Simulation analysis of different creatinine clearance estimation methods for dosing target-specific oral anticoagulants in overweight and obese patients: When does the method matter?

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BACKGROUND

- While less monitoring, fewer drug interactions, and faster onset of action compared to warfarin (Shamem 2013), characteristics and bleeding risk are not well described for obese patients in target-specific oral anticoagulants (TSOAC) literature. The clinical trials of these anticoagulants poorly describe subgroup analyses in obese and elderly patients. (Connolly 2009, ROCKET AF).
- Dosing for target-specific oral anticoagulants is currently based on creatinine clearance in dabigatran, edoxaban, rivaroxaban, and on serum creatinine, age, and body weight in apixaban (Pradaxa PI, Savaysa PI, Xarelto PI, and Eliquis PI).
- Current studies use total body weight to calculate clearance creatinine in dose determination (Connolly 2009, Lopes 2010, ROCKET AF). Using total body weight in obese patients may overestimate the creatinine clearance and lead to an overdose of these anticoagulants, ultimately leading to bleeding events. (Turpie 2011).

OBJECTIVE

To evaluate the effect of using TBW compared to IBW for estimating creatinine clearance (CrCl) on dosing magnitude in overweight and obese patients for four target-specific oral anticoagulants.

METHODS

- Simulation study using characteristics of 237 patients, with a subgroup analysis of BMI > 25
- Two CrCl calculations estimated for each patient using the CG equation: one with TBW and one with IBW.
- For elderly > 65 years of age, two additional eCrCl calculations were based on rounding the SCr to 0.8 and 1.
- Dosing groups for each of the four oral anticoagulants (i.e. dabigatran, apixaban, edoxaban, rivaroxaban) were assigned according to dosing recommendations from package inserts.
- Data analysis (i.e. t test for 2 samples assuming unequal variances) were performed to compare same dosing vs. different dosings for critical factors. Same dosing means that patients receive the same dose when either TBW or IBW was used. Patients receiving lower or higher doses if IBW was used instead of TBW are considered different dosings.

METHODS

Table 2. Dosing calculations for simulation study drugs

Dabigatran (Pradaxa) dosing for non-valvular atrial fibrillation (NVAF)

•CrCL ≥ 30 mL/min: 150 mg BID
•15 ≤ CrCL < 30 mL/min: 75 mg BID
• CrCL < 15 mL/min: 0 mg BID

Rivaroxaban (Xarelto) dosing for NVAF

•CrCL ≥ 50 mL/min: 20 mg QD
•15 ≤ CrCL < 50 mL/min: 15 mg QD
•CrCL < 15 mL/min: 0 mg QD

Edoxaban (Savaysa) dosing for NVAF

•50 < CrCL ≤ 95 mL/min: 60 mg QD
•15 ≤ CrCL ≤ 50 mL/min: 30 mg QD
•CrCL < 15 or > 95 mL/min: 0 mg QD

Apixaban (Eliquis) dosing for NVAF:
•SCr < 1.5 mg/dL: 5 mg BID
•Either (SCr ≥ 1.5 mg/dL AND age ≥ 80) **OR** (SCr ≥ 1.5 mg/dL AND TBW ≤ 60 kg) **OR** (age ≥ 80 AND TBW ≤ 60 kg): 2.5 mg BID

Table 1. Baseline characteristics of patient population (n = 237)

Characteristics	Mean (SD)		Median (Range)
Age (years)	68.6 (16.8)		70 (19-99)
≥ 65 years, %		138 (58.2)	
≥ 80 years, %		78 (32.9)	
Female, %		103 (43.4)	
BMI > 25 kg/m², %		122 (51.5)	
IBW (kg)	64.8 (11.6)		66.1 (44 – 89.1)
TBW (kg)	76.9 (20.2)		75 (39.7 – 167)
BMI (kg/m²)	26.3 (6.2)		25.4 (13.4 – 58.3)
BMI > 25 kg/m²	30.6 (5.3)		29.2 (25.1 – 58.3)
Height (inches)	67.3 (4.3)		67 (58 – 77)
SCr (mg/dL)	1.56 (1.52)		1.10 (0.4 – 12)
BUN (mg/dL)	26.9 (21.1)		20 (5 – 126)

RESULTS

Table 2. Dabigatran same vs different dosing using IBW or TBW (n = 104 vs 18, BMI>25 kg/m²), SCr not rounded

Variable (SAME)	IBW (n = 104)	TBW (n = 104)	p-value
Mean age (SD)	63.8 (1.7)	63.8 (1.7)	1
Mean weight (SD)	66.3 (1.1)	90.0 (1.7)	< **0.001**
Mean % IBW (SD)	137.5 (2.4)	137.5 (2.4)	1
Mean BMI (SD)	30.3 (0.5)	30.3 (0.5)	1
Mean modified SCr (SD)	1.38 (0.15)	1.38 (0.15)	1
Mean CrCL (SD)	65.1 (3.6)	87.7 (4.5)	**<0.001**

Variable (DIFFERENT)	IBW (n = 18)	TBW (n = 18)	p-value
Mean age (SD)	76.1 (3.7)	76.1 (3.7)	1
Mean weight (SD)	59.1 (2.8)	88.5 (5.1)	< **0.001**
Mean % IBW (SD)	152.7 (9.4)	152.7 (9.4)	1
Mean BMI (SD)	32.4 (1.8)	32.4 (1.8)	1
Mean modified SCr (SD)	2.06 (0.28)	2.06 (0.28)	1
Mean CrCL (SD)	25.7 (1.1)	38.7 (2.3)	**<0.001**

Table 3. Rivaroxaban same vs different dosing using IBW or TBW (n = 91 vs 31, BMI>25 kg/m²), SCr not rounded

Variable (SAME)	IBW (n = 91)	TBW (n= 91)	p-value
Mean age (SD)	62.9 (1.9)	62.9 (1.9)	1
Mean modified weight (SD)	66.8 (1.3)	89.0 (1.9)	< **0.001**
Mean % IBW (SD)	134.7 (2.4)	134.7 (2.4)	1
Mean BMI (SD)	29.8 (0.5)	29.8 (0.5)	1
Mean modified SCr (SD)	1.51 (0.18)	1.51 (0.18)	1
Mean CrCL (SD)	65.5 (4.2)	86.9 (5.4)	**<0.001**

Variable (DIFFERENT)	IBW (n = 31)	TBW (n= 31)	p-value
Mean age (SD)	73.9 (2.5)	73.9 (2.5)	1
Mean modified weight (SD)	60.4 (1.8)	92.1 (3.4)	< **0.001**
Mean % IBW (SD)	154.3 (6.0)	154.3 (6.0)	1
Mean BMI (SD)	33.1 (1.2)	33.1 (1.2)	1
Mean modified SCr (SD)	1.40 (0.16)	1.40 (0.16)	1
Mean CrCL (SD)	41.0 (1.6)	61.5 (2.2)	**<0.001**

Table 5. Edoxaban same vs different dosing using IBW or TBW (n = 72 vs 50, BMI>25 kg/m²), SCr not rounded

Variable (SAME)	IBW (n = 72)	TBW (n = 72)	p-value
Mean age (SD)	65.3 (2.1)	65.3 (2.1)	1
Mean modified weight (SD)	67.4 (1.5)	87.0 (1.9)	< **0.001**
Mean % IBW (SD)	130.4 (2.3)	130.4 (2.3)	1
Mean BMI (SD)	28.9 (0.4)	28.9 (0.4)	1
Mean modified SCr (SD)	1.65 (0.2)	1.65 (0.2)	1
Mean CrCL (SD)	62.2 (5.2)	79.6 (6.5)	**<0.001**

Variable (DIFFERENT)	IBW (n = 50)	TBW (n = 50)	p-value
Mean age (SD)	66.2 (2.4)	66.2 (2.4)	1
Mean modified weight (SD)	62.0 (1.5)	93.8 (2.9)	< **0.001**
Mean % IBW (SD)	153.1 (4.5)	153.1 (4.5)	1
Mean BMI (SD)	33.1 (0.9)	33.1 (0.9)	1
Mean modified SCr (SD)	1.24 (0.1)	1.24 (0.1)	1
Mean CrCL (SD)	55.0 (3.0)	81.7 (4.0)	**<0.001**

DISCUSSION & CONCLUSIONS

Study Limitations: Simulation study using relatively small patient population shows only how using TBW compared to IBW affect dosing determination. Appropriateness of doses to achieve therapeutic goal, or to avoid adverse events due to toxicity of TOACs in serum were not evidenced due to simulation format.

Strengths: This group of simulation patients reflect real-world patients seen in a mid-sized community hospital. **Future directions**: Compare the effects of lean body weight, IBW, and TBW on eCrCl in obese patients.

Conclusions: Using TBW for eCrCl may over-estimate the dosing needs for older patients with worse renal function receiving dabigatran, for older patients with modestly increased SCr and higher degrees of obesity receiving rivaroxaban, and for patients with higher degrees of obesity receiving edoxaban. Dose determination for apixaban was not affected by the eCrCl method.