- Saturable clearance within vascular endothelium
- Adipose tissue is less vascularized than lean tissue, therefore UFH is not well-distributed
- How to best account for additional vasculature seen in adipose tissue

Clin Pharm 1996;54:2517-21. Am J Health Sys Pharm 2001;58:2143-46.
Clin Pharm 1989;8:65-8. J Thromb Haemost 2021;19:1874-82.

UFH in Obesity

- Potential approaches to dosing:
  - Dosing weight
    - IBW + 0.4(ABW-IBW)
  - Modified dosing weight (average of IBW & ABW)
  - Actual weight with dose caps
  - Estimates of plasma volume

IBW = ideal body weight;
ABW = actual body weight

Select Study of UFH

- Retrospective (n = 273)
- Morbid obesity vs. overweight vs. normal/underweight
- Mean weight in morbidly obese group 141 kg
- No difference in time to first therapeutic aPTT
- Infusion rates needed to attain therapeutic aPTTs were lower in higher weight groups
- No difference in bleeding or mortality

Ann Pharmacother 2010;44:1141-51.

UFH Recommendations

- VTE prophylaxis – Bariatric surgery
  - Higher doses (i.e., 7,500 units SC tid) may be considered

- VTE prophylaxis – Non-bariatric surgery
  - Higher doses may be considered (i.e., 7,500 units SC tid for weight > 120 kg)

Chest 2008;133:381S-453S. Obes Surg 2004;14:731-77. Obes Surg 2005;15:1316-20. Am J Surg 2007;194:709-11.

UFH Recommendations

- VTE treatment
  - Use actual body weight with consideration of dose cap
  - Potential initial maximum doses:
    - Bolus: 80 units/kg (10,000 units)
    - Infusion: 14 units/kg/hr IV infusion

Pharmacother 2010;30:105-112e. Ann Pharmacother 2010;44:1141-51. Clin Pharm 1989;8:65-8.

Case #1

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Case #1 - Potential Therapeutic Options

- Bridge UFH IV or enoxaparin SC to warfarin
  - UFH IV bolus 60 U/kg (maximum of 10,000 units), then initiate IV infusion 14 U/kg/hr (maximum of 2,600 U/hr), monitor aPTT or anti-factor Xa

    OR
  - Enoxaparin 1 mg/kg (190 mg) SC q12 hrs, no monitoring

  - Warfarin 10 mg PO x 1, monitor INR

Case #1 - Potential Therapeutic Options

- DOAC
  - Rivaroxaban 20 mg daily with evening meal

    OR
  - Apixaban 5 mg bid

Conclusions and Summary Points

- Obesity alters the pharmacokinetics of anticoagulants, leading to uncertainty in optimal dosing
- Studies of UFH/LMWH and warfarin demonstrate the need for higher doses with careful monitoring
- Evolving evidence and guidelines support standard dose rivaroxaban or apixaban as warfarin alternatives

Questions