ashp MIDYEAR 2018
Clinical Meeting & Exhibition

Therapeutic Challenges: Direct Oral Anticoagulants in Special Populations

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Disclosures

- **Paul P. Dobesh:** BMS/Pfizer alliance: Consultant; Boehringer Ingelheim: Consultant; Daiichi Sankyo: Consultant; Janssen Pharmaceuticals: Consultant; Portola Pharmaceuticals: Consultant
- All other planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.

Learning Objectives

- Discuss clinical trials evaluating direct oral anticoagulants (DOACs) in obesity.
- Evaluate clinical trials of DOACs in patients with malignancy.
- Recommend DOAC dosing for end stage renal disease (ESRD).
- Select an appropriate DOAC therapy for patients with gastric bypass.

Case 1

A 72-year-old woman (64 kg) with chronic kidney disease is admitted for atrial fibrillation. Her heart rate is controlled on metoprolol and it is time to initiate oral anticoagulation therapy. Her CrCl is 23 mL/min (SCr 2.0 mg/dL).

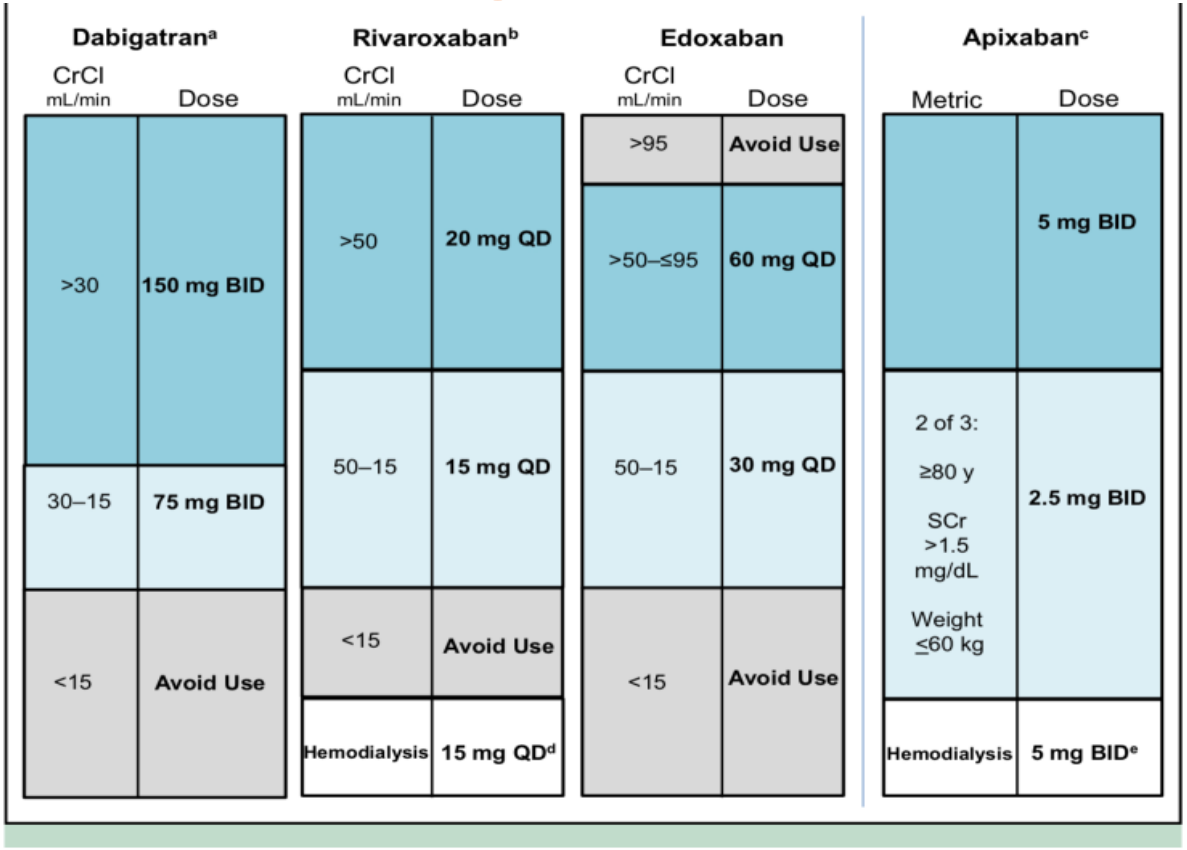
Which of the following is appropriate oral therapy?

a. Apixaban 5 mg twice daily
b. Dose-adjusted warfarin (INR goal = 2-3)
c. Edoxaban 60 mg once daily
d. Dabigatran 150 mg twice daily
e. Rivaroxaban 15 mg once daily

Renal Exclusion Criteria in Clinical Trials

DOAC	Renal Clearance	Pivotal Trial(s)	Renal Exclusion Criterion
Dabigatran	80%	RE-COVER RE-COVER II	CrCl < 30 mL/min
Rivaroxaban	36%	EINSTEIN DVT EINSTEIN PE	CrCl < 30 mL/min
Apixaban	25%	AMPLIFY	CrCl < 25 mL/min or SCr > 2.5 mg/dL
Edoxaban	35%	HOKUSAI-VTE	CrCl < 30 mL/min

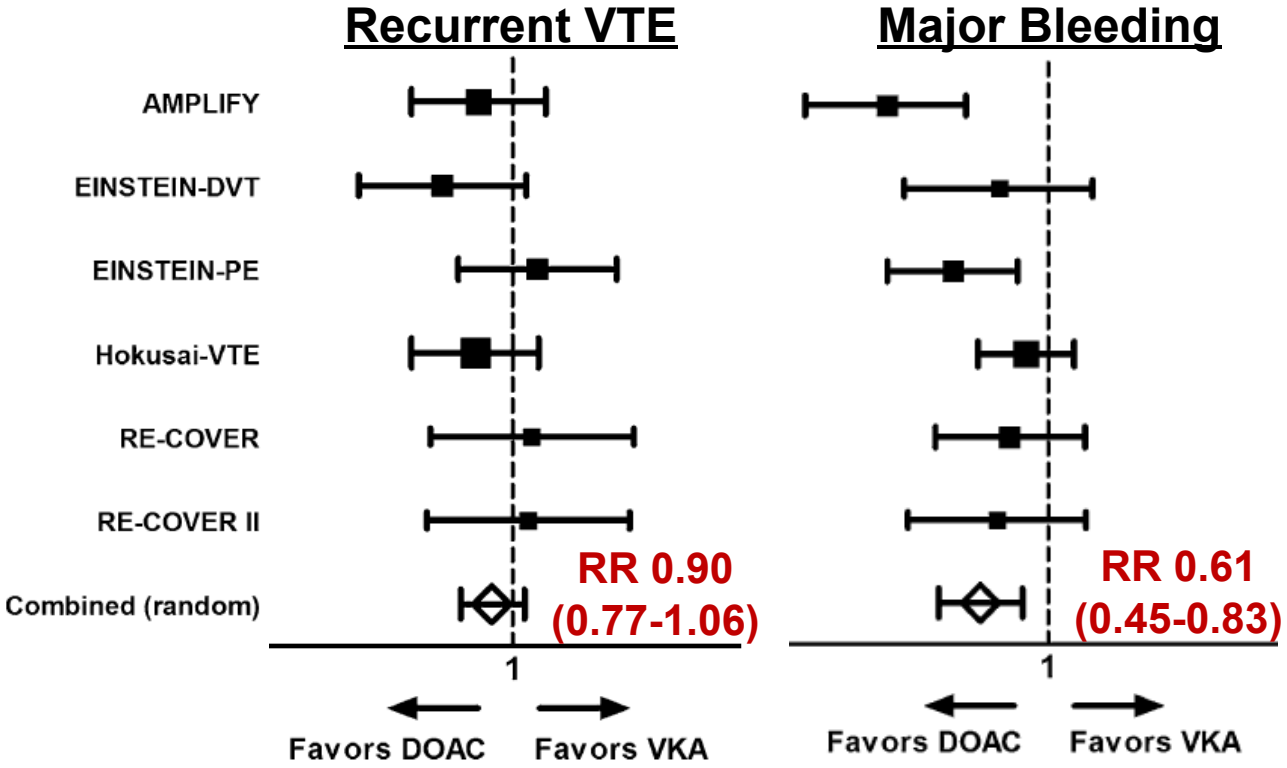
Dosing Guidelines



Dabigatran[a]		Rivaroxaban[b]		Edoxaban		Apixaban[c]	
CrCl mL/min	Dose	CrCl mL/min	Dose	CrCl mL/min	Dose	Metric	Dose
>30	150 mg BID	>50	20 mg QD	>95	Avoid Use		5 mg BID
				>50–≤95	60 mg QD		
30–15	75 mg BID	50–15	15 mg QD	50–15	30 mg QD	2 of 3: ≥80 y SCr >1.5 mg/dL Weight ≤60 kg	2.5 mg BID
<15	Avoid Use	<15	Avoid Use	<15	Avoid Use		
		Hemodialysis	15 mg QD[d]			Hemodialysis	5 mg BID[e]

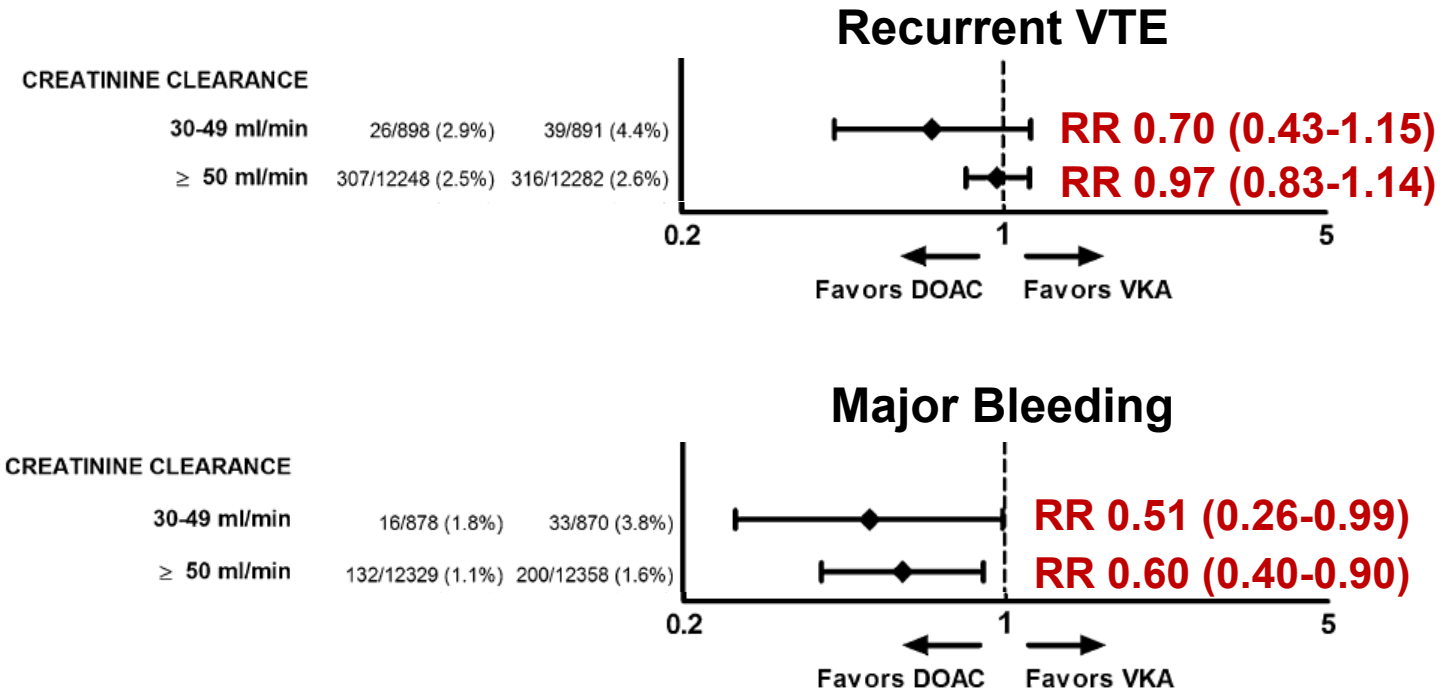
Fanikos J, et al. *Am J Med* 2017:130;1015-23.

Overall Results of VTE Trials



van Es N et al. *Blood* 2014; 124:1968-75

Results Stratified by Renal Function



van Es N et al. *Blood* 2014; 124:1968-75.

Phase III Non-Valvular Atrial Fibrillation DOAC Trials

GFR	Stroke/Systemic Embolism RR (95% CI)	Major Bleeding RR (95% CI)
50-80 mL/min	0.71 (0.62-0.81)	0.88 (0.80-0.97)
< 50 mL/min	0.79 (0.66-0.94)	0.80 (0.70-0.91)

Del-Carpio Munoz F et al. *Am J Cardiol* 2016;117:69-75.

Real-world studies: More data to come

Study	Population (n)	n
XALIA	Patients with VTE treated with rivaroxaban	5723
GARFIELD-VTE	Patients with VTE treated with DOACs or VKA	10,000 (target)
Dresden NOAC registry	Patients with VTE or NVAF treated with DOACs	2941
RE-COVERY DVT/PE	Patients with VTE treated with dabigatran or VKA	14,000 (target)

Beyer-Westendorf J et al. *Thromb Haemost*. 2016; 116(suppl 2):S13-S23.
Ageno W et al. *Thromb Haemost*. 2017; 117:415-21.

Evidence in Severe Renal Dysfunction (CrCl < 30 mL/min) or End-Stage Renal Disease

Warfarin in Severe CKD and Hemodialysis

- **Hemodialysis**
  - **Observational studies have shown a reduced risk of all cause death, CV events, stroke, and thromboembolism without increased bleeding in patients on dialysis of renal replacement therapy**
  - **Three large meta-analyses failed to show benefit of warfarin in ESRD or dialysis patients**
    - **Did not reduce mortality or thromboembolism rates**
    - **Did increase risk of all-cause or major bleeding**
  - **One meta-analysis (9,000 patients) and one study demonstrated increased risk in strokes**

Fanikos J, et al. *Am J Med* 2017;130:1015-1023.
Lee M, et a. *Medicine* 2016;95:e2741.

Apixaban Renal Data

2.7 Renal Impairment

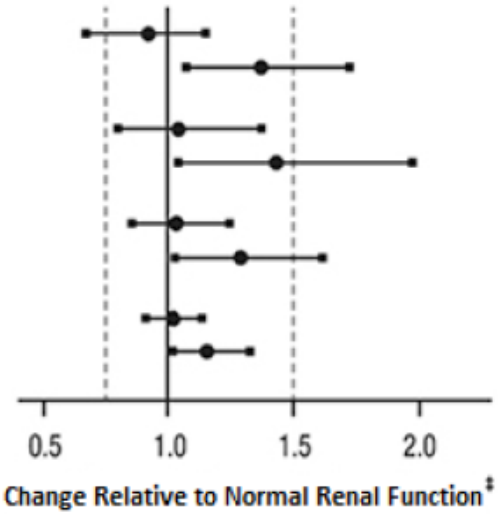
The dosing adjustment for moderate renal impairment is described above *[see Dosage and Administration (2.2)]*. The recommended dose for patients with end-stage renal disease (ESRD) maintained on hemodialysis is 5 mg twice daily. Reduce dose to 2.5 mg twice daily if one of the following patient characteristics (age ≥80 years or body weight ≤60 kg) is present *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

8.6 End-Stage Renal Disease Patients Maintained with Hemodialysis

Patients with ESRD with or without hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS; therefore, the dosing recommendation is based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis. The recommended dose for ESRD patients maintained with hemodialysis is 5 mg orally twice daily. For ESRD patients maintained with hemodialysis with one of the following patient characteristics, age ≥80 years or body weight ≤60 kg, reduce dose to 2.5 mg twice daily *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.2, 12.3)]*.

Apixaban Renal Data

Population Description	PK	Recommendation
End-Stage Renal Disease*/Normal	C_{max} AUC	No dose adjustment
Renal Impairment: Severe†/Normal	C_{max} AUC	No dose adjustment
Renal Impairment: Moderate/Normal	C_{max} AUC	No dose adjustment
Renal Impairment: Mild/Normal	C_{max} AUC	No dose adjustment



Abbreviations: ESRD, end-stage renal disease; PK, pharmacokinetic.
* ESRD subjects maintained with chronic and stable hemodialysis; reported PK findings are following single dose of apixaban post hemodialysis.
† Creatinine clearance 15 to 29 mL/min.
‡ Dashed vertical lines illustrate PK changes that were used to inform dosing recommendations.
Adapted from Eliquis Full Prescribing Information

Apixaban in Hemodialysis

5 mg twice daily for several days

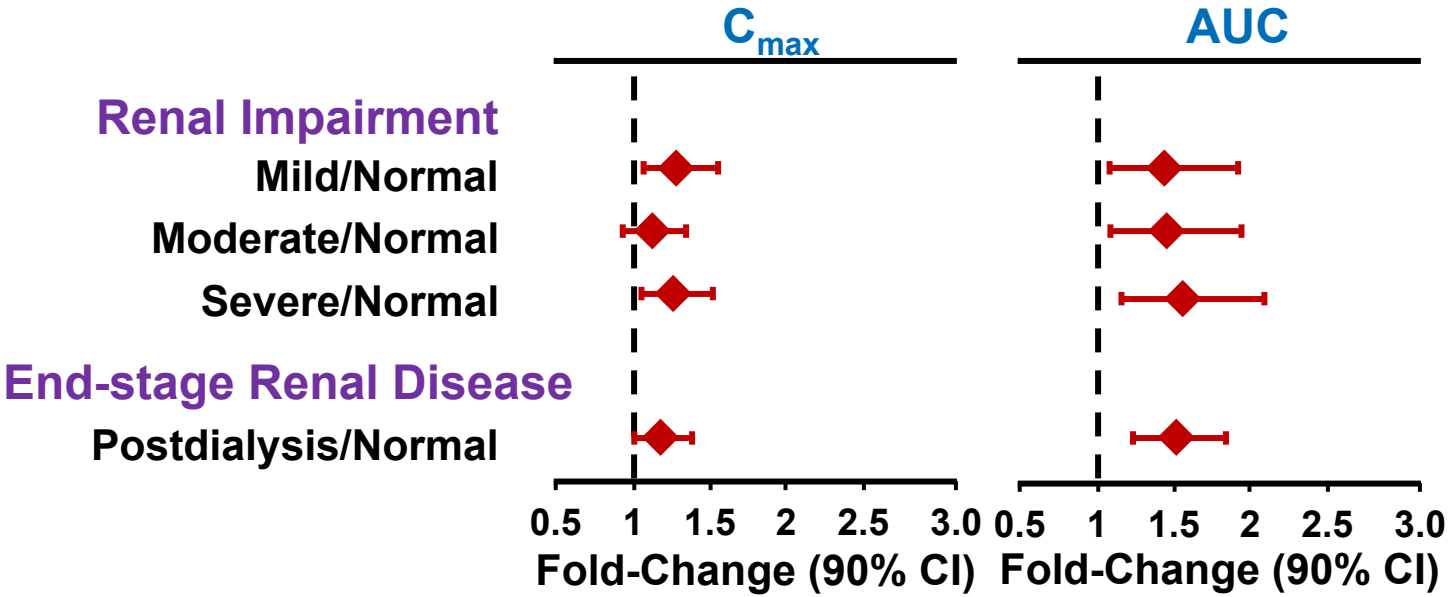
Apixaban 5 mg Twice Daily	Day 22	*P* Value	Reference Levels (for the 5 mg twice daily dose)
AUC_{0-12}, ng h/ml	3026.6±46.6% [2770.4]	0.03	[1474–1717][18]
AUC_{0-24}, ng h/ml	6053.2±46.6% (3505.5–9469.7)	0.03	3370 (2070–5250)[19]
C_{max}, ng/ml	307.0±39.4% (189.0–455.0)	0.02	171 (91–321)[a20]
$t_{max,}$, h	3.8±35.6% (2.5–6.0)	0.89	—
C_{min}, ng/ml	217.5±51.9% (91.0–337.4)	0.03	107 (56–203)[19]
$t_{1/2}$, h	17.4±51.3% (7.1–29.8)	0.13	—

Significant accumulation with approximately a 2-fold increase in Cmax and AUC

"Apixaban 5mg twice daily led to supratherapeutic levels in patients on hemodialysis and should be avoided."

Mavrakanas TA, et al. *J Am Soc Nephrol* 2017;28:2241-48.

Rivaroxaban in Patients on Chronic Hemodialysis

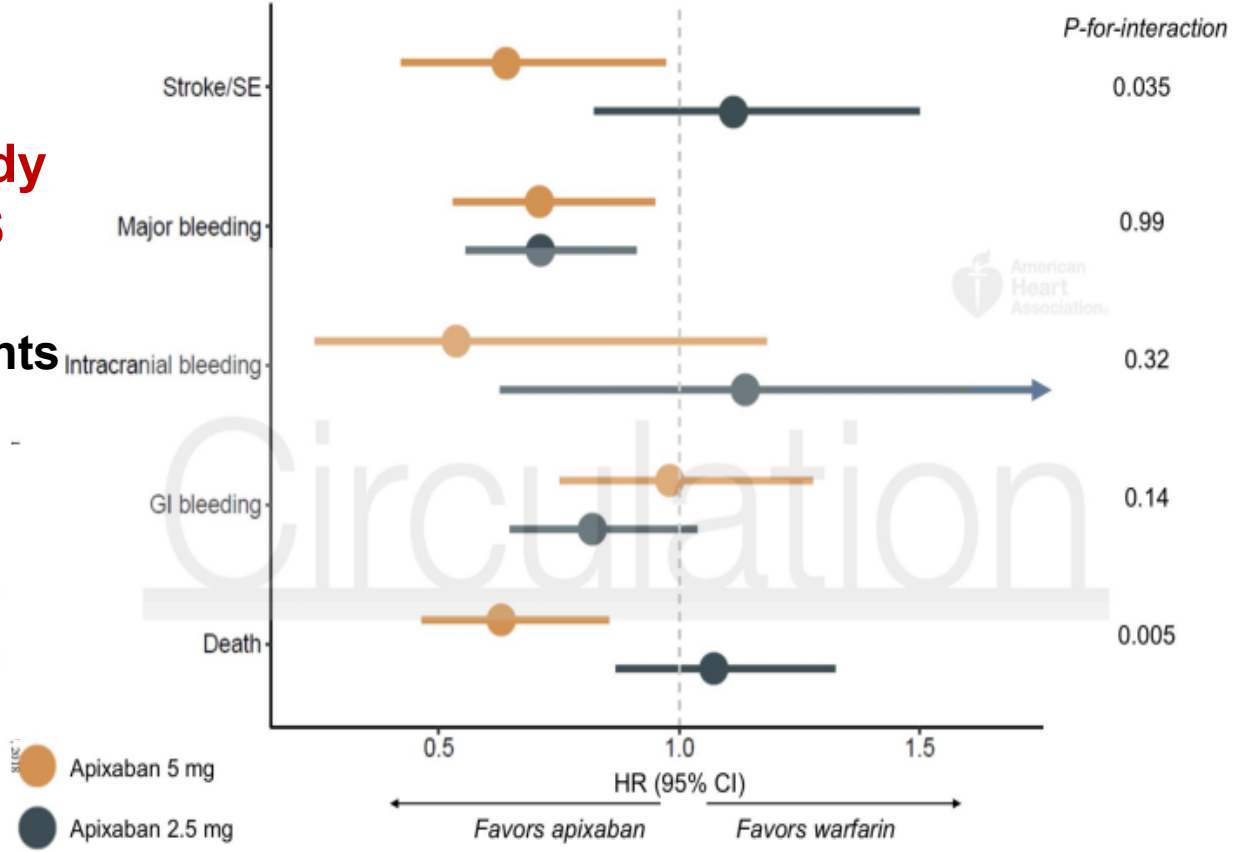


8 Patient Single-Dose Study
Reduced dose (15 mg once daily)

Dias C, et al. *Am J Nephrol* 2016;43:229–236.

Apixaban and Hemodialysis

- **2018 retrospective study from patients in the US Renal Data System**
  - **Mostly evaluate patients on apixaban and dialysis**
  - **Apixaban (n=2351)**
    - **5 mg BID (n=1035)**
    - **2.5 mg BID (n=1317)**
  - **Warfarin (n=23,172)**



Siontis KS, et al. *Circulation* 2018

Rivaroxaban in Patients with CKD 3b-4

Outcomes	Warfarin (TTR 67.6%) (n=100)	Rivaroxaban 15 mg Once Daily (n=247)
Stroke	25 (15 hemorrhagic) (10 ischemic)	0
VTE	5	0
GI bleeding	8	2
Minor bleeding	4	6

DiLullo L, et al. *J Neph* 2018; https://doi.org/10.1007/s40620-018-0501-7

Mean follow up 16 ± 0.3 months

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d. Dabigatran 150 mg twice daily
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Case

HW is a 60-year-old man who was diagnosed with stomach cancer about 6 months ago. Today he presents with a proximal DVT in his left leg. He has normal hepatic and renal function. He would like to avoid injectable therapy.

Which of the following is the best treatment for HW's DVT?

a. Warfarin for 6 months
b. Apixaban 10 mg twice daily x 21 days, then 5 mg twice daily
c. Edoxaban 30 mg once daily
d. Rivaroxaban 15 mg twice daily x 21 days, then 20 mg daily
e. Dabigatran 150 mg twice daily

ACCP Antithrombotic Guideline, 10th edition (AT 10)

AT 10 Choice of anticoagulant for long-term treatment of DVT and PE:

In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over VKA therapy (Grade 2B)

Remarks: Acute therapy with parenteral anticoagulation is given before dabigatran and edoxaban

In patients with DVT of the leg or PE who receive extended therapy, we suggest that there is no need to change the choice of anticoagulant after the first 3 months (Grade 2C).

Kearon C et al. *Chest.* 2016; 149:315-52.

ACCP AT 10 Guideline Statement

AT 10 Choice of anticoagulant for long-term treatment of DVT and PE:

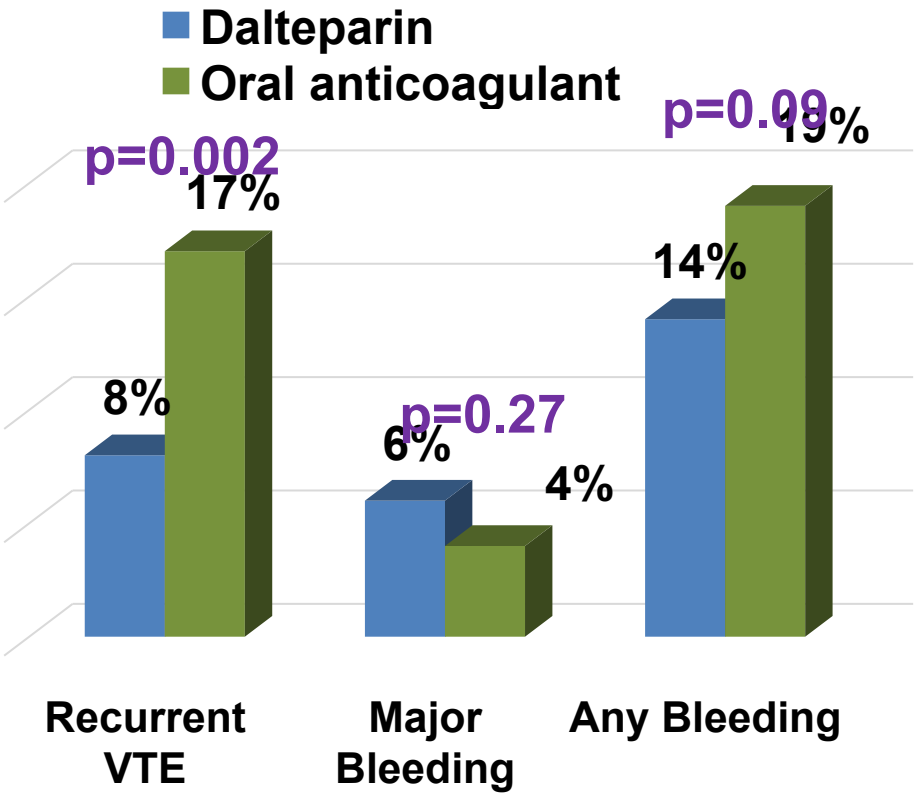
In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).
Remarks: Acute therapy with parenteral anticoagulation is given before dabigatran and edoxaban. See text for factors that influence choice of therapy.

Kearon C et al. *Chest.* 2016; 149:315-52.

VTE Treatment in Cancer Patients:

LMWH vs. Warfarin

- **Initial dalteparin dose 200 units/kg/day**
- **Randomized to dalteparin 150 units/kg/day or warfarin (INR 2-3)**
- **n = 676**
- **Significant reduction in VTE at 6 months with dalteparin**
- **Mortality: dalteparin 39% vs. dalt/warfarin 41% (p = 0.53)**



Lee A et al. *N Engl J Med.* 2003; 349:146-53.

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Remarks: Acute therapy with parenteral anticoagulation is given before dabigatran and edoxaban. See text for factors that influence choice of therapy.

Pages 324-325. "In patients with VTE and cancer who are not treated with LMWH, we do not have a preference for either a NOAC or VKA." There is no preference of one NOAC over another NOAC

Kearon C et al. *Chest.* 2016; 149:315-52.

DOAC VTE Trials and Dosing

- **RECOVER I and II**
  - At least 5 days of injectable anticoagulation followed by dabigatran 150 mg twice daily
- **EINSTEIN DVT and PE**
  - Rivaroxaban 15 mg twice daily for 21 days, then 20 mg daily
- **AMPLIFY**
  - Apixaban 10 mg twice daily for 7 days, then 5 mg twice daily
- **Hokusai – VTE**
  - At least 5 days of injectable anticoagulation followed by edoxaban 60 mg once daily

Acute VTE Treatment: Clinical Trial Comparisons

Characteristic	RE-COVER I	RE-COVER II	EINSTEIN – DVT	EINSTEIN – PE	AMPLIFY	Hokusai - VTE
Mean age (yr)	55	57	56	58	57	56
Male sex (%)	58	61	57	53	59	57
Weight (kg)	85	81	82	83	84	82
CrCl 30-50 mL/min (%)	NR	NR	6.8	8.2	5.7	6.6
Active cancer (%)	4.8	3.9	6.0	4.6	2.7	2.5
VTE history (%)	26	18	19	20	16	18
DVT only (%)	69	68	99	0	66	60
PE only (%)	21	23	0	75	25	30
DVT + PE (%)	10	9	1	25	9	10

Dobesh PP et al. *Drugs.* 2014; 74:2015-32.

NR = not reported

VTE Treatment in Cancer Patients:

LMWH vs. Warfarin

- Initial dalteparin dose 200 units/kg/day
- Randomized to dalteparin 150 units/kg/day or warfarin (INR 2-3)
- n = 676
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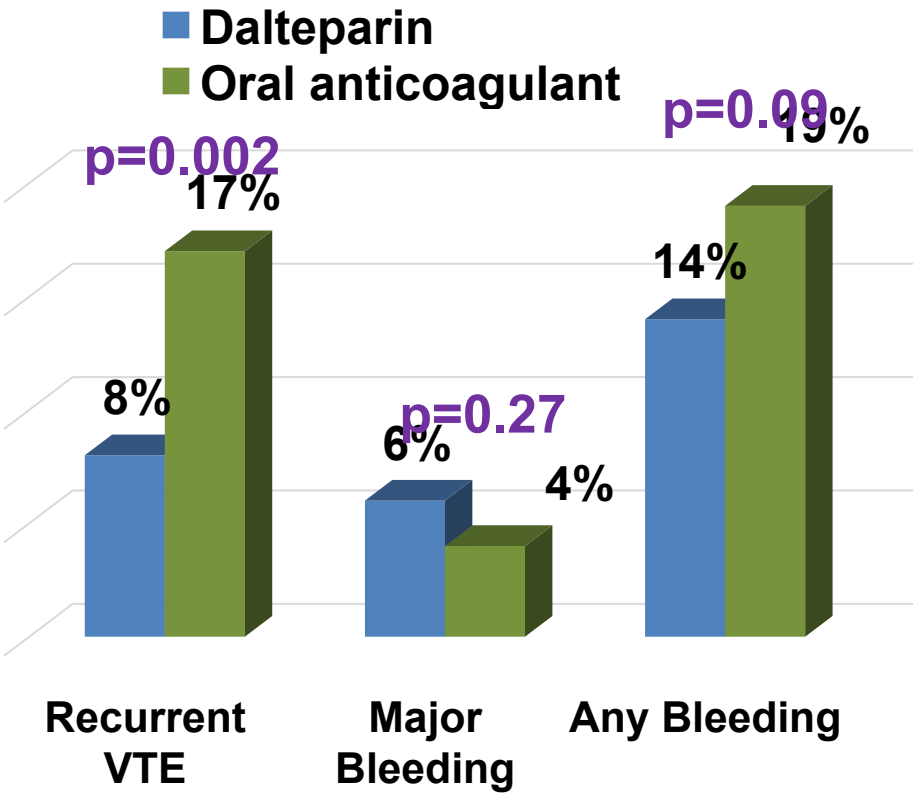
- Mortality: dalteparin 39% vs. dalt/warfarin 41% (p = 0.53)

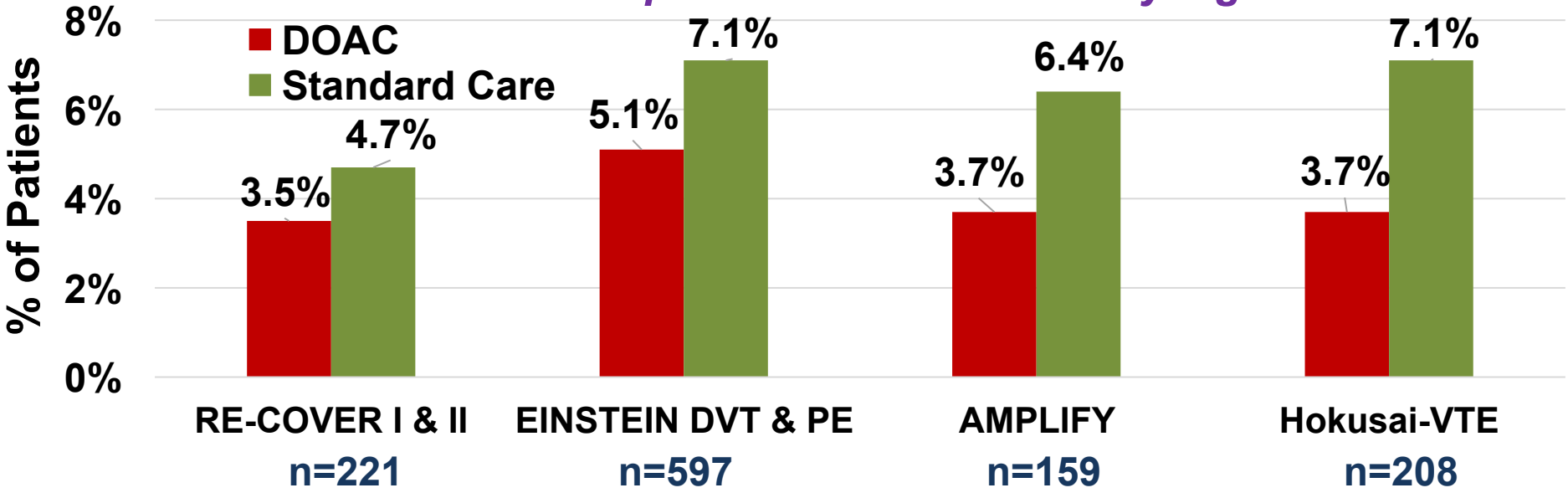


Lee A et al. *N Engl J Med.* 2003; 349:146-53.

Patients with Active Cancer

Primary Efficacy Endpoint

None of these comparisons are statistically significant

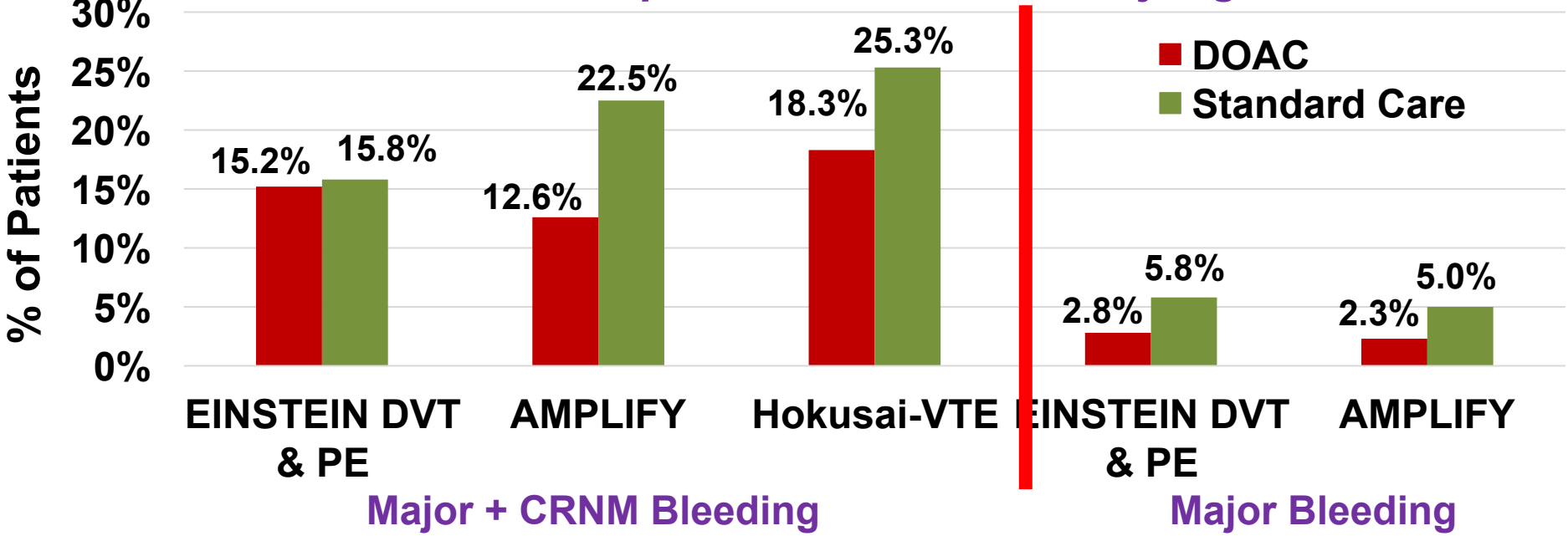


Schulman S, et al. *Circulation* 2014;129;764-772.; Prins MH, et al. *Thrombosis Journal* 2013;11.21.; Agnelli G, et al. *J Thromb Haemost* 2015;13:2187-2191.; The Hokusai-VTE Investigators. *N Engl J Med* 2013;369:1406-1415.

Patients with Active Cancer

Safety Endpoints

None of these comparisons are statistically significant



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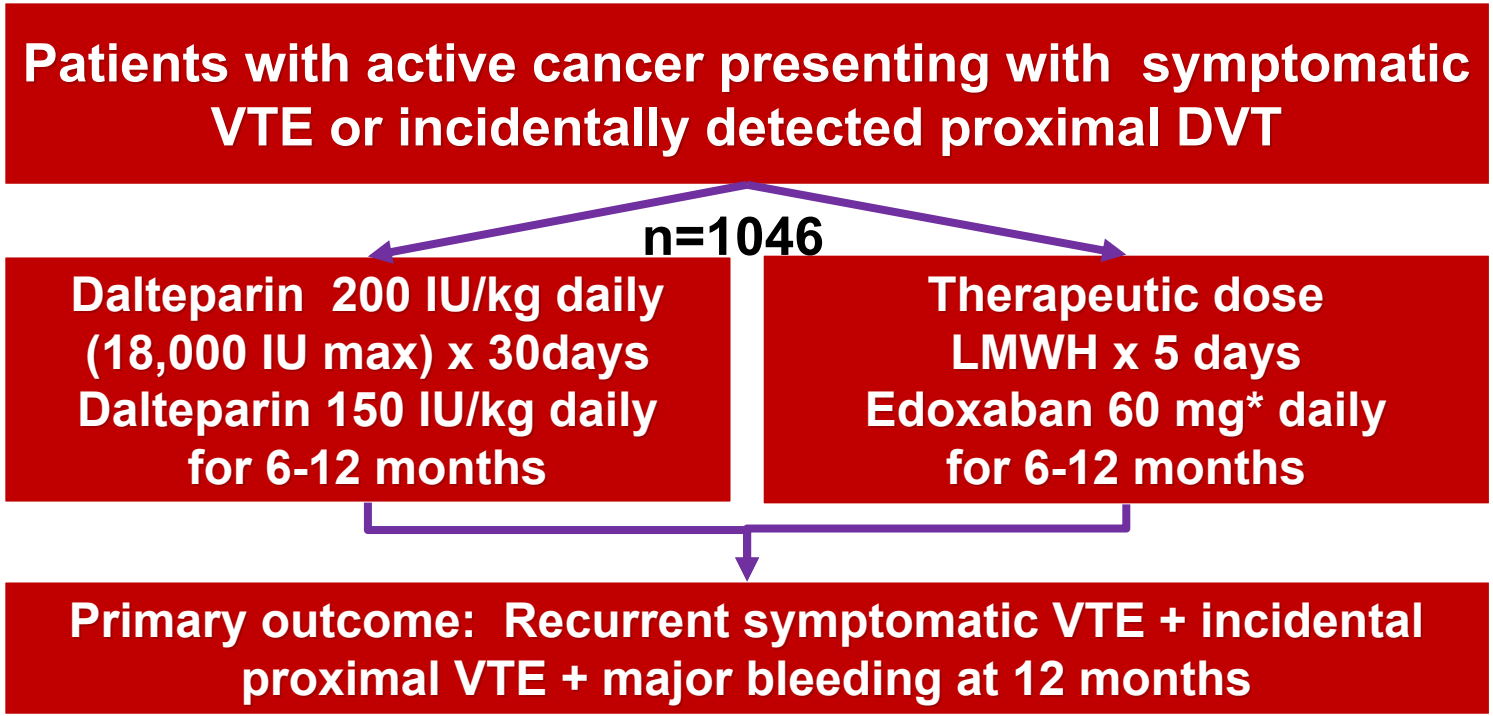
Hokusia VTE Cancer Trial



*** 30 mg daily was use in patients with CrCl 30-50, weight ≤ 60kg, or with us of potent P-gp inhibitors**

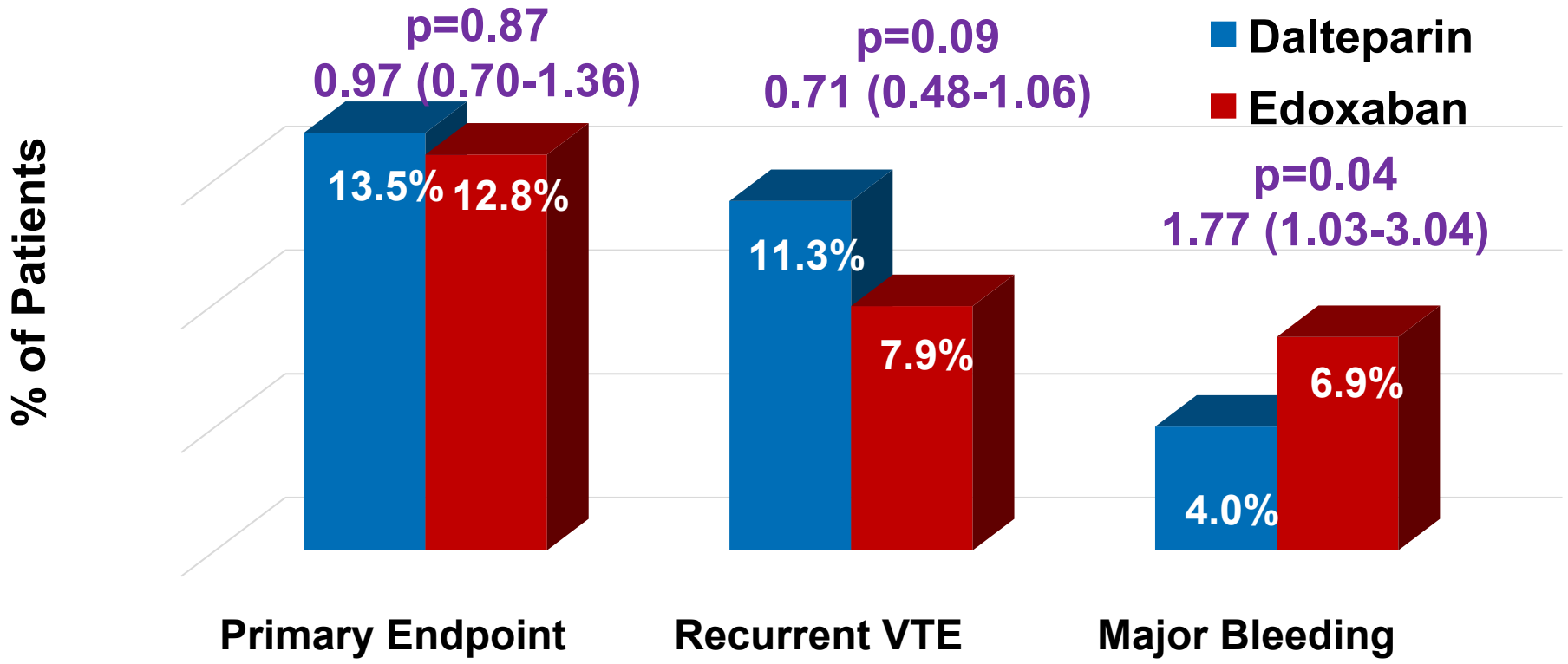
Roskob GE, et al. *N Engl J Med* 2018;378:615-624.

Hokusai VTE Cancer Trial

Characteristic	Dalteparin (n=524)	Edoxaban (n=522)
Age (years)	63.7 ± 11.7	64.3 ± 11.0
Male (%)	50.2	53.1
Reduced dose edoxaban (%)	22.3	23.4
CrCl 30-50 mL/min (%)	6.5	7.3
Symptomatic VTE (%)	67.0	68.0
Incidental VTE (%)	33.0	32.0
Previous VTE (%)	12.0	9.4
Active cancer (%)	97.5	98.3
Metastatic cancer (%)	53.4	52.5
Cancer treatment within 4 wks (%)	73.1	71.6

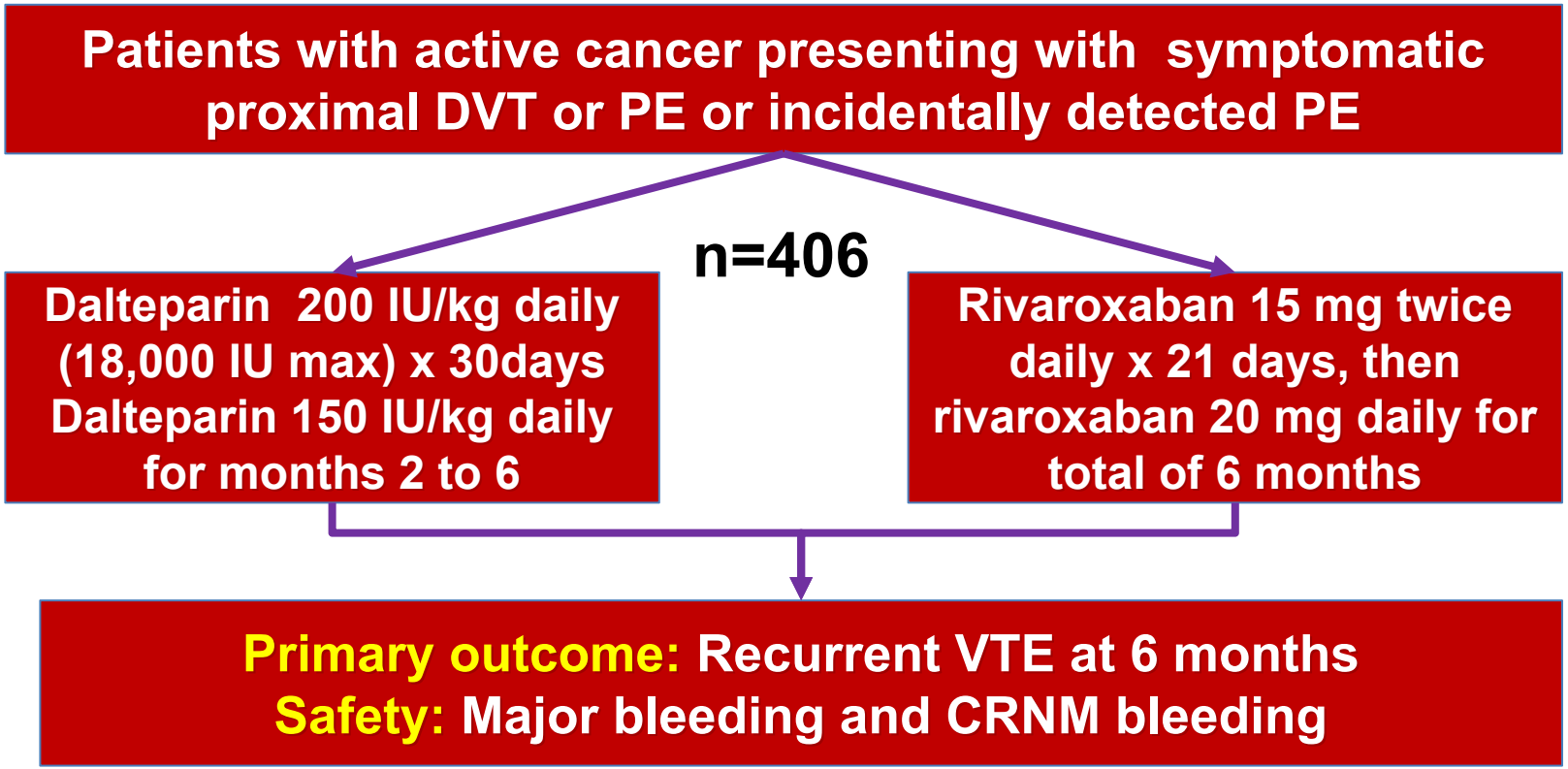
Roskob GE, et al. *N Engl J Med* 2018;378:615-624.

Hokusai VTE Cancer Trial



Roskob GE, et al. *N Engl J Med* 2018;378:615-624.

SELECT – D Trial

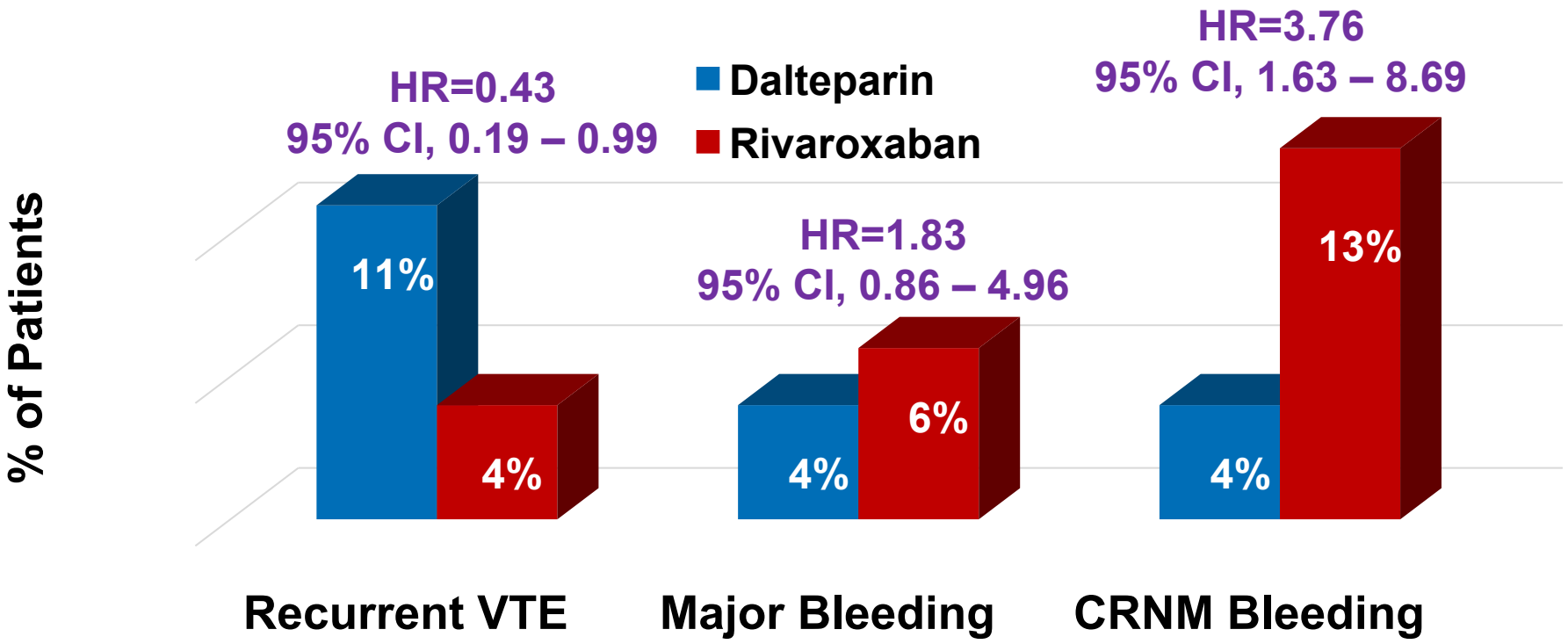


Young AM, et al. *J Clin Oncol* 2018;36:

SELECT – D Trial

Characteristic	Dalteparin (n=203)	Rivaroxaban (n=203)
Age (years)	67 [34-87]	67 [22-87]
Male (%)	48	57
Symptomatic VTE (%)	48	47
Incidental VTE (%)	52	53
Active cancer (%)	100	100
Metastatic cancer (%)	58	58
Current cancer treatment	70	69
VTE high-risk tumor type (%)	84	83

SELECT – D Trial



Major bleeding inpatients with esophageal or gastroesophageal cancer: 36% of major bleeding with rivaroxaban and 11% of dalteparin

DOACs in Cancer

- **DOACs vs. VKA (warfarin)**
  - Post hoc data (not randomized by presence of cancer)
  - Efficacy and safety seem to be similar
- **DOACS vs. LMWH (dalteparin)**
  - Two trials completed to date
    - Hokusai VTE Cancer (edoxaban)
      - Trend to better efficacy
      - significantly more major bleeding
    - SELECT-D (rivaroxaban)
      - Significantly better efficacy
      - Trend to more major bleeding
  - Combined data?
    - Recurrent VTE: 6.8% DOAC vs. 10.6% dalteparin (p=0.012) NNT=27
    - Major bleeding: 6.5% DOAC vs. 3.7% dalteparin (p=0.023) NNH=38
  - Role of GI cancer in bleeding?

Case

HW is a 60-year-old man who was diagnosed with stomach cancer about 6 months ago. Today he presents with a proximal DVT in his left leg. He has normal hepatic and renal function. He would like to avoid injectable therapy.

Which of the following is the best treatment for HW's DVT?

a. Warfarin for 6 months
b. Apixaban 10 mg twice daily x 21 days, then 5 mg twice daily
c. Edoxaban 30 mg once daily
d. Rivaroxaban 15 mg twice daily x 21 days, then 20 mg daily
e. Dabigatran 150 mg twice daily

Case

NT is a 45 year old female patient recovering from a hysterectomy surgery that was complicated by a post-operative infection. She is hospital day 5 and has been doing well on levofloxacin and thought she would go home today. She now demonstrates pain and swelling in her left leg. CUS confirms a proximal DVT, despite receiving UFH 5000 until three times daily. She is also receiving ranitidine and oxycodone. Her platelet count was 130 x 10^9/L upon admission and is now 70 x 10^9/L. UFH is discontinued and a SRA is sent for analysis

Which of the following is the best treatment for NT's DVT?

a. Enoxaparin bridged to warfarin
b. Argatroban bridged to warfarin
c. Fondaparinux bridged to warfarin
d. Rivaroxaban 15 mg twice daily x 21 days, then 20 mg daily
e. Argatroban followed by rivaroxaban

4T Score Calculation

Category	2 points	1 point	0 points
Thrombocytopenia	Platelet count fall > 50% AND platelet nadir ≥ 20 x 10^9/L	Platelet count fall 30%-50% OR platelet nadir 10-19 x 10^9/L	Platelet count fall < 30% OR platelet nadir < 10 x 10^9/L
Timing of platelet count fall	Clear onset between days 5 and 10 OR platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-10 fall, but not clear (e.g. missing platelet counts) OR onset after day 10 or fall ≤ 1 day (prior heparin exposure 30-100 days ago)	Platelet count fall < 4 days without recent heparin exposure
Thrombosis or other sequelae	New thrombosis (confirmed) OR skin necrosis at heparin injection sites OR acute systemic reaction after IV heparin bolus	Progressive or recurrent thrombosis OR non-necrotizing (erythematous) skin lesions OR suspected thrombosis (not proven)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

≤ 3 points: low probability for HIT (≤ 5% in study, < 1% in meta-analysis)
4-5 points: intermediate probability (~ 14% probability of HIT)
6-8 points: high probability (~ 64% probability of HIT)

Lo GK, et al. *J Thromb Haemost* 2006;4:759-765.

DOACs in HIT

- **Case series (n=9) in Singapore**
  - **4Ts score ≥ 4**
  - **All patients had HIT thrombosis**
  - **Positive IgG specific PF4/heparin complex assay or ELISA**
  - **Rivaroxaban as initial treatment (no fondaparinux or argatroban)**
    - **15 mg twice daily x 21 days, then 20 mg daily (n=4)**
    - **If CrCl < 15 mL/min – initial dose was 10 mg daily (n=5)**
  - **All patients had platelet recovery without progression or new thrombosis**
    - **Mean 14 days; median 8 days**
    - **No bleeding or amputations**
    - **6 of 9 eventually switched to warfarin**

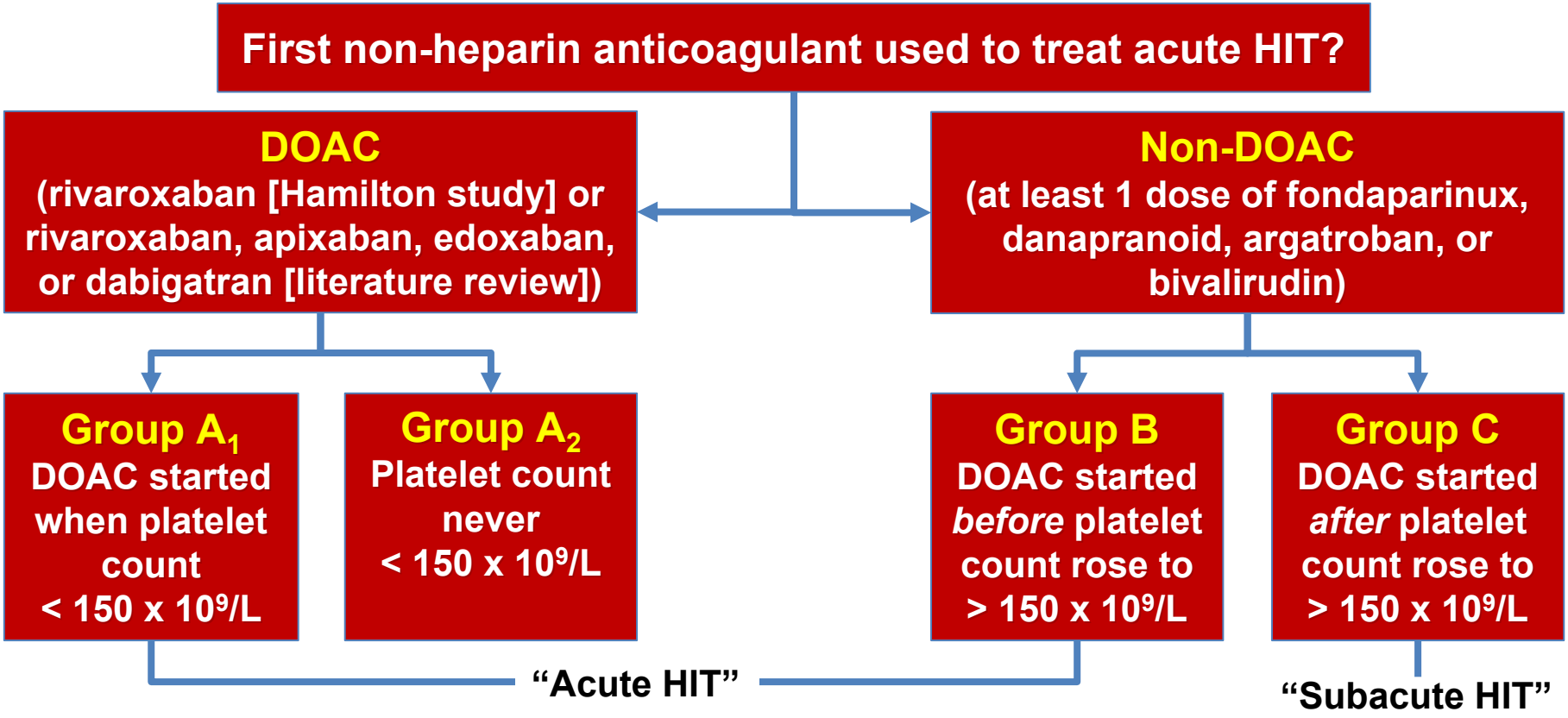
Ong SY, et al. *Ann Hematol* 2017;96:525-527.

DOACs in HIT

- **Case series (n=22) in Arizona**
  - **Reduction in platelet count < 100 x 10^9/L + recent heparin + PF4 ELISA or SRA**
  - **Short course argatroban (mean 32 hours), 2 hours off, then DOAC 3-6 months**
    - **Rivaroxaban 20 mg daily (n=11)**
    - **Dabigatran 150 mg twice daily (n=6)**
    - **Apixaban 5 mg twice daily (n=5)**
  - **20/22 had lab confirmed HIT; 2/22 were solely clinical diagnosis**
  - **Results**
    - **Platelet recovery in all patients (169 x 10^9/L → 82 x 10^9/L → 188 x 10^9/L)**
    - **5/22 (23%) had new DVT**
    - **No arterial thrombosis**
    - **No in-hospital death**
    - **No bleeding or limb loss**

Sharifi M, et al. *Throm Res* 2015;135:607-609.

The Hamilton Experience



Warkentin TE, et al. *Blood* 2017;130:1104-1113.

The Hamilton Experience

Study author	Reference	No. of patients	Group			Median platelet count at rivaroxaban start	HIT-associated thrombosis*		Outcome			
			A_1	A_2	B				Thrombosis		Bleed	
							No.	%	No.	%	No.	%
Rivaroxaban-Hamilton experience												
Linkins et al	17	12	3	2	7	56	6		1		0†	
This study		10	7	1	2	64	5		0		0	
Rivaroxaban-other (non-Hamilton) centers												
Kopolovic and Warkentin	28	1	0	0	1	30	0		0		0	
Ng et al, Ong et al‡	29, 36	9	9	0	0	64	9		0		0	
Sharifi et al§	30	9‡	0	0	9	90‡	4		0		0	
Hantson et al	31	1	0	0	1	30	1		0		0	
Abouchakra et al	32	1	1	0	0	25	1		0		0	
Sartori et al	33	1	0	1	0	150	1		0		0	
Casan et al	34	1	0	0	1	48	1		0		0	
Samoš et al	35	1	1	0	0	65	1		0		0	
Summary		46	21	4	21	73	29/46‖	63.0	1/46	2.2	0/46	0

Warkentin TE, et al. *Blood* 2017;130:1104-1113.

The Hamilton Experience

Study author	Reference	No. of patients	Group			Median platelet count at DOAC start	HIT-associated thrombosis*		Outcome			
			A_1	A_2	B				Thrombosis		Bleed	
							No.	%	No.	%	No.	%
Apixaban												
Sharifi et al†	30	5	0	0	5	90‡	1		0		0	
Larsen et al	37	1	1	0	0	112	0		0		0	
Delgado-García et al§	38, 39	1	1	0	0	25	1		0		0	
Kunk et al	40	5	0	0	5	111	3		0		0	
Total		12	2	0	10	90‡	5/12‖	41.7	0/12	0	0/12	0
Dabigatran												
Sharifi et al†	30	6	0	0	6	90‡	2		0		0	
Anniccherico et al	41, 42	1	0	0	1	120	1		0		0	
Mirdamadi§	43	1	1	0	0	32	1		0		0	
Tardy-Poncet et al	44	1	0	0	1	56	0		0		0	
Noel et al	45	1	0	1	0	216	1		1¶		0	
Bircan and Alanoglu§	46	1	1	0	0	52	1		0		0	
Total		11	2	1	8	58	6/11‖	54.5	1/11	9.1	0/11	0

Warkentin TE, et al. *Blood* 2017;130:1104-1113.

Case

NT is a 45 year old female patient recovering from a hysterectomy surgery that was complicated by a post-operative infection. She is hospital day 5 and has been doing well on levofloxacin and thought she would go home today. She now demonstrates pain and swelling in her left leg. CUS confirms a proximal DVT, despite receiving UFH 5000 until three times daily. She is also receiving ranitidine and oxycodone. Her platelet count was 130 x 10^9/L upon admission and is now 70 x 10^9/L. UFH is discontinued and a SRA is sent for analysis

Which of the following is the best treatment for NT's DVT?

a. Enoxaparin bridged to warfarin
b. Argatroban bridged to warfarin
c. Fondaparinux bridged to warfarin
d. Rivaroxaban 15 mg twice daily x 21 days, then 20 mg daily
e. Argatroban followed by rivaroxaban

Case

A 54 year-old obese man (160 kg, BMI 54 kg/m^2) is admitted to the hospital with a DVT, possible PE. He is initially managed with heparin. He is reluctant to take warfarin since his mother died of a hemorrhage while on warfarin. Which would you do?

A. Advise him to take long-term LMWH
B. Switch him to a DOAC
C. Calculate a subcutaneous heparin dose
D. Encourage warfarin therapy

FDA-approved Labeling for Obesity

Agent	Dosing for Obesity
Dabigatran	No dosage recommendation
Rivaroxaban	No dosage recommendation
Apixaban	No dosage recommendation
Edoxaban	No dosage recommendation

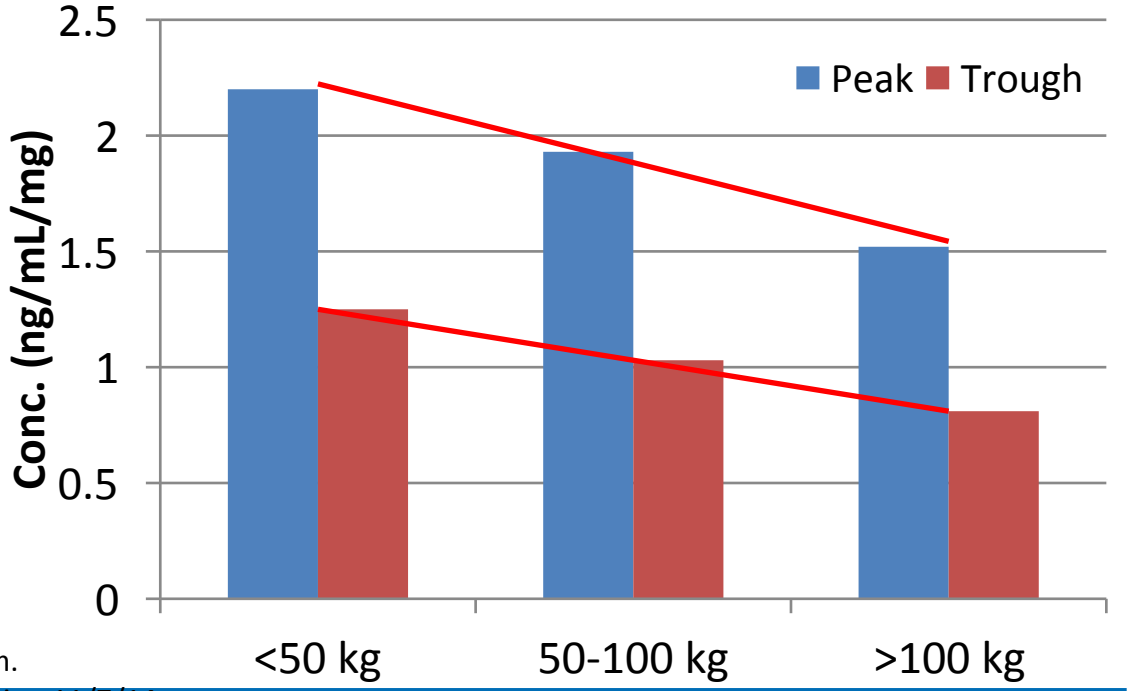
Weights in phase III trials

Medication	Clinical Trial	Weight breakout	Number (%)
Dabigatran	RE-COVER 1	≥ 100 kg BMI ≥ 35	502/2539 (20) 306/2539 (12)
	RE-COVER 2	> 100 kg BMI > 35	438/1280 (34.2) 302/1280 (23.6)
	RE-LY	≥ 100 kg	3099/18,113 (17.1)
Rivaroxaban	EINSTEIN DVT	> 100 kg	245/1731 (14.2)
	EINSTEIN PE	> 100 kg	345/2419 (14.3)
	ROCKET-AF	> 90 kg BMI > 35	2035/7131 (28.5) 972/7131 (13.6)
Apixaban	AMPLIFY	≥ 100 kg BMI > 35	522/2691 (19.4) 349/2691 (13.0)
	ARISTOTLE	BMI ≥ 40	1006/17,913 (5.6)
Edoxaban	HOKUSAI VTE	> 100 kg	611/4118 (14.8)

Martin K, et al. *J Thromb Haemost* 2016; 14: 1308-13

Dabigatran

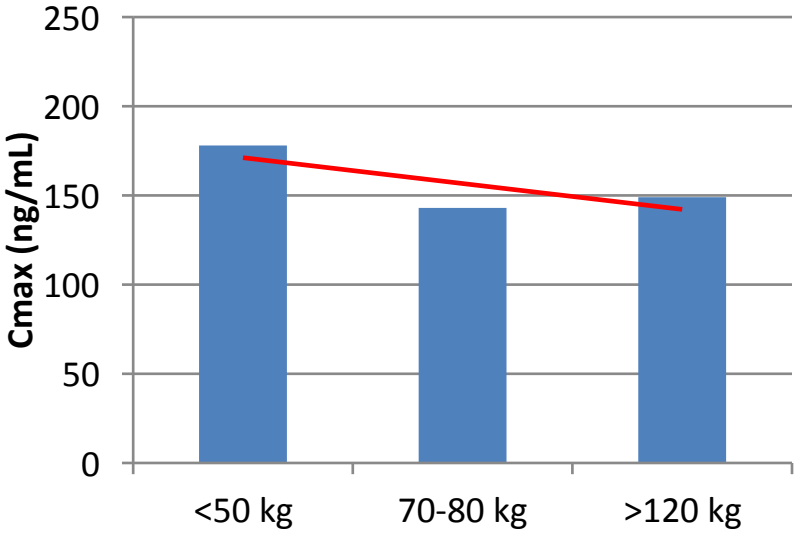
- Dose normalized plasma concentration (ng/mL/mg) of total dabigatran by body weight (kg)

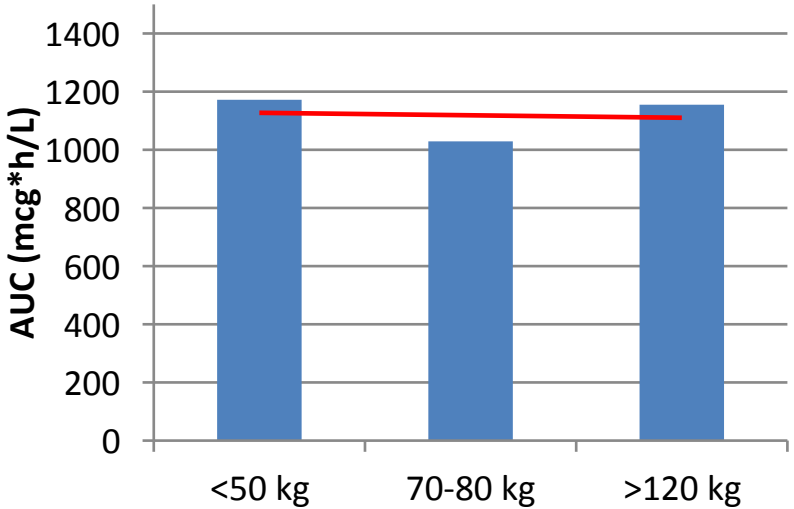


Boehringer Inhleheim.
Internal Communication 11/7/14

Rivaroxaban

Rivaroxaban		<50 kg	70-80 kg	>120 kg
	Cmax (ng/mL)	178	143	149
	AUC (mcg*h/L)	1172	1029	1155
	T ½ (hr)	9.6	7.2	7.3

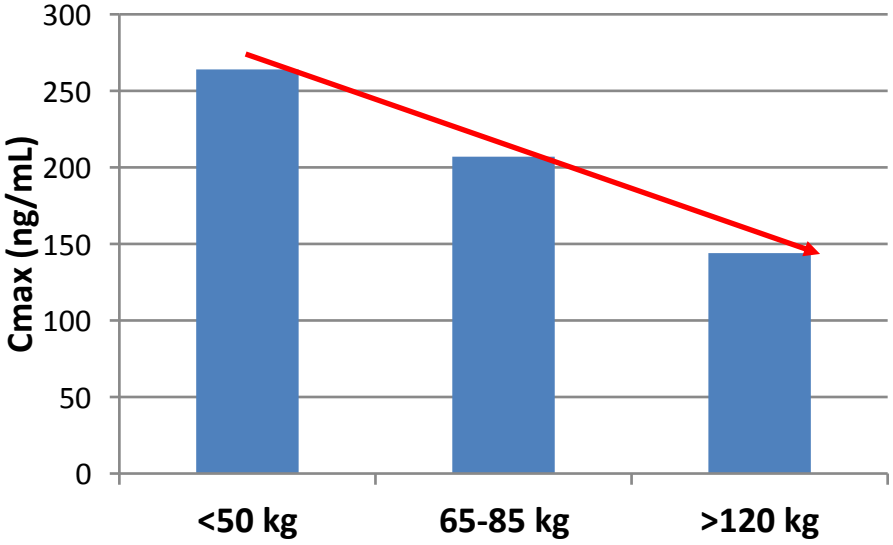


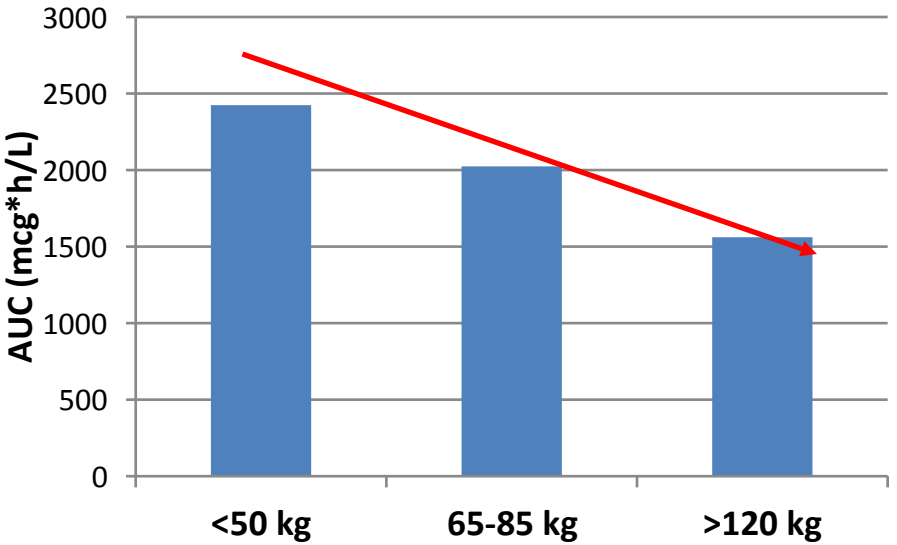


Xarelto® PI

Apixaban

Apixaban		<50 kg	65-85 kg	>120 kg
	Cmax (ng/mL)	264	207	144
	AUC (mcg*h/L)	2424	2024	1561
	T ½ (hr)	15.7	12.0	8.8





Upreti VV, et al. Br J Clin Pharmacol. 2013;76:908-16.

Kinetics of DOACs in Obesity

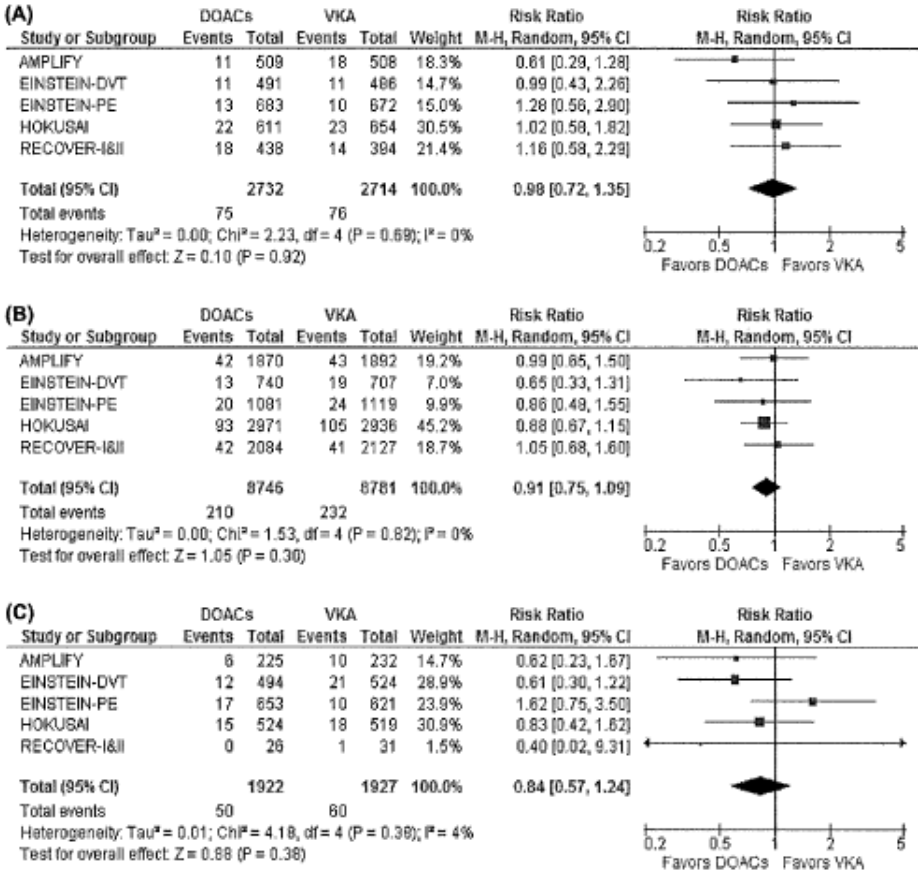
- Dabigatran
  - Kinetics show a decrease in concentration
- Rivaroxaban
  - No significant difference in kinetic profile
- Apixaban
  - Kinetics show a decrease in concentration
- Edoxaban
  - No formal kinetic studies

ISTH Statement on Obesity

- We recommend appropriate standard dosing on DOACs in patients with BMI ≤40 kg/m^2 and <120 kg.
- We suggest that DOACs should NOT be used in patients with a BMI >40 kg/m^2 or a weight of >120kg
  - Secondary to limited clinical data available for patients at the extreme of weight and the available PK/PD evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur in increasing weight, which raises concerns about underdosing
- If DOACs are used in patients with a BMI >40 kg/m^2 or a weight of >120kg, we suggest checking a drug-specific peak/trough level.
  - Continue the DOAC if it falls within the expected range but change to a VKA if the drug-specific level is found to be below the expected range

Martin K, et al. *J Thromb Haemost* 2016; 14: 1308-13

Clinical Reviews of DOACs in Obesity



High Body Weight

Normal Body Weight

Low Body Weight

Di Minno MN, et al. *Annals of Medicine* 2015;47:61-68

Clinical Reviews of DOACs in Obesity

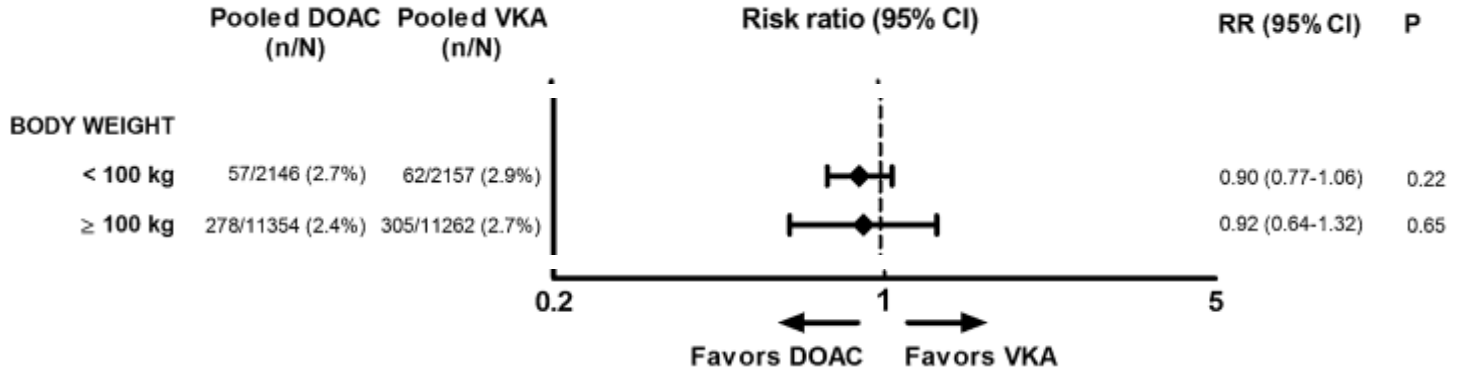
- Registry data from Germany

	Events (n)	Events/100 pt. yrs (95%CI)
BMI 30-35 (n= 731)		
Effectiveness endpoint	30	1.84 (1.24-2.63
ISTH major bleeding	34	2.09 (1.44-2.91
BMI 35-40 (n= 248)		
Effectiveness endpoint	9	1.56 (0.71-2.96)
ISTH major bleeding	13	2.23 (1.19-3.81)
BMI >40 (n= 98)		
Effectiveness endpoint	1	0.49 (0.01-2.71)
ISTH major bleeding	7	3.45 (1.39-7.12)

Tittl L. International Journal of Cardiology. 2018;262:85-91

Clinical Reviews of DOACs in Obesity

- Meta-analysis of DOACs vs. VKAs in phase III VTE trials



Van Es. Blood 2014;124:1968-75

Case

A 54 year-old obese man (160 kg, BMI 54 kg/m^2) is admitted to the hospital with a DVT, possible PE. He is initially managed with heparin. He is reluctant to take warfarin since his mother died of a hemorrhage while on warfarin. Which would you do?

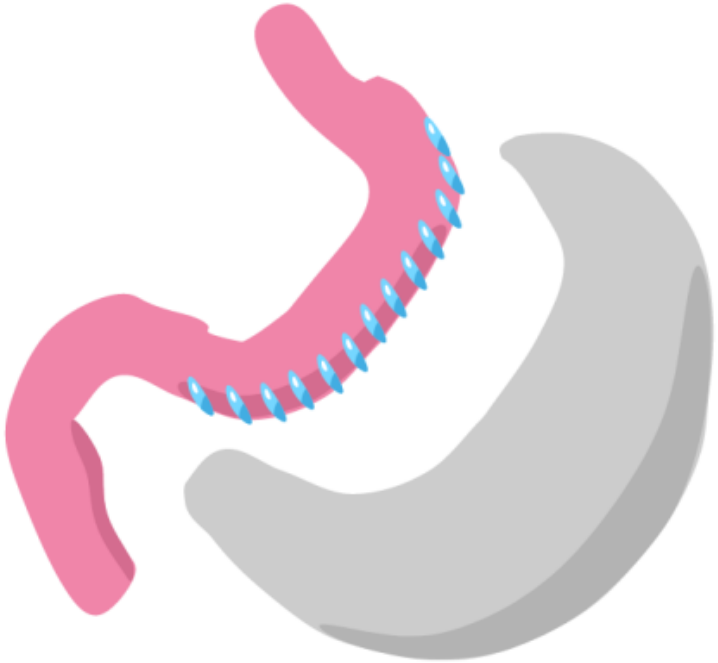
A. Advise him to take long-term LMWH
B. Switch him to a DOAC
C. Calculate a subcutaneous heparin dose
D. Encourage warfarin therapy

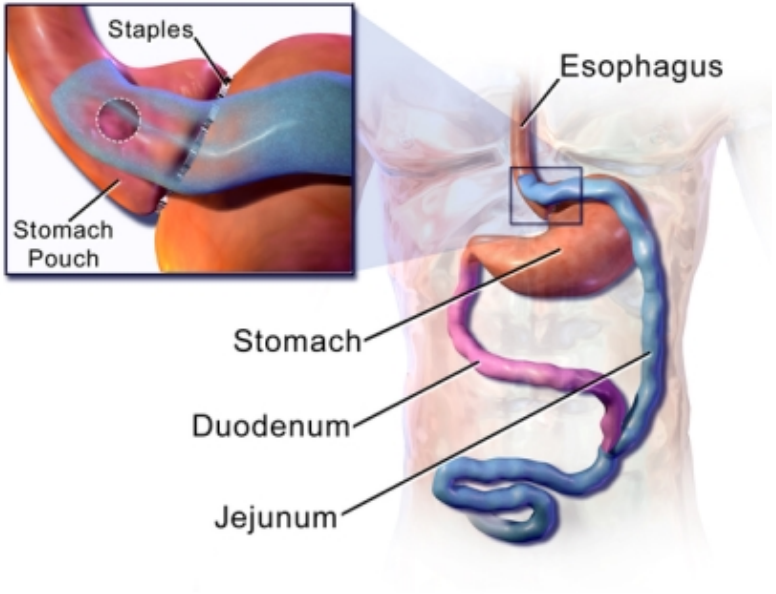
Case

A 44 year-old morbidly obese woman (119 kg, BMI 41 kg/m2) is on indefinite anticoagulation with warfarin for a history of recurrent VTE. She has undergone a Roux-En-Y gastric bypass procedure 4 months ago. She lives in a rural setting and has missed numerous INR appointments and has very fluctuating INR measurements. She wants to switch to a DOAC agent. What would you advise her?

A. Switch to apixaban
B. Switch to dabigatran
C. Switch to rivaroxaban
D. Do not switch, continue warfarin
E. Stop all anticoagulation since she has lost significant weight

Types of gastric bypass procedures





Roux-En-Y

Image from: Lina Wolf. Magenverkleinerung.tips

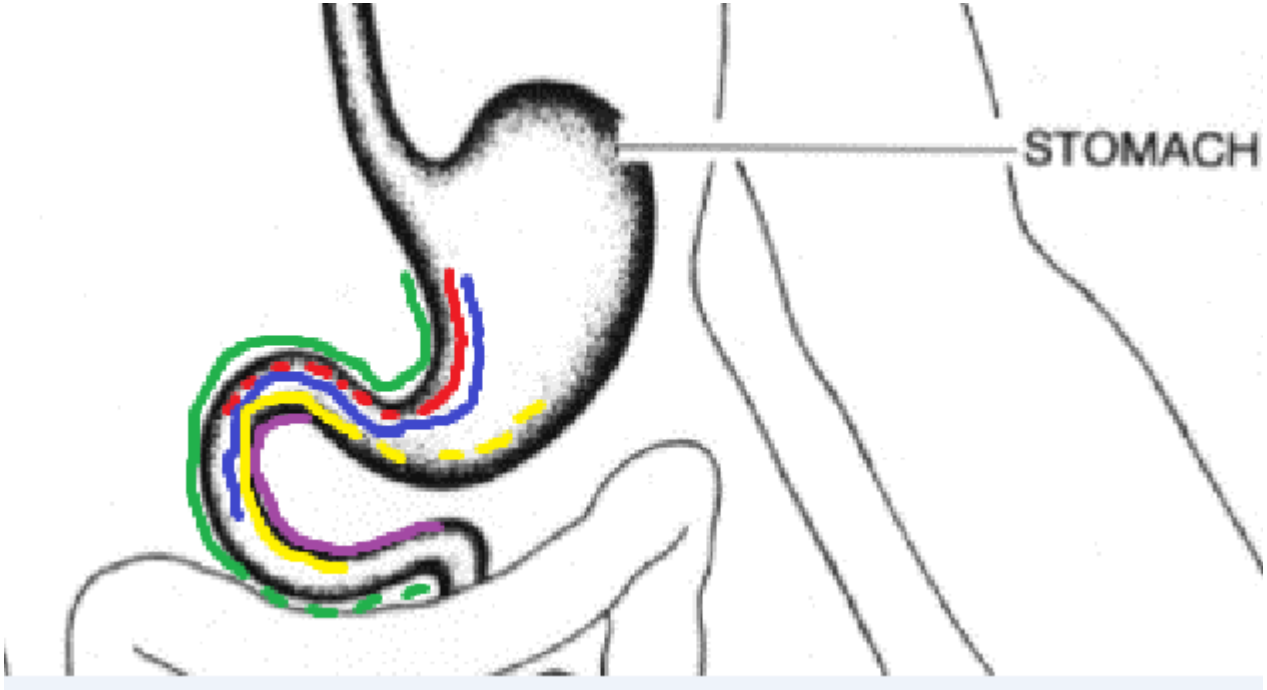
Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". *WikiJournal of Medicine* **1** (2). DOI:10.15347/wjm/2014.010.

Gastric Bypass

- No prospective trials of any DOACs in patients with gastric bypass therapy

- Site of absorption
  - Dabigatran
    - Likely absorbed in lower stomach and duodenum
  - Rivaroxaban
    - Likely absorbed primarily in the stomach, less absorption in the proximal small bowel
  - Apixaban
    - Likely absorbed in the proximal small bowel, little gastric and colonic absorption
  - Edoxaban
    - Likely absorbed in the proximal small bowel

DOAC sites of absorption



Adapted from: Martin KA. *The American Journal of Medicine* (2017)130,517-24.

Theorized potential of bariatric surgery on DOACs

- Reduction of rivaroxaban absorption, requires food for optimal absorption
- Reduction in gastric acid production raising pH
- Motility may be increased leading to inadequate absorption
- Surgeries that bypass the small intestine may alter enteric metabolism and efflux/influx of drugs
- Changes in Vd of drugs
- Alterations in body weight for weeks to months after procedure

Dabigatran following bariatric surgery

- 66 y.o. male with Roux-en-Y procedure and atrial fibrillation
  - Suffered ischemic stroke while on dabigatran
  - Coags: aPTT 26 secs, PT 13.7 secs, INR 1.1

- 67 y.o. female with Roux-en-Y procedure and atrial fibrillation
  - Serum dabigatran trough was measured and was 21 ng/ml (ref 31-225 ng/mL)
  - Was also receiving pantoprazole
  - No events but transitioned to warfarin

Lee D. *Journal of Cardiology Cases* (2013)8:e49-50.

Rivaroxaban following bariatric surgery

- 27 year old female patient, 181 kg (BMI = 61 kg/m^2)

Table 1 Rivaroxaban plasma concentrations, INR and aPTT values at baseline and throughout the day after intake of 20 mg od

	Baseline	3 h	6 h	12 h	24 h	Day 2 + 3 h
Rivaroxaban plasma concentrations (ng/ml)	n.a.	224.22	86.89	86.32	35.54	262.46
INR	1.51	3.86	2.93	2.78	2.42	5.84
aPTT (s; ULN 36 s)	30	39	36	36	34	44

Mahlmann A. *J Thromb Thrombolysis* (2013)36:533-35.

Bariatric Surgery on DOAC levels

- Cross-sectional, matched cohort study
- Identified patients receiving DOACs on the bariatric units of 2 hospitals

- Post-BS group patients were matched with patients
  - Age (+/- 5 years)
  - Sex
  - BMI (+/- 2 kg/m2)
  - SCr
  - DOAC agent

- DOAC levels measured at predicted peak levels and had to be at steady state

Rottenstreich A. Thrombosis Research 2018;163:190-95.

Bariatric surgery on DOAC levels

Drug levels	Post-BS (n=18)	Control (n= 18)	P-value
Apixaban (n= 9)	207 [164-271] ng/mL	212 [126-238] ng/mL	0.92
Rivaroxaban (n= 7)	159 [123-193] ng/mL	249 [231-311] ng/mL	0.02
Dabigatran (n= 2)	144 ng/mL	176 ng/mL	-

- 5 post-BS patients had peak DOAC levels below expected range vs. 0 in the control group (p=0.05)
  - All apixaban and dabigatran patients had levels in the expected range
  - 2/7 (28.6%) rivaroxaban patients had levels in the expected range

- Duration of DOACs was 1.7 years
  - No bleeding events in either group
  - One thrombotic event reported in the post-BS group receiving rivaroxaban

Rottenstreich A. Thrombosis Research 2018;163:190-95.

Clinical Guidance on DOACs in gastric bypass

- Recommend warfarin as first line agent
  - Can monitor INR
- Recommend patients on DOACs prior to gastric bypass be changed to warfarin
- If DOACs are used, check drug-specific levels (peaks/troughs)
  - Change to warfarin if the levels are not in the expected ranges instead of altering DOAC dose

- Remember, weight and absorption may continue to change in these patients for weeks to months after the procedure. You likely will need to check repeat levels.

Case

- A 44 year-old morbidly obese woman (119 kg, BMI 41 kg/m2) is on indefinite anticoagulation with warfarin for a history of recurrent VTE. She has undergone a Roux-En-Y gastric bypass procedure 4 months ago. She lives in a rural setting and has missed numerous INR appointments and has very fluctuating INR measurements. She wants to switch to a DOAC agent. What would you advise her?

A. Switch to apixaban
B. Switch to dabigatran
C. Switch to rivaroxaban
D. Do not switch, continue warfarin
E. Stop all anticoagulation since she has lost significant weight

Elderly patients in clinical trials (>75 years old)

Indication	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
NVAF	40%	31%	38%	41%
VTE	9.9%	13%	16%	14%

Pradaxa®, Xarelto®, Eliquis®, Savaysa® package inserts

Dabigatran in NVAF

Clinical Outcome	<75 y.o. HR (95% CI) N=10,855	75-79 y.o. HR (95% CI) N=4231	80-84 y.o. HR (95% CI) N=2305	≥ 85 y.o. HR (95% CI) N=722	P-value
Stroke/Sys Emb	0.63 (0.46-0.86)	0.65 (0.42-1.01)	0.67 (0.41-1.10)	0.70 (0.31-1.57)	0.996
Major bleeding	0.70 (0.57-0.86)	1.04 (0.81-1.35)	1.41 (1.02-1.94)	1.22 (0.74-2.02)	0.001
Intracranial major bleeding	0.43 (0.25-0.74)	0.23 (0.09-0.60)	0.55 (0.25-1.21)	0.61 (0.20-1.87)	0.481
Extracranial major bleeding	0.78 (0.62-0.97)	1.22 (0.93-1.61)	1.68 (1.18-2.41)	1.41 (0.80-2.49)	0.001
All-cause mortality	0.77 (0.64-0.93)	0.82 (0.63-1.07)	1.16 (0.87-1.55)	1.15 (0.74-1.79)	0.068

Lauw MN, et. al. *Heart* 2017 Jul;103(13):1015-1023

Rivaroxaban in NVAF

Clinical Outcome	<75 HR (95% CI) N=8007 (efficacy)	≥ 75 HR (95% CI) N=6164 (efficacy)	P-value
Stroke/Sys Emb	0.95 (0.76-1.19)	0.80 (0.63-1.02)	0.3131
Major bleeding	0.96 (0.78-1.19)	1.11 (0.92-1.34)	0.3357
Intracranial major bleeding	0.54 (0.33-0.89)	0.80 (0.50-1.28)	0.2654
GI major bleeding	1.5 (p=0.0136)	1.69 (p=0.0002)	NA

Halperin JL, et. al. *Circulation* 2014;130:138-146

Apixaban in NVAF

Clinical Outcome	<65 y.o. HR (95% CI) N=5417	65-74 y.o. HR (95% CI) N=7052	≥ 75 y.o. HR (95% CI) N=5678	≥ 80 y.o. HR (95% CI) N=2436	P-value
Stroke/Sys Emb	1.16 (0.77-1.73)	0.72 (0.54-0.96)	0.71 (0.53-0.95)	0.81 (0.51-1.29)	0.11
Major bleeding	0.78 (0.55-1.11)	0.71 (0.56-0.89)	0.64 (0.52-0.79)	0.66 (0.48-0.9)	0.63
Intracranial major bleeding	0.87 (0.43-1.74)	0.35 (0.20-0.60)	0.34 (0.20-0.57)	0.36 (0.17-0.77)	0.2
Any bleeding	0.73 (0.65-0.81)	0.70 (0.65-0.77)	0.71 (0.65-0.78)	NA	0.94
All-cause mortality	1.07 (0.84-1.35)	0.77 (0.64-0.94)	0.91 (0.77-1.07)	NA	0.43

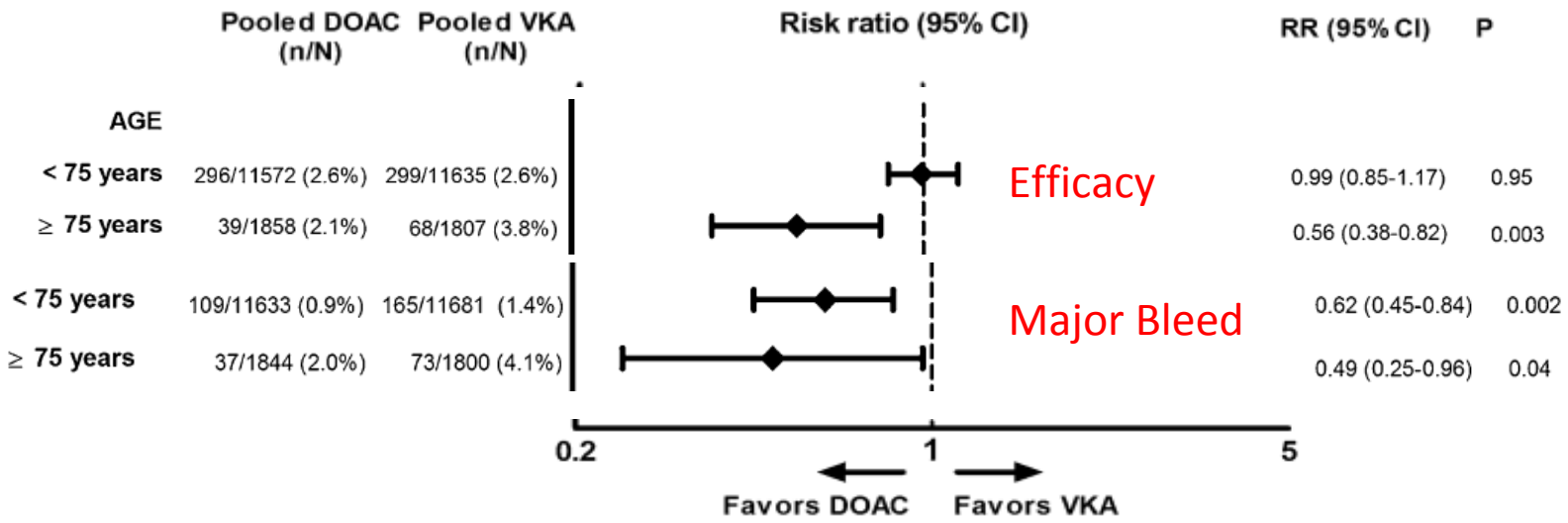
Halvorsen, et. al. *European Heart Journal* (2014) 35, 1864–1872

Edoxaban in NVAF

Clinical Outcome	<65 y.o. HR (95% CI) N=5497	65-74 y.o. HR (95% CI) N=7134	≥ 75 y.o. HR (95% CI) N=8474	P-value
Stroke/Sys Emb	0.94 (0.65-1.37)	0.89 (0.68-1.16)	0.83 (0.66-1.04)	0.84
Major bleeding	0.81 (0.58-1.12)	0.75 (0.60-0.94)	0.83 (0.70-0.99)	0.78
Intracranial major bleeding	1.03 (0.46-2.29)	0.42 (0.25-0.70)	0.40 (0.26-0.62)	0.11
GI bleeding	1.03 (0.63-1.66)	1.20 (0.86-1.69)	1.32 (1.01-1.72)	0.67

Kato ET, et. al. *J Am Heart Assoc* 2016;5: e003432 doi: 10.1161/JAHA.116.003432

Pooled analysis of DOACs vs VKA in VTE



Van Es. Blood 2014;124:1968-75

Assessment of bleeding risks on DOACs in octogenarians

Risk factors for bleeding in the patients treated with oral anticoagulants by a Cox proportional hazard model.

Variable	HR (95%CI)	*p*-value
BMI <18.5 (kg/m^2)	3.26 (1.65–6.50)	< 0.01
BW ≤ 50 (kg)	0.85 (0.42–1.71)	0.64
Age ≥ 85 (years)	1.14 (0.65–1.99)	0.64
HAS-BLED score ≥ 3	1.34 (0.70–2.55)	0.38
Chronic kidney disease	1.17 (0.66–2.08)	0.59
Hemoglobin <10.0 (ng/dl)	1.38 (0.78–2.45)	0.27
Use of warfarin (%)	0.80 (0.43–1.47)	0.47
Antiplatelet therapy (%)	1.32 (0.66–2.66)	0.44

Shinohara M. *Journal of Cardiology* 2018. doi.org/10.1016/j.jjcc.2018.05.012

KEY TAKEAWAYS

- Use of anticoagulants continues to be a struggles in patients with chronic renal disease, but data continues to demonstrate promising results with DOACs
- DOACs continue to demonstrate potential use in patients with malignancy and HIT
- Use of DOACs in morbidly obese patients continues to be a challenge
  - ISTH Statement preferring VKA
  - Watch total body weight >120 kg
- Use of DOACs in patients with a history of gastric bypass
  - Little evidence, check levels