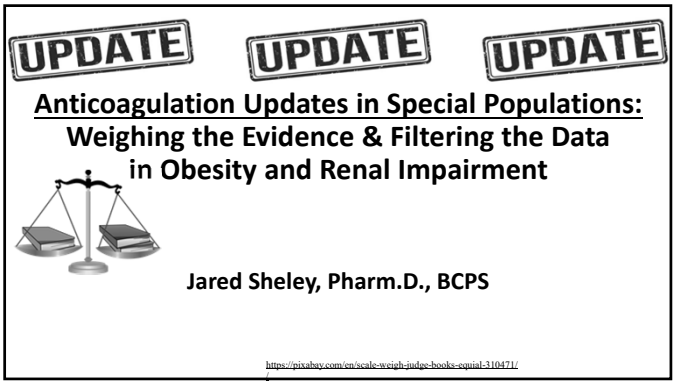

Anticoagulation Updates in Special Populations: Weighing the Evidence & Filtering the Data in Obesity and Renal Impairment

Jared Sheley, Pharm.D., BCPS

https://pixabay.com/en/scale-weigh-judge-books-equal-310471/

Objectives

Pharmacists

- Identify limitations in applying weight-based dosing of parenteral anticoagulants in obese patients and when alterations may be necessary
- Describe current recommendations and existing data for direct oral anticoagulant (DOAC) use in obese patients
- Explain the limitations in data with direct oral anticoagulants (DOAC) use in patients with renal impairment

Technicians

- Discuss why obese patients require different dosing strategies of parenteral anticoagulants than non-obese patients
- Describe why there are concerns with direct oral anticoagulants (DOAC) in obese patients
- Identify patients, by history or laboratory measures, in whom there may be concern for using direct oral anticoagulants (DOAC)

Technician Question

Why would obese patients require different dosing strategies of parenteral anticoagulants than non-obese patients?

A. Parenteral anticoagulants are given at fixed doses, so obese patient may be underdosed
B. Parenteral anticoagulants are given at fixed doses, so obese patients may be overdosed
C. Parenteral anticoagulants are given at weight-based doses, so obese patients may be underdosed
D. Parenteral anticoagulants are given at weight-based doses, so obese patients may be overdosed

Technician Question

Describe why there are concerns with direct oral anticoagulants (DOAC) in obese patients

A. DOAC are given at fixed doses, so obese patient may be underdosed
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C. DOAC are given at weight-based doses, so obese patients may be underdosed
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Technician Question

Which of the following would be a reason for concern with DOAC use?

A. Feeding tube status
B. Hemodialysis status
C. Tricare prescription insurance
D. Elevated blood glucose

Pharmacist Question

Which of the following scenarios likely requires intervention by the pharmacist upon receiving the medication order?

A. 90 kg patient (BMI = 31) with new proximal DVT ordered enoxaparin 1 mg/kg subQ BID
B. 180 kg patient (BMI = 55) with new PE ordered enoxaparin 1 mg/kg subQ BID
C. 90 kg patient (BMI = 31) with A Fib started on unfractionated heparin w/ IV bolus dose 80 units/kg/hr and IV infusion rate 18 unit/kg/hr
D. 180 kg patient (BMI = 55) with ACS started on unfractionated heparin w/ IV bolus dose 4,000 units and IV infusion rate 1,000 unit/hr

Pharmacist Question

Which of the following is consistent with the guidance from the International Society of Thrombosis and Haemostasis (ISTH) on use of the direct oral anticoagulants (DOAC) in obese patients?

A. DOACs are recommended to be used at standard doses for all patients due to data suggesting obesity does not effect drug concentrations
B. DOACs are recommended to be used at double the dose for patients with extreme obesity due to data suggesting similar drug concentrations
C. DOACs are suggested to be avoided in patient with BMI >30 kg/m2 or weight > 90 kg due to exclusion from trials
D. DOACs are suggested to be avoided in patients with BMI > 40 kg/m2 or weight > 120 kg due to data suggesting decreased drug concentrations

Pharmacist Question

Which of the following is true regarding data on DOAC in patients with renal impairment?

A. Some DOAC with labeled indications for patients on dialysis now have robust data showing safety and efficacy in this patient population
B. Patients with ESRD on dialysis or CrCl < 25 ml/min were excluded from all clinical trials of DOAC
C. Patients with CrCl < 50 ml/min were excluded from all clinical trials of DOAC
D. Renal function is not a relevant consideration w/ DOAC use

Obesity in the US

- Obesity prevalence in adults *(BMI > 30 kg/m2)* = **40%**
- Extreme / morbid obesity in adults *(BMI > 40 kg/m2)* = **8%**
- Increasing annually for > 20 years

- Obesity known to be an independent risk factor for many conditions that require anticoagulation
  - Venous Thromboembolism (VTE)
  - Atrial Fibrillation (A Fib)

National Center for Health Statistics, 2016
Hales CM, et al. NHANES 2017

Parenteral Anticoagulants in Obesity

- Normally recommended dosing

	"Full anticoagulation" (DVT, PE, Valve)	**Acute Coronary Syndromes (ACS)**
Unfractionated Heparin (UFH)	Bolus: 80 unit/kg IV Infusion: 18 unit/kg/hr IV	Bolus: 60 unit/kg IV Infusion: 12 unit/kg IV
Enoxaparin (Lovenox)	1 mg/kg BID	1 mg/kg BID

- Concerns with weight based dosing
  - Weight based dosing meant to provide enough drug for increase in blood volume
  - Blood volume of adipose tissue is less than lean tissue

Holbrook, et al. CHEST 2012; 141(2)(Suppl):e1525–e184S
O'Gara, et al. Circulation 2013. 127:e362-e425.
Amsterdam, et al. J Am Coll Cardiol. 2014 Dec 23;64(24):e139-e228.

Parenteral Anticoagulants in Obesity

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- Obesity Recommendations

	"Full anticoagulation" (DVT, PE, Valve)	**Acute Coronary Syndromes (ACS)**
Unfractionated Heparin (UFH)	***None***	Bolus: **Maximum 4,000 units** Infusion: **Maximum 1,000 units/hr**
Enoxaparin (Lovenox)	***None***	***None***

Holbrook, et al. CHEST 2012; 141(2)(Suppl):e1525–e184S
O'Gara, et al. Circulation 2013. 127:e362-e425.
Amsterdam, et al. J Am Coll Cardiol. 2014 Dec 23;64(24):e139-e228.

Unfractionated Heparin Data in Obesity

Study	**Methods**	**Findings in Obese Patients**
Barletta J, et al. 2008	Compared initial aPTT values BMI > 40 vs BMI < 40	Higher aPTT; BMI >40 independent RF for elevated aPTT
Gerlach A, et al. 2013	Omitted bolus dose, use reduced infusion rate 16 unit/kg/hr in obese, 12 unit/kg/hr in morbidly obese	Similar times to reach therapeutic range Avg dose 11 unit/kg/hr in obese vs 16 unit/kg/hr in non-obese
Hohner E, et al. 2015	Retrospective review of therapeutic doses	Lower weight-based dosing in >130 kg, 13 unit/kg/hr vs 16 unit/kg/hr
Shin S, et al. 2015	Retrospective review of therapeutic doses Grouped patients by weight	Longer time to therapeutic range Lower doses needed for therapeutic level Avg. dose for >150 kg = 11 unit/kg/hr vs. 16 unit/kg/hr for <100 kg

Barletta J., et al. Surg Obes Relat Dis. 2008 Nov-Dec;4(6):748-53.
Gerlach A, et al. Int J Crit Illn Inj Sci. 2013 Jul;3(3):195-9.
Hohner E, et al. J CritCare. 2015 Apr;30(2):395-9.
Shin S, et al. Blood Coagul Fibrinolysis. 2015Sep;26(6):655-60.

Low Molecular Weight Heparin Data in Obesity

- Enoxaparin

Study	Patients	Methods	Findings in Obese Patients
Deal E, et al. 2011	BMI > 40 *n=26*	Retrospective review	Avg dose for therapeutic level was 0.74 mg/kg 0 below goal, 38% above goal
Thompson-Moore N, et al. 2015	BMI > 40 or Wt > 140 kg *n=41*	Retrospective review	Median therapeutic dose 0.83 mg/kg Median supratherapeutic dose 0.98 mg/kg
Lee Y, et al. 2015	BMI > 40 or Wt > 150 kg *n=99*	Retrospective review Used 1 mg/kg ABW	> 50% were supratherapeutic
Lalama J, et al. 2015	BMI >40 *n=31*	Prospective study, dosed 0.74 mg/kg	48% therapeutic, 36% above goal, 16% below Avg. therapeutic dose 0.71 mg/kg

Deal E, et al. J Thromb Thrombolysis. 2011Aug;32(2):188-94.
Thompson-Moore N, et al.. Clin Appl Thromb Hemost. 2015 Sep;21(6):513-20.
Lee Y, et al.. Pharmacotherapy. 2015 Nov;35(11):1007-15.
Lalama J, et al. J ThrombThrombolysis. 2015 May;39(4):516-21.

Technician Question

Why would obese patients require different dosing strategies of parenteral anticoagulants than non-obese patients?

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Which of the following scenarios likely requires intervention by the pharmacist upon receiving the medication order?

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Direct Oral Anticoagulants (DOAC) in Obesity

Drug	Mechanism	Indications
Dabigatran (Pradaxa ®)	Direct Thrombin Inhibitor	NVAF, VTE treatment, Post-ortho surg VTE prevention
Rivaroxaban (Xarelto ®)	Factor Xa Inhibitor	NVAF, VTE treatment, Post-ortho surg VTE prevention
Apixaban (Eliquis ®)		NVAF, VTE treatment, Post-ortho surg VTE prevention
Edoxaban (Savaysa ®)		NVAF, VTE Treatment
Betrixaban (Bevyxxa ®)		VTE prevention

Direct Oral Anticoagulants (DOAC) in Obesity

- Data from normal weight patients

Drug	Volume of Distribution (L)	Protein Binding (%)
Dabigatran (Pradaxa ®)	50 - 70	35
Rivaroxaban (Xarelto ®)	50	92
Apixaban (Eliquis ®)	21	87
Edoxaban (Savaysa ®)	107	55
Betrixaban (Bevyxxa ®)	32	60

Direct Oral Anticoagulants (DOAC) in Obesity

- Concerns with DOAC in obese patients
  - Prescribed at fixed doses
  - Would expect increased Vd and clearance → decreased drug exposure → ?? efficacy
  - No monitoring to determine level of anticoagulation

Pharmacokinetic Data

Drug	PK Data in "Obesity"
Dabigatran	**21 – 35% decrease in mean concentration**
Rivaroxaban	Cmax & AUC relatively unchanged Slight decrease half-life
Apixaban	**30-45% decrease in Cmax** **23-36% decrease in AUC** **27-44% decrease in half-life**
Edoxaban	**No data exists**
Betrixaban	

Reilly PA, et al..J Am Coll Cardiol. 2014 Feb 4; 63(4):321-8.
Kubitza D, et al. J Clin Pharmacol 2007; 47: 218-26.
Upreti VV, et al. Br J Clin Pharmacol. 2013;76:908-16.

Clinical Data - Dabigatran

Trial	Weight threshold reported (kg)	% Patients (#)	BMI Threshold Reported (kg/m2)	% Patients (#)
RE-LY	≥ 100	17.1%	≥ 28	49.5%
RE-COVER I & II (pooled data)	>100	17.2% (438)	> 35	12.3% (302)
RE-MEDY	≥ 100	20.9% (299)		
RE-SONATE	≥ 100	17.9% (122)		
Eriksson, et al. Pooled data from RE-NOVATE I & II, RE-MODEL			≥40	10% (58)

Connolly SJ, et al. N Engl J Med. 2009 Sep 17;361(12):1139-51.
Schulman S, et al. N Engl J Med. 2009 Dec 10;361(24):2342-52.
Eriksson B, et al. Thromb Res. 2012 Nov;130(5):818-20.

Clinical Data - Dabigatran

- No significant differences in weight/BMI subgroups in reported data
- RE-LY highest BMI group >28 kg/m2, highest weight > 100 kg
- Reilly P, et al. 2014 Analysis of RE-LY data
  - Peak and through levels for 76% & 70% of patients
  - **21-35% decrease in mean drug concentration in >100 kg**
  - **Risk of ischemic stroke inversely related to through plasma concentrations (p=0.045)**

Connolly S, et al. N Engl J Med. 2009;361(12):1139–51.
Reilly PA, et al..J Am Coll Cardiol. 2014 Feb 4; 63(4):321-8.

Clinical Data - Dabigatran

- VTE rates numerically increasing with increasing weight & BMI

		Rate of VTE / death for dabigatran	Rate of VTE / death for warfarin
RE-COVER & RE-COVER II (pooled data)	50 – 100 kg	2.0%	1.9%
	>100 kg	4.1%	3.6%
	BMI < 25	1.5%	2.2%
	BMI 25 - < 30	2.3%	1.7%
	BMI > 35	3.3%	2.2%
RE-MEDY	50 – < 100 kg	1.6%	1.3%
	≥ 100 kg	2.7%	1.0%

Schulman S, et al. Circulation. 2014 Feb 18;129(7):764-72.
Schulman S, et al. N Engl J Med. 2013 Feb 21;368(8):709-18.

Clinical Data - Dabigatran

- Clinical outcomes in VTE prevention studies (ortho surg)

BMI	VTE/VTE death Dabigatran	VTE/VTE death Enoxaparin	Odds Ratio
20-25 kg/m^2	2.1%	4.3%	**0.48 (0.24-0.97)**
25-30 kg/m^2	3.0%	4.5%	0.67 (0.41-1.09)
>30 kg/m^2	2.7%	2.9%	0.92 (0.49-1.74)

Eriksson B, et al. Thromb Res. 2012 Nov;130(5):818-20.

Clinical Data - Rivaroxaban

Trial	Weight threshold reported (kg)	% Patients (#)	BMI Threshold Reported (kg/m2)	% Patients (#)
ROCKET-AF	> 90	28.5% (2,035)	> 35	13.6% (972)
EINSTEIN DVT	>90	28.3% (491)		
	> 100	14.2% (245)		
EINSTEIN PE	> 90	28.3% (683)	≥ 30	30.8% (741)
	> 100	14.3% (345)		
RECORD 1-4	Not reported			

Patel MR, et al. N Engl J Med. 2011 Sep 8;365(10):883-91.
EINSTEIN Investigators. N Engl J Med. 2010 Dec 23;363(26):2499-510.
EINSTEIN–PE Investigators. N Engl J Med. 2012 Apr 5;366(14):1287-97.
Eriksson B. NEJM 2008;358:2765-75.
Kakkar A. Lancet 2008;372,9632:31-59.
Lassen M. NEJM 2008;358:2776-86.
Turpie A. Lancet 2009;373,9676:1673-80.

Clinical Data - Rivaroxaban

- No significant differences in weight/BMI subgroups in reported data
  - Highest weight group > 90 kg
  - Highest BMI group > 30 kg/m2 for VTE
    > 35 kg/ m2 for A Fib

Clinical Data - Apixaban

Trial	Weight threshold reported (kg)	% Patients (#)	BMI Threshold Reported (kg/m2)	% Patients (#)
ARISTOTLE			≥ 30	40%
			≥ 40	5.6%
AVERROES	Not reported			
AMPLIFY	≥ 100	19.4% (522)	> 35	13.0% (349)
ADVANCE trials (pooled)			≥30	16.9% (1149)

Granger CB. N Engl J Med. 2011 Sep 15;365(11):981-92.
Connolly SJ. N Engl J Med. 2011 Mar 3;364(9):806-17.
Agnelli G, et al. N Engl J Med. 2013 Aug 29;369(9):799-808.
Pineo G, et al. J Thromb Haemost. 2013 Mar;11(3):444-51.

Clinical Data - Apixaban

- Higher BMI correlated w/ lower major bleeding in ARISTOTLE (p=0.039)
  - 1.38%/year for BMI > 40 vs. 2.04-2.26% for other BMI subgroups
- No other significant differences in weight/BMI subgroups in reported data
  - Highest weight group > 100 kg, highest BMI group > 35 kg/m2 for efficacy data
    (> 30 kg/m2 for A Fib and VTE ppx)

Granger CB. N Engl J Med. 2011 Sep 15;365(11):981-92.
Connolly SJ. N Engl J Med. 2011 Mar 3;364(9):806-17.
Agnelli G, et al. N Engl J Med. 2013 Aug 29;369(9):799-808.
Pineo G, et al. J Thromb Haemost. 2013 Mar;11(3):444-51.

Clinical Data - Edoxaban

Trial	Weight threshold reported (kg)	% Patients	BMI Threshold Reported (kg/m2)	% Patients
ENGAGE AF-TIMI 48	Not Reported			
HOKUSAI VTE	>100	14.8% (611)		

Giugliano R. N Engl J Med. 2013 Nov;369:2093-104.
Hokusai-VTE Investigators. N Engl J Med 2013;369:1406-15.

Clinical Data - Edoxaban

- No significant differences in weight/BMI subgroups in reported data
  - Not reported for A Fib
  - Highest weight group > 100 kg for VTE

Note CrCl > 95 ml/min = Contraindication due to increased stroke risk in A Fib

Clinical Data - Betrixaban

Trial	Weight threshold reported (kg)	% Patients	BMI Threshold Reported (kg/m2)	% Patients
APEX	Not reported			

- No reporting of outcome data by weight or BMI

Cohen A. N Engl J Med. 2016 Aug 11;375(6):534-44.

Obesity Paradox in Atrial Fibrillation

- Obese patients with Atrial Fibrillation have shown better prognosis vs. normal weight patients
  - Lower rate of stroke / systemic embolism
  - Lower rate of major bleeding
  - Lower rate of CV death / all-cause death

Cambeiro G, et al. J Atr Fibrillation. 2015 Aug 31;8(2):1259.
Sandhu R, et al. Eur Heart J. 2016; 37, 2869–2878.
Lavie C, et al.. Prog Cardiovasc Dis. 2016;58(5):537-47.
Proietti M, et al. Stroke. 2017;48:857-866.

ISTH SSC Guidance Statement

- **We recommend appropriate standard dosing of the DOACs in patients with a BMI less than or equal to 40 kg m^{-2} and weight less than or equal to 120 kg for VTE treatment, VTE prevention, and prevention of ischemic stroke and systemic arterial embolism in non-valvular AF**
- **We suggest that DOACs should <u>not</u> be used in patients with a BMI of > 40 kg m^{-2} or a weight of > 120 kg**
  - Limited clinical data available for patients at the extreme of weight
  - Available PK/PD evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives with increasing weight
  - Concerns about underdosing

Martin K, et al. J Thromb Haemost. 2016 Jun;14(6):1308-13.

ISTH SSC Guidance Statement

- **If DOACs are used in a patient with a BMI of > 40 kg m^{-2} or a weight of > 120 kg, we suggest checking a drug-specific peak and trough level**
  - Anti-FXa for apixaban, edoxaban, and rivaroxaban; ecarin time or dilute thrombin time with appropriate calibrators for dabigatran; or mass spectrometry drug level for any of the DOACs.
  - If the level falls within the expected range, continuation of the DOAC seems reasonable
  - If the drug-specific level is found to be below the expected range, we suggest changing to a VKA rather than adjusting the dose of the DOAC

Martin K, et al. J Thromb Haemost. 2016 Jun;14(6):1308-13.

Technician Question

Describe why there are concerns with direct oral anticoagulants (DOAC) in obese patients

A. DOAC are given at fixed doses, so obese patient may be underdosed
B. DOAC are given at fixed doses, so obese patients may be overdosed
C. DOAC are given at weight-based doses, so obese patients may be underdosed
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Pharmacist Question

Which of the following is consistent with the guidance from the International Society of Thrombosis and Haemostasis (ISTH) on use of the direct oral anticoagulants (DOAC) in obese patients?

A. DOACs are recommended to be used at standard doses for all patients due to data suggesting obesity does not effect drug concentrations
B. DOACs are recommended to be used at double the dose for patients with extreme obesity due to data suggesting similar drug concentrations
C. DOACs are suggested to be avoided in patient with BMI >30 kg/m2 or weight > 90 kg due to exclusion from trials
D. DOACs are suggested to be avoided in patients with BMI > 40 kg/m2 or weight > 120 kg due to data suggesting decreased drug concentrations

DOAC in Renal Impairment

Drug	% Renal Clearance
Dabigatran (Pradaxa ®)	80%
Rivaroxaban (Xarelto ®)	36%
Apixaban (Eliquis ®)	27%
Edoxaban (Savaysa ®)	50%
Betrixaban (Bevyxxa ®)	11% ?

Pradaxa [package insert]. Ridgefield, CT, Boehringer Ingelheim; 2017.
Xarelto [package insert]. Titusville, NJ. Janssen Pharmaceuticals; 2017.
Eliquis [package insert]. Princeton, NJ. Bristol-Myers Squibb; 2018.
Savaysa [package insert]. Basking Ridge, NJ. Daiichi Sankyo; 2017.
Bevyxxa [package insert]. San Franscico, CA. Portola Pharmaceutical; 2017.

DOAC in Renal Impairment

Drug	Manufacturer Recommendations
Dabigatran (Pradaxa ®)	A Fib: No dose adjustment CrCl >30, 50% reduction in CrCl 15-30 VTE: Avoid CrCl < 30
Rivaroxaban (Xarelto ®)	A Fib: CrCl 15 – 50 reduce dose from 20 mg to 15 mg daily VTE: Avoid in CrCl < 30
Apixaban (Eliquis ®)	A Fib: Reduce dose 50% if 2 of 3: Age ≥ 80, Wt ≤ 60 kg, SCr ≥ 1.5 A Fib & VTE No dose adjustment recommended for renal impairment including those w/ ESRD on dialysis
Edoxaban (Savaysa ®)	A Fib & VTE: 50% dose reduction in CrCl 15-50 ml/min
Betrixaban (Bevyxxa ®)	VTE prevention: 50% dose reduction in CrCl 15 – 30 ml/min

Pradaxa [package insert]. Ridgefield, CT, Boehringer Ingelheim; 2017.
Xarelto [package insert]. Titusville, NJ. Janssen Pharmaceuticals; 2017.
Eliquis [package insert]. Princeton, NJ. Bristol-Myers Squibb; 2018.
Savaysa [package insert]. Basking Ridge, NJ. Daiichi Sankyo; 2017.
Bevyxxa [package insert]. San Franscico, CA. Portola Pharmaceutical; 2017.

DOAC in Renal Impairment- *Manufacturer vs. Data*

Drug	Manufacturer Recommendations	Clinical Trial Data
Dabigatran	A Fib: 50% reduction in CrCl 15-30	**Excluded CrCl < 30 ml/min**
Rivaroxaban	A Fib: Reduce dose 20 mg to 15 mg in CrCl 15-50	**Excluded CrCl < 30 ml/min**
Apixaban	A Fib: Reduce dose 50% if 2 of 3: Age ≥ 80, Wt ≤ 60 kg, SCr ≥ 1.5 A Fib & VTE No dose adjustment recommended for renal impairment including those w/ ESRD on dialysis	**Excluded CrCl < 25 ml/min (30 ml/ml VTE prevention) or SCr > 2.5**
Edoxaban	A Fib & VTE: 50% dose reduction in CrCl 15-50	**Excluded CrCl < 30 ml/min**
Betrixaban	VTE prevention: 50% dose reduction in CrCl 15 – 30	**Excluded CrCl < 30 ml/min**

Connolly SJ, et al. N Engl J Med. 2009 Sep 17;361(12):1139-51.
Patel MR, et al. N Engl J Med. 2011 Sep 8;365(10):883-91.
Granger CB. N Engl J Med. 2011 Sep 15;365(11):981-92.
Agnelli G, et al. N Engl J Med. 2013 Aug 29;369(9):799-808.
Connolly SJ. N Engl J Med. 2011 Mar 3;364(9):806-17.
Hokusai-VTE Investigators. N Engl J Med 2013;369:1406-15.
Giugliano R. N Engl J Med. 2013 Nov;369:2093-104.

Dabigatran in Renal Impairment

So if they weren't included in clinical trials, what data do we have?

- Single dose PK data

CrCl (ml/min)	AUC Increase	Cmax Increase	Half-life (hr)
≥ 80	1 X	1 X	13
50-80	1.5 X	1.1 X	15
30-50	3.2 X	1.7 X	18
15-30	6.3 X	2.1 X	27

- aPTT time curve
  - 75 mg dose in CrCl 15-30 higher than 150 mg dose in CrCl 30-50
- *PK simulation test – estimated 12% ↑ peak & 39% ↑ trough*

Pradaxa [package insert]. Ridgefield, CT, Boehringer Ingelheim; 2017.
J Clin Pharmacol. 2012 Sep;52(9):1373-8.

Rivaroxaban in Renal Impairment

So if they weren't included in clinical trials, what data do we have?

- CrCl 30-50 ml/min received 15 mg daily in ROCKET-AF
  - No difference in outcomes
- CrCl 15-30: AUC increase 64%, Factor Xa inhibition increase 100%
- HD patients:
  - **Single** 15 mg dose in 8 patients → 56% increased AUC vs. normal renal function
  - 10 mg **single** dose → "similar drug exposure" to 20 mg in normal renal function
  - 10 mg x 7 days --> "no accumulation"

Patel MR, et al. N Engl J Med. 2011 Sep 8;365(10):883-91.
Kubitza D, et al. Br J Clin Pharmacol. 2010 Nov;70(5):703-12.
Dias C, et al.. Am J Nephrol. 2016;43(4):229-36.
De Vriese A, et al. Am J Kidney Dis. 2015 Jul;66(1):91-8.

Apixaban in Renal Impairment

So if they weren't included in clinical trials, what data do we have?

- **Single dose** PK study in **8 patients** on hemodialysis
  - After HD: **AUC ↑ 36%**
  - Before HD: **AUC ↑17%**

  ⇒ FDA Approval (2014)
- Repeated dosing in **7 patients** on hemodialysis x 8 days showed accumulation
  - Suggests 5 mg BID should be avoided
  - 2.5 mg BID reasonable ??
- 4-7% of drug removed w/ HD session
- **Single dose** PK study→ regression showed **AUC ↑44%** with CrCl 15 ml/min

Wang X, et al. J Clin Pharmacol. 2016May;56(5):628-36.
Mavrakanas T, et al. J Am Soc Nephrol. 2017Jul;28(7):2241-2248
Chang M, et al. J Clin Pharmacol. 2016 May;56(5):637-45.

Apixaban in Renal Impairment

So if they weren't included in clinical trials, what data do we have?

- Retrospective review of patients on apixaban or warfarin with CrCl <25, SCr >2.5, or on dialysis at single hospital (n= 73 each)
  - *27% on dialysis, 10% ESRD not on dialysis, 63% non-ESRD*
  - *46% apixaban new starts, 0% warfarin new starts*
  - No difference in major bleeding (9.6% vs. 17.8%)
  - No difference in composite bleeding (21.9% vs. 27.4%)
  - No difference in stroke rate (7.5% vs. 7.5%) or VTE (0%)

Stanton B, et al. Pharmacotherapy. 2017 Apr;37(4):412-419.

Apixaban in Renal Impairment

So if they weren't included in clinical trials, what data do we have?

- Retrospective review of ESRD pts- 40 apixaban vs. 120 warfarin
  - 58% on 2.5 mg dose (all qualified for 5 mg dose per labeling)
  - No differences in bleeding events
    - 0% vs. 5.8% major
    - 12.5% vs. 5.8% clinical relevant nonmajor
  - *Relied mostly on paper chart documentation for bleeding events*

Sarratt S, et al.]Ann Pharmacother. 2017Jun;51(6):445-450..

Apixaban in Renal Impairment

So if they weren't included in clinical trials, what data do we have?

- Retrospective review of hospitalized ESRD pts on apixaban (n=114)
  - 46% new starts
  - **15% bleeding rate over average LOS 6 days**
    - 6% ISTH major bleeding, 11% ISTH major or clinically relevant)
  - **Risk Factors for bleeding:**
    - **Higher cumulative apixaban exposure**
    - **Hospital LOS**
    - **Total daily dose (OR 1.72)**
    - **Total number of HD sessions (OR 2.04)**
    - **Continuation of outpatient apixaban (OR 13.07)**

Steuber T, et al. AnnPharmacother. 2017 Nov;51(11):954-960.

Edoxaban in Renal Impairment

So if they weren't included in clinical trials, what data do we have?

- Manufacturer PK data – CrCl <30 had 93% increase drug exposure vs normal renal function

Savaysa [package insert]. Basking Ridge, NJ. Daiichi Sankyo; 2017.

Betrixaban in Renal Impairment

So if they weren't included in clinical trials, what data do we have?

- Manufacturer PK data – eGFR (MDRD) 15-30 ml/min/1.73 m2 had 2.63 fold increase drug exposure vs normal renal function

Bevyxxa [package insert]. San Franscico, CA. Portola Pharmaceutical; 2017.

Technician Question

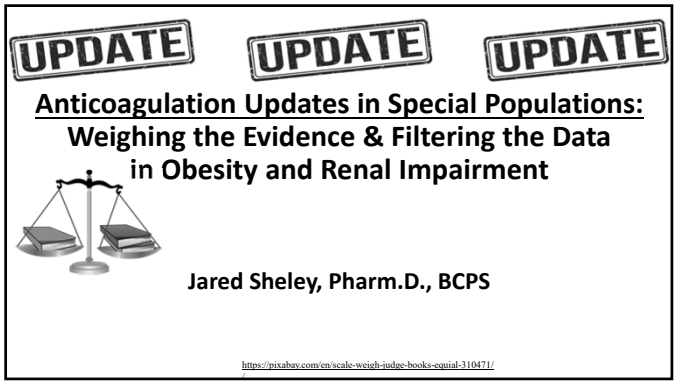
Which of the following would be a reason for concern with DOAC use?

A. Feeding tube status
B. Hemodialysis status
C. Tricare prescription insurance
D. Elevated blood glucose

Pharmacist Question

Which of the following is true regarding data on DOAC in patients with renal impairment?

A. Some DOAC with labeled indications for patients on dialysis now have robust data showing safety and efficacy in this patient population
B. Patients with ESRD on dialysis or CrCl < 25 ml/min were excluded from all clinical trials of DOAC
C. Patients with CrCl < 50 ml/min were excluded from all clinical trials of DOAC
D. Renal function is not a relevant consideration w/ DOAC use


UPDATE
UPDATE
UPDATE
Anticoagulation Updates in Special Populations:
Weighing the Evidence & Filtering the Data
in Obesity and Renal Impairment
Jared Sheley, Pharm.D., BCPS
https://pixabay.com/en/scale-weigh-judge-books-equial-310471/