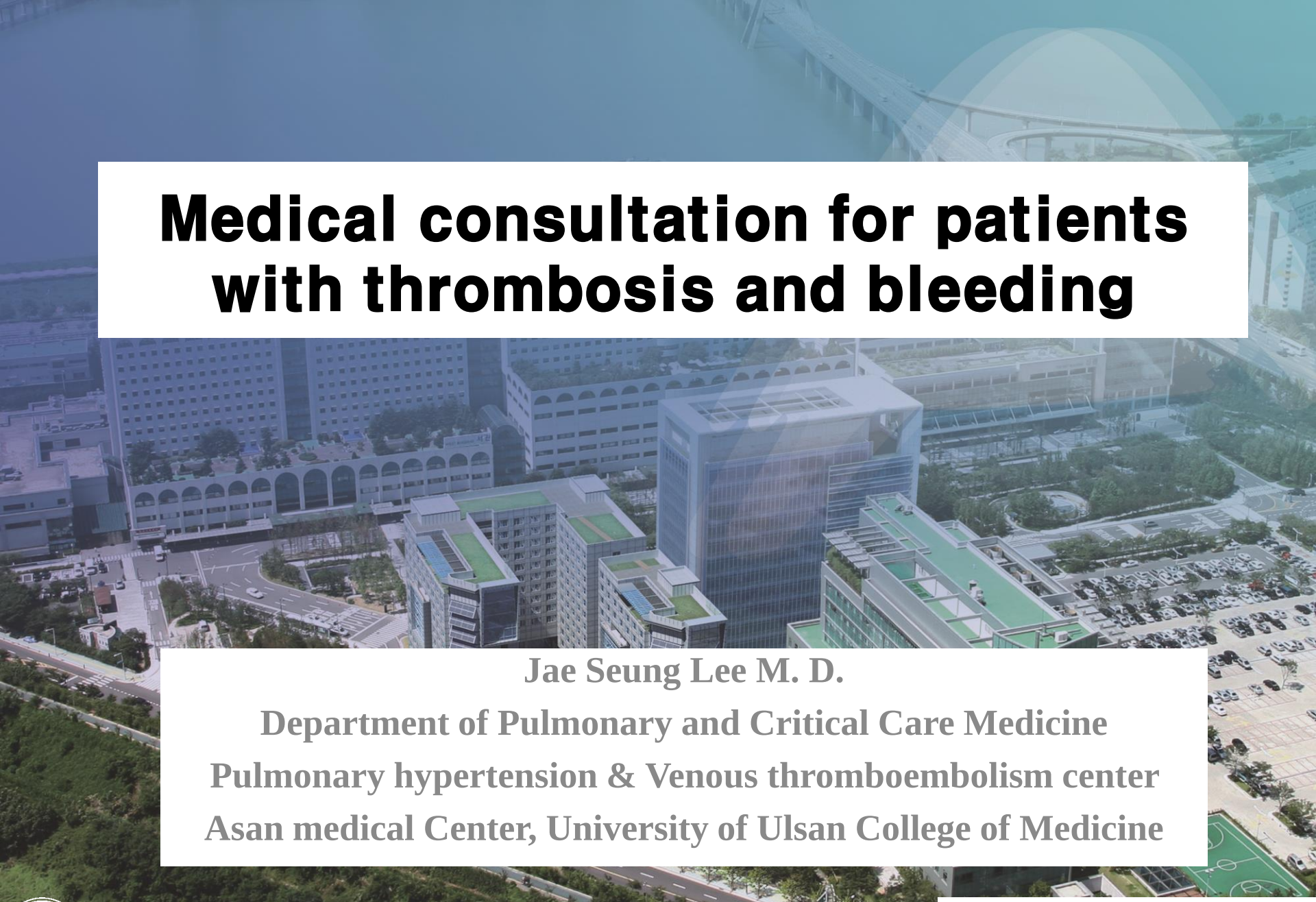
Medical consultation for patients with thrombosis and bleeding



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폐고혈압·정맥혈전센터

Case . (73/F)

Chief complaint : **Hematuria**

Present illness :

2009. Varicose vein with DVT로 3개월 warfarin 복용

2013.11 소화기내과에서 시행한 liver dynamic CT에서 우연히 발견된 **acute PE 소견으로 warfarin 재복용**

2016.11 hematuria, conjuctival hemorrahge 소견으로 내원

P. M. Hx: **HBV LC (Child-Pugh class A)**

P/Ex.: **BP 130/83 mmHg PR 89 /m RR 18/m**

Initial Laboratory data

CBC WBC 4200 /mm3 , **Hb 12.0 g/dL , PLT 113×10^3/mm3**

Coagulation battery **PT 43.4 s (3.71 INR)** **aPTT 43.4 s** (25-35)

Chemical & electrolyte battery

Ca/P (mg/dL) 8.5/3.6 Glucose (mg/dL) 140

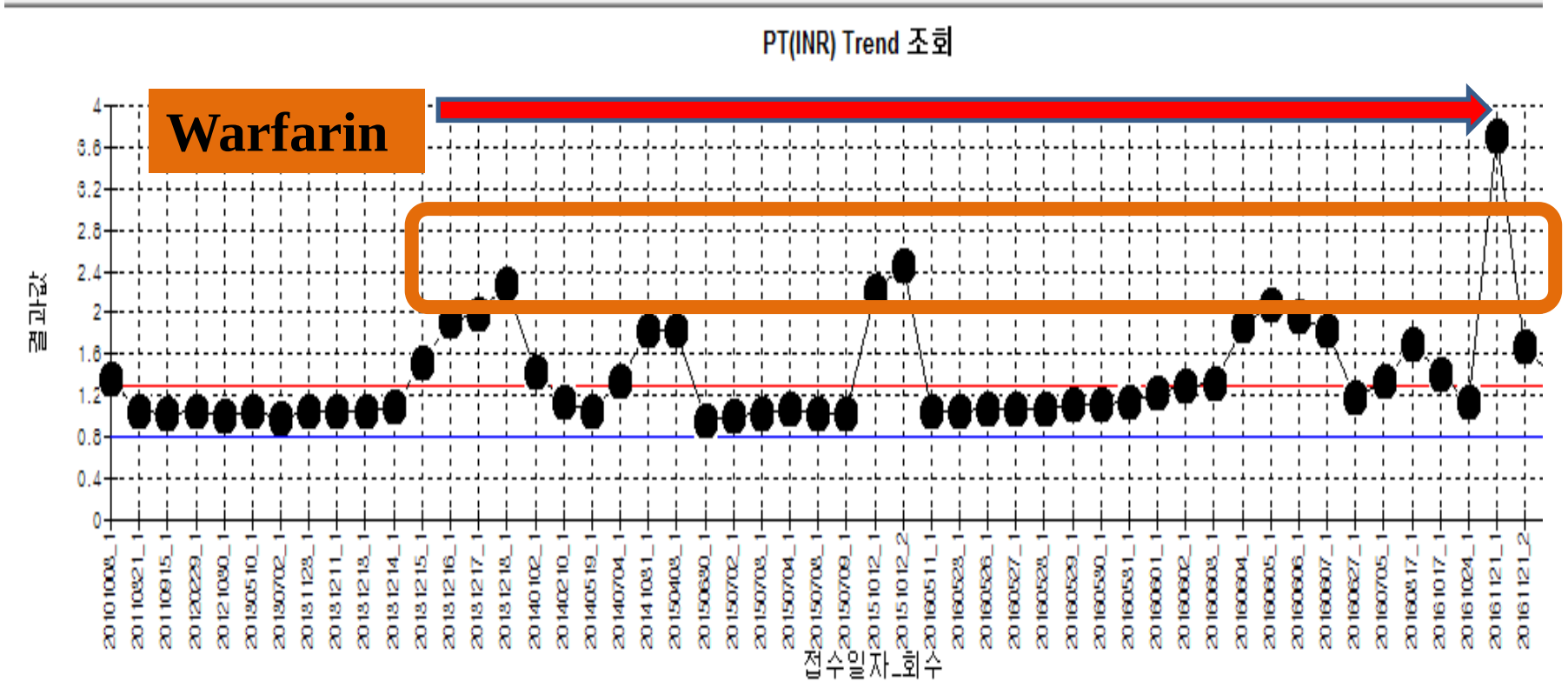
BUN/Cr (mg/dL) 13/0.5 Protein/albumin (mg/dL) 6.3/**2.8**

AST/ALT (IU/L) 40/25 ALP/r-GT (IU/L) 109

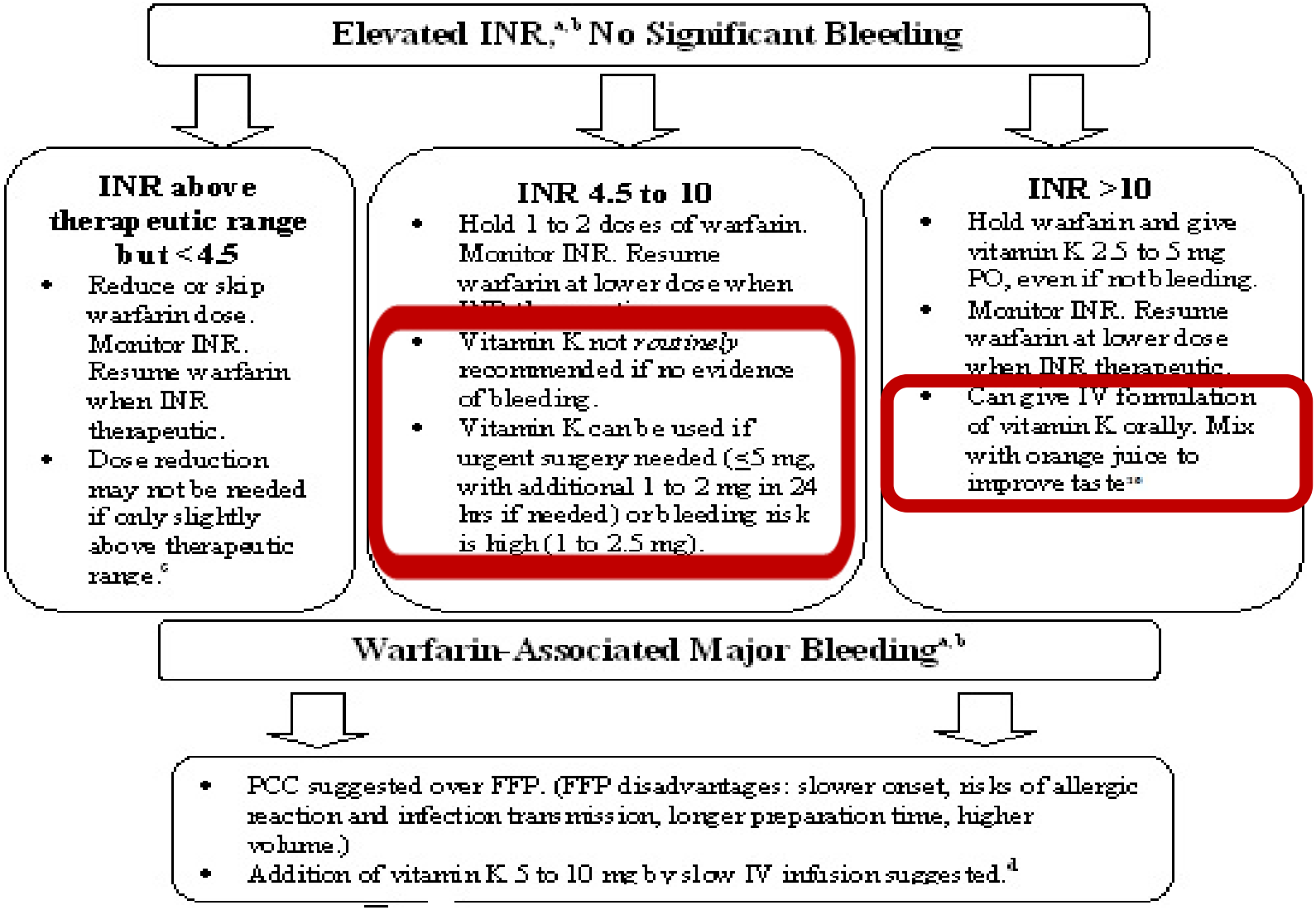
T.bil (mg/dl) 1.1

U/A **Occult blood ++++** **WBC (-)**

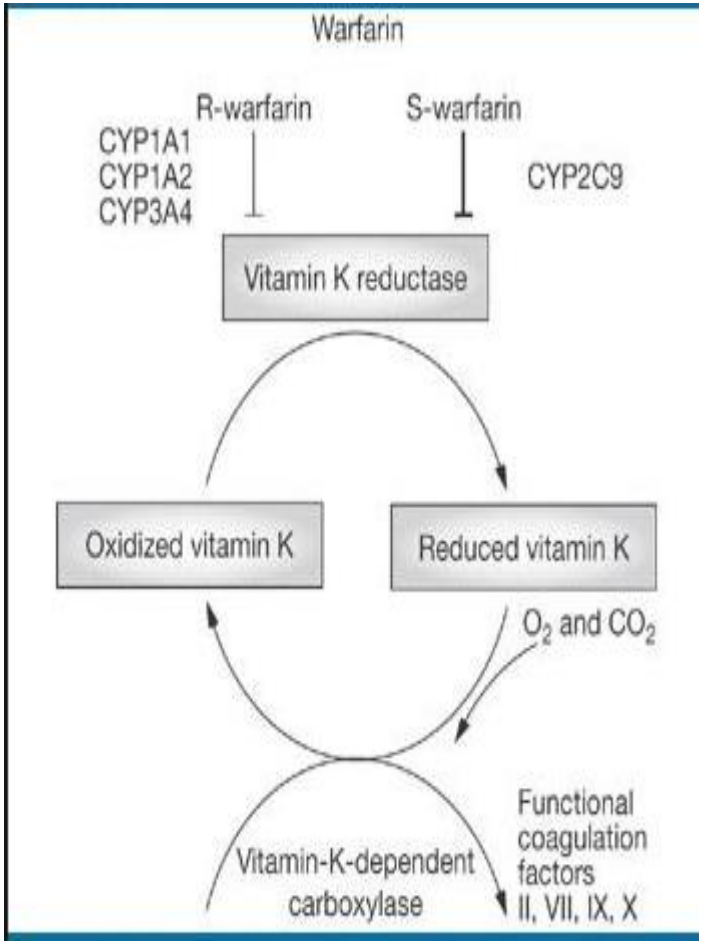
PT INR during warfarin treatment

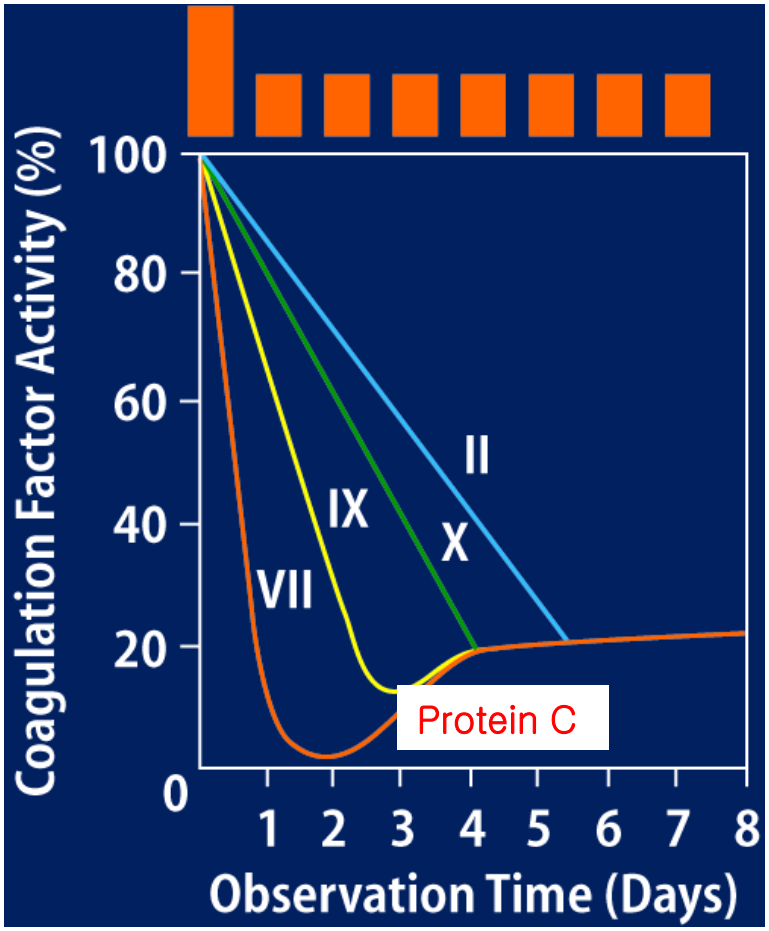


Management of an elevated INR



Warfarin Mechanism of Action





Characteristics of Therapies for Warfarin Reversal

Product	Time to Effect (After Administration)	Duration of Effect	Evidence of Efficacy for Warfarin Revesal	Risk of Thrombosis
Oral vitamin K	24 h	Days	++++	NS
Intravenous vitamin K	8–12 h	Days	++++	NS
Fresh frozen plasma	Immediate	12–24 h	++	NS
PCC	Immediate	12–24 h	+++	+ (Higher with activated PCC)
Recombinant factor VIIa	Immediate	2–6 h	+	++

Vitamin K

- Needed several hours to maximum therapeutic effects (INR reduction)
- **Slow IV infusion d/t anaphylactic reaction**

- The ASTH guideline mentions that the **injectable preparation of vitamin K can be administered orally.**

- The taste of undiluted vitamin K can be unpleasant, and **mixing it with orange juice** can mask this taste.

Prothrombin Complex Concentrates (PCC)

- Originally developed to restore hemostasis in hemophilia B (Factor IX deficiency)
- (also) TOC to reverse anticoagulation with VKAs

- 4-factor PCC (4-F PCC) : Factor II, VII, IX, X
- 3-factor PCC (3-F PCC) : Factor II, (VII), IX, X
- Activated PCC

Fresh Frozen Plasma (FFP)

- **Commonly used to reverse warfarin therapy**
- **Not recommended it for DOAC reversal**
- Contain all coagulation factors (fibrinogen variable concentrations)
- Recommended dose : 15-20 ml/kg

Advantages	**Easy available** **Low cost**
Disadvantages	**Human product → Allergic reaction, Transfusion Related Lung Injury (TRALI), needed ABO compatibility** **A long time to prepare d/t defrost** **High infusion volume (1500ml ↑) in order to increase coagulation factor concentration → Caution in Renal failure and/or Heart failure**

Recombinant Factor VII activated (rFVIIa)

- Hemostatic agent at vascular injury site
  → rFVII combine tissue factor at injury site
  → Factor X Activating, locally
  → Platelet activating
  → Thrombin ↑
  → Hemostasis

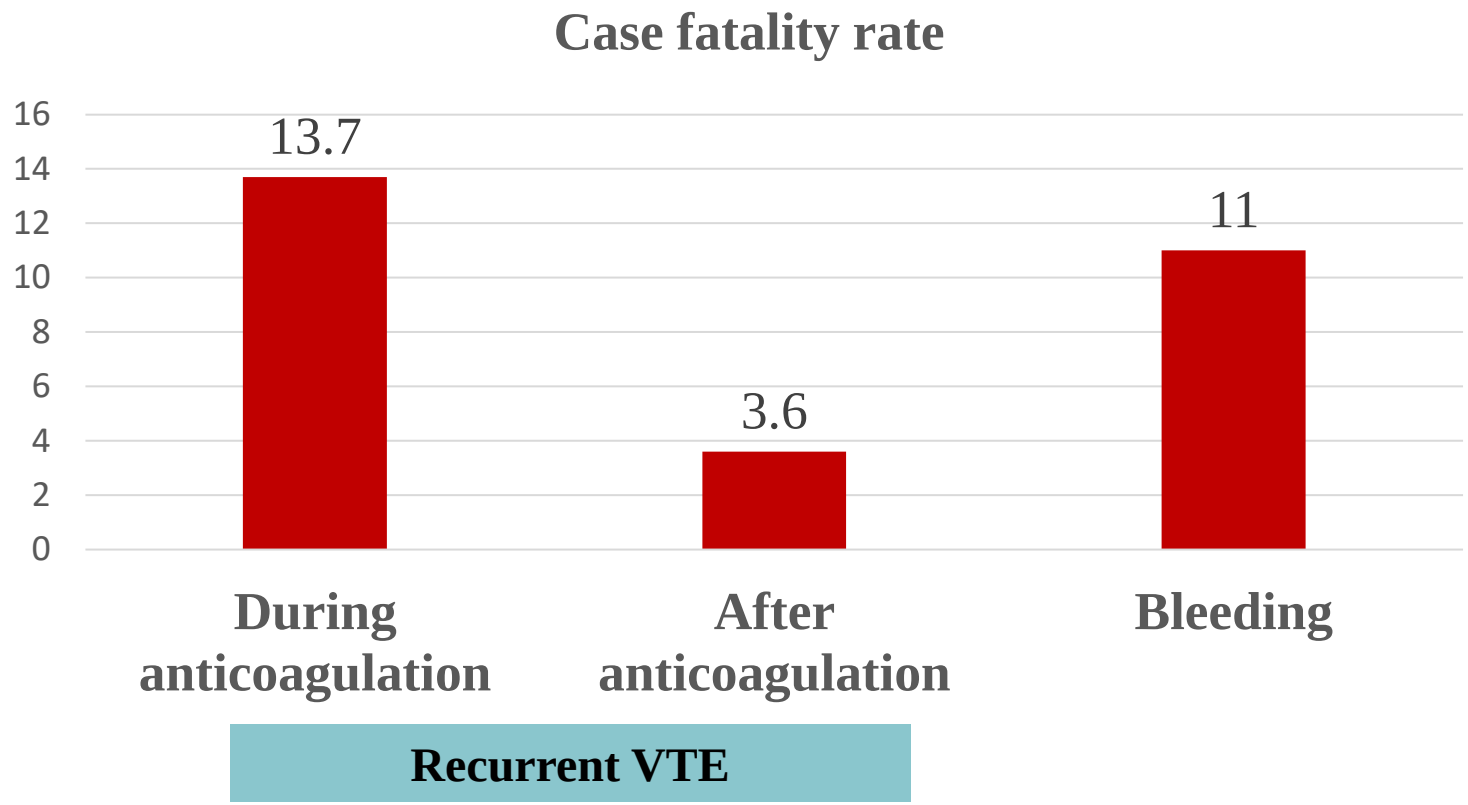
Recombinant Factor VIIa (NovoSeven)

- Local reaction → systemic activation

Risk and benefit of anticoagulation in VTE

Case fatality of recurrent VTE and major bleeding

Systematic review



Carrier M, et al. Ann Intern Med. 2010;152:578-589.

Risk of long-term recurrence

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[b]
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

ESC guidelines. Eur heart J 2019

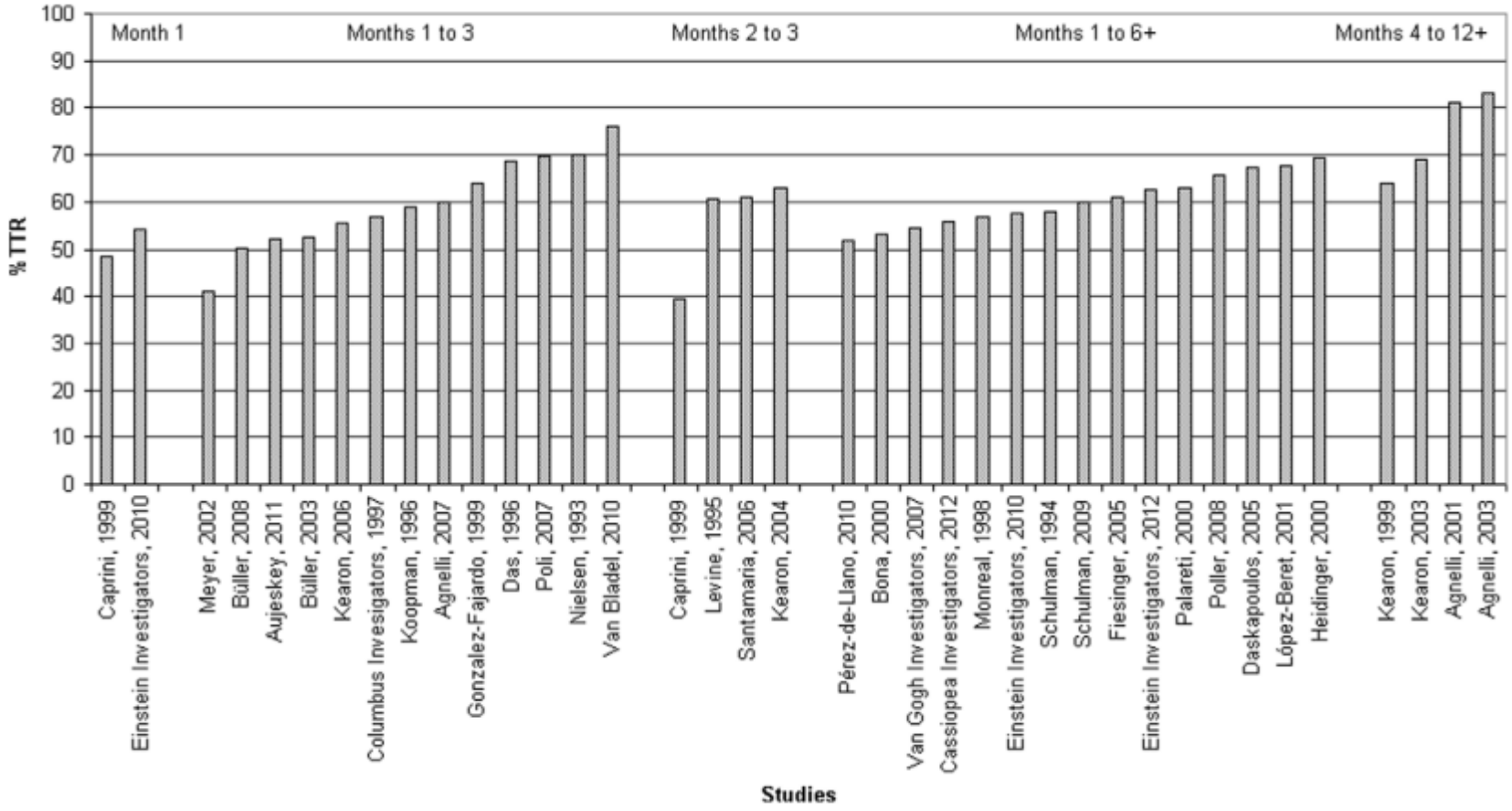
Risk factors for bleeding with anticoagulation therapy in VTE

Age> 65 y	Cancer	Anti-platelet therapy
Age >75y	Metastatic cancer	Poor anticoagulant control
Previous bleeding	Renal failure	Recent surgery
Comorbidity and reduced functional capacity	Thrombocytopenia	Frequent falls
Previous stroke	Anemia	Alcohol abuse
Diabetes		

0 risk factor : low risk
1 risk factor- moderate risk
2 risk factors: High risk

Chest 2012;141 :e419-e494

Time in Therapeutic Range in VTE treated with warfarin



Erken PMG, et al. PLoS One. 2012; 7(9): e42269

Bleeding and mortality : INR variability and iTTR

Quartiles	1	2	3	4
Bleeding total				
iTTR	Ref	1.41 (1.11–1.78)	2.56 (2.06–3.19)	4.03 (3.20–5.08)
Variability	Ref	1.25 (0.98–1.60)	2.06 (1.63–2.61)	3.80 (3.01–4.79)
Death				
iTTR	Ref	1.65 (1.28–2.13)	2.43 (1.90–3.11)	5.54 (4.36–7.04)
Variability	Ref	0.98 (0.76–1.26)	1.66 (1.31–2.11)	3.45 (2.75–4.33)

iTTR, individual time in therapeutic range; Ref, reference. For iTTR, the quartiles are: 1 (> 84%), 2 (73%-84%), 3 (57%-73%), 4 (≤ 57%). For INR variability, the quartiles are: 1 (≤ 0.66), 2 (0.66–0.85), 3 (0.85–1.05), 4 (>1.05).

Sanden P, et al.Thromb Haemost. 2017 Jan 5;117(1):27–32

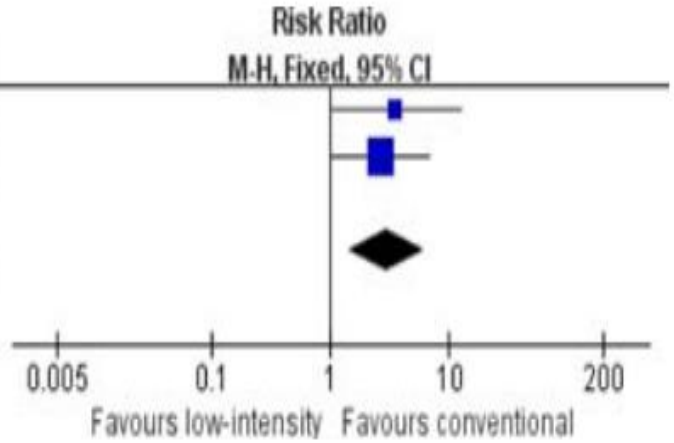
Low vs conventional intensity warfarin

Risk of VTE: RR 2.96 ↑

Study or Subgroup	Low-intensity Events	Low-intensity Total	Conventional-intensity Events	Conventional-intensity Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Clive Kearon 2003	11	337	3	324	33.8%	3.53 [0.99, 12.52]
Clive Kearon 2008	16	369	6	369	66.2%	2.67 [1.06, 6.74]
Total (95% CI)		**706**		**693**	**100.0%**	**2.96 [1.40, 6.24]**
Total events	27		9			

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%

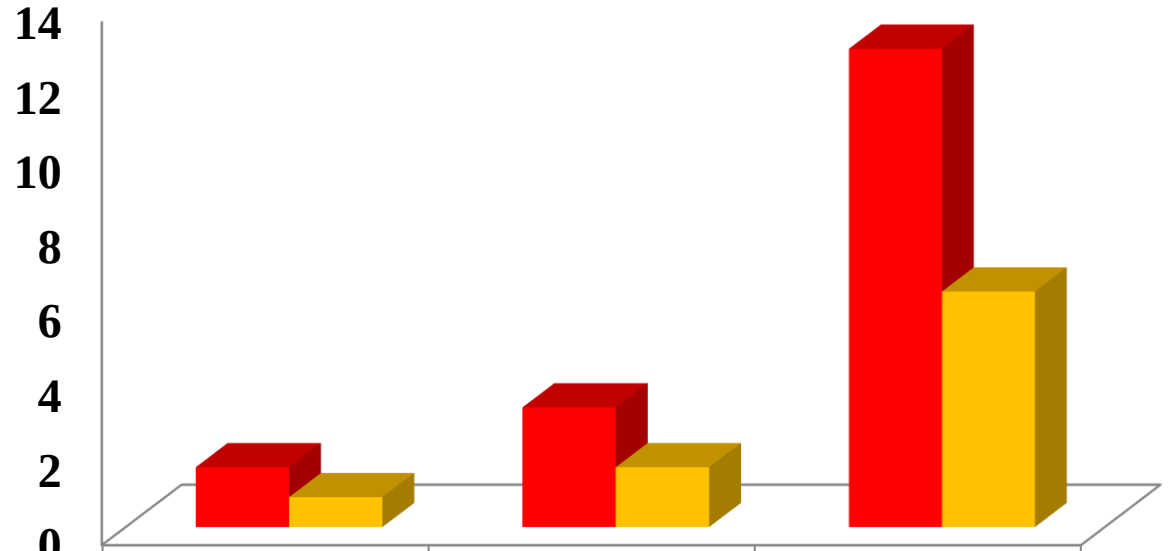
Test for overall effect: Z = 2.84 (P = 0.004)



There was no significant difference in the frequency of overall bleeding between the 2 groups (HR, 1.3; 95% CI, 0.8 to 2.1)

Jiang R, et al.Clin Respir J. 2018;12(7):2170-2177

Estimated absolute risk of major bleeding



	Low risk	Moderate risk	High risk
Anticoagulation 0-3 mo	1.6	3.2	12.8
anticoagulation after first3 mo	0.8	1.6	6.3

Chest 2012;141 :e419-e494

Bleeding risk score model in VTE

The IMPROVE score

Age		
≥85 yrs	○	3.5 Points
40-84 yrs	○	1.5 Points
<40 yrs	○	0 Points
Gender		
Male	○	1 Point
Female	○	0 Points
Renal Function		
Normal Renal Function [GFR ≥60 ml/min/m^2	○	0 Points
Moderate Renal Failure [GFR 30-59 ml/min/m^2	○	1 Point
Severe Renal Failure [GFR <30 ml/min/m^2	○	2.5 Points
Liver Function		
Normal Liver Function [INR ≤ 1.5]	○	0 Points
Liver Failure [INR > 1.5]	○	2.5 Points
Platelet Count		
≥50 x 10^9/L	○	0 Points
<50 x 10^9/L	○	4 Points
Admission to ICU or CCU		
	○	2.5 Points
Central Venous Catheter		
	○	2 Points
Active Gastric or Duodenal Ulcer		
	○	4.5 Points
Prior Bleeding within previous 3 months		
	○	4 Points
Rheumatic Disease		
	○	2 Points
Active Malignancy		
	○	2 Points

<7	**Not at increased risk of bleeding**
≥7	**Increased risk of bleeding**

The VTE-BLEED score

Active Cancer		
○	Yes	2 Points
Male Patient with Uncontrolled Hypertension [Systolic BP ≥140mm Hg]		
○	Yes	1 Point
Anaemia [Hb <130g/L Men. Hb <120g/L Women]		
○	Yes	1.5 Points
History of Bleeding [Major or non-major clinically relevant bleeding]		
○	Yes	1.5 Points
Renal Dysfunction [CrCl 30-60ml/min]		
○	Yes	1.5 Points
Age ≥60 yrs		
○	Yes	1.5 Points

<2	Low bleeding risk
≥2	High bleeding risk

Decousus H, et al. Chest. 2011; 139: 69-79.

Klok FA, et al. Eur Respir J. 2016; 48: 1369-76

Contraindications to therapeutic anticoagulation : ASCO 2020 guideline

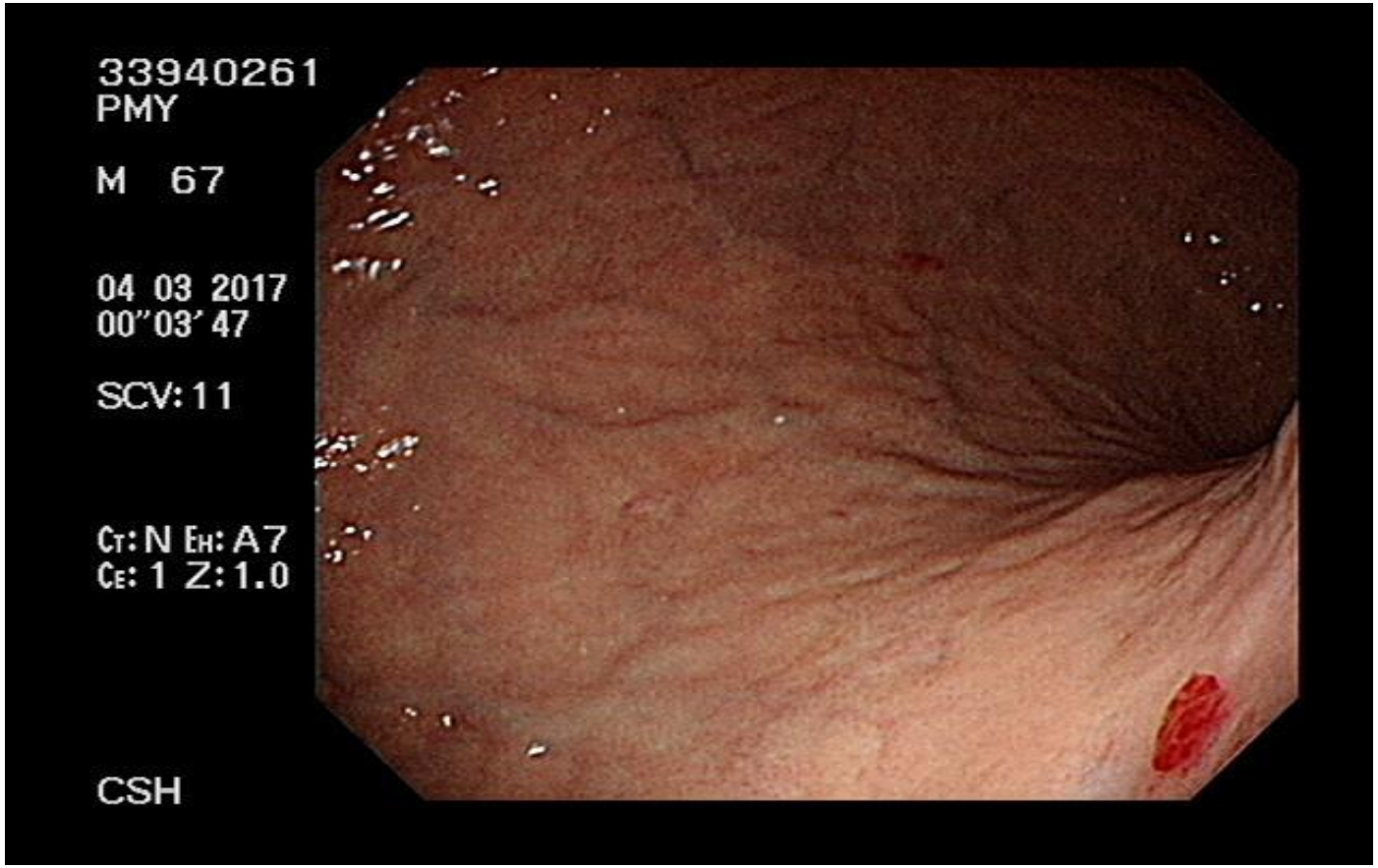
Absolute	Relative
- **Active major, serious, or potentially life-threatening bleeding not reversible with medical or surgical intervention** - Severe, uncontrolled malignant hypertension - **Severe, uncompensated coagulopathy (e.g., liver failure)** - Severe platelet dysfunction or inherited bleeding disorder - **Persistent, severe thrombocytopenia (, 20,000/mL)** - **High-risk invasive procedure in a critical site**	- **Intracranial or spinal lesion at high risk for bleeding** - Active GI ulceration at high risk of bleeding - **Active but non–life-threatening bleeding** (e.g., trace hematuria) - **Intracranial or CNS bleeding within past 4 weeks** - **Recent high-risk surgery or bleeding event** - **Persistent thrombocytopenia (, 50,000/mL)**

Key NS, et al. J Clin Oncol. 2020;38(5):496–520.

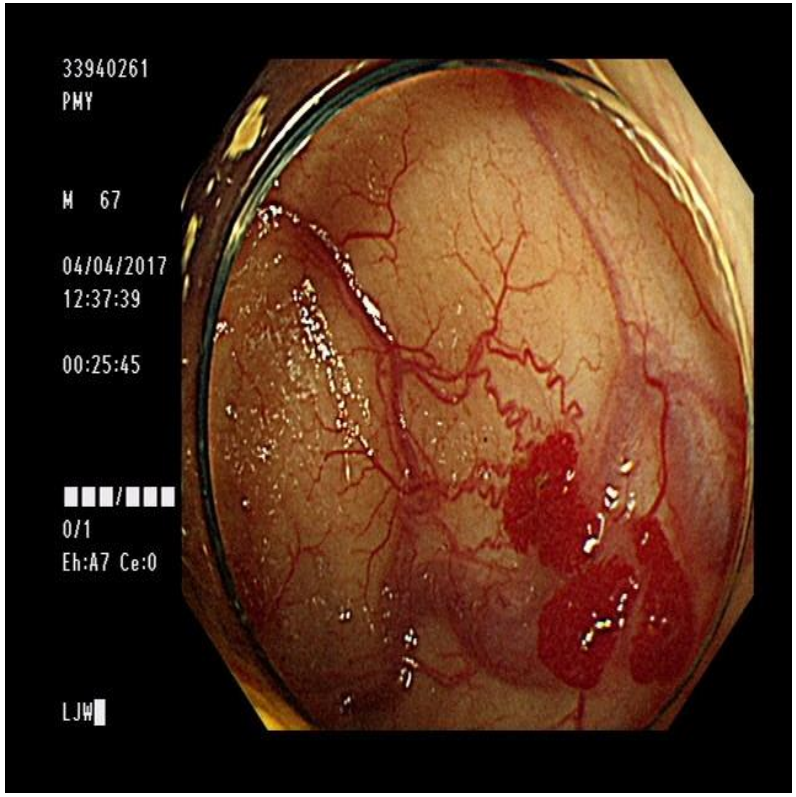
Case 2. (67/M)

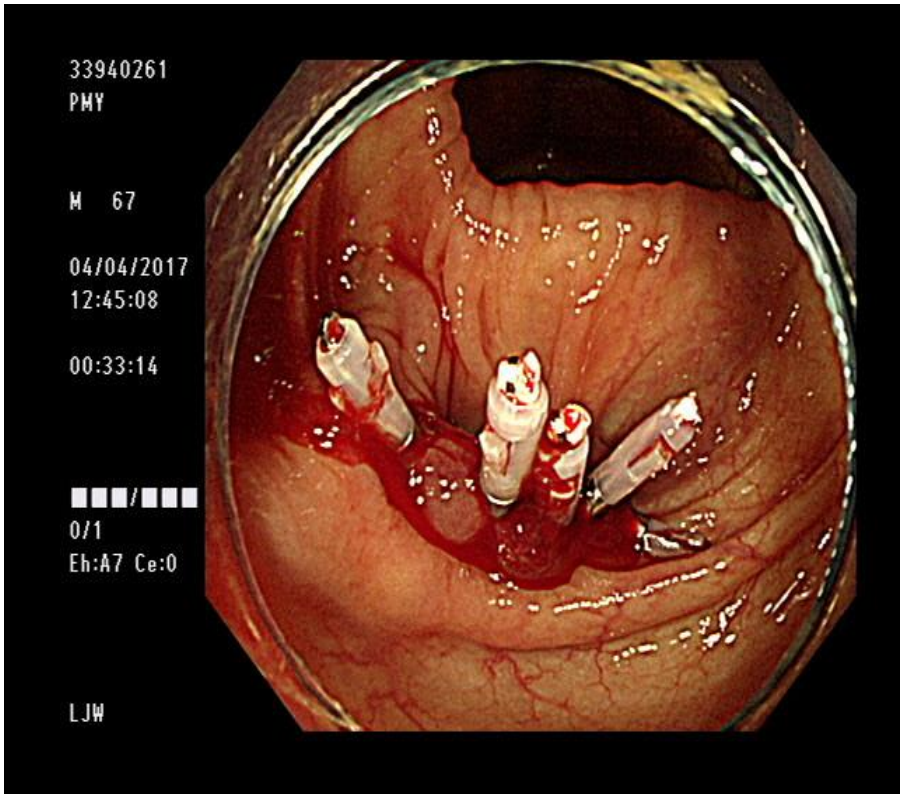
- **1달전 Unprovoked PTE 진단 rivaroxaban 복용 중 melena로 내원**
- **BP 93/68 mmHg PR 166/m, RR 20/m**
- **Hb 6.8 (←10.4) g/dL**

Gastroscopy



Colonoscopy



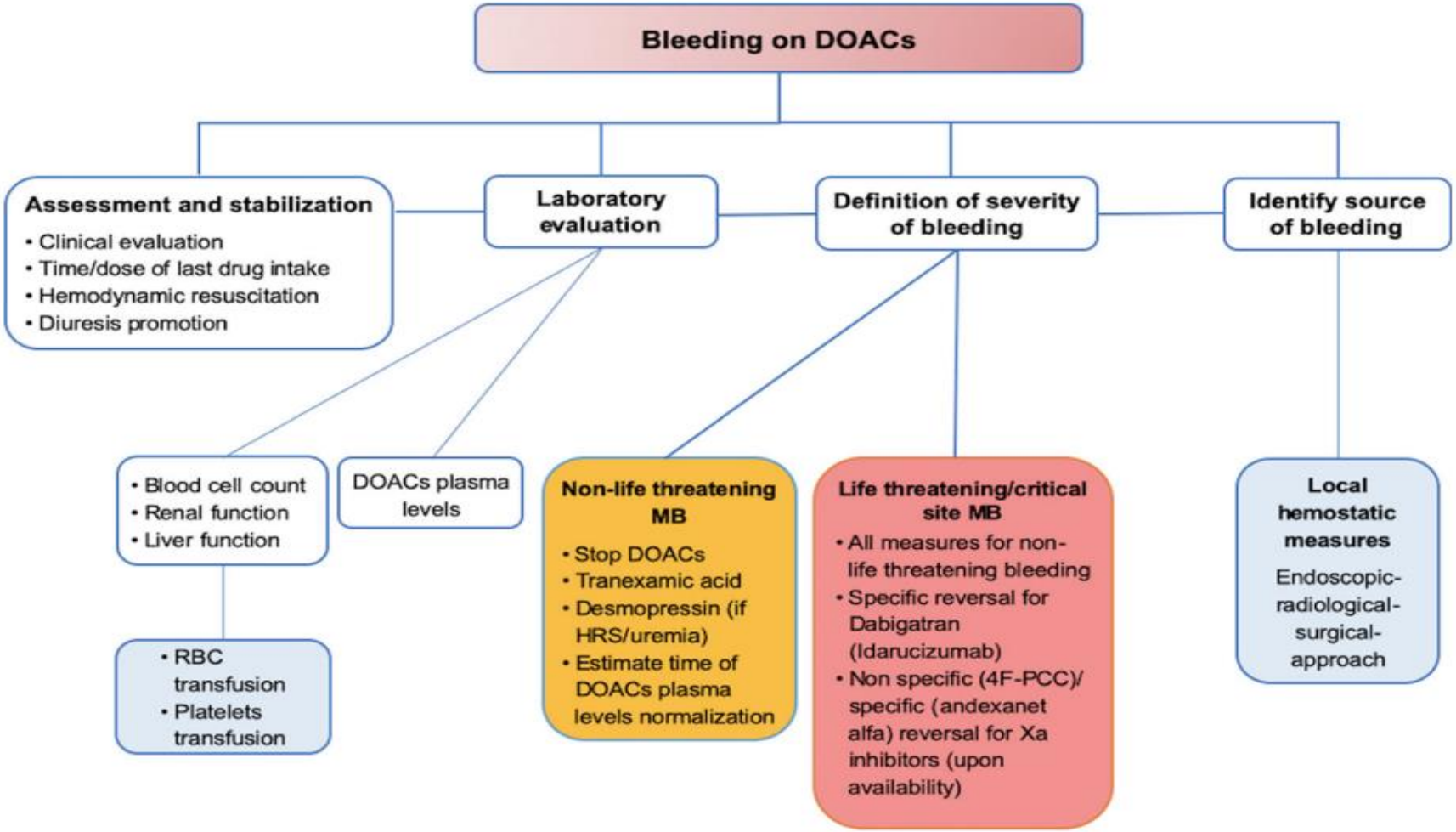


Lower GI bleeding d/t ascending colon angiodysplasia

-> Hemoclipping

Rivaroxaban 20mg qd -> apixaban 5mg bid

Management of bleeding complications on DOACs



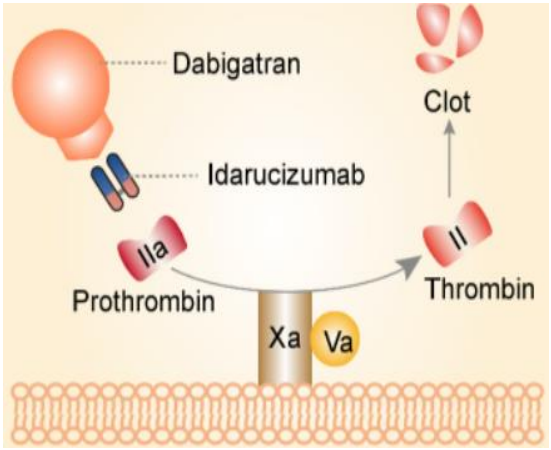
Ballestri S, et al. Adv Ther. 2022;16;1–26.

Idarucizumab

- **Humanized monoclonal antibody**, binding both unbound dabigatran and thrombin-bound dabigatran
  → promptly neutralizing anticoagulant activity

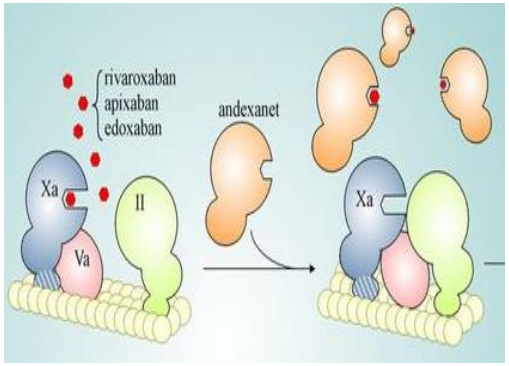
- 2 bolus each of 2.5g, 10-15min apart.

- Approved by the U.S. FDA and the EMA

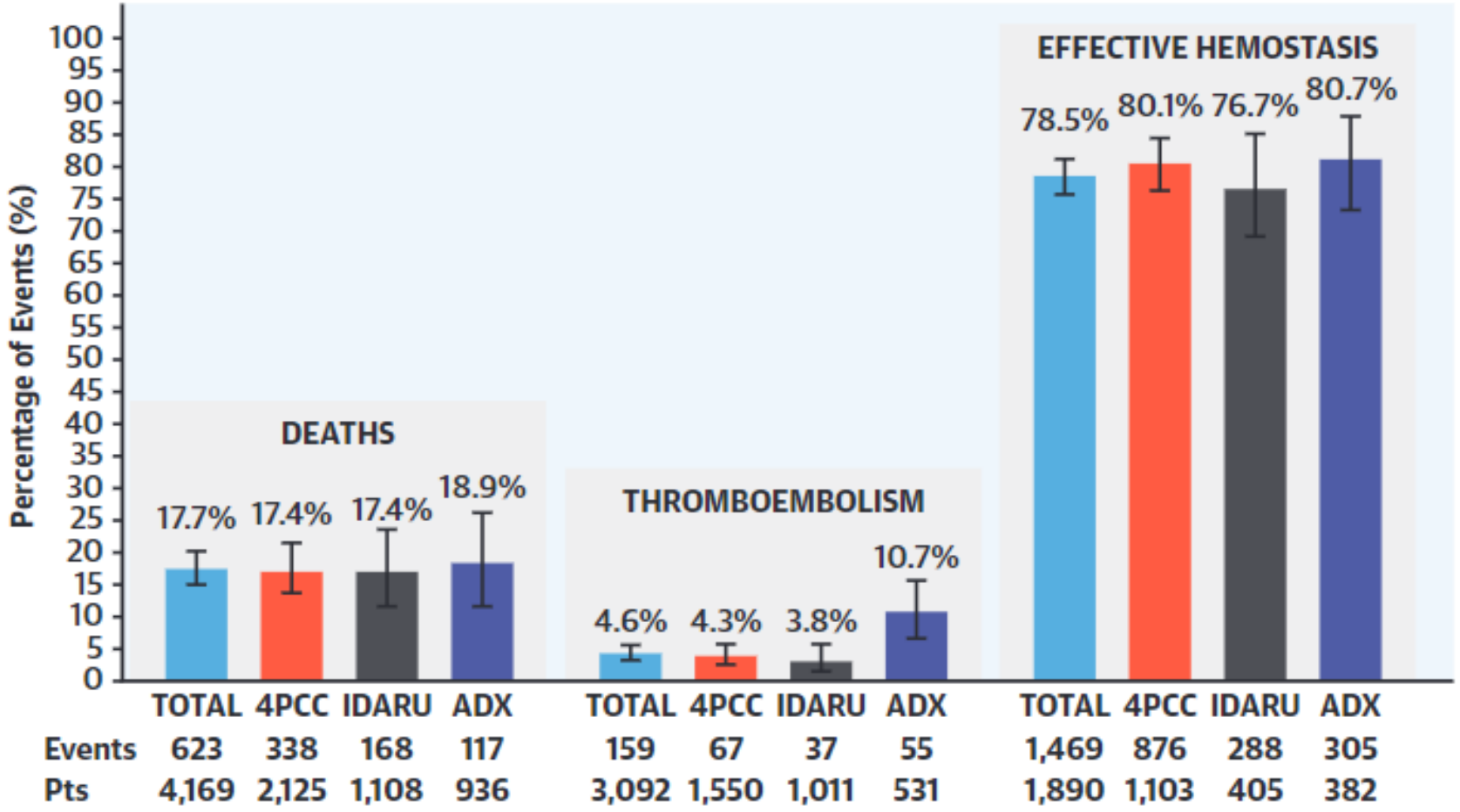


Andexanet alfa

- Recombinant protein with high affinity binding to FXa inhibitors
- Rivaroxaban & Apixaban : effective
- 7hrs ↑: 400mg bolus over 15-30mins → 480mg infusion over 2hrs
- 7hrs ↓ or unknown : 800mg bolus over 15-30mins → 960mg infusion over 2hrs



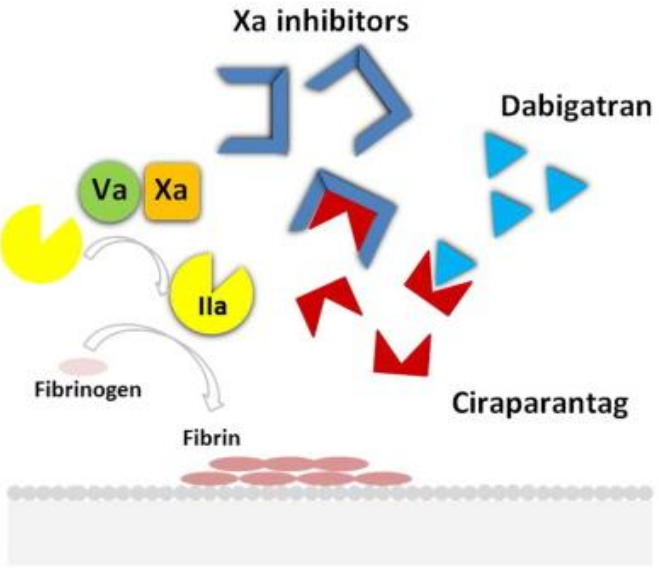
Meta-Analysis of Reversal Agents for Severe Bleeding Associated With DOACs



Gómez-Outes, A. et al. J Am Coll Cardiol. 2021;77(24):2987-3001.

Ciraparantag: universal antidote

- a synthetic, small, cationic, water-soluble molecule
- Binding : **FXa, FIIa, LMWH, fondaparinux uFH**
- **VKA : No binding → No effect**



Phase 1 and 2 trials show very fast onset of action without procoagulant effect and no known drug-drug interactions.

Risk of bleeding with DOACs versus warfarin in RCT

	Dabigatran RE-COVER (150 mg) [17]	Rivaroxaban EINSTEIN DVT-PE [18–20]	Apixaban AMPLIFY [21]	Edoxaban Hokusai-VTE [22]
Recurrent VTE	=	=	=	=
MB or CRNMB	↓	=	↓	↓
MB	=	↓	↓	=
ICH	↓*	↓*	↓*	↓*
MGIB	↑*	=*	↓*	=*

Ballestri S, et al. Adv Ther. 2022;16;1–26.

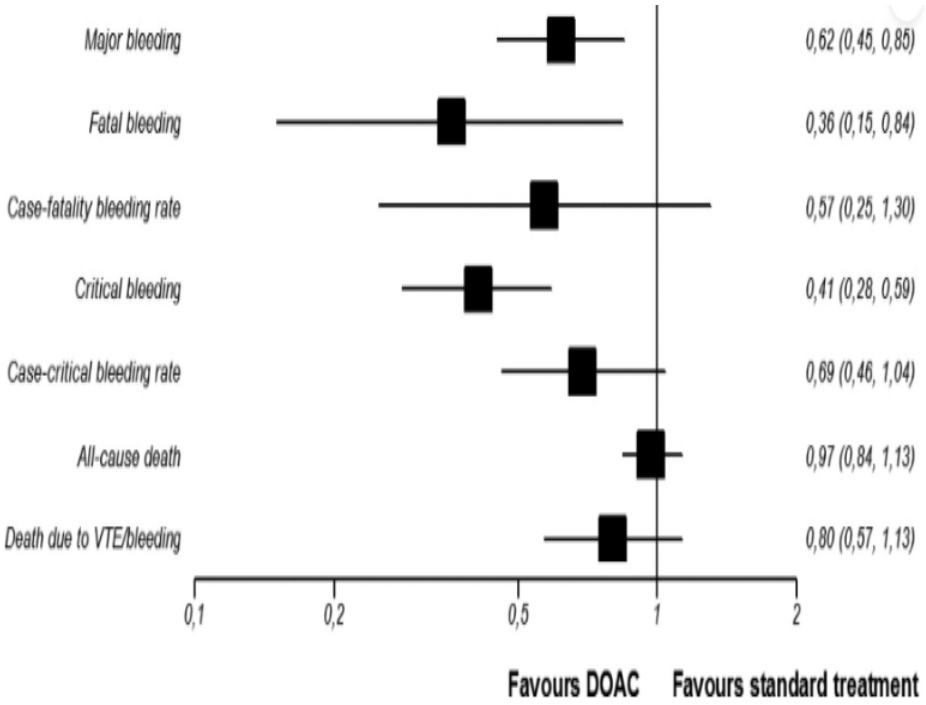
Risk of bleeding with DOACs versus warfarin in real-world data

	Dabigatran [23-25]	Rivaroxaban [23, 24, 26-28]	Apixaban [24, 28-31]	Edoxaban
Recurrent VTE	=	=	=↓	-
CRNMB	=	-	↓	-
MB	=	=	↓	-
ICH	-	↓	=↓	-
GIB	=	=	↓	-

Ballestri S, et. Adv Ther. 2022;16;1-26. al

Major and case fatality bleeding during initial treatment: DOAC vs warfarin

Meta-analysis of 6 RCT: RE-COVER I and II, EINSTEIN-DVT, EINSTEIN-PE, AMPLIFY, and HOKUSAI-VTE

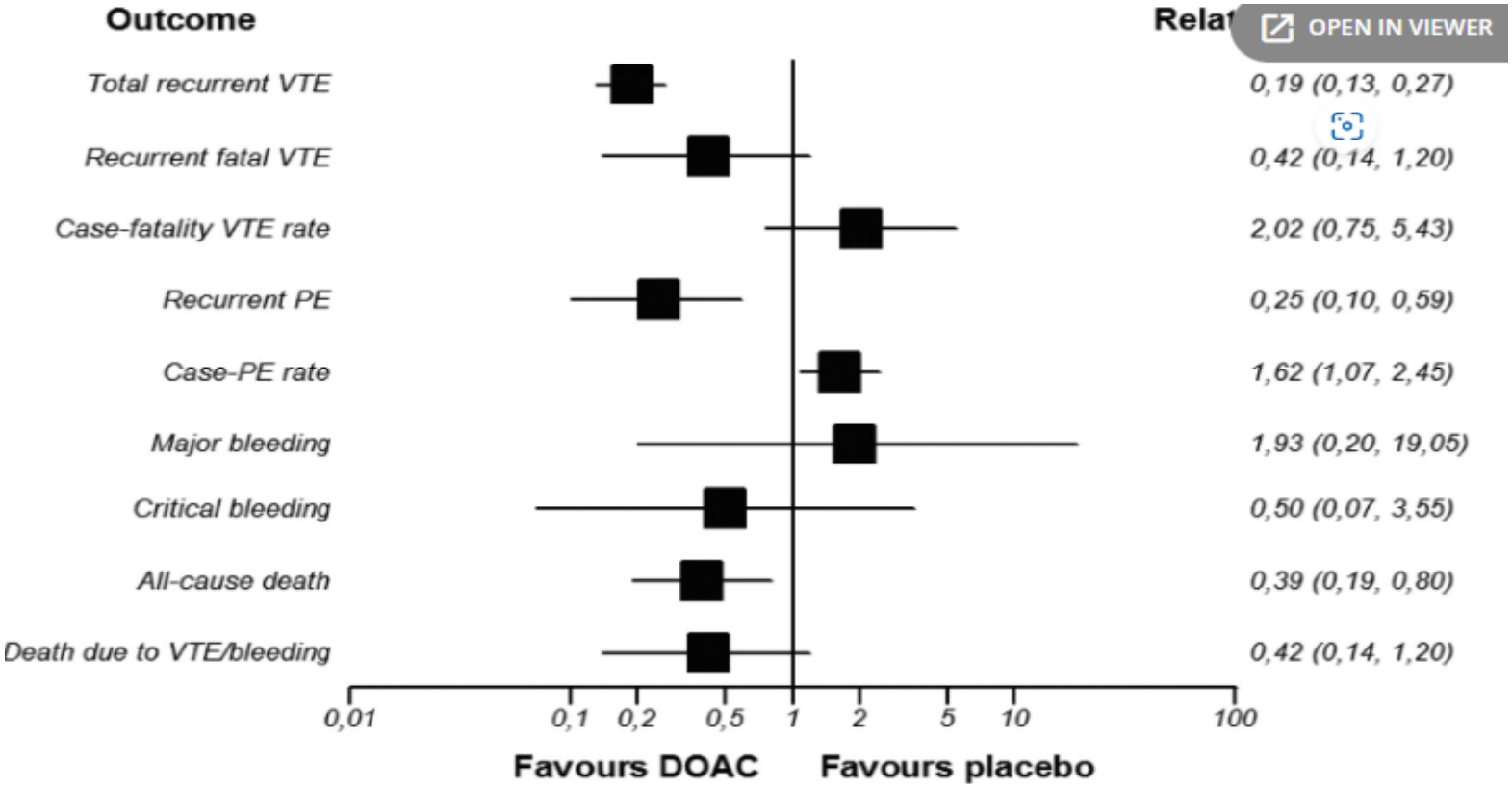


Total major bleeding (95%CI), events per 100 patient-years	1.8 (1.3-2.4)	3.1 (2.1-4.2)
Fatal bleeding (95%CI), events per 100 patient-years	0.1 (0.04-0.2)	0.3 (0.2-0.4)
Case fatality bleeding rate (95%CI), %	6 (3-10)	10 (5-16)
Critical bleeding (95%CI), events per 100 patient-years	0.5 (0.4-0.7)	1.24 (0.9-1.64)
Case critical bleeding rate (95%CI), %	29 (21-37)	42 (33-53)
All-cause death (95%CI), events per 100 patient-years	3.6 (3.2-4.0)	3.8 (3.3-4.4)
Death due to VTE/bleeding (95%CI), events per 100 patient-years	0.7 (0.6-0.9)	0.8 (0.6-1.2)

Wu C, et al. J Cardiovasc Pharmacol Ther. 2015;20(5):490–500.

Outcomes during extended therapy: DOAC vs placebo

- **EINSTEIN-Extension and AMPLIFY-EXT**



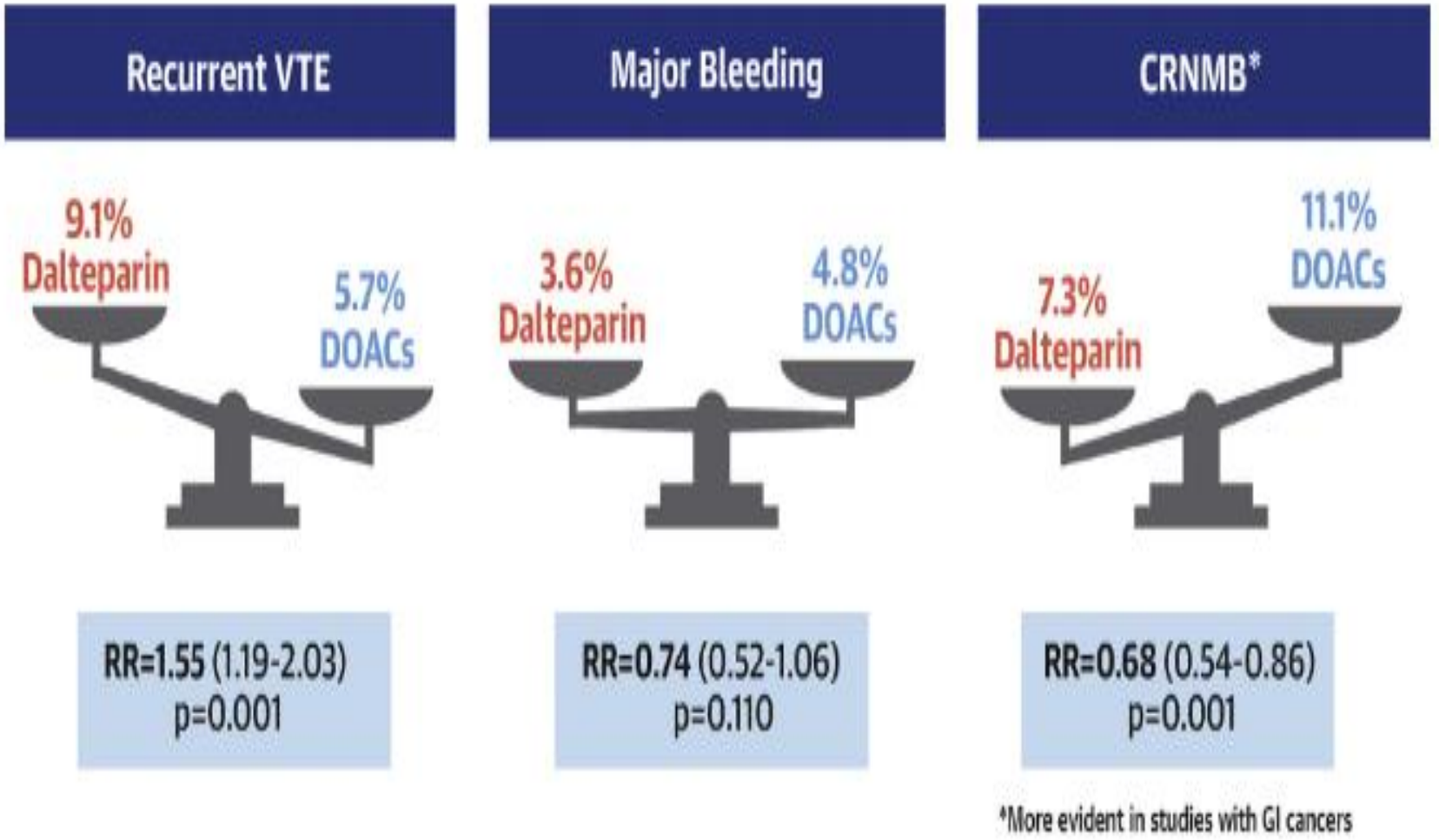
Wu C, et al. J Cardiovasc Pharmacol Ther. 2015;20(5):490–500.

Risk of bleeding of extended VTE treatment with DOACs

	Dabigatran		Rivaroxaban			Apixaban	
	RE-MEDY (versus VKA) [35]	RE-SONATE (versus placebo) [35]	EINSTEIN-EXT (versus placebo) [18]	EINSTEIN-CHOICE (versus ASA 100 mg) [36]		AMPLIFY-EXT (versus placebo) [37]	
	150 mg	150 mg	20 mg	20 mg	10 mg	5 mg	2.5 mg
Recurrent VTE	=	↓	↓	↓	↓	↓	↓
MB or CRNM	↓	↑	↑	=	=	=	=
MB	=	–	–	=	=	=	=
GIB	–	–	–	–	–	–	–
ICH	–	–	–	–	–	–	–

Ballestri S, et al. Adv Ther. 2022;16;1–26.

DOAC vs LMWH in patients with cancer-VTE



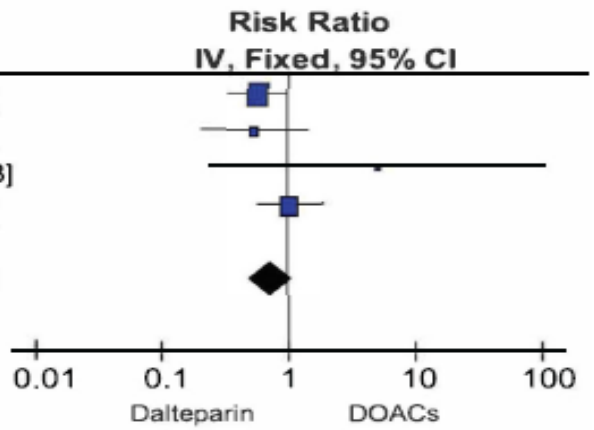
Sabatino, J. et al. J Am Coll Cardiol CardioOnc. 2020;2(3):428–40

DOAC vs LMWH in patients with cancer-VTE

A **Major bleeding**

Study	Dalteparin Events	Dalteparin Total	DOACs Events	DOACs Total	P value	Risk Ratio
Hokusai VTE	21	524	36	522	0.043	0.58 [0.34, 0.98]
Cancer SELECT-D	6	203	11	203	0.223	0.55 [0.21, 1.45]
ADAM VTE	2	150	0	150	0.298	5.00 [0.24, 103.28]
CARAVAGGIO	23	579	22	576	0.893	1.04 [0.59, 1.84]
Total (95% CI)	**52**	**1,456**	**69**	**1,451**	**0.110**	**0.74 [0.52, 1.06]**

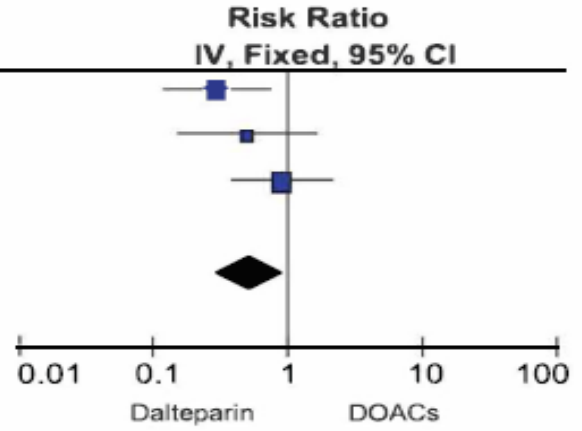
Heterogeneity: Chi² = 4.08, df = 3 (P = 0.253); I² = 26%



B **Gastrointestinal bleeding**

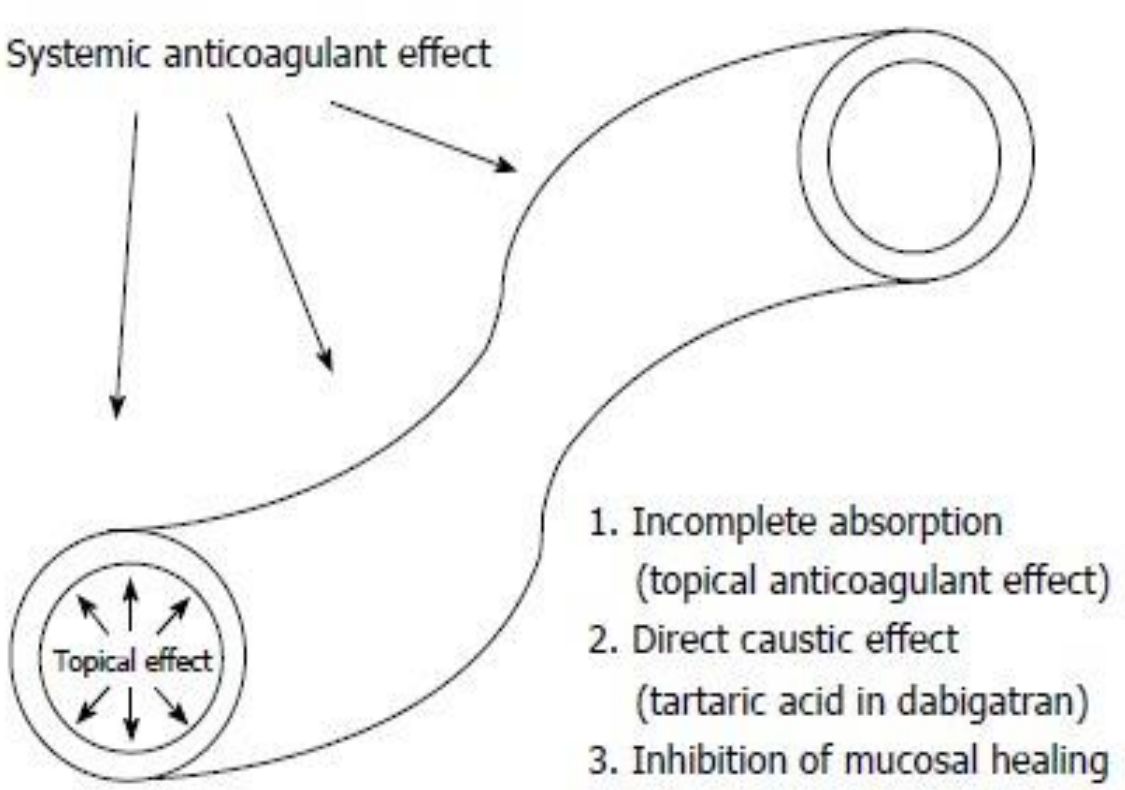
Study	Dalteparin Events	Dalteparin Total	DOACs Events	DOACs Total	P value	Risk Ratio
Hokusai VTE Cancer	6	524	20	522	0.009	0.30 [0.12, 0.74]
SELECT D	4	203	8	203	0.251	0.50 [0.15, 1.63]
CARAVAGGIO	10	579	11	576	0.816	0.90 [0.39, 2.11]
Total (95% CI)	**20**	**1,306**	**39**	**1,301**	**0.020**	**0.53 [0.31, 0.92]**

Heterogeneity: Chi² = 3.07, df = 2 (P = 0.21); I² = 35%



Sabatino, J. et al. J Am Coll Cardiol CardioOnc. 2020;2(3):428–40

Mechanisms of DOACs-related GI Bleeding



Warfarin, rivaroxaban
Upper GI

Dabigatran
Lower GI

Why rivaroxaban causes more bleeding ?

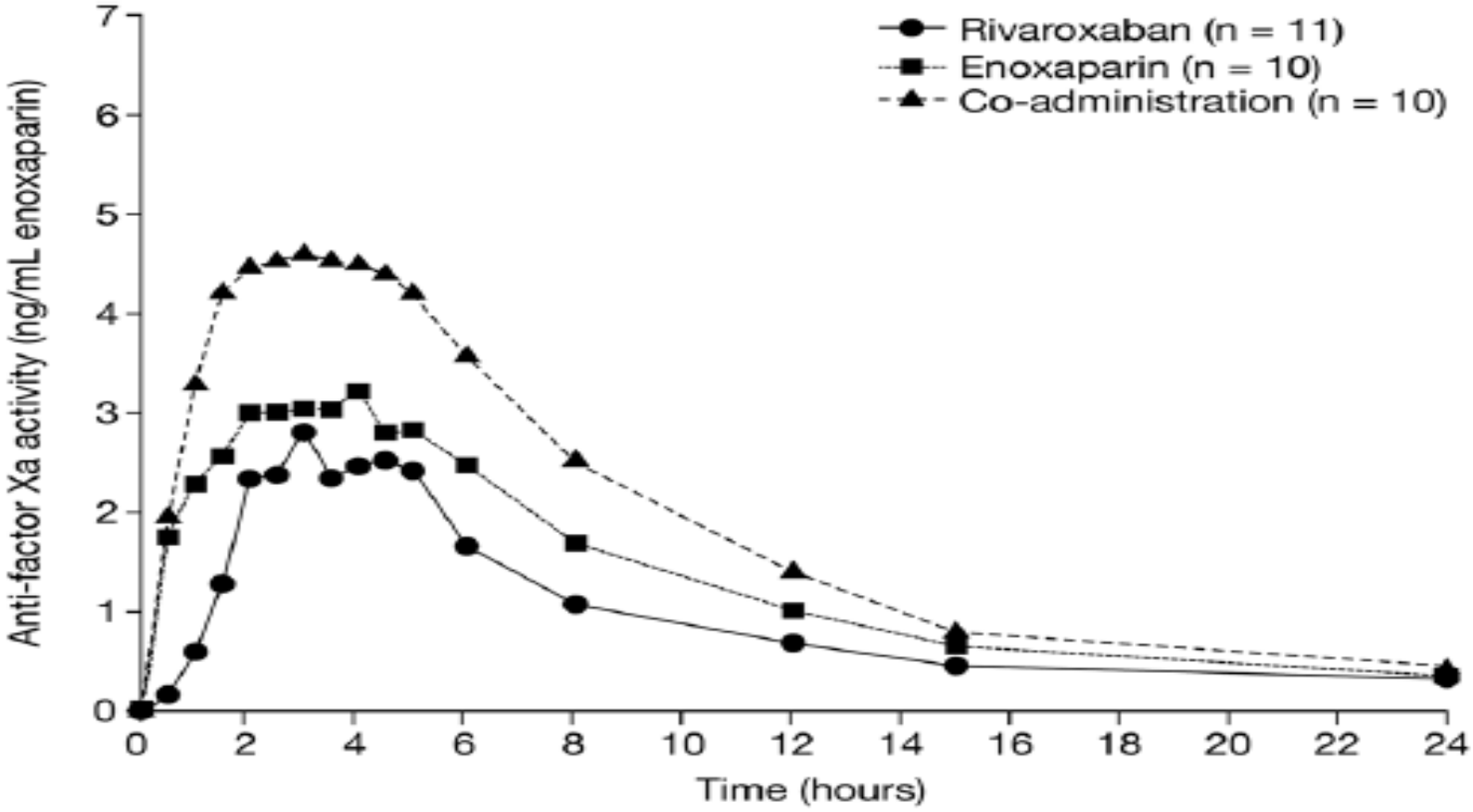
Both rivaroxaban and apixaban are factor Xa inhibitors, administered in active form, and have similar bioavailability. However, these two agents differ in the risk of GIB, **which may be related to the higher peak level of once-daily dosing of rivaroxaban than the twice-daily dosing of apixaban**.

Similarly, the once-daily dosing of rivaroxaban may also account for the higher GIB risk observed in the head-to-head study of rivaroxaban and dabigatran.

PK/PD of DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Anti-thrombin	Anti-factor Xa	Anti-factor Xa	Anti-factor Xa
Bioavailability	7%	66%	50%	60%
Tmax (h)	1.5	2.5	3	1-5
T½ (h)	9-17	6-13	12	12
Dosing	b.i.d	once daily	b.i.d	once daily
Renal excretion	High	Moderate	Moderate	Moderate
Hepatic metabolism	Low	Moderate	Moderate	Moderate
Reversal agents	Idarucizumab[1]	Andexanet alfa	Andexanet alfa	Andexanet alfa
	Aripazine	Aripazine	Aripazine	Aripazine

Anti-factor Xa activity of rivaroxaban and enoxaparin



Kubitza D et al. Br J Clin Pharmacol 2010;70-703-712

PK/PD of apixaban and rivaroxaban

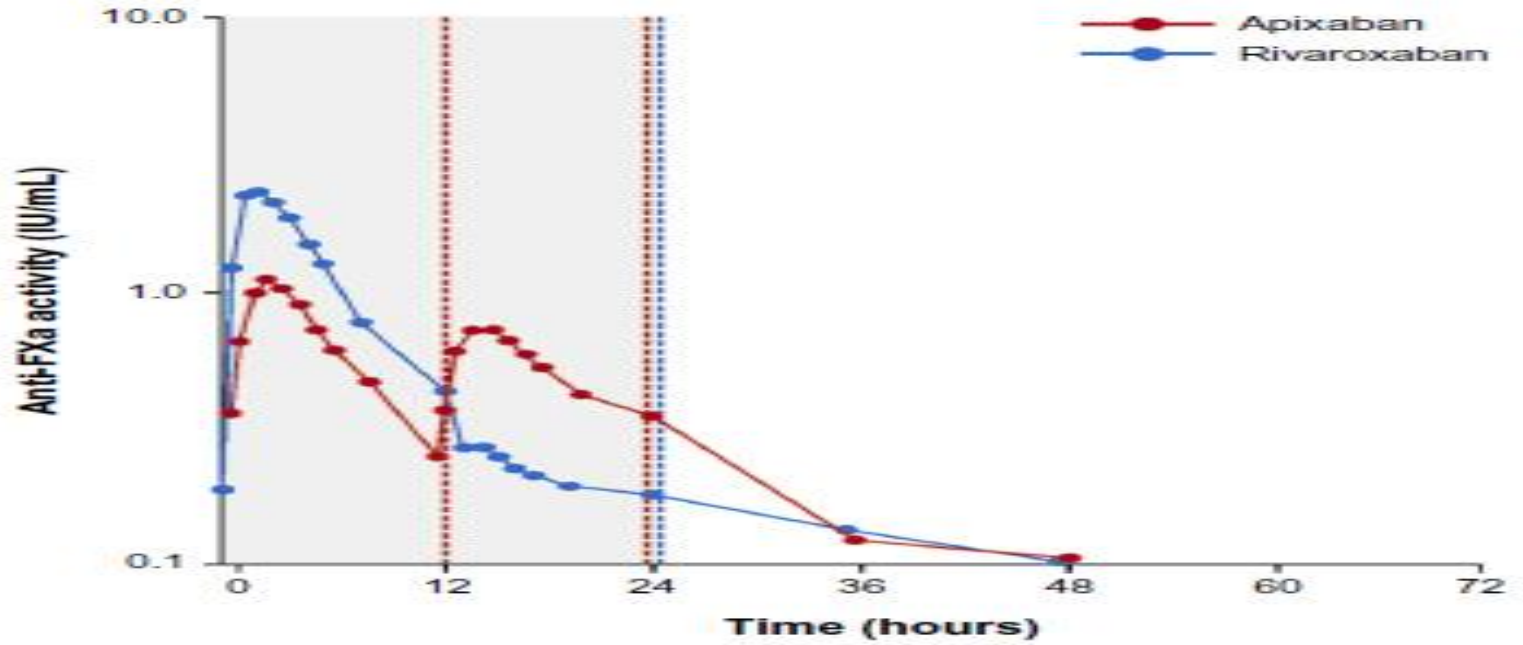


Table 3 Summary statistics: steady state anti-FXa activity of rivaroxaban and apixaban

N=14	Peak (IU/mL) G mean (CV)	Trough (IU/mL) G mean (CV)	Peak:trough G mean (CV)	T_{peak} (h) median (min–max)	$AUC_{(0-12)}$ (IU·h/mL) G mean (CV)	$AUC_{(0-24)}$ (IU·h/mL) G mean (CV)	$T_{1/2}$ (h) Mean (SD)
Rivaroxaban 10 mg QD (0–24 h)	2.82 (51)	0.170* (32)	16.5* (57.4)	2.00 (1.00–3.00)		17.8 (29)	NE#
Apixaban 2.5 mg BID (0–12 h)	1.12 (21)	0.240 (22)	4.7 (19.5)	2.00 (1.00–3.00)	7.42 (21)	13.3 (22)	8.91 (2.46)‡

Frost C. et al. Clin Pharmacol. 2014

Case 3. (61/M)

Chief complaint :abdominal pain

Present illness :

내원 4일전부터의 abdominal pain으로 외부병원에서 초음파 시행하여
Acute cholecystitis with stone 으로 소화기내과 입원하여 biliary CT시행
-> **asymptomatic PE** 발견되어 호흡기내과 의뢰

P. M. Hx: (-)

P/Ex.: **BP 107/72 mmHg PR 94 /m RR 18/m**

Initial Laboratory data

CBC WBC 4500 /mm3 , Hb 15.7 g/dL , PLT 126×10^3/mm3

Coagulation battery PT 11.1s (0.96 INR) aPTT 27.5 s

Chemical & electrolyte battery

Ca/P (mg/dL) 9.0/2.4 Glucose (mg/dL) 98

BUN/Cr (mg/dL) 23/0.9 Protein/albumin (mg/dL) 6.5/3.5

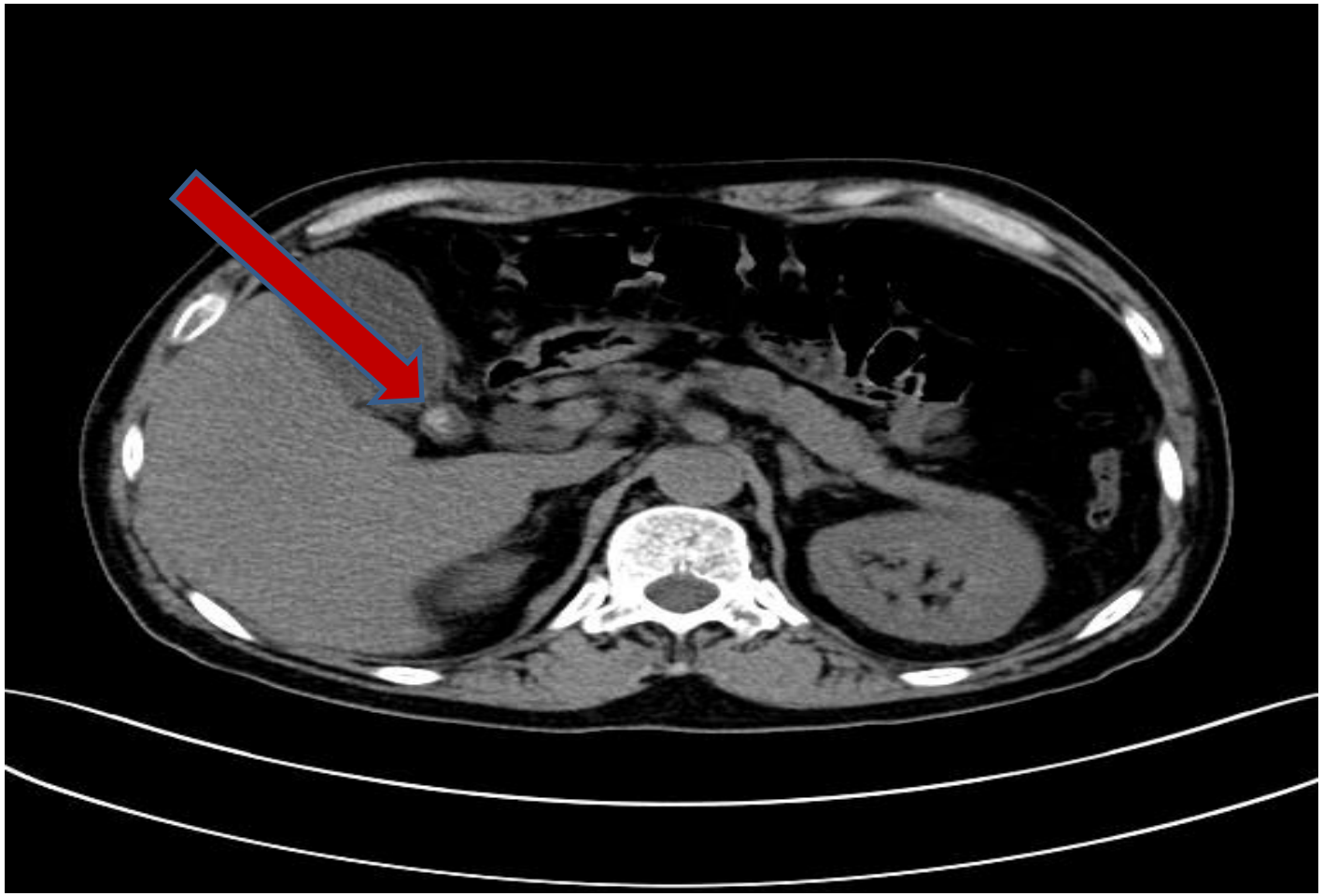
AST/ALT (IU/L) 45/88 **ALP/r-GT (IU/L) 87/361**

T.bil/D. Bil (mg/dl) 1.0/0.7 amylase/lipase U/L 60/90

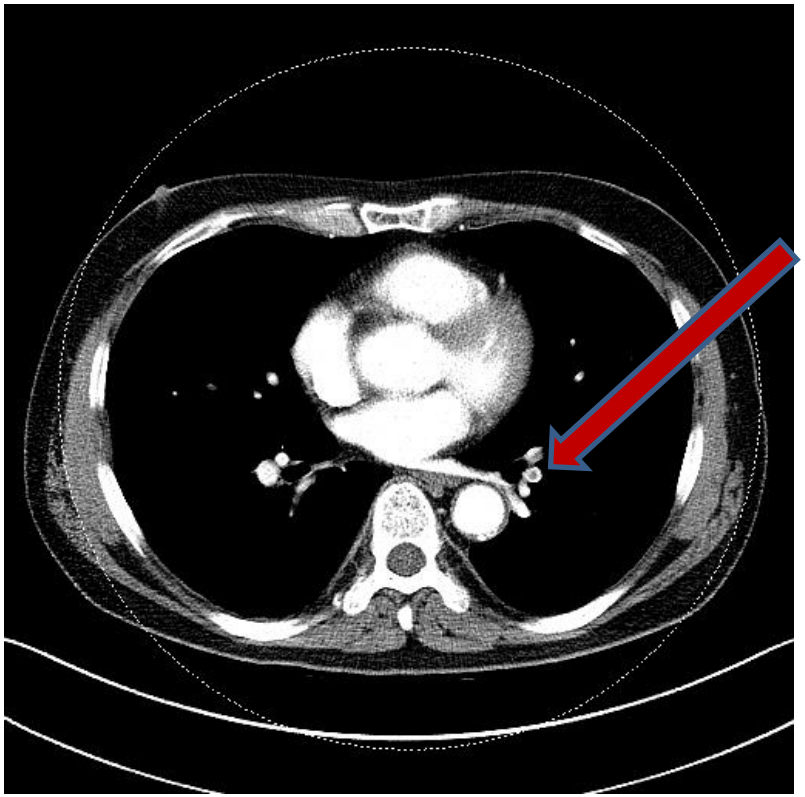
D-dimer 2.10 ug/mL

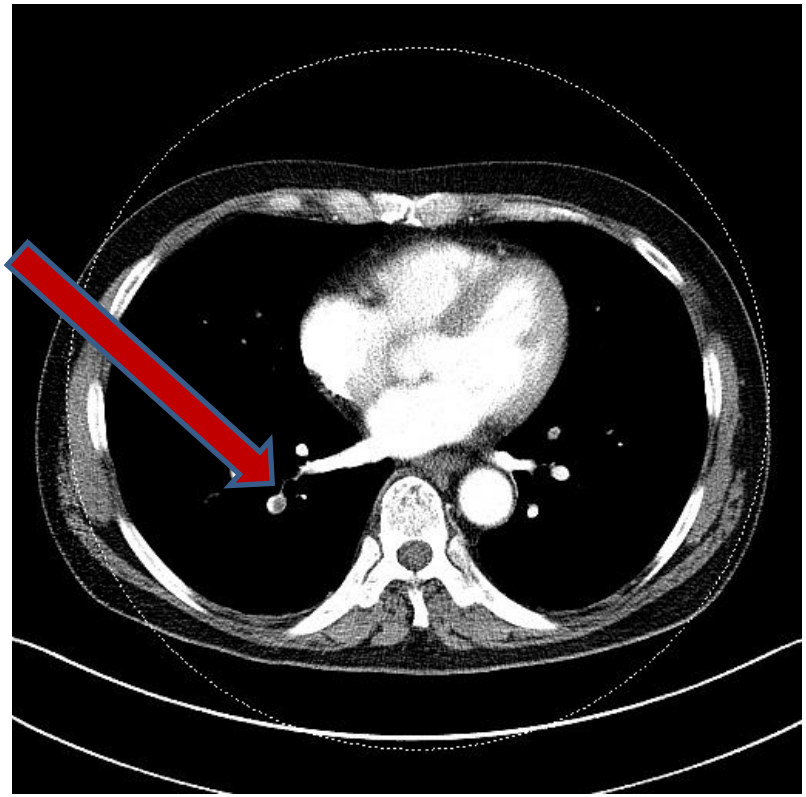
BNP 99 pg/mL **Tn-I 0.006 ng/mL CK-MB 0.2 ng/mL**

Abdomen CT: CBD stone



HD#2: Chest CT (2017.05.13)



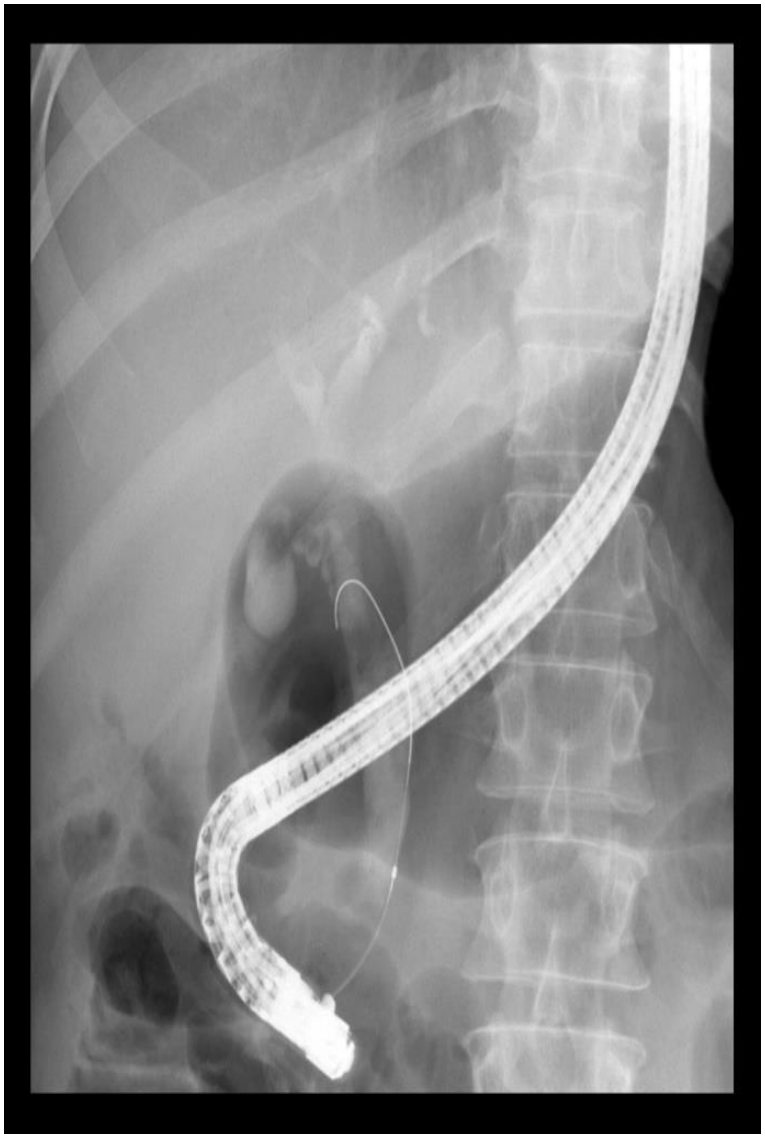


HD#3
UFH

HD#4:
ERCP & EST & stone removal

HD#5
Enoxaparin
1mg/kg bid SQ

HD#6
Apixaban 5mg bid



HD#6: Tubography

S: Sx (-)

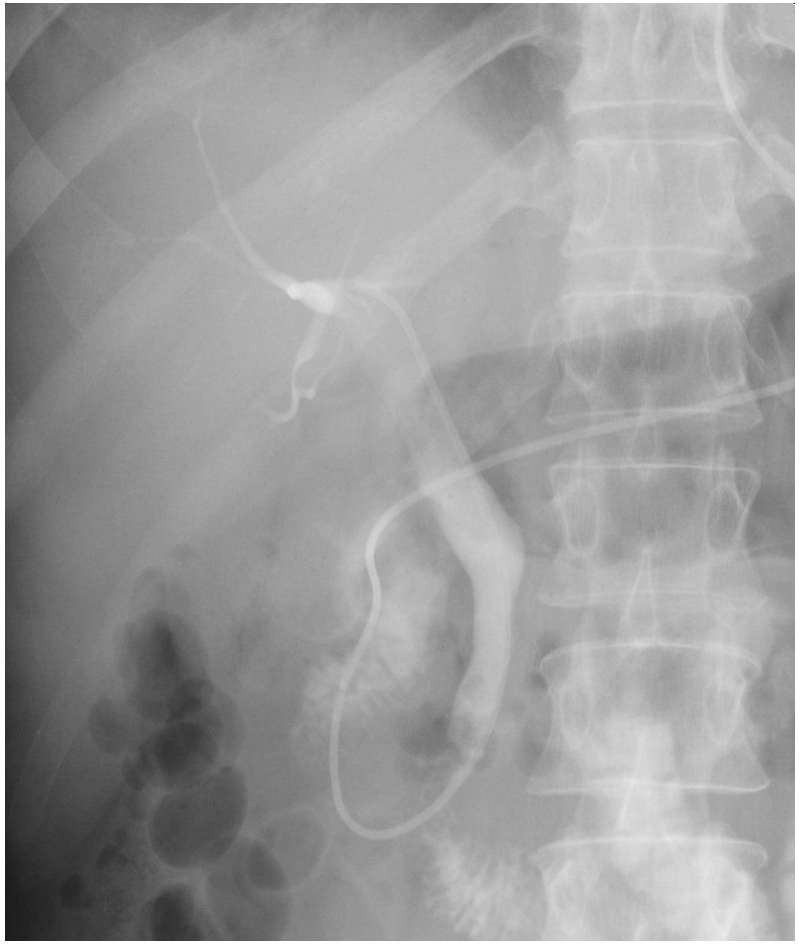
O: tubogram-

residual stone

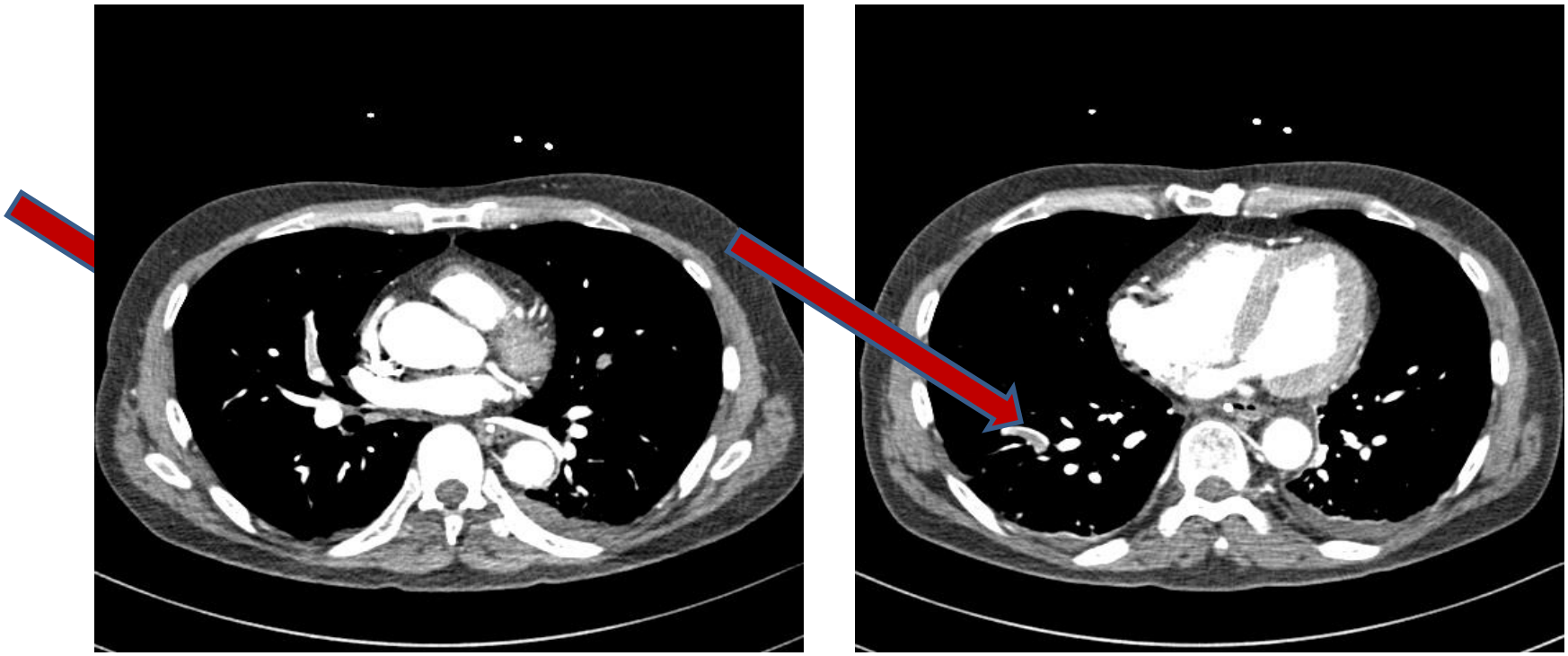
Management

: **ERCP 시행 위해**

apixaban 중단



HD#7: Lt. pleuritic chest pain



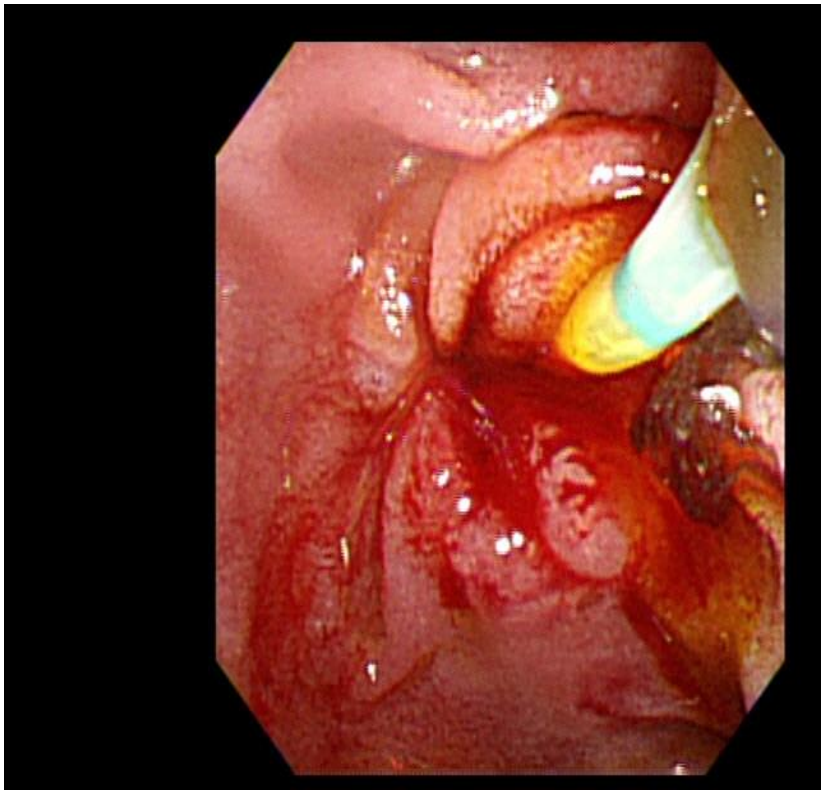
Newly developed filling defect in the right middle lobar artery.
Increased extent of filling defect in the lateral basal artery of RLL
Increased left pleural effusion

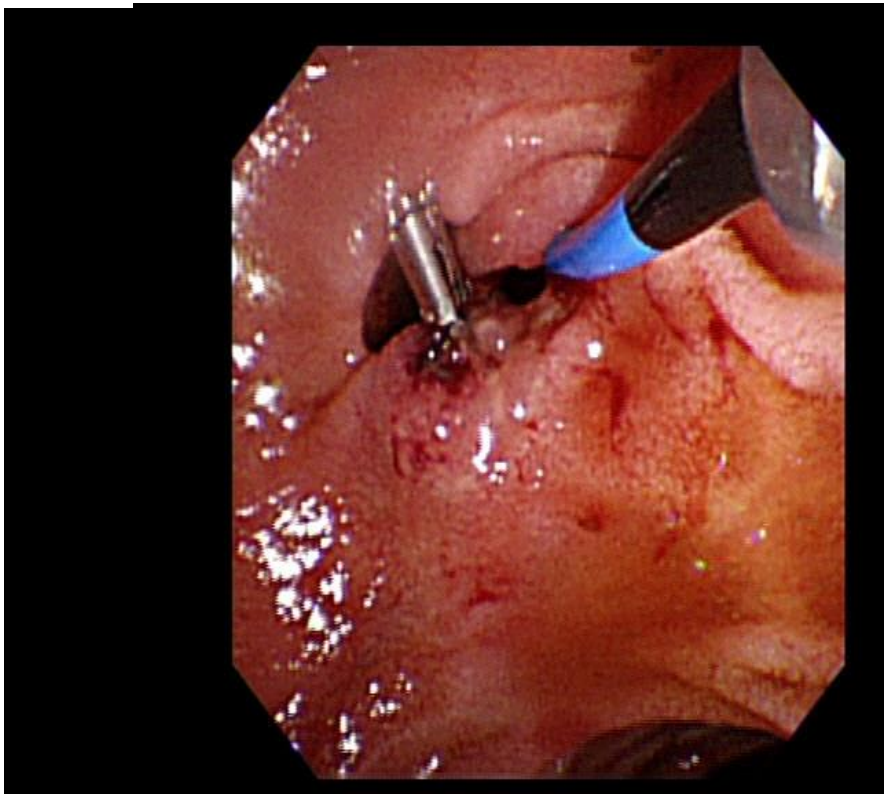
Management: Enoxaparin restart

HD#8: Hematochezia

Hb 14.3 -> 10.0 d/dL

EST site bleeding -> Clipping

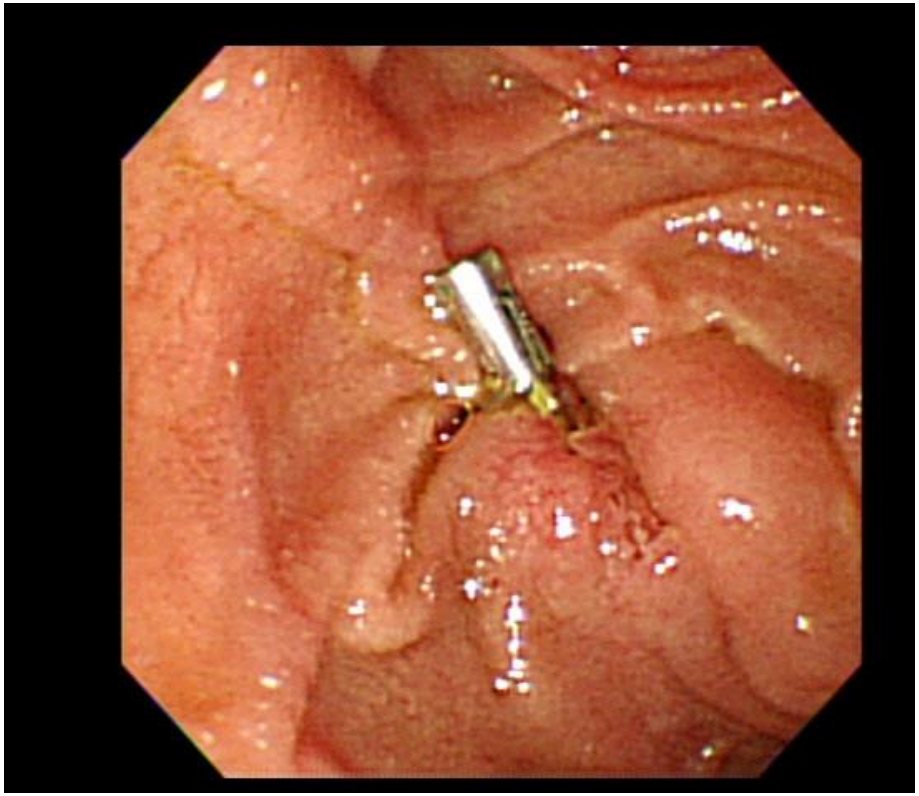




HD#11 f/u Gastroscopy

S: Sx (-)

O: Hb 10.4 g/dL



Management

: Enoxaparin 1일 투여

Apixaban 5mg bid 변경

2-month after apixaban treatment

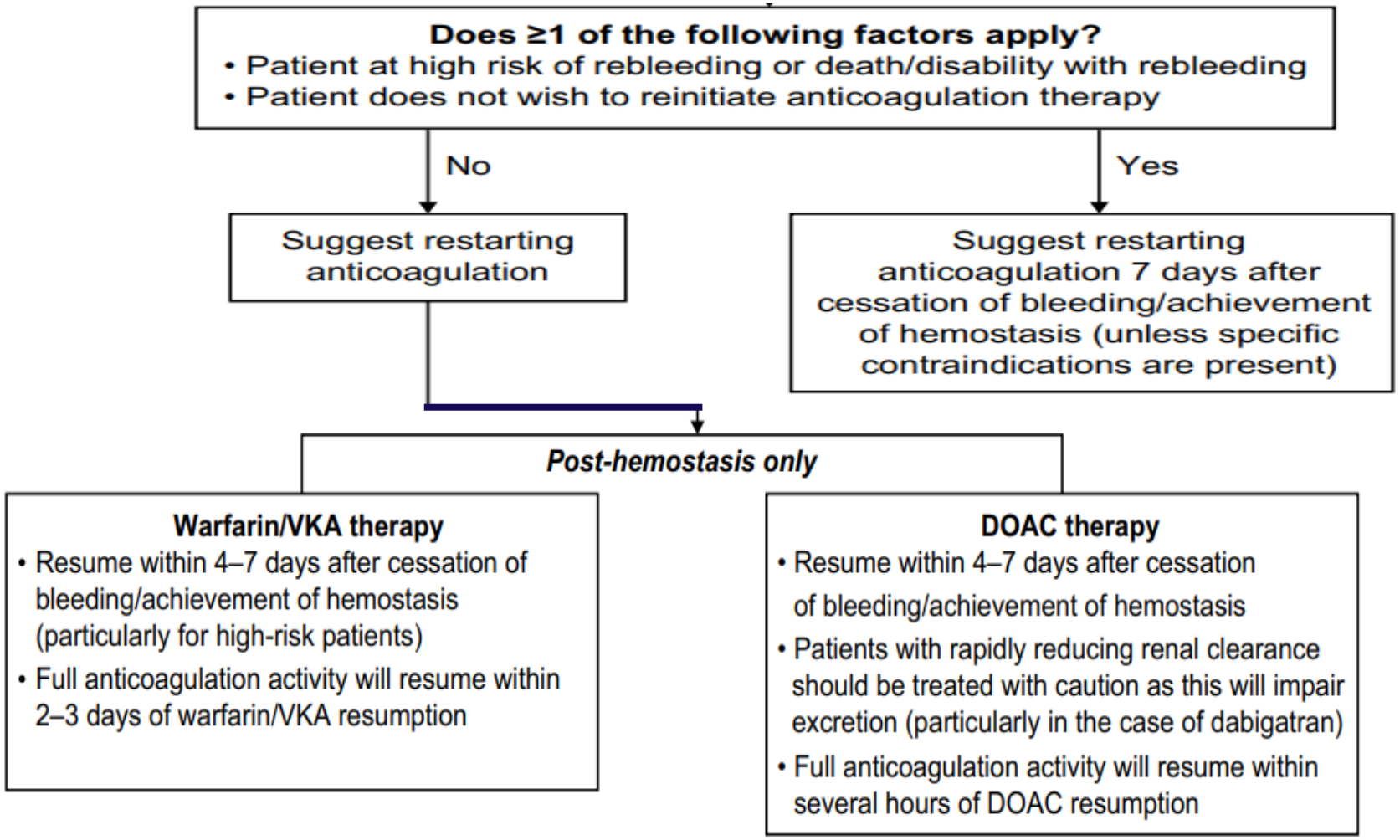
S: No bleeding events

O: Hb 12.1 g/dL

Management

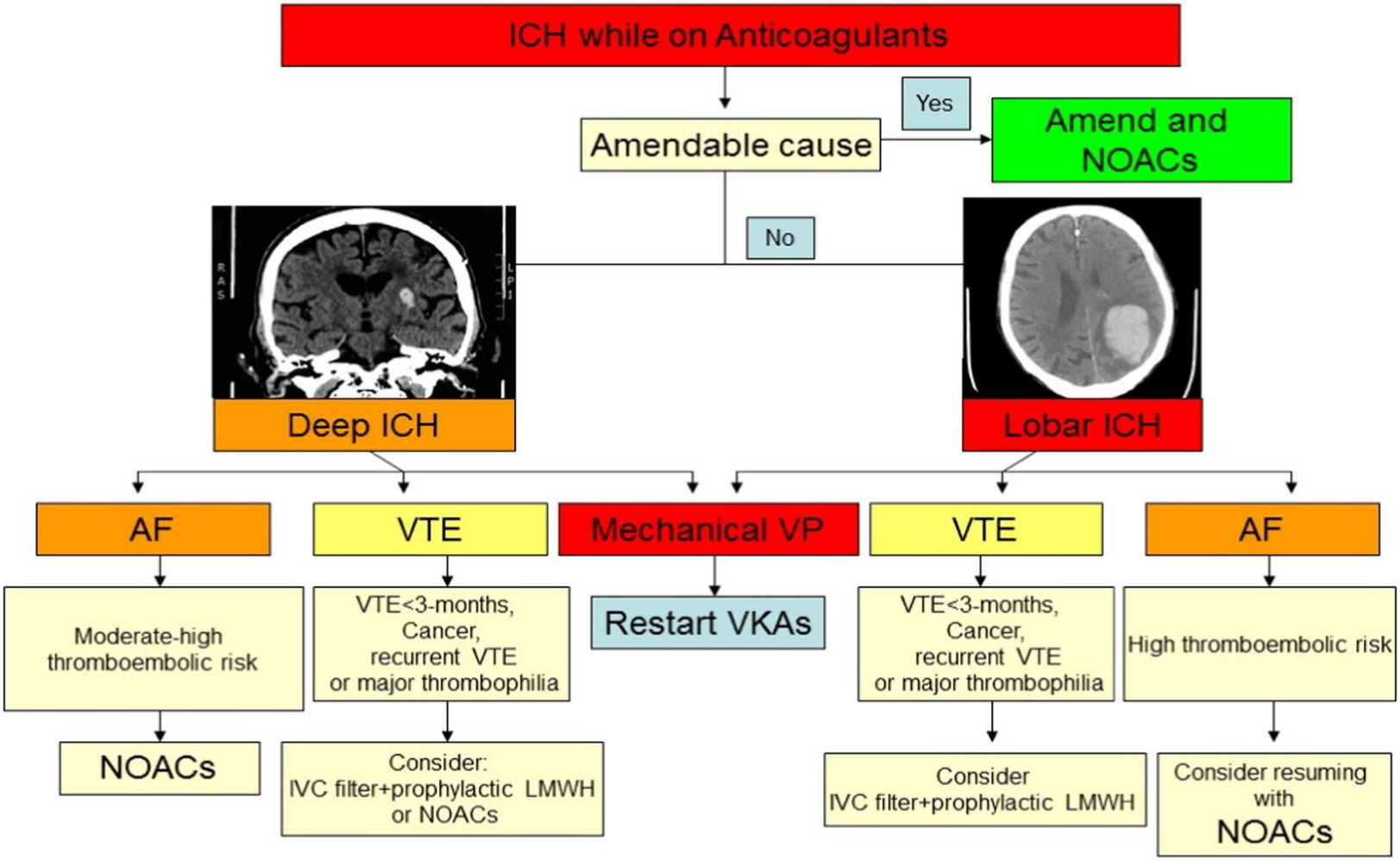
: apixaban 2일 중단하고 elective LLC

Resumption of anticoagulant after achieving hemostasis with GI bleeding



Milling TJ, et al. Dig Dis Sci. 2021;66(11):3698-3714

Resumption of anticoagulants after ICH



Becattini C, et al. Vascul Pharmacol. 2016;84:15-24.

Prophylactic-Dose Heparin for VTE Prevention in Patients With Acute Hemorrhagic Stroke and Restricted Mobility

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)
Overall mortality	114 (2 studies[a]) 10 d	Low[b-d] due to risk of bias, imprecision	RR, 1.05 (0.46-2.36)
PE (fatal and nonfatal)	10,681 (8 studies[e]) 14-90 d	Moderate[c,d,f] due to imprecision	RR, 0.7 (0.47-1.03)[e]
Symptomatic DVT	914 (8 studies[e]) 2-52 wk	Moderate[d,f,h] due to inconsistency	RR, 0.31 (0.21-0.42)[e]
Rebleeding	189 (3 studies[i]) 7-10 d[j]	Low[c,d,k] due to risk of bias, imprecision	RR, 0.24 (0.05-1.13)[l]

In patients with acute primary intracerebral hemorrhage and restricted mobility, we suggest prophylactic-dose subcutaneous heparin (UFH or LMWH) started between days 2 and 4 or intermittent pneumatic compression devices over no prophylaxis (Grade 2C)

CHEST 2012; 141(2)(Suppl):e601S–e636S

Inferior vena cava filters

Recommendations	Class[a]	Level[b]
IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C
IVC filters should be considered in cases of PE recurrence despite therapeutic anticoagulation.	IIa	C
Routine use of IVC filters is not recommended.[302–304]	III	A

ESC guidelines. Eur heart J 2019

Vena caval filters : PREPIC I trial

- **400 patients with proximal DVT** +/- PE
- Two-by-two factorial design
- Randomized: +/- **permanent IVC filter**, UFH or LMWH
- Outcomes: recurrent VTE, death, major bleeding (day 12 and 2 years)

Day 12 : PE ↓

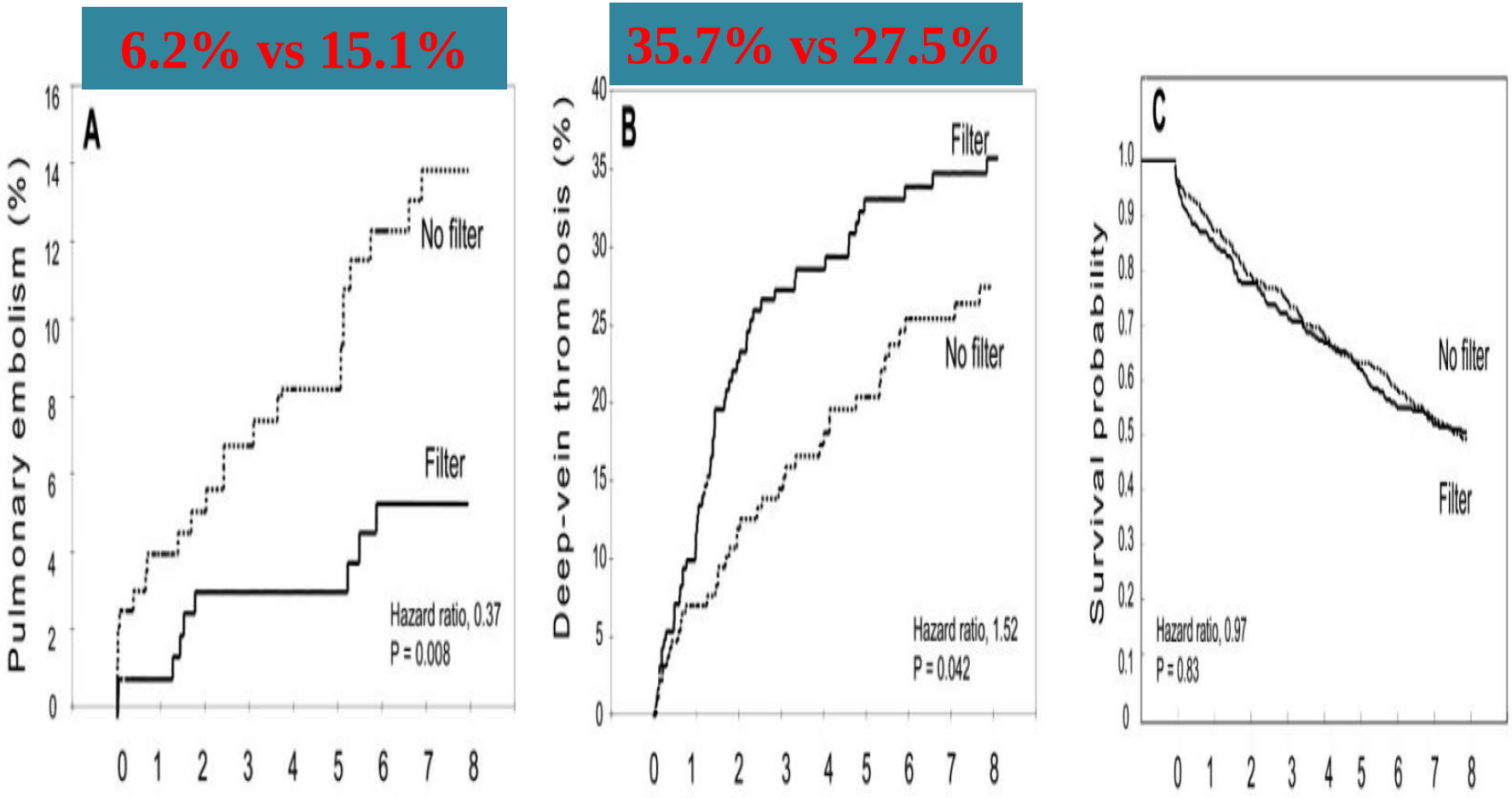
End Point	Filter	No Filter	Odds Ratio (95% CI)*	P Value
	number (percent)			
Pulmonary embolism				
Symptomatic†	2	5		
Asymptomatic	0	4		
All‡	2 (1.1)	9 (4.8)	0.22 (0.05–0.90)	0.03
Major bleeding	9 (4.5)	6 (3.0)	1.49 (0.53–4.20)	0.44
Death	5 (2.5)	5 (2.5)	0.99 (0.29–3.42)	0.99

2 year : PE ≈ , DVT ↑

Event and Time of Occurrence	Filter	No Filter	Odds Ratio (95% CI)	P Value
	number (percent)			
Symptomatic pulmonary embolism†				
Enrollment–3 mo	2	6		
>3 mo–1 yr	0	4		
>1–2 yr	4	2		
All	6 (3.4)	12 (6.3)	0.50 (0.19–1.33)	0.16
Recurrent deep-vein thrombosis				
Enrollment–3 mo	9	6		
>3 mo–1 yr	8	7		
>1–2 yr	20	8		
All	37 (20.8)	21 (11.6)	1.87 (1.10–3.20)	0.02
Major bleeding				
Enrollment–3 mo	11	10		
>3 mo–1 yr	5	8		
>1–2 yr	1	4		
All	17 (8.8)	22 (11.8)	0.77 (0.41–1.45)	0.41
Death				
Enrollment–3 mo	15	10		
>3 mo–1 yr	12	12		
>1–2 yr	16	18		
All	43 (21.6)	40 (20.1)	1.10 (0.72–1.70)	0.65

Decousus NEJM 1998; 338:409–415

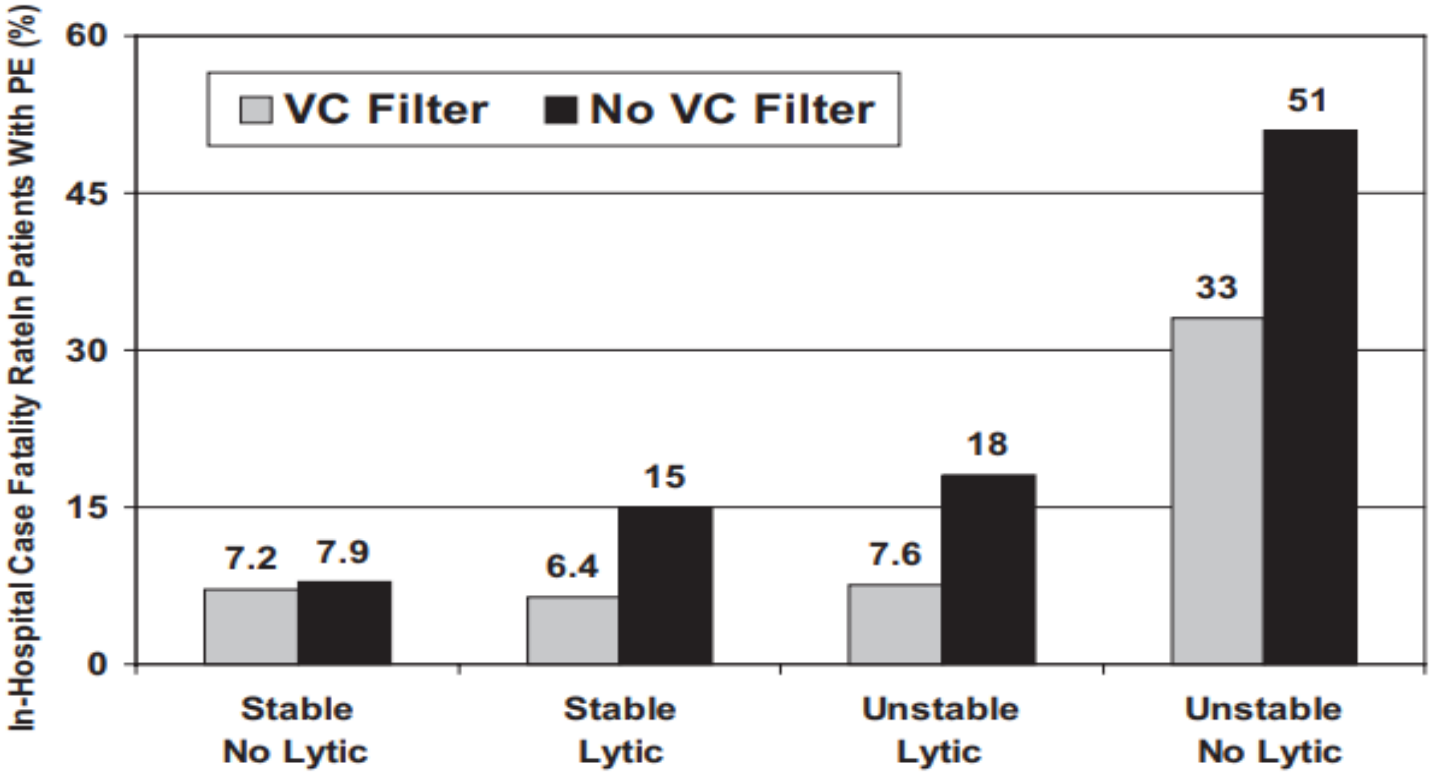
Vena caval filters : PREPIC I trial
8 year follow-up



PREPIC study group Circulation 2005;112:416-422

Impact of vena cava filters on in-hospital case fatality rate from PE

Data from the US Nationwide Inpatient Sample



Stein PD, et al. Am J Med. 2012;125(5):478-84

IVC filter in patients wit VTE and a significant bleeding risk

Propensity score–matched analysis of the RIETE study

Death ≈, PE-related death ↓, recurrent VTE ↑

	30-Day Outcome	Filter	No Filter	OR (95% CI)	p Value
Any VTE					
	Death	23/344 (6.6)	35/344 (10.2)	0.63 (0.36–1.12)	0.12
	PE-related death	6/344 (1.7)	17/344 (4.9)	0.35 (0.15–0.43)	0.03
	Major bleeding	13/344 (3.8)	18/344 (5.2)	0.71 (0.35–1.46)	0.35
	Recurrent VTE	21/344 (6.1)	2/344 (0.6)	11.12 (2.56–48.19)	<0.001
Any DVT*					
	Death	8/134 (6.0)	15/134 (11.2)	0.53 (0.20–1.44)	0.21
	Major bleeding	5/134 (3.7)	5/134 (3.7)	NC†	
	Recurrent VTE	4/134 (3.0)	2/134 (1.5)	NC†	
Any PE					
	Death	15/210 (7.1)	24/210 (11.4)	0.60 (0.19–1.21)	0.15
	Major bleeding	8/210 (3.8)	14/210 (6.7)	0.55 (0.23–1.32)	0.18
	Recurrent VTE	17/210 (8.1)	2/210 (1.0)	9.16 (2.24–32.48)	<0.001

Muriel A, et al. J Am Coll Cardiol 2014;63:1675–83

Effect of a Retrievable Inferior Vena Cava Filter Plus Anticoagulation vs Anticoagulation Alone : PREPIC2 trial

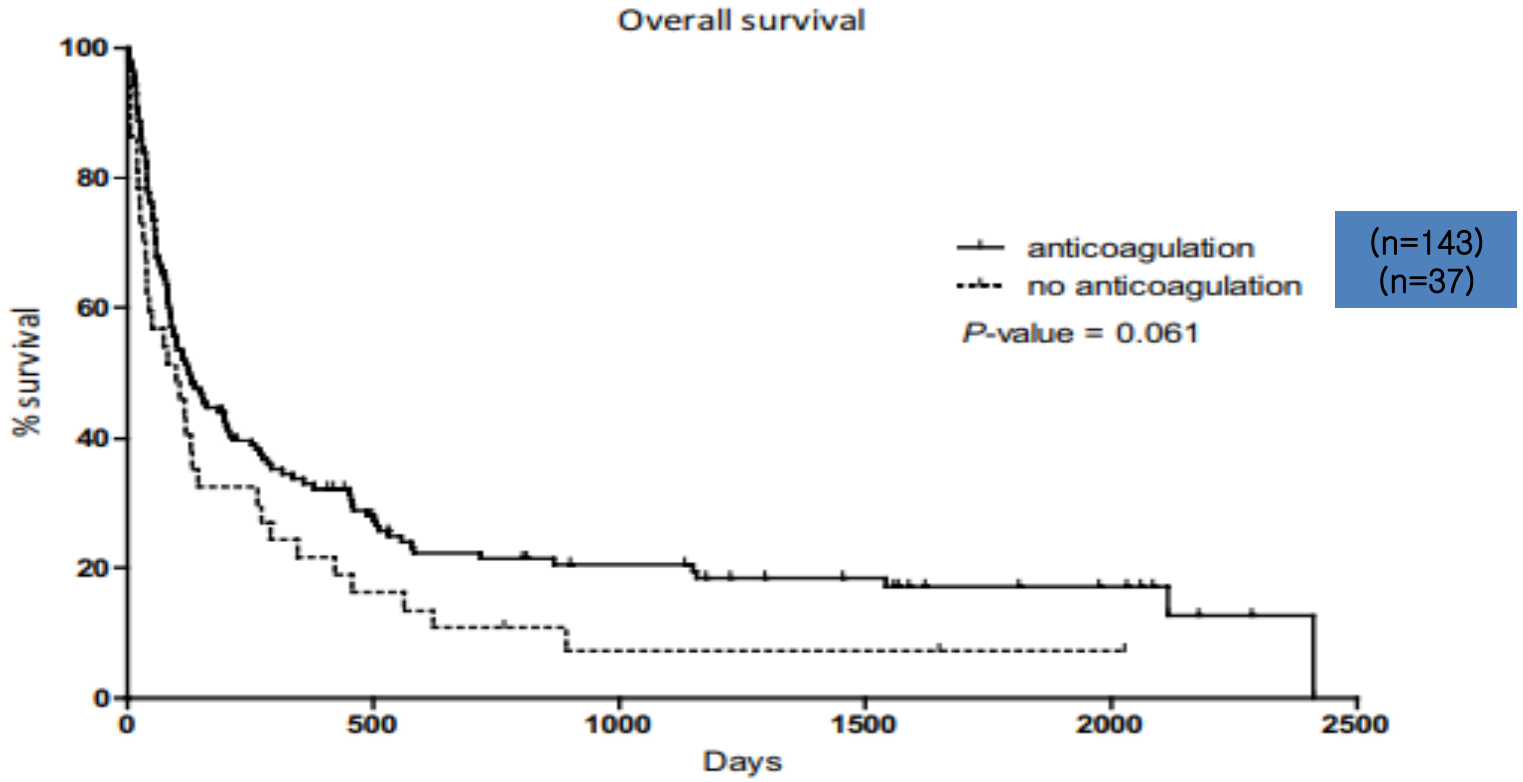
A randomized, open-label, blinded end point trial with hospitalized patients with acute, symptomatic PE associated with lower-limb DVT and at least 1 criterion for severity

Clinical Outcomes	Group, No. With Events (%)		Relative Risk, % (95% CI)	*P* Value[b]
	Filter (n = 200)[a]	Control (n = 199)		
At 3 Months				
Recurrent pulmonary embolism (primary efficacy outcome)[c]	6 (3.0)	3 (1.5)	2.00 (0.51-7.89)	.50
Fatal	6 (3.0)	2 (1.0)		
Nonfatal	0 (0.0)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	1 (0.5)	1.00 (0.06-15.9)	>.99
Recurrent venous thromboembolism	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.36
Major bleeding	8 (4.0)	10 (5.0)	0.80 (0.32-1.98)	.63
Death	15 (7.5)	12 (6.0)	1.25 (0.60-2.60)	.55
At 6 Months				
Recurrent pulmonary embolism[c]	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.54
Fatal	6 (3.0)	3 (1.5)		
Nonfatal	1 (0.5)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	2 (1.0)	0.50 (0.05-5.47)	>.99
Recurrent venous thromboembolism	8 (4.0)	6 (3.0)	1.33 (0.47-3.77)	.59
Major bleeding	13 (6.5)	15 (7.5)	0.87 (0.42-1.77)	.69
Death	21 (10.6)	15 (7.5)	1.40 (0.74-2.64)	.29

JAMA. 2015;313(16):1627-1635

Effect of post-filter anticoagulation on mortality in patients with cancer-associated PE

- **A retrospective cohort study of patients with a solid tumor and vena cava filter inserted because of PE at Asan Medical Center**



Kang J, et al. Int J Clin Oncol. 2018;23(5):1007-1013.

Complications of IVC filters

Complication	Rate (%)
Complication from insertion	4-11
Insertion site thrombosis	2-28
IVC thrombosis	6-30
Filter Migration	3-69
IVC Perforation	9-24
Post thrombotic Syndrome	5-70

Anticoagulation and heavy menstrual bleeding

HMB/AUB effects:
- 30% of women at some point
- 70% of women on warfarin

Which medicine should I take?

Observational studies of rivaroxaban have demonstrated[6]:
- Prolonged menstrual bleeding >8 days (27%)
- Unscheduled contact with a provider for vaginal bleeding (41%)
- Medical or surgical interventions for vaginal bleeding (25%)
- Adaptation of anticoagulant treatment (15%)

Incidence of Major or Clinically Relevant Nonmajor Uterine Bleeds in Randomized Controlled Trials of Direct Oral Anticoagulants[7,8]

Drug	Incidence	OR (vs warfarin)
Rivaroxaban	9.5%	2.1
Edoxaban	9.0%	1.26
Apixaban	5.4%	1.18
Dabigatran	5.9%	0.59

Godin R, et al. Vascul Pharmacol. 2017;93-95:1-5.
Huisman MV, et al. J Thromb Haemost. 2018;16:1775-1778.

Risk of VTE in Anticoagulated Women on Hormonal Therapies

- the EINSTEIN DVT and PE trials

Hormonal Therapy	VTE Risk (%/year)
None	4.7
Estrogen-containing	3.7
Progestin-only	3.8
Any therapy	3.7

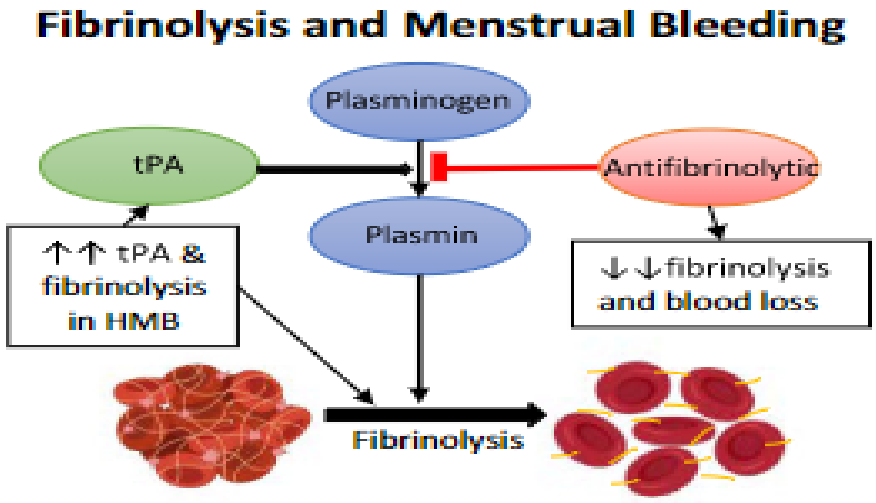
HR of 0.56 (95% CI, 0.23-1.39)

Martinell, et al. Blood. 2016;127:1417-1425.

Tranexamic acid in menstrual bleeding

Tranexamic acid is effective for the treatment of HMB

- 40% reduction in menstrual blood loss
- Improved quality of life
- Contraindicated in the setting of acute thrombosis
- Not studied in women on anticoagulation or with a history of VTE



Holding or discontinuing anticoagulation early

- Increases the risk of recurrent VTE
- Is not proven to reduce menstrual blood loss
- Is not recommended

Possible benefit of switching from a "higher risk" anticoagulant such as rivaroxaban to a "lower risk" anticoagulant such as dabigatran or apixaban is the subject of ongoing studies.

Bannow BS, et al. Res Pract Thromb Haemost. 2021;5(5):e12570.

Takeaway messsage

- It is generally not adequate to ascribe the bleeding to the effect of the anticoagulant.

- Occult bleeding in the individual receiving DOACs should be systematically evaluated.