How to choose an anticoagulant in various clinical situations

-Anticoagulation for PE in special population-

Seung-Ick Cha, MD, PhD
Kyungpook National University Hospital
Pulmonology, Internal Medicine

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- Anticoagulation in CKD or ESRD
- Anticoagulation in CLD or cirrhosis
- Anticoagulation in patients undergoing enteral nutrition and gastrectomy

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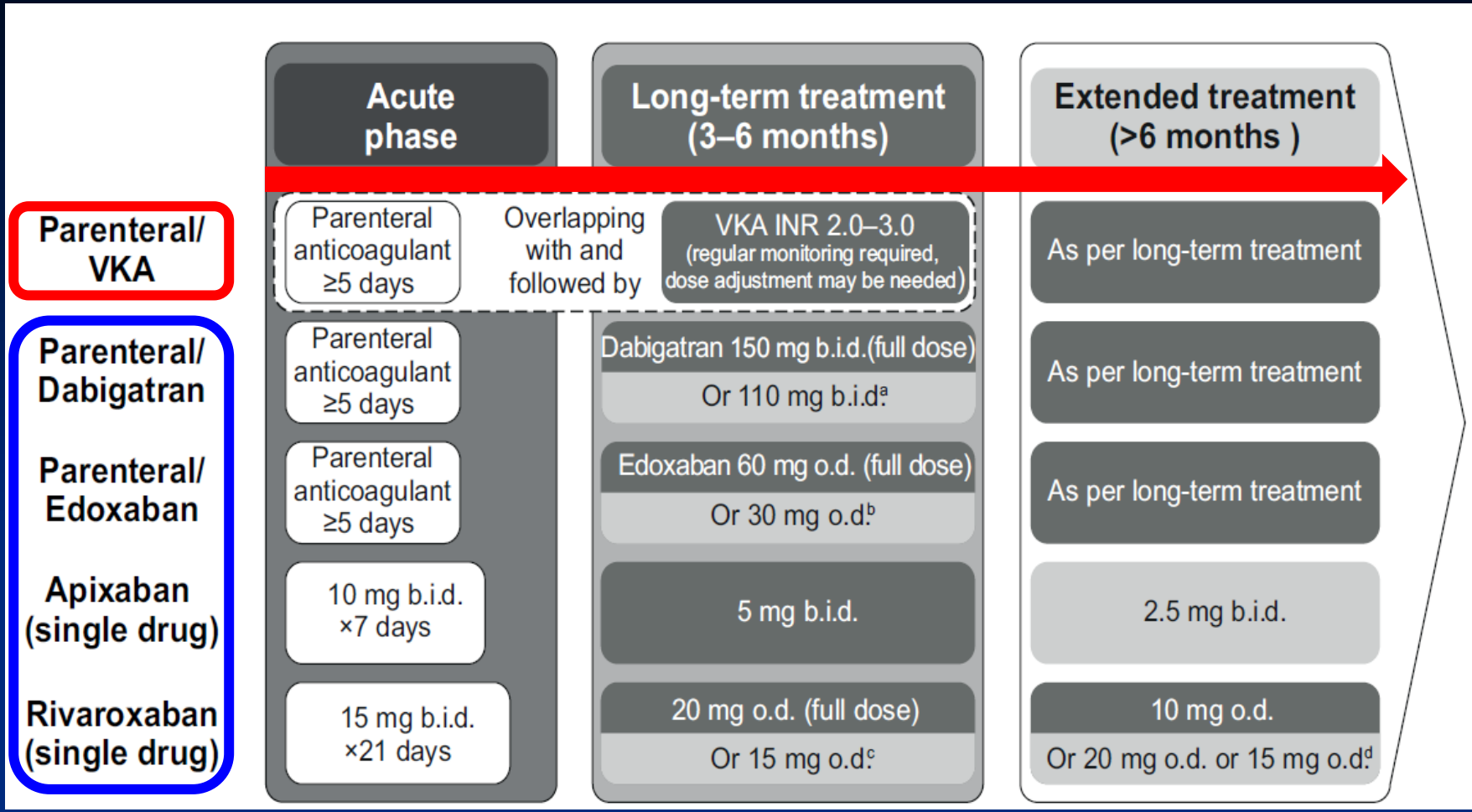
Anticoagulation for PE



Bavalia et al. Thromb Haemost 2020;20:899

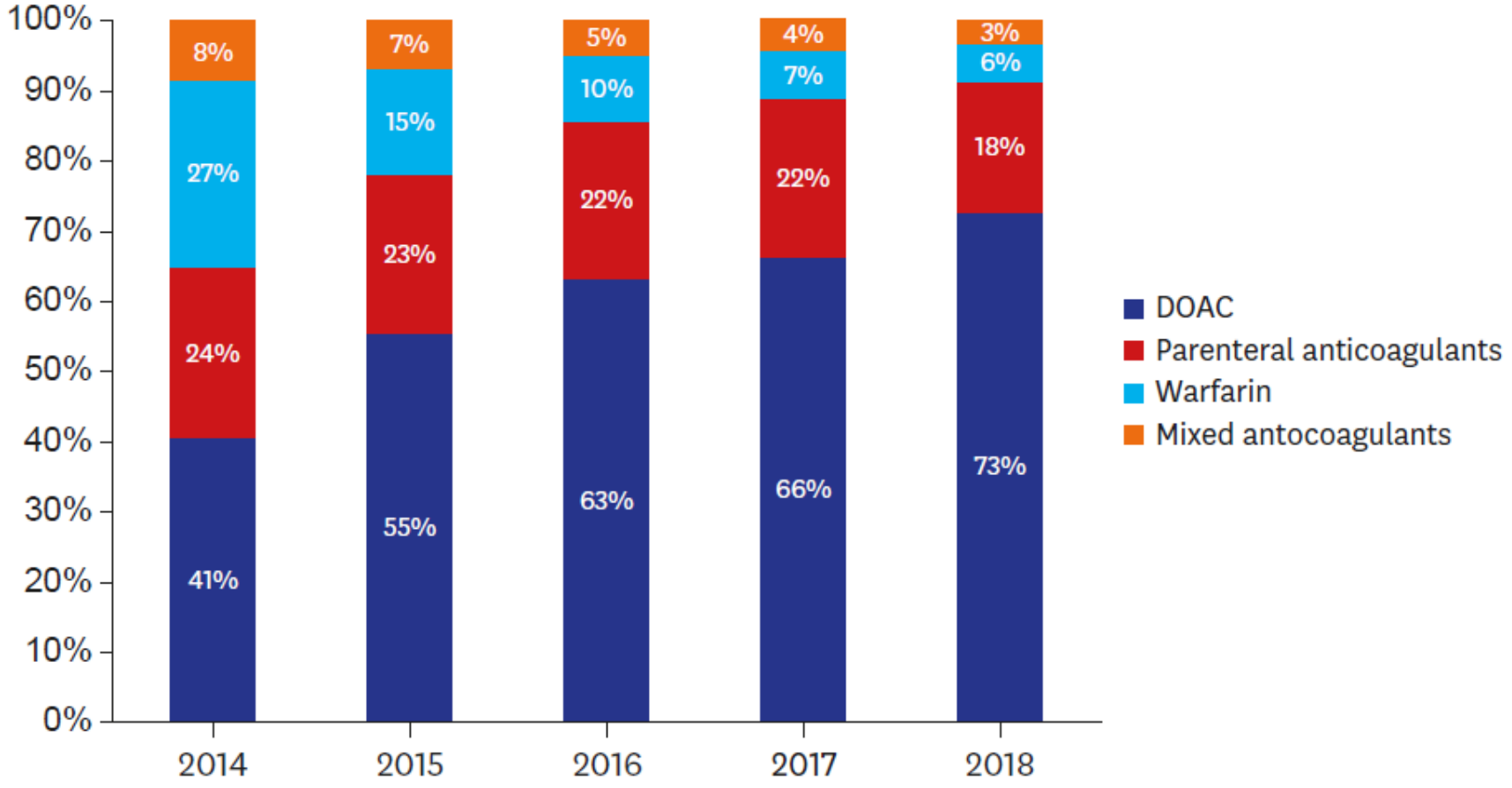


Fig. 1. Anticoagulation trend for venous thromboembolism from 2014 to 2018.
DOAC = direct oral anticoagulants.

Hwang et al. J Korean Med Sci 2022;37:e130

DOAC vs VKA

- For patients with DVT and/or PE, the ASH guideline panel suggests using DOACs over VKAs

- DOAC < VKA
  - ✓ Renal insufficiency (CrCl < 30 mL/min)
  - ✓ Moderate to severe liver disease
  - ✓ Antiphospholipid syndrome
  - ✓ Inhibitors/inducers of P-glycoprotein, or strong inhibitors/inducers of cytochrome P450 3A4
  - ✓ Bariatric surgery (gastrectomy?) and short gut
  - ✓ Cost of DOACs and patient preference

ASH guideline 2020

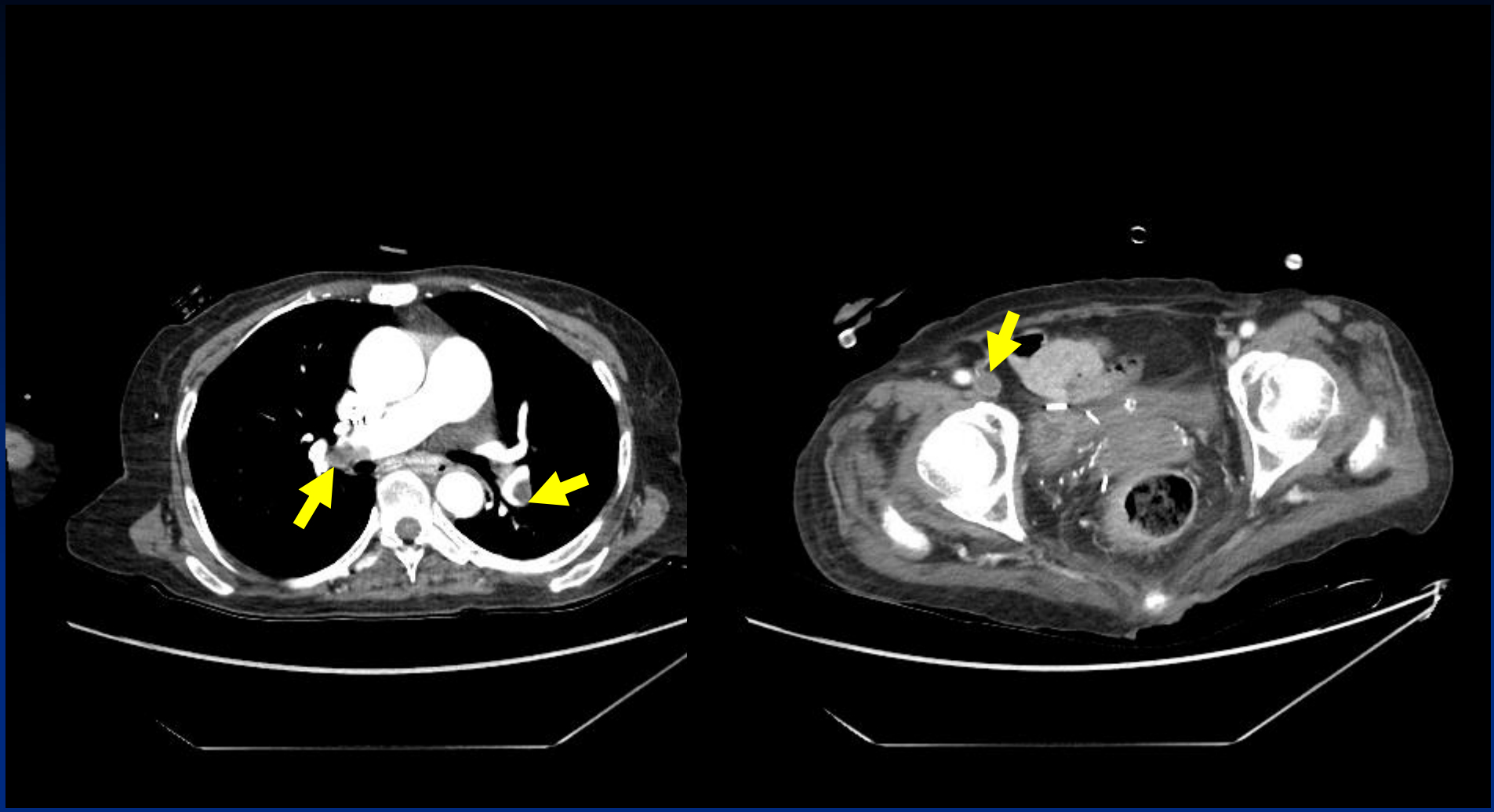
Case 1

- F 67
- CKD due to diabetic nephropathy → HD (요양병원)
  hypertension, ICA occlusion, peripheral arterial occlusive disease

  21.11.25. left total knee replacement → bedridden status
  22.2.14. right leg swelling → DVT suspected
  XX.X.XX. anticoagulation (rivaroxaban 10 mg bid)
  22.2.21. KNUH 혈관외과 visit → ER
- Anticoagulation: Yes or No ?

  In patients with a high clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (ACCP 9th guidelines, 2012)

Case 1 (II)



CT scan (22.2.21.)

Case 1 (III)

- **CBC: 8980/4.0/12.2/278000**
- **LFT: albumin 2.3, otherwise normal range**
- **BUN/Cr: 84/3.17 (CKD-EPI eGFR 14)**
- **Troponin I 9.51 pg/mL (<34)**
- **NT-proBNP 3182 pg/mL (<533)**
- **UGI endoscopy: no active bleeding focus**
- **Colonoscopy: limited study due to blood clot**

- **Medication**

Famotidine 20 mg qd
Chlorpheniramine 2 mg bid
레날민정 (multivitamin) qd
Trimebutine 100 mg bid
Ferrous sulfate 256 mg qd

Nortriptyline 11.4 mg qd
Gemigliptin 68.9 mg qd
Gliclazide 60 mg qd
Furosemide 40 mg bid
Acetaminophen + tramadol

Case 1 (IV)

- **22.2.21. IVC filter insertion**
  22.2.27. Enoxaparin 1 mg/kg qd + warfarin 5 mg started
  22.3.04. IVC filter removed
  22.3.10. Transferred to 요양병원 (warfarin 4 mg)

- **DOACs vs VKA?**

PE in patients with CKD and ESRD

- **Healthcare Cost and Utilization Project's Nationwide Inpatient Sample**

	Normal kidney function	CKD	ESRD
PE admission /100,000 persons	66	204	527
Severe PE	3951 (2.8)	429 (4.3)	89 (5.5)
Mortality	4523 (3.2)	666 (6.7)	106 (6.7)
Length of stay	5 (3-7)	6 (4-8)	7 (4-10)

Severe PE: use of mechanical ventilation, vasopressor, or thrombolytic agents on the day of admission or the second hospital day.

Kumar et al. Clin J Am Soc Nephrol 2012;7:1584

CKD and PE

- **Renal insufficiency:**
  a predictor of recurrent PE, 30 d-mortality, major bleeding

- **Increased risk of VTE**
  - **Activation of coagulation cascade (factor VII, VIII, IX, X, XI, XII, VWF)**
  - **Decreased AT and PC**
  - **Elevated homocysteine level**
  - **Increased PAI, D-dimer, CRP, fibrinogen**
  - **Coagulation and platelet activation within HD machine**

- **Bleeding risk:**
  - **Uremic platelet dysfunction, platelet-vessel wall interaction**
  - **2-fold increase (eGFR <30 mL/min/1.73 m^2)**

Rivera-Bebron et al. Thromb Res 2021;204:101
Lamarche et al. Curr Opin Pulm Med 2021;27:311
Cheung et al. Ann Pharmacother 2021;55:711

VTE characteristics in renal disease

	Effect on VTE incidence	Effect on VTE outcomes	Therapeutic consideration
Renal disease	Increased VTE risk	Worse outcomes; Increased bleeding complications	VKA is preferred anticoagulant. LMWH may increase bleeding. DOACs not indicated in CrCl < 30 mL/min or dialysis.

Nguyen et al. Clin Chest Med 2018;39:515

VKA in ESRD patients with AF

- Minimal renal excretion
  Unaffected by dialysis

- The role of warfarin in patients with CKD-5 or ESRD and AF is not well established.
  A lack of net clinical benefit
  ← a lack of efficacy and increased risk of bleeding

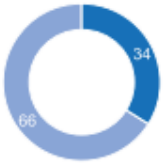
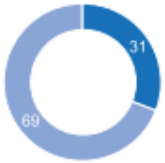
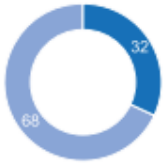
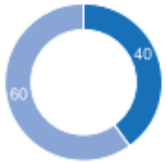
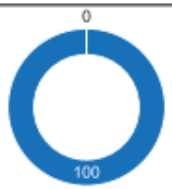
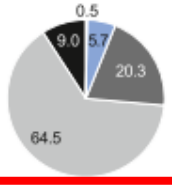
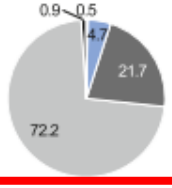
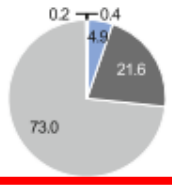
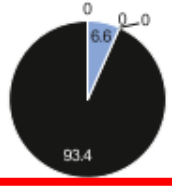
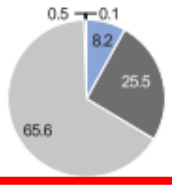
- A risk of calciphylaxis (calcific uremic arteriolopathy)
  : inhibition of the matrix Gla protein,
  which can lead to an increased risk of ischemic stroke

- Warfarin metabolism is affected by uremia through p450 system → difficult to control INR

- Significant interpatient variability in response to warfarin

Starr et al. Ann Pharmacother 2022;56:691

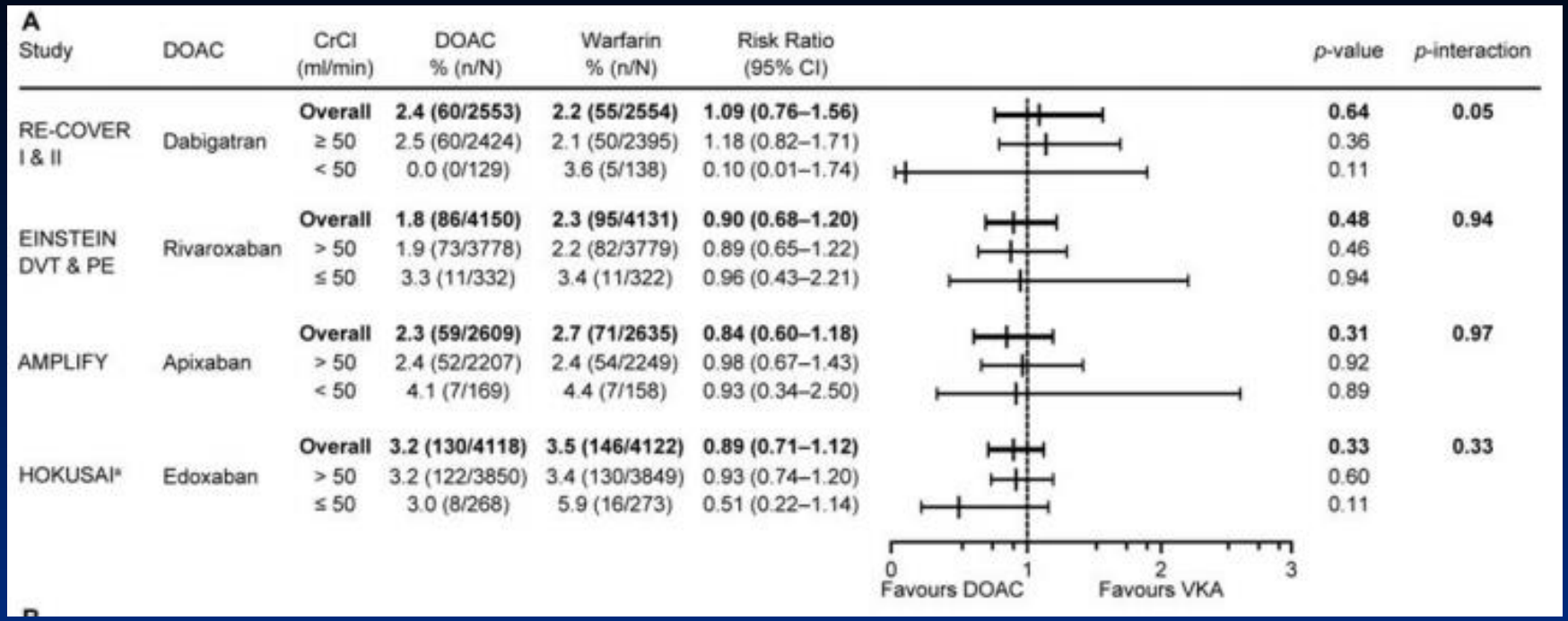
RCTs of DOACs for VTE Tx

	AMPLIFY [28] (N = 5395)	RE-COVER [29] (N = 2539)	RE-COVER II [30] (N = 2568)	Hokusai-VTE [31] (N = 8240)	EINSTEIN PE [32] (N = 4832)
Initial regimen for acute-phase treatment	Apixaban 10 mg twice daily for 1 week	LMWH for ≥5 days	LMWH for ≥5 days	LMWH or UFH for ≥5 days	Rivaroxaban 15 mg twice daily for 3 weeks
Regimen for long-term treatment	Apixaban 5 mg twice daily	Dabigatran 150 mg twice daily	Dabigatran 150 mg twice daily	Edoxaban 60 mg or 30 mg* daily	Rivaroxaban 20 mg daily
Design	Double-blind	Double-blind, double-dummy	Double-blind, double-dummy	Double-blind, double-dummy	Open-label
Type of index event (%) PE (with or without DVT) / DVT					
PE (with or without DVT, %)	34.0	31.0	31.8	40.0	100.0
CrCl (mL/min) ≤30 mL/min / >30 to ≤50 mL/min / >50 to ≤80 mL/min / >80 mL/min / Missing or NR					
≤30 mL/min	29 (0.5)	13 (0.5)	9 (0.4)	NI	6 (0.1)
>30 to ≤50 mL/min	309 (5.7)	120 (4.7)	125 (4.9)	541 (6.6)	398 (8.2)
>50 to ≤80 mL/min	1093 (20.3)	551 (21.7)	555 (21.6)	NR	1230 (25.5)
>80 mL/min	3478 (64.5)	1833 (72.2)	1875 (73.0)	NR	3172 (65.6)
Missing or NR	486 (9.0)	22 (0.9)	4 (0.2)	–	26 (0.5)

Exclusion CrCl, mL/min <25 <30 <30 <30 <30

Rivera-Bebron et al. Thromb Res 2021;204:101

Rates of recurrent VTE with DOAC vs VKA

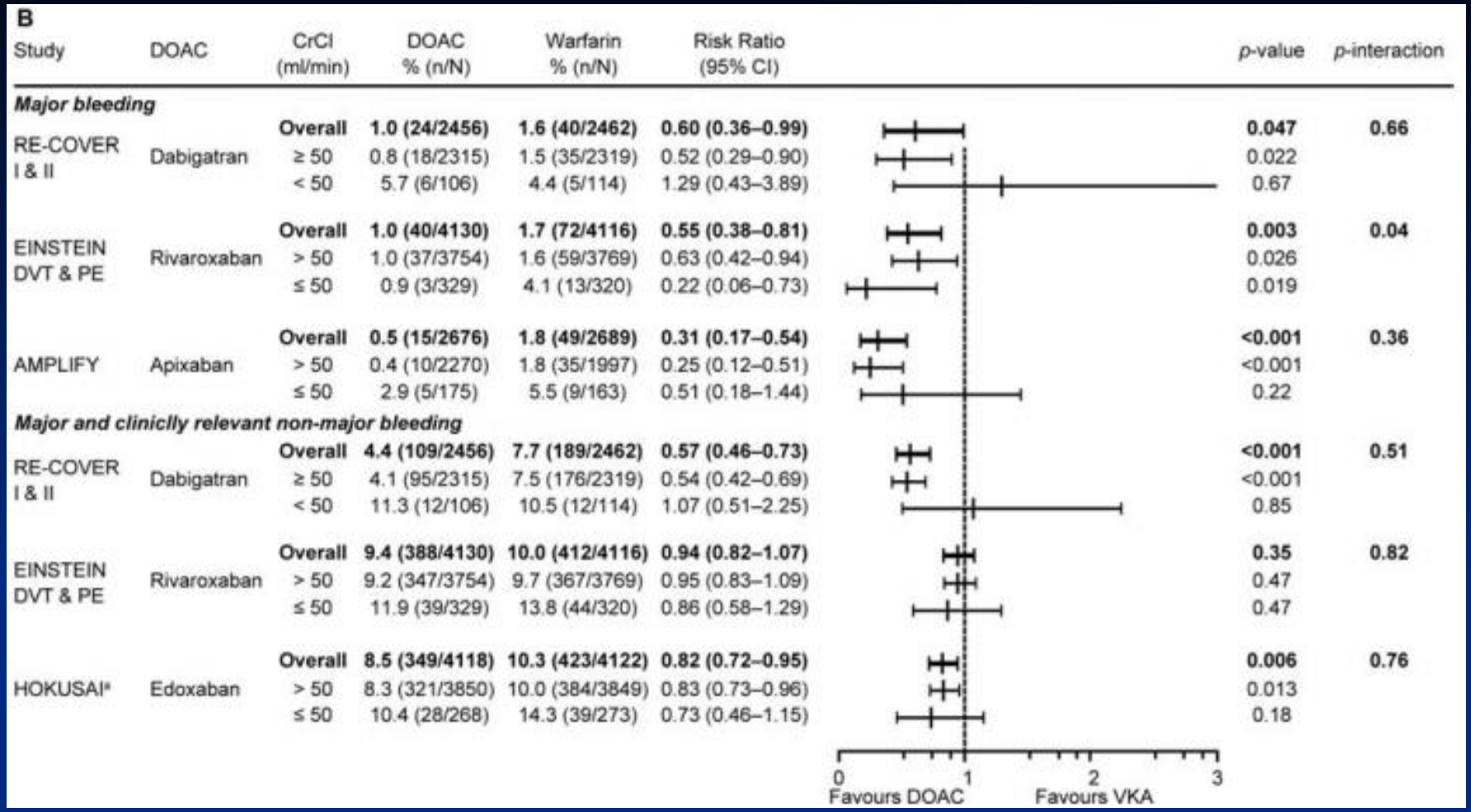


A

Study	DOAC	CrCl (ml/min)	DOAC % (n/N)	Warfarin % (n/N)	Risk Ratio (95% CI)	p-value	p-interaction
RE-COVER I & II	Dabigatran	**Overall**	**2.4 (60/2553)**	**2.2 (55/2554)**	**1.09 (0.76–1.56)**	**0.64**	**0.05**
		≥ 50	2.5 (60/2424)	2.1 (50/2395)	1.18 (0.82–1.71)	0.36	
		< 50	0.0 (0/129)	3.6 (5/138)	0.10 (0.01–1.74)	0.11	
EINSTEIN DVT & PE	Rivaroxaban	**Overall**	**1.8 (86/4150)**	**2.3 (95/4131)**	**0.90 (0.68–1.20)**	**0.48**	**0.94**
		> 50	1.9 (73/3778)	2.2 (82/3779)	0.89 (0.65–1.22)	0.46	
		≤ 50	3.3 (11/332)	3.4 (11/322)	0.96 (0.43–2.21)	0.94	
AMPLIFY	Apixaban	**Overall**	**2.3 (59/2609)**	**2.7 (71/2635)**	**0.84 (0.60–1.18)**	**0.31**	**0.97**
		> 50	2.4 (52/2207)	2.4 (54/2249)	0.98 (0.67–1.43)	0.92	
		< 50	4.1 (7/169)	4.4 (7/158)	0.93 (0.34–2.50)	0.89	
HOKUSAI*	Edoxaban	**Overall**	**3.2 (130/4118)**	**3.5 (146/4122)**	**0.89 (0.71–1.12)**	**0.33**	**0.33**
		> 50	3.2 (122/3850)	3.4 (130/3849)	0.93 (0.74–1.20)	0.60	
		≤ 50	3.0 (8/268)	5.9 (16/273)	0.51 (0.22–1.14)	0.11	

Bavalia et al. Thromb Haemost 2020;120:899

Rates of bleeding with DOAC vs VKA



B

Study	DOAC	CrCl (ml/min)	DOAC % (n/N)	Warfarin % (n/N)	Risk Ratio (95% CI)	*p*-value	*p*-interaction
Major bleeding							
RE-COVER I & II	Dabigatran	**Overall**	**1.0 (24/2456)**	**1.6 (40/2462)**	**0.60 (0.36–0.99)**	**0.047**	**0.66**
		≥ 50	0.8 (18/2315)	1.5 (35/2319)	0.52 (0.29–0.90)	0.022	
		< 50	5.7 (6/106)	4.4 (5/114)	1.29 (0.43–3.89)	0.67	
EINSTEIN DVT & PE	Rivaroxaban	**Overall**	**1.0 (40/4130)**	**1.7 (72/4116)**	**0.55 (0.38–0.81)**	**0.003**	**0.04**
		> 50	1.0 (37/3754)	1.6 (59/3769)	0.63 (0.42–0.94)	0.026	
		≤ 50	0.9 (3/329)	4.1 (13/320)	0.22 (0.06–0.73)	0.019	
AMPLIFY	Apixaban	**Overall**	**0.5 (15/2676)**	**1.8 (49/2689)**	**0.31 (0.17–0.54)**	**<0.001**	**0.36**
		> 50	0.4 (10/2270)	1.8 (35/1997)	0.25 (0.12–0.51)	<0.001	
		≤ 50	2.9 (5/175)	5.5 (9/163)	0.51 (0.18–1.44)	0.22	
Major and clinicly relevant non-major bleeding							
RE-COVER I & II	Dabigatran	**Overall**	**4.4 (109/2456)**	**7.7 (189/2462)**	**0.57 (0.46–0.73)**	**<0.001**	**0.51**
		≥ 50	4.1 (95/2315)	7.5 (176/2319)	0.54 (0.42–0.69)	<0.001	
		< 50	11.3 (12/106)	10.5 (12/114)	1.07 (0.51–2.25)	0.85	
EINSTEIN DVT & PE	Rivaroxaban	**Overall**	**9.4 (388/4130)**	**10.0 (412/4116)**	**0.94 (0.82–1.07)**	**0.35**	**0.82**
		> 50	9.2 (347/3754)	9.7 (367/3769)	0.95 (0.83–1.09)	0.47	
		≤ 50	11.9 (39/329)	13.8 (44/320)	0.86 (0.58–1.29)	0.47	
HOKUSAI[a]	Edoxaban	**Overall**	**8.5 (349/4118)**	**10.3 (423/4122)**	**0.82 (0.72–0.95)**	**0.006**	**0.76**
		> 50	8.3 (321/3850)	10.0 (384/3849)	0.83 (0.73–0.96)	0.013	
		≤ 50	10.4 (28/268)	14.3 (39/273)	0.73 (0.46–1.15)	0.18	

Bavalia et al. Thromb Haemost 2020;120:899

Pharmacology of DOACs

	VKA	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Bioavailability	100%	3-7%	80-100% (10 mg dose), 66% or more (20 mg dose)	50%	62%
Renal elimination of unchanged drug	0%	80%	36%	27%	50%
Dialyzable	Not	50-60%	Not	Not	Not
Protein binding	98-99%	35%	92-95%	87%	55%

Klil-Drori et al. Semin Thromb Hemost 2018;44:353

PK study for apixaban in subjects with ESRD on HD

- **Single dose study**
  Increased overall exposure in patients with ESRD of 36%
  4-hour HD → reduced exposure by 14%,
  closer to that of the healthy volunteers
  5 mg bid dose of apixaban
  - Safe
  - Equal efficacy in patients with ESRD vs those without it

Wang et al. J Clin Pharmacol 2016;56:628

- **Serial dosing** of apixaban over 8 days
  5 mg dose → unacceptable supratherapeutic drug levels
  2.5 mg dose → acceptable AUC and trough levels

Mavrakanas et al. J Am Soc Nephrol 2017;28:2241

Weber et al. Eur J Haematol 2019;102:312

Apixaban vs warfarin in VTE patients with CKD

- Using 5 US insurance claims databases

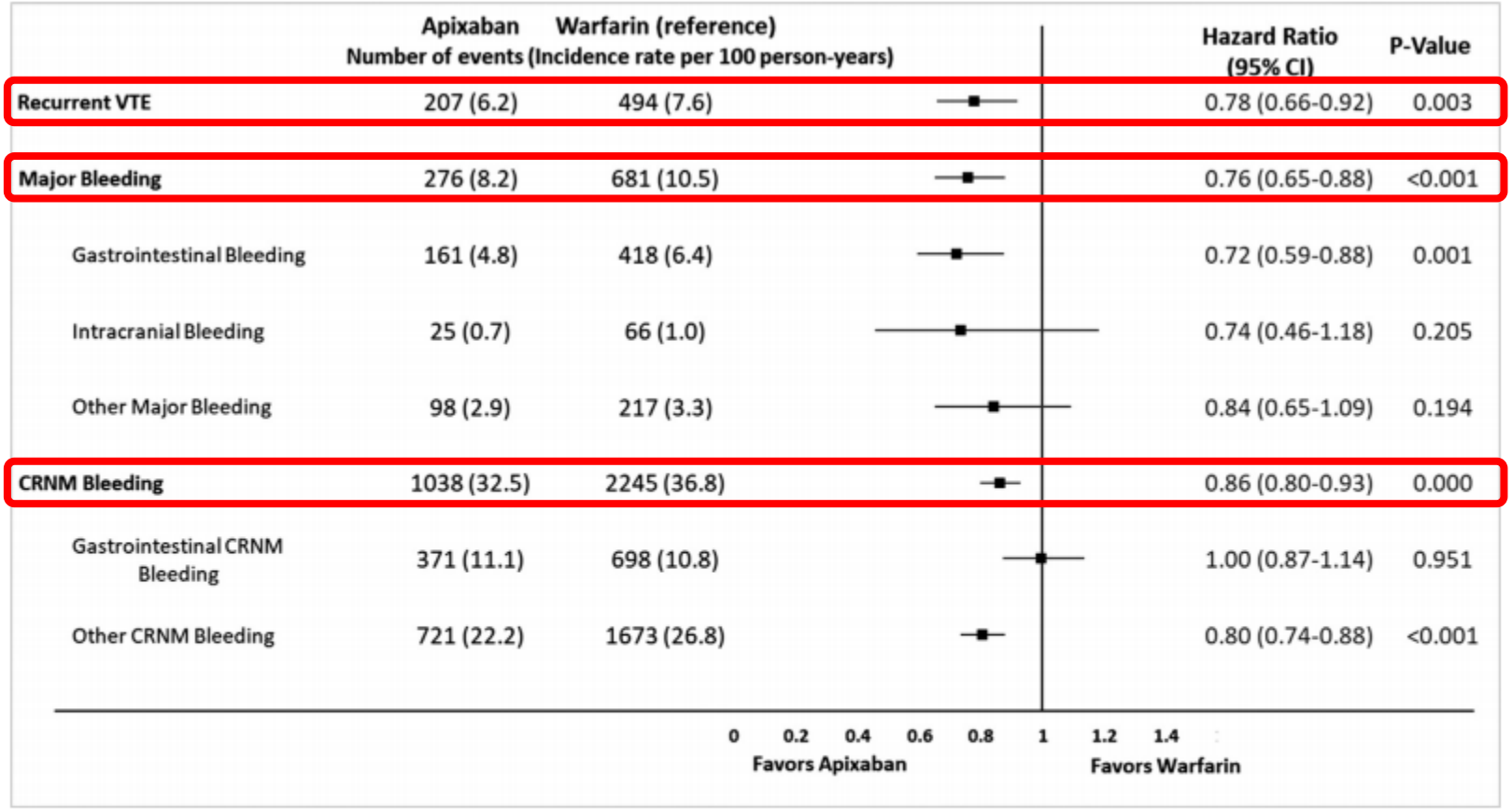


Fig. 2 Risk of recurrent venous thromboembolism (VTE), major bleeding, and clinically relevant nonmajor bleeding among patients with chronic kidney disease prescribed apixaban or warfarin to treat VTE. The figure shows a forest plot of the risks of recurrent VTE, major bleeding, and CRNMB. The patient population consisted of patients with CKD being treated for VTE with apixaban or warfarin during the study period. The number of events and the incidence per 100 person-years are listed for each outcome and treatment. Risk is indicated by an HR and 95% CI. The degree of risk is indicated along the *x*-axis. *Black squares* indicate the hazard ratio; *solid black lines* indicate the 95% CI. CI, confidence interval; CKD, chronic kidney disease; CRNMB, clinically relevant nonmajor bleeding; HR, hazard ratio; VTE, venous thromboembolism.

Cohen et al. Thromb Haemost 2022;122:926

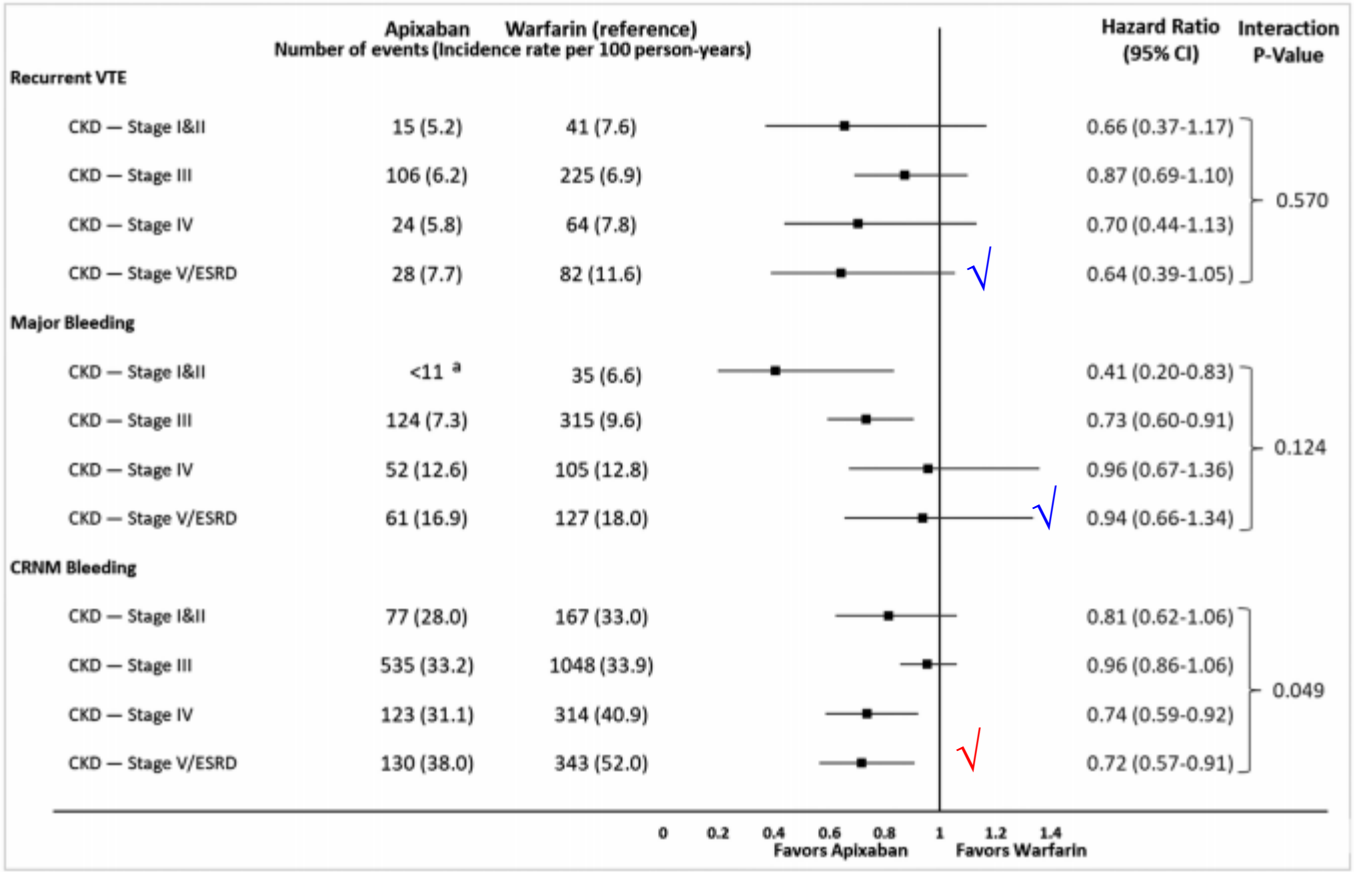


Fig. 3 Risk of recurrent venous thromboembolism (VTE), major bleeding, and clinically relevant nonmajor bleeding among patients with chronic kidney disease prescribed apixaban or warfarin to treat VTE, stratified by CKD stages. The figure shows a forest plot of the risks of recurrent VTE, major bleeding, and CRNMB. The patient population consisted of patients with CKD being treated for VTE with apixaban or warfarin during the study period, stratified by the stage of CKD (stage I/II, stage III, stage IV, stage V/ESRD). The number of events and the incidence per 100 person-years are listed for each outcome, stage, and treatment. Risk is indicated by an HR and 95% CI. The degree of risk is indicated along the *x*-axis. The *p*-value for interaction indicates the association between CKD stages and treatment effects on a specific outcome. *Black squares* indicate the hazard ratio; *solid black lines* indicate the 95% CI. CI, confidence interval; CKD, chronic kidney disease; CRNMB, clinically relevant nonmajor bleeding; ESRD, end-stage renal disease; HR, hazard ratio; VTE, venous thromboembolism. [a] <11 used due to agreements with commercial providers to assure privacy for very small number of events; interaction is significant if $p<0.10$.

Stage I/II: 8.2%
Stage III: 49.4%
Stage IV: 12.8%
Stage V:12.0%
Stage unspecified: 17.6%

Cohen et al. Thromb Haemost 2022;122:926

Apixaban vs warfarin for treatment of VTE in patients receiving long-term dialysis

- n=12206
- Retrospective cohort study of Medicare fee-for-service receiving dialysis using US Renal Data System data from 2013 to 2018

	Warfarin n=9086	Apixaban n=3130	Standardized difference*
Modality			
HD catheter	4399 (48)	1520 (49)	-0.3
HD AVG	1392 (15)	473 (15)	0.5
HD AVF	2756 (30)	957 (31)	-0.3
PD	530 (6)	180 (6)	0.4
VTE type			
DVT only	6711 (74)	2304 (74)	0.6
PE +/- DVT	2376 (26)	827 (26)	-0.6

*Difference of >10% is considered to suggest meaningful imbalance.

Wetmore JB et al. CJASN 2022;17:693

Outcome	Analysis	Warfarin Crude N events	Warfarin Event rate per 100 PY	Apixaban Crude N events	Apixaban Event rate per 100 PY	HR (95% CI)
Recurrent VTE	ITT	305	8.3	56	4.9	0.58 (0.43, 0.77)
	CAS	185	10.5	30	6.5	0.55 (0.36, 0.82)
Major bleeding	ITT	402	11.1	103	8.8	0.78 (0.62, 0.98)
	CAS	255	14.6	60	11.7	0.74 (0.55, 0.99)
All-cause mortality	ITT	1457	39.1	499	41.2	1.04 (0.94, 1.16)
	CAS	594	33.7	194	39.3	1.08 (0.91, 1.28)

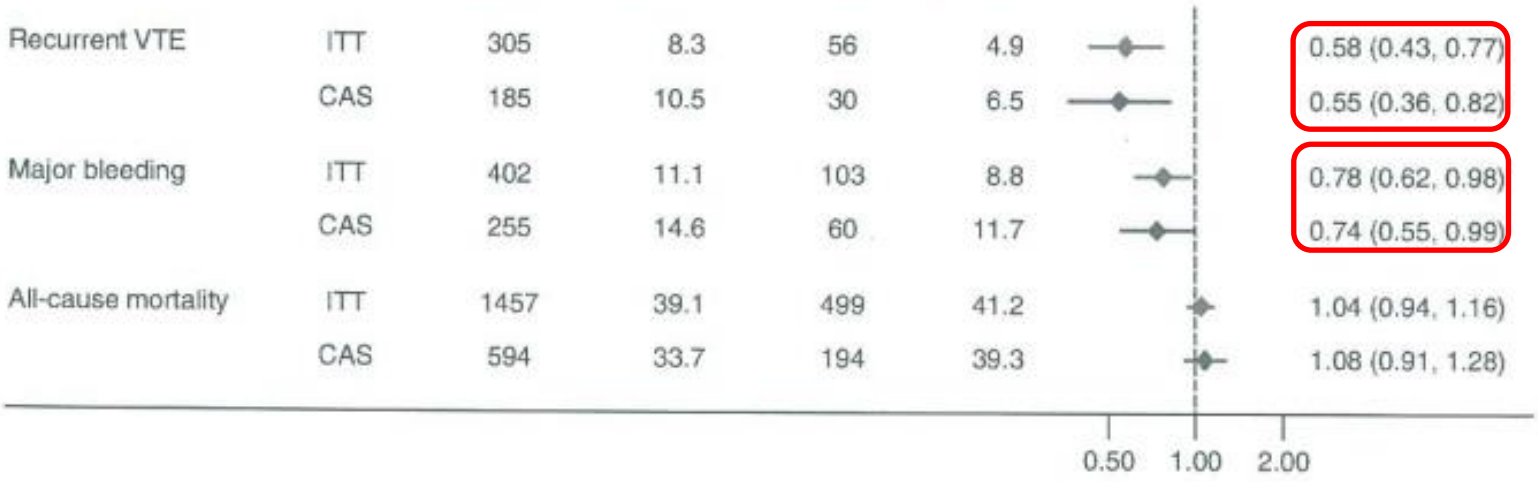


Figure 2. | Comparisons, adjusted using the inverse probability of treatment (IPT) and the inverse probability of censoring (IPC) weighting for sociodemographic factors, comorbid conditions, disability proxy score, concomitant medications, and health care utilization, for apixaban versus warfarin in the 6-month follow-up analysis. CAS, censored-at-drug-switch-or-continuation; 95% CI, 95% confidence interval; HR, hazard ratio; ITT, intention-to-treat; PY, person-years.

Wetmore JB et al. CJASN 2022;17:693

Standard vs reduced dose apixaban for the treatment of VTE in patients with severe renal disease

Table 1
Baseline characteristics.

	Standard (n = 125)	Reduced (n = 78)	p-Value
Male, n (%)	62 (49.6)	37 (47.4)	0.77
Age (years), mean [SD]	60.2 [18.9]	61.0 [16.8]	0.77
Weight (kg), mean [SD]	79.8 [24.2]	75.2 [19.5]	0.14
CrCl (mL/min)[a], mean [SD]	22.8 [20.0]	18.3 [16.1]	0.01
SCr (mg/dL), mean [SD]	5.2 [3.3]	5.75 [4.7]	0.36
CKD 4 (CrCl 15–29 mL/min), n (%)	53 (42.4)	28 (35.9)	0.46
CKD 5 (CrCl <15 mL/min), n (%)	72 (57.6)	49 (62.8)	0.46
Apixaban loading dose[b], n (%)	44 (35.2)	2 (2.6)	<0.01
Concurrent antiplatelets, n (%)	48 (38.4)	38 (48.7)	0.19
Apixaban treatment duration (days), mean [SD]	148.2 [56.9]	151.4 [51.2]	–
<3 months, n (%)	24 (19.2)	12 (15.4)	–
3–6 months, n (%)	101 (80.8)	66 (84.6)	–
VTE bleed score[c], mean [SD]	4.51 [1.2]	4.53 [1.4]	0.92
Active cancer, n (%)	11 (8.8)	10 (12.8)	0.48
Uncontrolled hypertension, n (%)	48 (38.4)	29 (37.2)	0.88
Anemia, n (%)	108 (86.4)	66 (84.6)	0.83
History of bleed, n (%)	28 (22.4)	15 (19.2)	0.72
Age ≥60 years, n (%)	71 (56.8)	44 (56.4)	>0.99
CrCl ≤60 mL/min, n (%)	125 (100)	78 (100)	–

- Multicenter retrospective cohort
- Severe or end stage renal disease

Knueppel P, et al. Thromb Res 2022;220:91

Clinically relevant bleeding

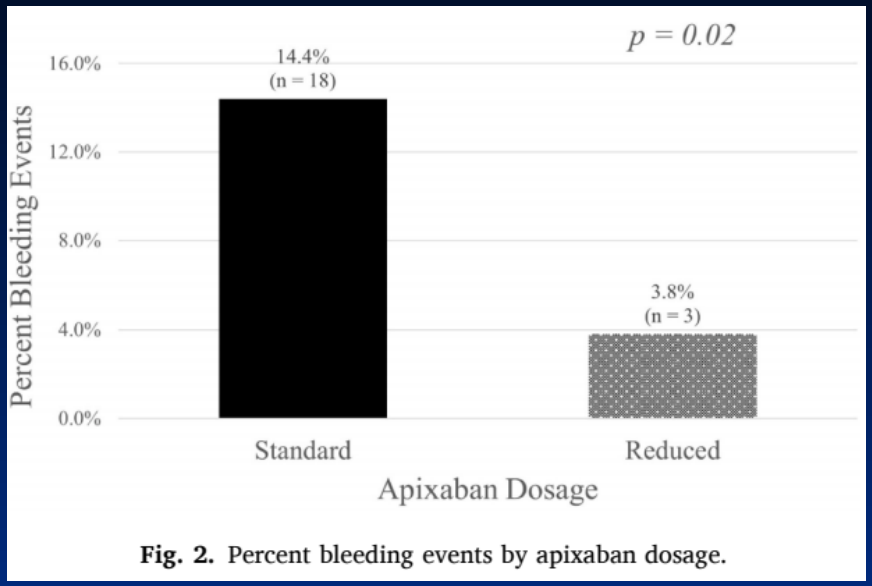


Fig. 2. Percent bleeding events by apixaban dosage.

VTE recurrence rate

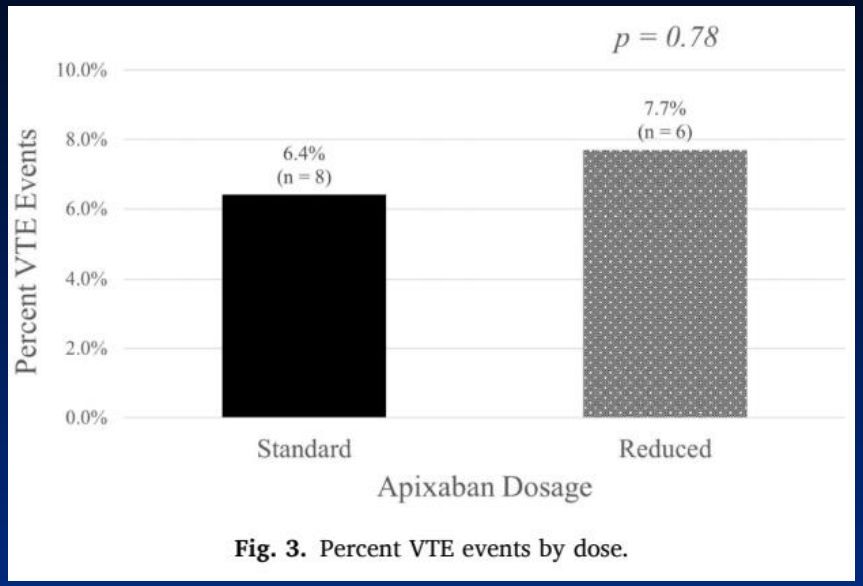


Fig. 3. Percent VTE events by dose.

Knueppel P, et al. Thromb Res 2022;220:91

Table 3. US Food and Drug Administration recommended dosing of DOACs based on renal function and indication [5–8]

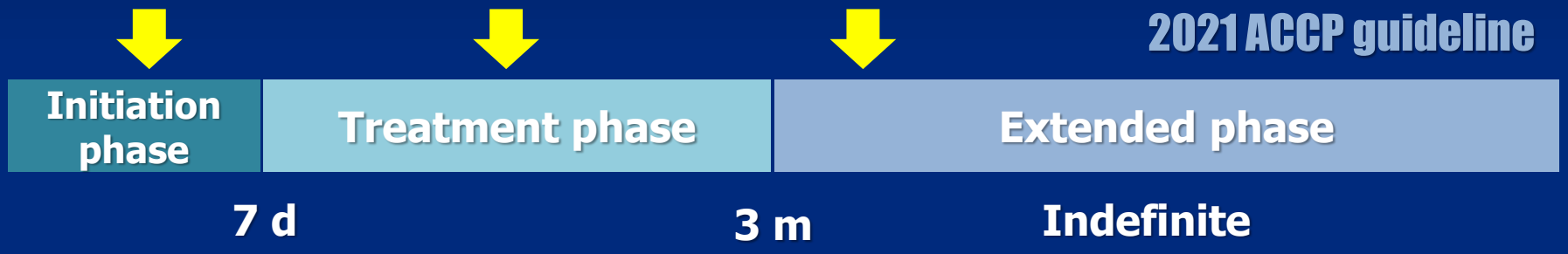
	Creatinine Clearance Categories (ml/min)			
	>50	30–50	15–29	<15 or dialysis
Treatment of venous thromboembolism (for the first 3–6 months)				
Rivaroxaban	15 mg b.i.d. x 21 days then 20 mg daily	15 mg b.i.d. x 21 days then 20 mg daily	15 mg b.i.d. x 21 days then 20 mg daily	not recommended
Apixaban	10 mg b.i.d. x7 days then 5 mg b.i.d.	10 mg b.i.d. x7 days then 5 mg b.i.d.	10 mg b.i.d. x7 days then 5 mg b.i.d.	10 mg b.i.d. x7 days then 5 mg b.i.d.
Edoxaban	LMWH[a] 5–10 days then 60 mg or 30 mg daily based on weight[b]	LMWH[a] 5–10 days then 30 mg daily	LMWH[a] 5–10 days then 30 mg daily	not recommended
Dabigatran	LMWH[a] 5–10 days then 150 mg b.i.d.	LMWH[a] 5–10 days then 150 mg b.i.d.	not recommended	not recommended
Treatment of atrial fibrillation				
Rivaroxaban	20 mg daily	15 mg daily	15 mg daily	15 mg daily
Apixaban	5 mg b.i.d.[c]	5 mg b.i.d.[c]	5 mg b.i.d.*	5 mg b.i.d.[c]
Edoxaban	60 mg daily[b,d]	30 mg daily	30 mg daily	not recommended
Dabigatran	150 mg b.i.d.	150 mg BID	75 mg b.i.d.	not recommended

b.i.d., twice daily; LMWH, low molecular weight heparin.
[a]LMWH or alternate parenteral anticoagulant.
[b]Use 30 mg daily if patient's weight ≤60 kg.
[c]Dose reduce to 2.5 mg b.i.d. if patient has at least two of the following 3: weight ≤60 kg, age ≥80 years, or serum creatinine ≥1.5 mg/dl (133 μmol/l).
[d]Do not use if CrCl > 95 ml/min.

Lamarche et al. Curr Opin Pulm Med 2021;27:311

Unanswered questions

- Use of apixaban from day 1 implies a higher dosage of 10 mg twice daily for 1 week or LMWH, switching to apixaban?
- Optimal maintenance dose: 5 mg bid vs 2.5 mg bid?
- Drug monitoring: anti-Xa assay?
- Unprovoked VTE: indefinite anticoagulation?
- High risk of recurrence: active malignancy, recurrent VTE?
- Use of antiplatelet therapy?

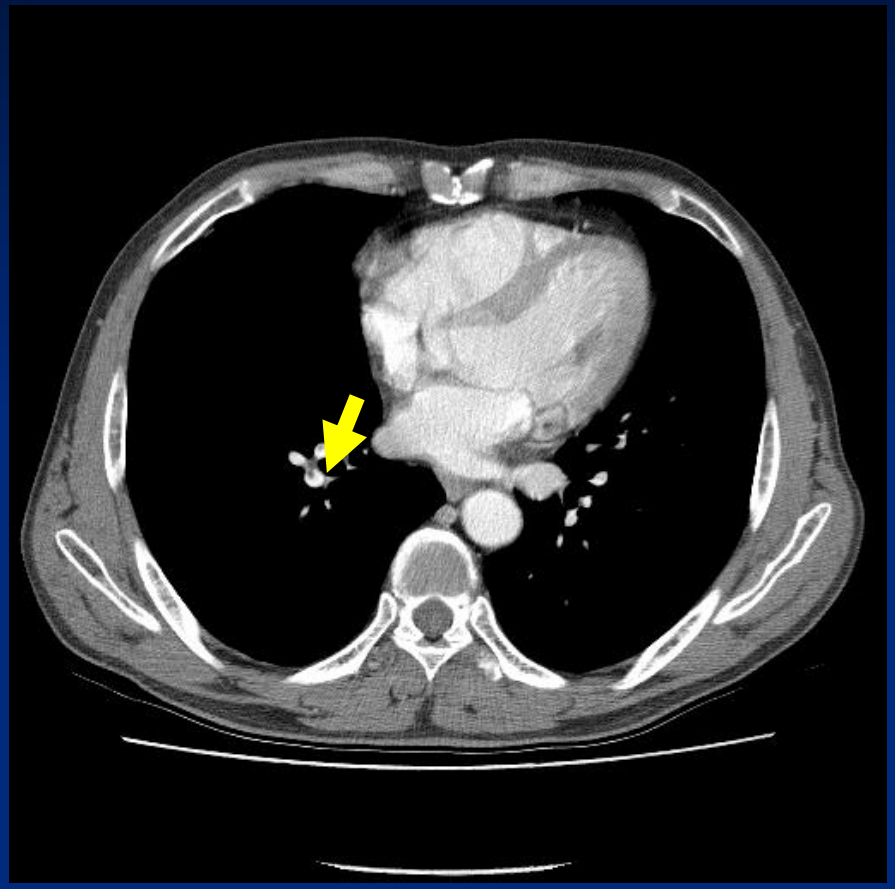


Mavrakanas TA. Clin J Am Soc Nephrol 2022;17:623

Case 2

- M 59
- C.C: dyspnea for 1 d
- Comorbidity: Parkinson's disease, alcoholic liver cirrhosis (Child 6, class A), hypertension

- d-Dimer 1410 pg/mL
- PT 24, INR 2.1
- Bilirubin 0.4 mg/dL
- Albumin 4.5 g/dL
- BUN 12.4 mg/dL
- Cr 0.75 mg/dL



Case 2 (II)

- **Anticoagulation ?**
  1) Enoxaparin + warfarin
  2) Rivaroxaban
  3) Apixaban
  4) Edoxaban
  5) Dabigatran

Coagulation in patients with cirrhosis

- Patients with cirrhosis are "autoanticoagulated": misconception
- Elevated INR due to coagulopathy
  At higher risk for bleeding and thrombosis
- A 2-fold increase in the incidence of unprovoked DVT/PE

Sogaard et al. Am J Gastroenterol 2009;104:96

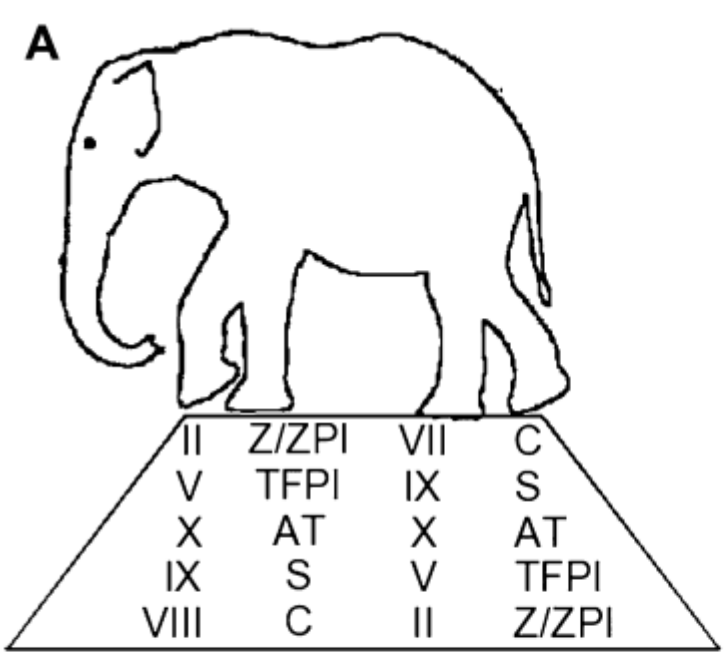
- 50% of VTE cases occurred in cirrhotic patients with INR > 1.6
  The risk of VTE existed in patients with INR > 2.2

Dabbagh et al. Chest 2010;137:1145

- Decreased factors II, V, VII, IX, X, XI → bleeding
  Decreased AT, PC, PS, increased factor VIII, vWF → thrombosis

Ha et a. Ann Pharmacol 2016; 50:402

- **Hemostatic balance:** higher buffer zone in noncirrhotic patients
- **Hemostatic instability:** smaller buffer zone in cirrhotic patients



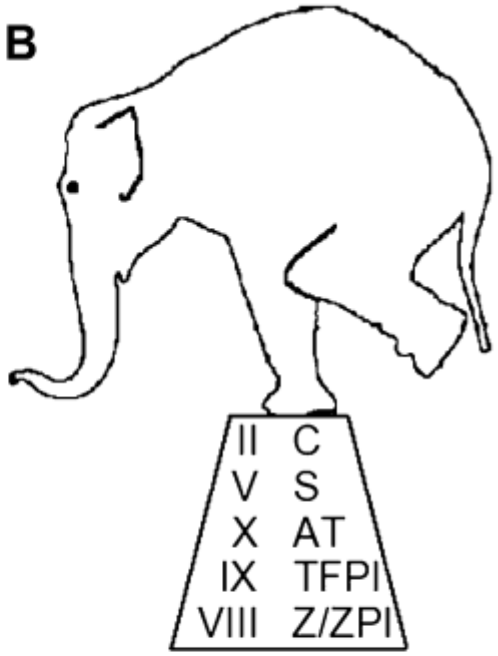


Fig. 4. Hemostatic balance. (*A*) Under normal conditions there are higher levels of pro- and anticoagulant proteins than are needed for minimal hemostatic function. This functional "excess" allows for a high degree of stability—the hemostatic balance tends to be maintained even under stress. (*B*) When the levels of the pro- and anticoagulant factors are reduced by hepatic insufficiency, there may not be a tendency to hemorrhage or thrombosis/DIC. However, the hemostatic balance is much harder to maintain in the face of stressors such as infection.

Monroe et al. Clin Liver Dis 2009;13:1

Effects of cirrhosis on coagulation tests

	INR	aPTT	Anti-Xa
Effect of cirrhosis	↑	↑	↓

- INR should not be used as an indicator of efficacy in cirrhotic
- The aPTT test has not been assessed in cirrhotic:
  targeted aPTT range is unclear.
  → UFH dosing guidelines & nomogram should differ.
- Increasing severity of cirrhosis was correlated with decreased AT levels → correlated with decreased anti-Xa levels

Ha et a. Ann Pharmacol 2016; 50:402

VTE characteristics in liver disease

	Effect on VTE incidence	Effect on VTE outcomes	Therapeutic consideration
Cirrhosis	Increased VTE risk	Increased LOS and hospitalization cost	LMWH is preferred over VKA

Nguyen et al. Clin Chest Med 2018;39:515

DOACs in patients with cirrhosis: systemic review

Study	Treatment groups	Recurrent VTE in patients with VTE	VTE clot progression in patients with VTE	Major bleeding in all patients
De Gottardi et al 2016	DOAC (n=36)			1/36 (3)
Kunk et al. 2016	DOAC (n=69)		3/47 (6)	8/69 (12)
Intagliata et al. 2016	DOAC (n=20) LMWH/VKA (n=19)			1/20 (5) 2/19 (11)
Hum et al. 2017	DOAC (n=27) LMWH/VKA (n=18)	0/12 (0) 0/8 (0)	1/12 (8) 1/8 (13)	1/27 (4) 5/18 (28)
Nagaoki et al. 2017	DOAC (n=20) LMWH/VKA (n=30)			3/20 (15) 2/30 (7)

- **Major bleeding: 3-15% in DOAC vs 7-28% in LMWH/VKA**
  - In phase III DOAC trials: MB, 1.1% in DOAC vs 1.8% in VKA

Hoolwerf et al. Thromb Res 2018;170:102

Anticoagulation in cirrhosis with DOAC

- The AUC, coagulation parameters, renal clearance, and half-life of a single dose of 150 mg dabigatran etexilate were comparable between patient with Child-Pugh class B and healthy controls, suggesting that dabigatran may be given at a similar dose in patients with cirrhosis compared to those without cirrhosis.
  ← Clearance by hepatobiliary pathways represent 20% of total clearance.

- The AUC after a single dose of 5 mg apixaban has been slightly elevated in patients with cirrhosis (Child-Pugh A and B) compared with healthy controls.

  For apixaban, hepatobiliary clearance represents 73% of total clearance, but only approximately 25% of apixaban is metabolized by various CYP450 enzymes into multiple metabolites.

Mendell et al. J Clin Pharmacol 2015;55:1395
Hoolwerf, et al. Thromb Res 2018;170:102

Anticoagulation in cirrhosis with DOAC (II)

- Moderate (but not mild) hepatic impairment reduced total body clearance of rivaroxaban after a single 10 mg dose, leading to increased rivaroxaban exposure and pharmacodynamic effects.
  ← 33% of total dose is excreted renally as unchanged drug; 60% is metabolized to active and inactive metabolites

- Once absorbed, approximately 50% of edoxaban is cleared by renal elimination, and 50% is cleared by hepatobiliary pathways with minimal metabolism (<4%) by CYP450 enzymes.

The use of edoxaban in patients with moderate or severe hepatic impairment (Child-Pugh B and C) is not recommended as these patients may have intrinsic coagulation abnormalities.

Hoolwerf, et al. Thromb Res 2018;170:102
Mendell et al. J Clin Pharmacol 2015;55:1395

Table 2. US Food and Drug Administration recommendations for DOAC use in cirrhosis [5–8]

	Child-Pugh Class			Hepatic disease associated coagulopathy
	A	B	C	
Rivaroxaban	usual dose	not recommended	not recommended	not recommended
Apixaban	usual dose	use with caution	not recommended	not recommended
Edoxaban	usual dose	not recommended	not recommended	not recommended
Dabigatran	usual dose	use with caution	not recommended	not recommended

Lamarche et al. Curr Opin Pulm Med 2021;27:311

Safety and efficacy of DOACs in patients with moderate to severe liver cirrhosis

Table 1. Characteristics of Included Patients.[a]

Patient characteristic	DOAC (n = 69)	Traditional (n = 32)	*P* value
Age, years	61 ± 14	67 ± 14	NS
Gender, male, n (%)	50 (72)	22 (69)	NS
Weight, kg	86 ± 19	90 ± 21	NS
Hemoglobin, g/dL	10 ± 2	11 ± 3	NS
Platelets, U/μL	199 ± 182	195 ± 92	NS
MELD score	15 ± 5	19 ± 5	0.001
CTP score	9 ± 2	8 ± 1	0.019
CTP B, n (%)	59 (86)	30 (94)	NS
Diagnosis of malignancy, n (%)	19 (28)	6 (19)	NS
Diagnosis of CKD, n (%)	19 (28)	8 (25)	NS
On antiplatelet therapy prior,[b] n (%)	17 (25)	22 (69)	<0.001
Cirrhosis etiology (many patients had >1 cirrhosis etiology)			
Cryptogenic, n (%)	18 (26)	13 (41)	NS
ETOH, n (%)	25 (36)	4 (13)	<0.001
NASH, n (%)	6 (9)	7 (22)	NS
HCV, n (%)	8 (12)	3 (10)	NS
Cardiac cirrhosis, n (%)	5 (7)	5 (16)	NS
HCC, n (%)	6 (9)	0	0.001
Other,[c] n (%)	6 (9)	1 (3)	NS
Indication for anticoagulation (many patients had >1 indication for anticoagulation)			
Atrial fibrillation, n (%)	24 (35)	19 (59)	NS
VTE, n (%)	45 (65)	9 (28)	0.003
PE (subset of VTE), n (%)	11 (16)	3 (9)	NS
Acute thromboembolism, n (%)	12 (17)	2 (6)	NS
Historic thromboembolism, n (%)	29 (42)	7 (22)	0.049
Other,[d] n (%)	1 (1)	4 (13%)	0.034
Anticoagulant			
Apixaban, n (%)	57 (83)	—	—
Rivaroxaban, n (%)	10 (14)	—	—
Dabigatran, n (%)	2 (3)	—	—
Warfarin, n (%)	—	31 (97)	—
Enoxaparin, n (%)	—	1 (3)	—

Oldham et al. Ann Pharmacother 2022;56:782

Table 2. Bleeding and Thromboembolic Outcomes.[a]

	DOACs	Traditional	
	n = 69	n = 32	*P* value
Bleeding events	25 (36)	7 (22)	0.149
Thromboembolic events	3 (4)	0	0.55
By severity of bleeding event			
	n = 25	n = 7	
ISTH major	6 (24)	3 (43)	NS
CRNMB	14 (56)	3 (43)	NS
Clinically nonrelevant	5 (20)	1 (14)	NS
By location of bleeding event			
	n = 25	n = 7	
Gastrointestinal	13 (52)	4 (57)	NS
Epistaxis	2 (8)	1 (14)	NS
Brain	0	1 (14)	NS
Other[b]	10 (40)	1 (14)	NS

Oldham et al. Ann Pharmacother 2022;56:782

Rates of bleeding and discontinuation of DOACs in patients with decompensated cirrhosis

Table 2. Baseline Characteristics of Study Cohort

Characteristic	n (total = 138)	Percent of population
Child-Turcotte-Pugh class		
A	45	32.6
B	70	50.7
C	23	16.7
Indication for DOAC		
DVT/PE	47	34.1
Atrial fibrillation	44	31.9
Portal vein thrombosis	39	28.3
Other	8	5.8
DOAC used		
Apixaban	94	68.1
Rivaroxaban	32	23.2
Dabigatran	12	8.7

Table 3. Type of Bleeding Events in Cirrhosis Patients on Direct Oral Anticoagulants

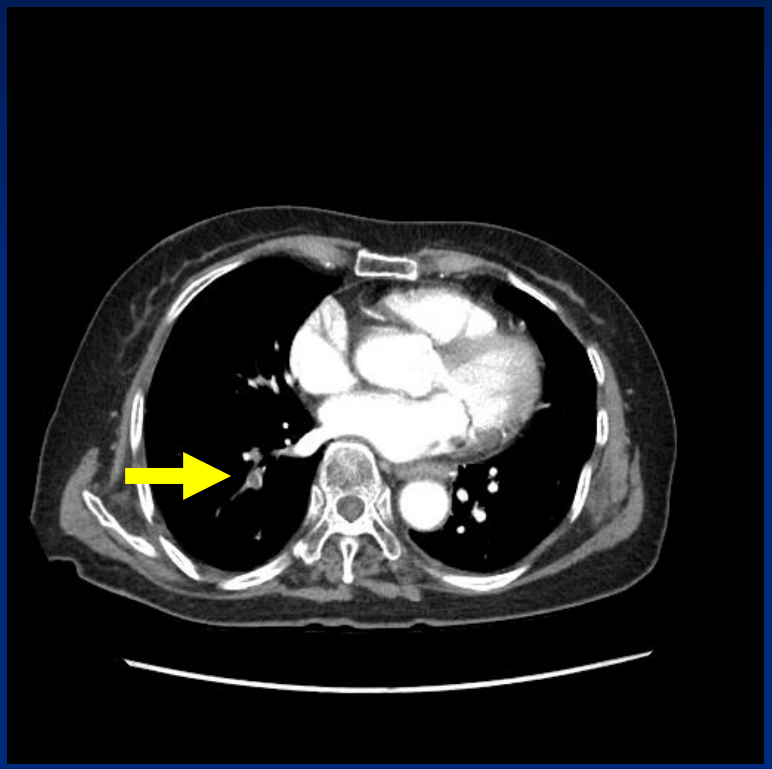
	n	Percent	Annualized rate (%)
Any bleeding	45	32.6	25.1
Major bleeding	11	8.0	6.2
Fatal bleeding	0	0	0
Central nervous system bleeding	1	0.7	0.6
Hemoglobin drop ≥2 g/dL or ≥2 units packed red blood cells	10	7.2	6.2
CRNMB	22	15.9	12.2
Minor bleeding	12	8.7	6.7
DOAC discontinuation due to bleeding	29	21	16.5

Anticoagulation duration: mean 427 d

Mort et al. Clin Gastroenterol Hepatol 2021;19:1436

Case 3

- F 81
- C.C.: chest discomfort
- Comorbidity:
  gastrectomy (2016, gastric cancer)
  primary CNS lymphoma
  2021.1.6-5.4. R-MVP CTx #5
- 2022.5.13. ER visit



Case 3 (II)

- **Anticoagulation?**

  22.5.13. enoxaparin
  22.5.16. DOAC vs VKA?

DOAC absorption locations

DOAC	Absorption location	Note
Apixaban	55% in distal SB and some proximal colon; some gastric and proximal SB	pH independent absorption
Dabigatran	Lower stomach and duodenum	Prodrug requires acidic environment for absorption (formulated with tartaric acid). 20% reduction was seen when given with antacids: thought to be clinically insignificant.
Edoxaban	Upper GIT (proximal SB)	pH dependent solubility Highly soluble in an acidic pH Food intake causes a modest but clinically insignificant effect
Rivaroxaban	Primarily stomach with reduced absorption in the proximal SB	Lipophilicity and limited aqueous solubility: 20 mg/15 mg tablets must be taken with a sufficient caloric intake

Hakeam et al. J Thromb Thrombolysis 2017;43:343

Transporter consideration

- All DOACs, substrates of P-gp
  Apixaban & rivaroxaban, substrates of CYP3A4.

- P-gp concentration is lowest in the duodenum and highest in the distal ileum and colon.
  Bypassing the proximal portions of the GIT could lead to decreased drug absorption due to increased efflux of DOAC back into the gut lumen.

- CYP3A4 is located along the entire small intestine with slightly increased expression from the duodenum to the middle section of the jejunum with gradually reduced expression in the distal jejunum and ileum.
  Bypassing the proximal segments of the GIT could result in a significant increase in oral bioavailability of substrates due to decreased metabolism.

Impact of surgical intervention on DOACs bioavailability

	Total gastrectomy	Partial gastrectomy	RYGB	Distal resection/ SBS	Colectomy
Rivaroxaban	Reduced up to 56%	Possibly reduced	Possibly reduced	Unlikely affected	Unlikely affected
Dabigatran	Possibly reduced	Possibly reduced	Possibly reduced	Possibly reduced	Unlikely affected
Apixaban	Unlikely affected	Unlikely affected	Possibly reduced	Possibly reduced	Possibly reduced
Edoxaban	Possibly reduced	Possibly reduced	Possibly reduced	Unlikely affected	Unlikely affected

SBS, short bowel syndrome

Modified from Hakeam et al. J Thromb Thrombolysis 2017;43:343

Absorption of DOACs in cancer patients after gastrectomy

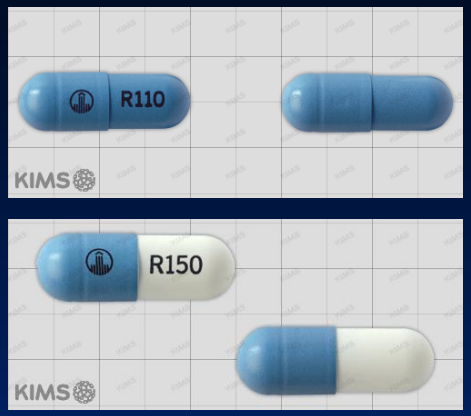
Table 2. Trough and peak DOAC concentrations and coagulation parameters.

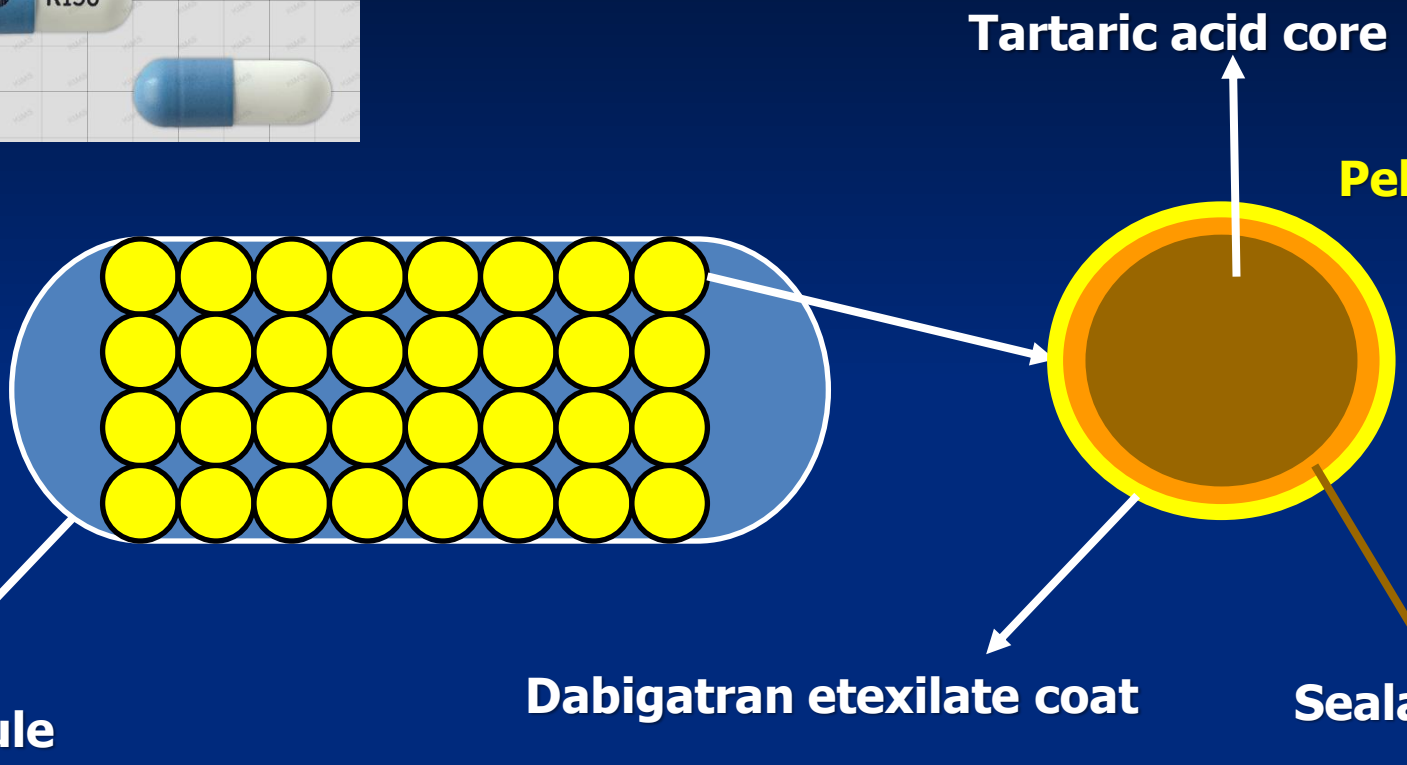
				Trough Level				Peak Level			
Patient Number	DOAC	Dosage (mg)	Creatinine Clearance (mL/min)	DOAC Level (ng/mL)	Expected Range * (ng/mL)	PT INR	aPTT (s)	DOAC Level (ng/mL)	Expected Range * (ng/mL)	PT INR	aPTT (s)
1	Edoxaban	1 × 60	78	51	19–62	1.1	39.5	195	125–245	1.2	47.7
2	Edoxaban	1 × 30	40	n.d.	4–20	1.2	40.4	171	60–120	1.3	49.9
3A	Edoxaban	1 × 30	68	n.d.	4–20	1.2	28.8	83	60–120	1.3	33.6
3B	Rivaroxaban	1 × 20	87	22	6–87	1.2	29.9	39	189–419	1.2	31.2
4	Rivaroxaban	1 × 20	88	45	6–87	1.0	34.1	210	189–419	1.0	44.3
5	Rivaroxaban	1 × 20	94	27	6–87	1.0	30.4	437	189-419	1.1	39.4
6	Rivaroxaban	1 × 20	68	65	6–87	1.3	34.5	257	189–419	1.4	43
7	Rivaroxaban	1 × 20	55	40	6–87	1.1	32.8	228	189–419	1.2	40.8
8	Apixaban	2 × 2.5	58	26	11–90	1.0	35	65	30–153	1.1	38
9	Apixaban	2 × 2.5	41	45	34–162	1.0	36.3	126	69–221	1.1	38.6
10	Apixaban	2 × 5	99	92	22–177	1.0	31.3	261	59–302	1.0	33.6
11A	Dabigatran	2 × 110	64	18	28–155	1.0	31.5	53	52–275	1.0	37.9
11B	Dabigatran	2 × 150	61	21	61–143	1.1	36.2	46	117–275	1.1	40.4
11C	Apixaban	2 × 5	63	99	41–230	1.1	33.5	217	91–321	1.1	35.3

Abbreviations: n.d.—not detectable, PT INR—prothrombin time based international normalized ratio, aPTT–activated partial thromboplastin time (reference range 27.0—41.0 seconds), creatinine clearance estimated by the Cockcroft-Gault equation. * Expected ranges differ depending on the DOAC and the respective dosage and indication [20].

Puhr et al. Pharmaceutics 2022;14:662

Dabigatran etexilate capsule structure





NG tube feeding: DOACs

- **Dabigatran: is not applied as a tablet (that can be crushed) but as a capsule which contains pellets of the prodrug. The oral bioavailability of dabigatran etexilate increases by 75% when the pellets are taken without the capsule shell.**

- **Rivaroxaban: administration of a 20 mg tablet administered orally as a crushed tablet mixed in applesauce or suspended in water and administered via a NG tube followed by a liquid meal resulted in AUC comparable to the AUC after standard application.**

Beyer-Westendorf J. Hamostseologie 2021;41:35
Kim SA, et al. JKMS 2019;34:e52

NG tube feeding: DOACs (II)

- **Apixaban**: oral administration of 10 mg of apixaban as two crushed 5 mg tablets suspended in water or mixed with applesauce resulted in an AUC reduction of only 16%. Suspension of a crushed 5 mg table in tube nutrition resulted in a drug exposure similar to that seen other clinical trials involving healthy volunteers receiving a single oral 5 mg tablet dose

- **Edoxaban**: administration of a crushed 60 mg tablet, either mixed into applesauce or suspended in water and given through a NG tube resulted in an AUC comparable to the AUC after standard application

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Given via nasogatric tube	No	Yes	Yes	Yes

Beyer-Westendorf J. Hamostseologie 2021;41:35
Kim SA, et al. JKMS 2019;34:e52

Summary

DOACs vs VKA in therapeutic anticoagulation for PE

- **ESRD:**
  Apixaban
- **Liver cirrhosis:**
  Child-Pugh A → All 4 DOACs
  Child-Pugh B → dabigatran and apixaban
- **Gastrectomy: apixaban**
- **NG tube feeding: rivaroxaban, apixaban, and edoxaban, except dabigatran**