Anticoagulation in the Patient with Obesity

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Disclosures

- I have received research support from the Heart Rhythm Society and the Pfizer-Bristol Myers Squibb Alliance
- I have served on an advisory board for Merck, Inc.
- I have served as a consultant to the Pfizer-Bristol Myers Squibb Alliance

- All the relevant financial relationships listed have been mitigated.

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.

Anticoagulation in Obesity: Disclaimer

- Evidence is limited and often of low quality
  - Clinical trial exclusions: morbid obesity, relatively few patients exceeded 100 kg
  - Multiple guidelines/expert opinion
- Optimal dosing is not well-established
- Focus of this presentation:
  - Warfarin and DOACs
  - Treatment (i.e., VTE, Afib)

Obesity: Background

- U.S. obesity prevalence in 2017-18 (NHANES):
  - 42.4%
- Severe obesity
  - 9.2%
- Projected prevalence by 2030:
  - 50% obese
  - 25% severely obese

NHANES = National Health and Nutrition Examination Survey

https://www.cdc.gov/nchs/data/factsheets/factsheet_nhanes.pdf;2017.
N Engl J Med 2019;381:2440-50.

Obesity: Implications for Anticoagulation

- 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

VTE = venous thromboembolism; Afib = atrial fibrillation; CVD = cardiovascular disease

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.

Warfarin in Obesity: Key Considerations

- 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.

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 in Obesity: Pharmacokinetics

Increasing body weight on DOAC concentrations		BMI > 40 kg/m^2 on DOAC concentrations
Apixaban	Lower peak	Lower AUC or no change
Dabigatran	Lower peak	No data available
Edoxaban	No data available	No data available
Rivaroxaban	No change or lower peak	No data available

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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

BW = body weight

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DOACs in Morbid Obesity: Selected Clinical Evidence (VTE Treatment)

Study	Design/No. Patients (morbid obesity)	Inclusion	Recurrent VTE	Major Bleeding
Kushnir et al., 2019	Retrospective chart review, n = 366	BMI ≥ 40	2.1% (A) vs. 2% (R), vs. 1.2% (W); p = 0.74	2.1% (A) vs. 1.3% (R), vs. 2.4% (W); p = 0.77
Perales et al., 2019	Retrospective chart review, n = 176	BMI > 40, > 120 kg	4.2% (R) vs. 6.4% (W); p = 0.61	6.3% (R) vs. 3.2% (W); p = 0.65
Spyropoulos et al., 2019	Retrospective cohort, propensity-matched, claims, n = 5,780	ICD codes: morbid obesity	16.8% (R) vs. 15.9% (W); p = 0.84	**1.8% (R) vs 2.5% (W); p = 0.04**
Cohen et al., 2021	Retrospective cohort, propensity-matched, claims, n = 19,751	ICD codes: morbid obesity	**5.3 (A) vs. 8.1 (W) per 100 person-yrs; HR, 0.63 (95% CI, 0.52-0.78)**	**4.5% (A) vs. 6.2% (W); HR, 0.70 (95% CI, 0.56-0.89)**
Crouch et al., 2022	Retrospective, multicenter, n = 1,099	BMI ≥ 40, ≥ 120 kg	**4.5% (A) vs. 8.7% (W); p = 0.02**	3.8% (A) vs. 3.3% (W); p = 0.72

A = apixaban; R = rivaroxaban; W = warfarin

Lancet Haematol 2019;6:e359-65. Ann Pharmacother 2020;54:344-50. Thrombosis Research 2019;182:159-66. Cureus 2021;13:e14572. J Clin Med 2021;10:200. Pharmacotherapy 2022;42:119-33.

Clinical Practice Guidelines: Obesity

SSH of the ISTH

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

SSH = Scientific and Standardization Committee
ISTH = International Society on Thrombosis and Haemostasis

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DOACs in Morbid Obesity: Selected Clinical Evidence (Atrial Fibrillation)

Study	Design/No. Patients (morbid obesity)	Inclusion	Thrombotic Outcome	Bleeding Outcome
Peterson et al., 2019	Retrospective, propensity-matched, claims, n = 3,563	ICD code: morbid obesity; rivaroxaban vs. warfarin	Stroke/SE: (R), OR, 0.88, 95% CI (0.60-1.28)	Major: (R), OR, 0.80, 95% CI, 0.59-1.08
Kido, et al., 2019	Retrospective, n = 128	BMI > 40 or > 120 kg; DOAC vs. warfarin	Stroke/TIA: RR, 0.84 (95% CI, 0.23-3.14)	Major: RR, 0.44 (95% CI, 0.15-1.25)
Costa et al., 2020	Retrospective, cohort, claims, n = 18,034	BMI ≥ 40; rivaroxaban vs. warfarin	Stroke/SE: (R), HR, 0.87 (95% CI, 0.68-1.12)	**Major: (R), HR, 0.75 (95% CI, 0.64-0.89)**
Deitelzweig et al., 2020 (ARISTOPHANES)	Retrospective, propensity-matched, claims, n = 34,942	ICD codes: morbid obesity or BMI ≥ 40; DOAC vs. warfarin	Stroke/SE: (A), HR, 0.72 (95% CI, 0.48-1.08)	**Major: (A), HR, 0.53, 95% CI, 0.44-0.64)**

ISTH = International Society on Thrombosis and Haemostasis; SE = systemic embolism
TIA = transient ischemic attack

Am Heart J 2019;212:113-9. Ann Pharmacother 2019;53:165-70. Curr Med Res Opin. 2020;36:1081-1088. J Clin Med 2020;9:1633.

DOACs in Morbid Obesity: Selected Clinical Evidence (Atrial Fibrillation)

Study	Design/No. Patients (morbid obesity)	Inclusion	Thrombotic Outcome	Bleeding Outcome
Wiethorn et al., 2021	Retrospective, n = 318	≥ 120 kg vs. < 120 kg; Apixaban, dabigatran, rivaroxaban	Stroke/DVT/PE/MI: 2.5% vs. 3.1%; p = 0.63	ISTH major or clinically relevant non-major: 5.3% vs. 6.6%; p = 0.50
Barakat et al., 2021	Retrospective, n = 3,924	NVAF across BMI categories (≥ 40 & < 18.5 kg/m^2); DOAC vs. warfarin	**Stroke: HR, 0.75 (95% CI, 0.64-0.87)**	**Significant (hospitalization): HR, 0.43 (95% CI, 0.20-0.94)**
O'Kane et al., 2022	Retrospective, n = 299	Morbidly obese (BMI ≥ 50 vs. non-obese; apixaban, rivaroxaban	Stroke: RR, 0.65 (95% CI, 0.38-1.82)	ISTH major: RR, 0.60 (95% CI, 0.34-2.29)
Chugh et al., 2023	Retrospective, n = 269	BMI ≥ 40 with AF and HF; apixaban, dabigatran, rivaroxaban	Stroke/SE (admission): 9.3% (R) vs. 3.7% (A) vs. 8.5% (D); p = 0.44	**Bleeding (admission): 15.5% (R) vs. 11.1% (A) vs. 31.4% (D); p = 0.01**

DVT = deep vein thrombosis; PE = pulmonary embolism; MI = myocardial infarction; ISTH = International Society on Thrombosis and Haemostasis; SE = systemic embolism; AF = atrial fibrillation; HF = heart failure

Am J Cardiovasc Drugs 2021;21:545-51. J Am Coll Cardiol EP 2021;7:649-58. Pharmacotherapy 2022;42:112-18. Pacing Clin Electrophysiol 2023;46:50-58.

Conclusions and Summary Points: Obesity

- Obesity alters the pharmacokinetics of anticoagulants, leading to uncertainty in optimal dosing
- Studies of warfarin demonstrate the need for higher doses with careful monitoring
- Apixaban or rivaroxaban are at least non-inferior to warfarin, with a signal of improved safety, in morbidly obese patients with VTE or Afib
- Paucity of evidence: BMI ≥ 50 kg/m^2 and/or weight > 150 kg

J Thromb Haemost 2021;19:1874-82.