GÓT CHÂN ACHILLES CỦA NOACs?

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Thuốc chống đông – nền tảng trong dự phòng và điều trị các bệnh lý liên quan đến huyết khối

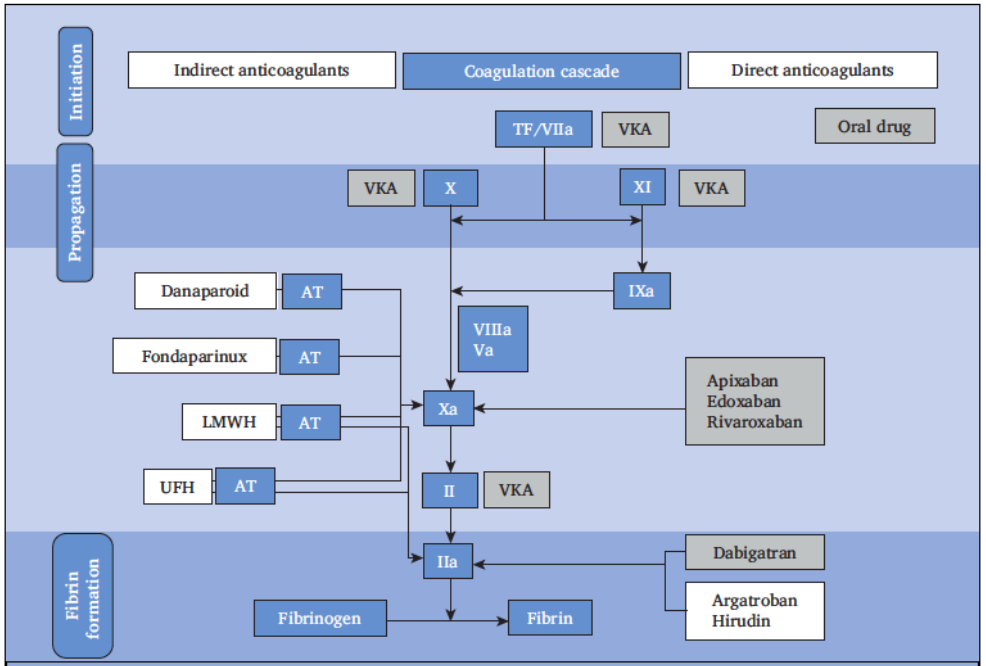


Figure 2. The three phases of the coagulation cascade (initiation, propagation, and fibrin formation) and targets for anticoagulants. Indirect anticoagulants, which require the presence of antithrombin (AT), are shown on the left. Direct anticoagulants, which do not require the presence of antithrombin, are shown on the right. These agents directly inhibit factor Xa or factor IIa (thrombin) and include hirudin, argatroban, and the direct oral anticoagulant dabigatran. Apixaban, edoxaban, and rivaroxaban are direct oral anticoagulants that directly inhibit factor Xa. VKA = vitamin K antagonist; TF = tissue factor; LMWH = low molecular weight heparin; UFH = unfractionated heparin. Modified with permission from Bauersachs, 2008.[83]

1. Các thuốc chống đông đường tiêm (UFH; LMWH-Enoxaparin…): **chủ yếu dùng trong thời gian ngắn.**

2. Các thuốc chống đông đường uống (OACs): điều trị lâu dài.

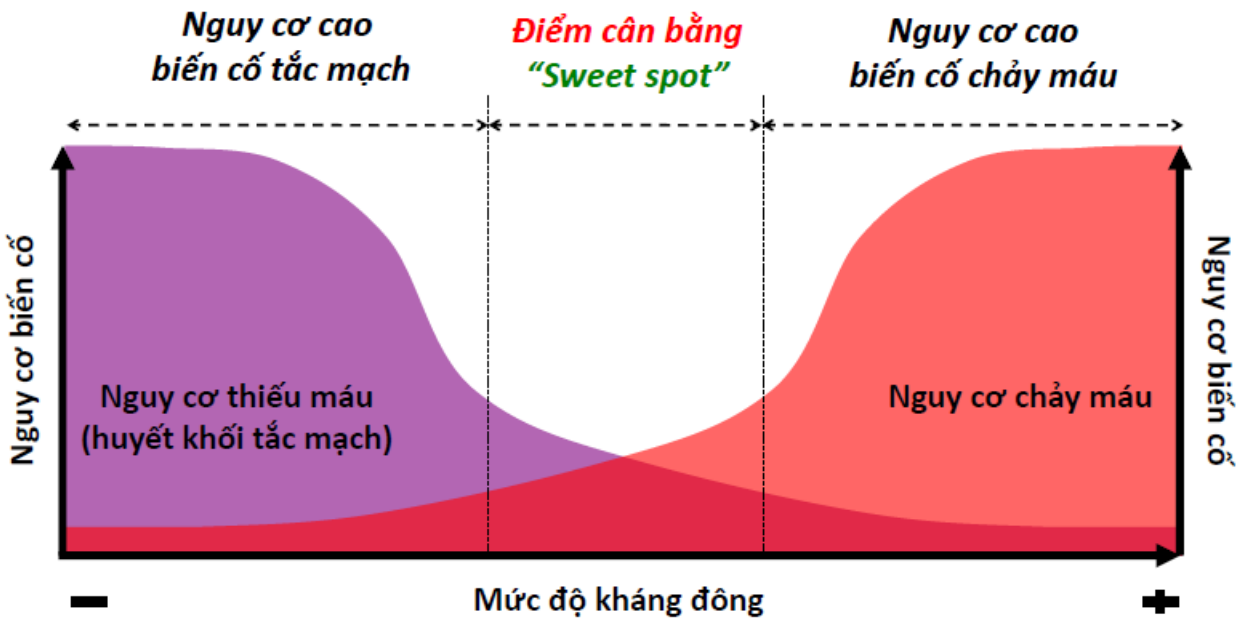
* Kháng Vitamin K (**VKAs**): Acenocoumarol, …

* Chống đông đường uống trực tiếp **(DOACs)**/không phải kháng Vitamin K **(NOACs)**:

- Ức chế trực tiếp Thrombin (IIa): Dabigatran.
- Ức chế Xa: Rivaroxaban, Apixaban, Edoxaban.

Stavros K. Kakkos et al. European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. *Eur J Vasc Endovasc Surg* (2021) 61, 9-82

Tối ưu hiệu quả-an toàn của kháng đông



Ferreiro JL, et al. Thromb Haemost. 2010;103:1128-1135.

DOACs/NOACs trong điều trị NVAF

So với VKA, NOACs:

- Giảm 19 % nguy cơ đột quỵ và tắc mạch hệ thống.

- Giảm 16 % nguy cơ chảy máu nặng (p = 0,06).

- Giảm # 50 % nguy cơ chảy máu nội sọ.

- Giảm 10 % nguy cơ tử vong chung.

Meta-Analysis of NOACs vs Warfarin

Efficacy

Result	Risk Ratio	95% CI	*P* Value
Stroke/SEE	0.81	0.73, 0.91	< .0001
Ischemic stroke	0.92	0.83, 1.02	.10
Hemorrhagic stroke	0.49	0.38, 0.64	< .0001
MI	0.97	0.78, 1.20	.77
All-cause mortality	0.90	0.85, 0.95	.0003

Safety

Result	Risk Ratio	95% CI	*P* Value
Major bleeding	0.86	0.73, 1.00	.06
ICH	0.48	0.39, 0.59	< .0001
GI bleeding	1.25	1.01, 1.55	.043

Ruff CT, et al. *Lancet*. 2014;383:955-962.

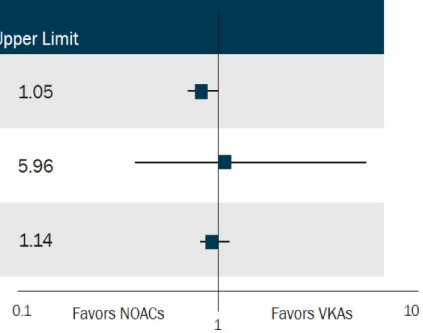
Recommendations	Class[a]	Level[b]
For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis).[423,424]	I	A

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) *European Heart Journal* (2020) doi:10.1093/eurheartj/ehaa612

DOACs/NOACs trong điều trị VTE

DOACs vs Warfarin for VTE
Efficacy

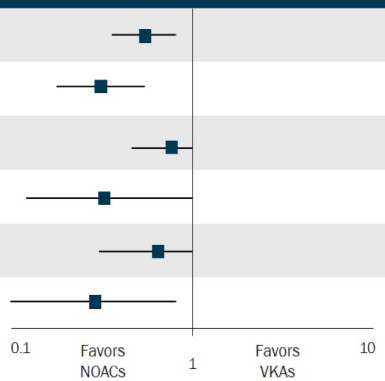
Outcome	RR	Lower Limit	Upper Limit
Recurrent VTE	0.88	0.74	1.05
Fatal PE	1.02	0.39	5.96
Overall mortality	0.97	0.83	1.14



van der Hulle T, et al. *J Thromb Haemost*. 2014;12:320-328.

DOACs vs Warfarin for VTE
Safety

Outcome	RR	Lower Limit	Upper Limit
Major bleeding	0.60	0.41	0.88
Nonfatal bleeding at a critical site	0.36	0.23	0.62
CRNM bleeding	0.76	0.58	0.99
Nonfatal intracranial bleeding	0.39	0.16	0.94
Major GI bleeding	0.68	0.36	1.30
Fatal bleeding	0.36	0.15	0.87



van der Hulle T, et al. *J Thromb Haemost*. 2014;12:320-328.

- Các kết cục về hiệu quả tương đương.
- Các kết cục về an toàn (chảy máu) tốt hơn.

DOACs/NOACs trong điều trị VTE

NOACs in Current Guidelines

When oral anticoagulation is started in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a VKA.[260,261,312–314]

I	A

2. 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 vitamin K antagonist (VKA) therapy (all Grade 2B).

a. Konstantinides SV, et al. *Eur Heart J*. 2020;41:543-603. b. Kearon C, et al. *Chest*. 2016;149:315-352.

Recommendation 16

For patients with provoked proximal deep vein thrombosis, treatment with a direct oral anticoagulant is recommended over a vitamin K antagonist for the principal treatment phase.

Class	Level	Reference
I	A	Kakkos *et al.* (2014)[129]

Recommendation 19

For patients with unprovoked proximal deep vein thrombosis, treatment with a direct oral anticoagulant is recommended over treatment with low molecular weight heparin followed by a vitamin K antagonist for the principal treatment phase.

Class	Level	Reference
I	A	Kakkos *et al.* (2014)[129]

Recommendation 40

For patients with calf deep vein thrombosis requiring anticoagulation, direct oral anticoagulants are recommended over low molecular weight heparin followed by vitamin K antagonists.

Class	Level	Reference
I	C	Kakkos *et al.* (2014)[129]

Stavros K. Kakkos et al. *Eur J Vasc Endovasc Surg* (2021) 61, 9-82

DOACs/NOACs trong điều trị CAT

Randomized Trials in CAT

Study	Drug	GI Cancer, %	Recurrent VTE, %	Major Bleeding, %	CRNM Bleeding, %	All-Cause Mortality, %
Hokusai-VTE Cancer[a] (2018)	Edoxaban, n = 522	6.3	7.9	6.9	14.6	39.5
	Dalteparin, n = 524	4.0	11.3	4.0	11.1	36.6
SELECT-D[b] (2018)	Rivaroxaban, n = 203	3.0	3.9	5.4	12.3	NR
	Dalteparin, n = 203	2.0	8.9	3.0	3.4	NR
ADAM VTE[c] (2019)	Apixaban, n = 145	4.8	0.7	0	6.2	16.0
	Dalteparin, n = 142	2.7	6.3	1.4	6.3	11.0
Caravaggio[d] (2020)	Apixaban n, = 576	4.0	5.6	3.8	12.2	23.4
	Dalteparin n, = 597	5.4	7.9	4.0	9.7	26.4
		Trends With NOACs	↓ ~30%	↑ ~30%*		↔

*Major bleeding occurred predominantly in patients with cancer in the GI tract.
a. Raskob GE, et al. *N Engl J Med*. 2018;378:615-624; b. Young AM, et al. *J Clin Oncol*. 2018;36:2017-2023; c. McBane RD 2nd, et al. *J Thromb Haemost*. 2020;18:411-421; d. Agnelli G, et al. *N Engl J Med*. 2020;382:1599-1607.

Khuyến cáo	Nhóm	Mức độ bằng chứng
Khuyến cáo ưu tiên heparin TLPT thấp để điều trị TTHKTM có triệu chứng hoặc phát hiện tình cờ, ở BN ung thư, đặc biệt ung thư đường tiêu hóa hoặc BN ung thư có tổn thương đường tiêu hóa	I	A
BN bị TTHKTM liên quan đến ung thư và có nguy cơ xuất huyết tiêu hóa hoặc tiết niệu sinh dục thấp được khuyến cáo điều trị bằng NOACs thuộc nhóm ức chế yếu tố Xa (Apixaban, Rivaroxaban, Edoxaban) nếu không dùng heparin TLPT thấp	I	A
Cân nhắc giảm một nửa liều Heparin TLPT thấp khi điều trị TTHKTM ở BN ung thư có số lượng tiểu cầu từ 25 - 50.000/µl	IIb	C
Điều trị chống đông ở BN ung thư bị TTHKTM nên được kéo dài ít nhất 6 tháng hoặc tới khi ung thư đã được chữa khỏi	IIb	B
Khuyến cáo điều trị chống đông tối thiểu 3 tháng, ở BN ung thư bị huyết khối trong ống thông (catheter) ngầm, và tiếp tục kéo dài nếu vẫn duy trì ống thông.	I	C

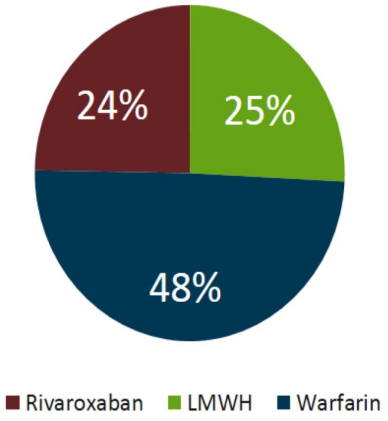
(1) Theo một số Hiệp hội quốc tế, các NOAC thuộc nhóm ức chế yếu tố Xa được ưu tiên lựa chọn điều trị TTHKTM ở BN ung thư, trừ BN có tiểu cầu < 50.000/µl; tổn thương gan tiến triển (men gan > 2 lần ngưỡng trên của giá trị bình thường); MLCT < 15 ml/phút; đang điều trị thuốc chuyển hóa qua con đường P-glucoprotein hay CYP3A4; ung thư đường tiêu hóa hoặc nguy cơ cao xuất huyết tiêu hóa.

Khuyến cáo của VNHA về chẩn đoán, điều trị và dự phòng TT HKTM – cập nhật 2023

Thực tế điều trị CAT:
OAC được ưa thích & tuân trị tốt hơn

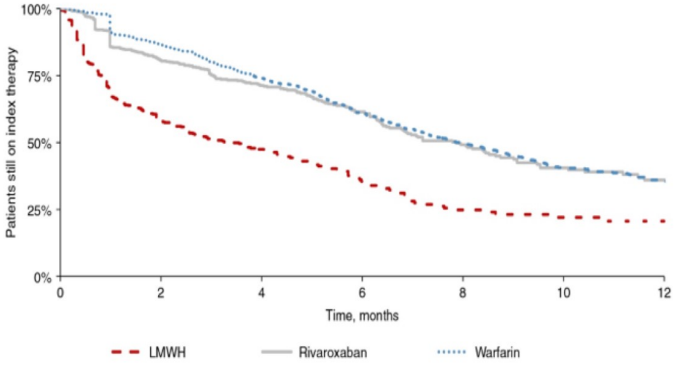
Oral Anticoagulants Are Preferred

2941 Patients With New VTE and Cancer (Humana Database, 2007-2014)



Khorana AA, et al. *Res Pract Thromb Haemost.* 2017;1:14-22.

Patient Persistence With Anticoagulation: *LMWH vs Oral Agents*



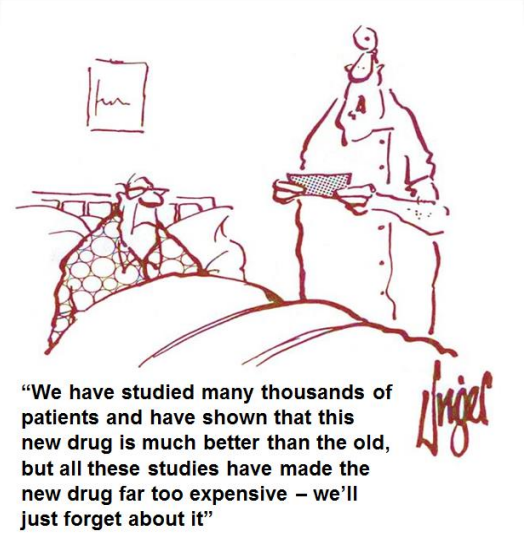
Cohort	Median treatment duration	Kaplan-Meier rates	
		6 months	12 months
LMWH	3.3	37%	21%
Warfarin	7.9	61%	35%
Riva roxaban	7.9	61%	36%

*Discontinuation was defined has a gap of more than 60 days between the end of the days of supply of a dispensing and the start date of the next dispensing of the index therapy, if any.

Khorana AA, et al. *Res Pract Thromb Haemost*. 2017;1:14-22. © 2017 The Authors. Research and Practice in Thrombosis and Haemostasis published by Wiley Periodicals, Inc on behalf of International Society on Thrombosis and Haemostasis.

The game is over???

The Paradox of Progress



"A cynic is a man who knows the price of everything but the value of nothing."

Oscar Wilde
Lady Windermere's Fan
(1892)

If the price is everything then the value is nothing

”Phát súng cảnh báo” đầu tiên: RE-ALIGN

METHODS

In this phase 2 dose-validation study, we studied two populations of patients: those who had undergone aortic- or mitral-valve replacement within the past 7 days and those who had undergone such replacement at least 3 months earlier. Patients were randomly assigned in a 2:1 ratio to receive either dabigatran or warfarin. The selection of the initial dabigatran dose (150, 220, or 300 mg twice daily) was based on kidney function. Doses were adjusted to obtain a trough plasma level of at least 50 ng per milliliter. The warfarin dose was adjusted to obtain an international normalized ratio of 2 to 3 or 2.5 to 3.5 on the basis of thromboembolic risk. The primary end point was the trough plasma level of dabigatran.

RESULTS

The trial was terminated prematurely after the enrollment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group. In the as-treated analysis, dose adjustment or discontinuation of dabigatran was required in 52 of 162 patients (32%). Ischemic or unspecified stroke occurred in 9 patients (5%) in the dabigatran group and in no patients in the warfarin group; major bleeding occurred in 7 patients (4%) and 2 patients (2%), respectively. All patients with major bleeding had pericardial bleeding.

CONCLUSIONS

The use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk. (Funded by Boehringer Ingelheim; ClinicalTrials.gov numbers, NCT01452347 and NCT01505881.)

N Engl J Med 2013;369:1206-14

BIẾN CỐ TIM MẠCH

(HUYẾT KHỐI/TẮC MẠCH…)

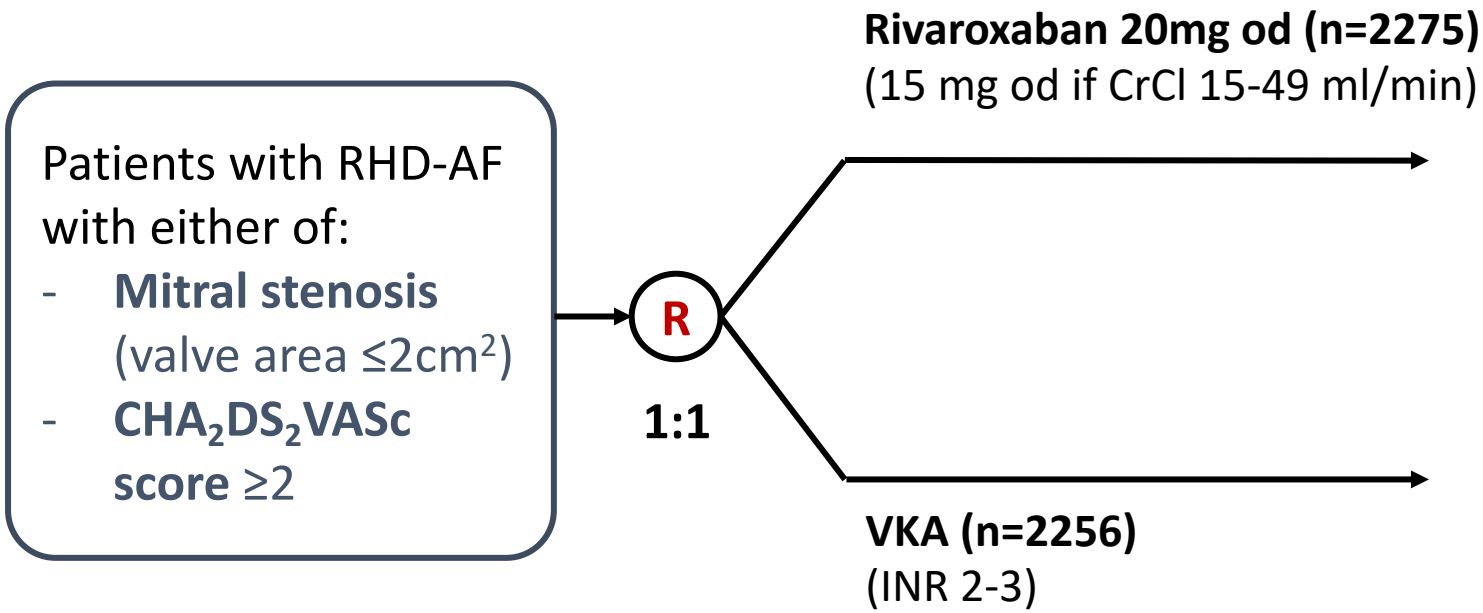
Rivaroxaban for rheumatic heart disease associated atrial fibrillation - INVICTUS

Ganesan Karthikeyan, Stuart Connolly*, Mpiko Ntsekhe, Bongani Mayosi* and Salim Yusuf**, for the INVICTUS Steering Committee and investigators

28th August 2022

**PI, **Steering committee chair*

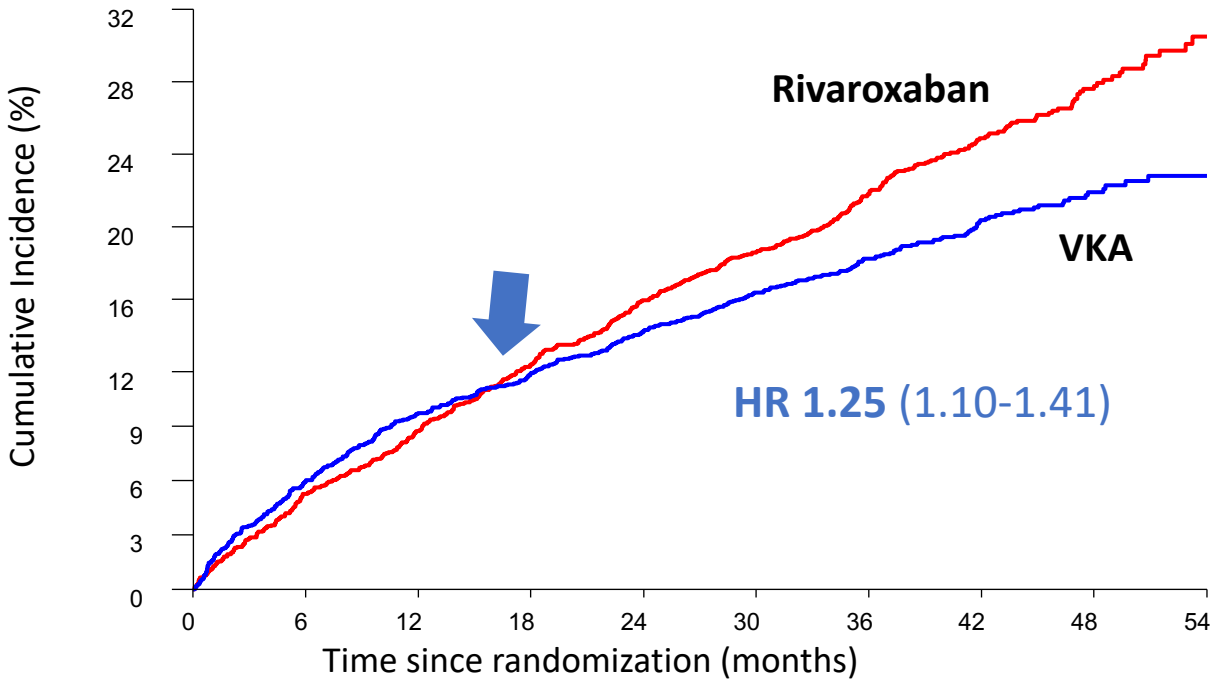
Patients and interventions



Am Heart J 2020;225:69-77

Results: Stroke, SE, MI or death (vascular or unknown)

4531 patients, 97% follow-up, average of 3.1 years



Proportional hazards assumption NOT met

Results: Efficacy - Intention-to-treat

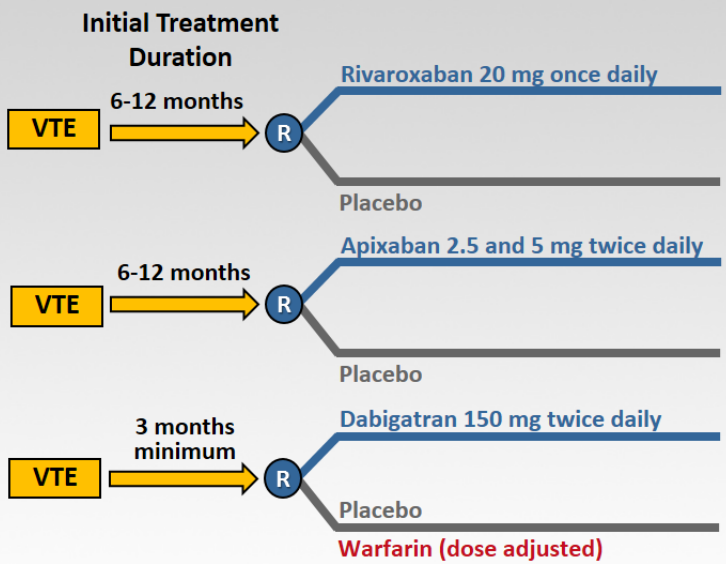
Outcomes % per year (n)	**Rivaroxaban** (n=2275)	**VKA** (n=2256)	**HR** (95% CI)	**RMST difference,** days (95% CI)	**p value (RMST)**
Primary composite	**8.2** (560)	**6.5** (446)	**1.25** (1.10-1.41)	**-76** (-121, -31)	0.001
Death	**8.0** (552)	**6.4** (442)	**1.23** (1.09-1.40)	**-72** (-117, -28)	0.001
Ischemic stroke	**1.1** (74)	**0.7** (48)	**1.53** (1.06-2.20)	**-23** (-40, -6)	0.01

Few systemic embolism (16), and MI (8) events

On-treatment analysis showed similar results

Điều trị mở rộng VTE: NOACs vs giả dược?

NOAC VTE Extension Trials



EINSTEIN Investigators. *N Engl J Med*. 2010;363:2499-2510.
Agnelli G, et al. *N Engl J Med*. 2013;368:699-708.
Schulman S, et al. *N Engl J Med*. 2013;368:709-718.

Medscape EDUCATION

Incidence of Recurrent VTE in Extension VTE Trials

Trial	Agent	Incidence of Recurrent VTE		
		NOAC, %	Warfarin, %	HR (95% CI)
RE-MEDY[a]	Dabigatran	1.8	1.3	1.44 (0.78-2.64)
RE-SONATE[a]	Dabigatran	0.4	5.6*	0.08 (0.02-0.25)
EINSTEIN-EXT[b]	Rivaroxaban	1.3	7.1	0.18 (0.09-0.39)
AMPLIFY-EXT[c]	Apixaban 2.5 mg	1.7	8.8	0.19 (0.11-0.33)
AMPLIFY-EXT[c]	Apixaban 5 mg	1.7	8.8	0.20 (0.11-0.34)

*Placebo comparator

a. Schulman S, et al. *N Engl J Med*, 2013;368:709-718[8]; b. EINSTEIN Investigators. *N Engl J Med*. 2010;363:2499-2510[3]; c. Agnelli G, et al. *N Engl J Med*. 2013;368:699-708.[9]

Incidence of Major Bleeding in Extension VTE Trials

Trial	Agent	Incidence of Major Bleeding		
		NOAC, %	Warfarin, %	HR (95% CI)
RE-MEDY[a]	Dabigatran	0.9	1.8	0.52 (0.27-1.02)
RE-SONATE[a]	Dabigatran	0.3	0*	Not estimable
EINSTEIN-EXT[b]	Rivaroxaban	0.7	0	Not estimable
AMPLIFY-EXT[c]	Apixaban 2.5 mg	0.2	0.5	0.49 (0.09-2.64)
AMPLIFY-EXT[c]	Apixaban 5 mg	0.1	0.5	0.25 (0.03-2.24)

*Placebo comparator

a. Schulman S, et al. *N Engl J Med*, 2013;368:709-718[8]; b. EINSTEIN Investigators. *N Engl J Med*. 2010;363:2499-2510[3]; c. Agnelli G, et al. *N Engl J Med*. 2013;368:699-708.[9]

Điều trị mở rộng VTE: Dabigatran không được khuyến cáo?

Nếu có chỉ định điều trị kéo dài thuốc chống đông sau 6 tháng, BN bị TTHKTM (không liên quan đến ung thư) có thể được cân nhắc dùng Rivaroxaban 10mg/ngày hoặc Apixaban 2,5 mg x 2 lần/ngày	IIa	A
Nếu BN bị TTHKTM chỉ định dùng thuốc chống đông kéo dài nhưng không dung nạp hoặc từ chối dùng thuốc chống đông, có thể cân nhắc sử dụng Aspirin hoặc Sulodeoxide	IIb	B
Với BN điều trị thuốc chống đông kéo dài, cần phải định kỳ đánh giá lợi ích và nguy cơ khi dùng thuốc	I	C

Khuyến cáo của VNHA về chẩn đoán, điều trị và dự phòng TT HKTM – cập nhật 2023

Tại sao?

Table 2. Efficacy and Safety Outcomes in the Active-Control Study.*

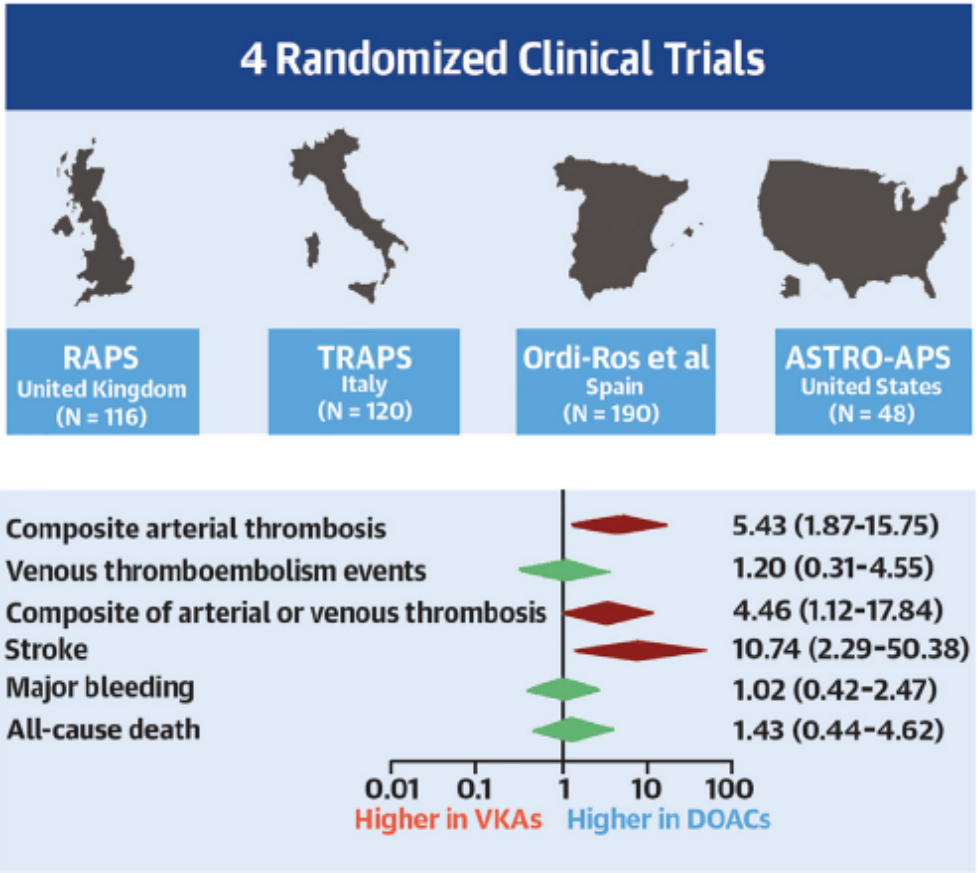
Outcome	Dabigatran (N=1430)	Warfarin (N=1426)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Efficacy analysis†				
Primary end point of recurrent or fatal venous thrombo-embolism	26 (1.8)	18 (1.3)	1.44 (0.78–2.64)	0.01‡
Secondary end points				
Symptomatic deep-vein thrombosis	17 (1.2)	13 (0.9)	1.32 (0.64–2.71)	0.46
Symptomatic nonfatal pulmonary embolism	10 (0.7)	5 (0.4)	2.04 (0.70–5.98)	0.19
Death related to venous thromboembolism	1 (0.1)	1 (0.1)	1.01 (0.06–16.2)	0.99
All deaths	17 (1.2)	19 (1.3)	0.90 (0.47–1.72)	0.74
Safety analysis§				
Major bleeding event¶	13 (0.9)	25 (1.8)	0.52 (0.27–1.02)	0.06
Fatal event	0	1		
Bleeding into critical organ	8	13		
Event resulting in fall in hemoglobin level or need for blood transfusions	9	18		
Major or clinically relevant bleeding event	80 (5.6)	145 (10.2)	0.54 (0.41–0.71)	<0.001
Any bleeding event	277 (19.4)	373 (26.2)	0.71 (0.61–0.83)	<0.001
Adverse event	1029 (72.0)	1010 (70.8)		0.53
Adverse event leading to discontinuation of study drug	145 (10.1)	126 (8.8)		0.26
Serious adverse event	227 (15.9)	224 (15.7)		0.97
Acute coronary syndrome				
During treatment	13 (0.9)	3 (0.2)		0.02
Within 30 days after treatment	1 (0.1)	3 (0.2)		
ALT >3× ULN	24 (1.7)	26 (1.8)		
ALT >3× ULN and bilirubin >2× ULN	2 (0.1)	1 (0.1)		

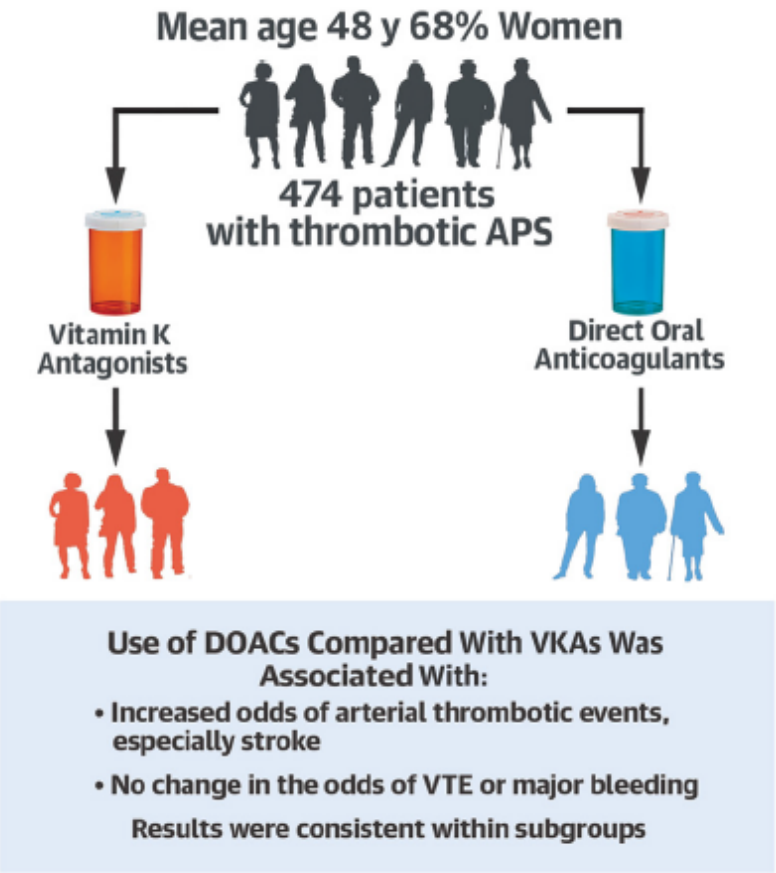
Table 3. Efficacy and Safety Outcomes in the Placebo-Control Study.

Outcome	Dabigatran (N=681)	Placebo (N=662)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Efficacy analysis*				
Primary end point of recurrent or fatal venous thrombo-embolism or unexplained death	3 (0.4)	37 (5.6)	0.08 (0.02–0.25)	<0.001
Secondary end points				
Symptomatic deep-vein thrombosis	2 (0.3)	22 (3.3)†		
Symptomatic nonfatal pulmonary embolism	1 (0.1)	14 (2.1)†		
Unexplained death	0	2 (0.3)‡		
Safety analysis§				
Major bleeding event¶	2 (0.3)	0	Not estimable	1.0
Event resulting in fall in hemoglobin level or need for blood transfusions	2	0		
Major or clinically relevant bleeding event	36 (5.3)	12 (1.8)	2.92 (1.52–5.60)	0.001
Any bleeding event	72 (10.5)	39 (5.9)	1.82 (1.23–2.68)	0.003
Adverse event	346 (50.6)	324 (49.2)		
Adverse event leading to discontinuation of study drug	50 (7.3)	81 (12.3)		
Serious adverse event	47 (6.9)	60 (9.1)		
Acute coronary syndrome during treatment‖	1 (0.1)	1 (0.2)		
Cerebrovascular event during treatment**	2 (0.3)	1 (0.2)		
ALT >3× ULN††	4 (0.6)	4 (0.6)		

N Engl J Med 2013;368:709-18

NOACs trong HC kháng phospholipid?





Khairani CD, et al. J Am Coll Cardiol. 2023;81(1):16-30.

J Am Coll Cardiol 2023;81:16–30

Điều trị HKTMS ở BN có bệnh lý tăng đông

Recommendation 66		
For patients with deep vein thrombosis and high risk thrombophilia (e.g., antiphospholipid syndrome, homozygous factor V Leiden mutation, or deficiencies of protein C or S, or antithrombin), full dose extended anticoagulant therapy is recommended with periodic re-evaluation.		
Class	Level	References
I	C	Tektonidou *et al.* (2019),[69] Nicolaides *et al.* (2013)[117]

Recommendation 67		
For patients with deep vein thrombosis and antiphospholipid syndrome who are triple positive or have a history of arterial or small vessel thrombosis, direct oral anticoagulants should not be used.		
Class	Level	References
III	B	Tektonidou *et al.* (2019),[69] Pengo *et al.* (2018),[395] Malec *et al.* (2020),[396] Ordi-Ros *et al.* (2019)[397]

Recommendation 68		
For patients with deep vein thrombosis and triple positive antiphospholipid syndrome, treatment with a vitamin K antagonist titrated to maintain a target international normalised ratio between 2–3 should be considered.		
Class	Level	Reference
IIa	B	Pengo *et al.* (2018)[395]

Recommendation 69		
For patients with deep vein thrombosis and a high risk thrombophilia, long term follow up by a thrombophilia expert is recommended.		
Class	Level	Reference
I	C	Consensus

66. BN HKTM sâu và bệnh lý tăng đông nguy cơ cao (ví dụ, ***hội chứng kháng phospholipid***, đột biến yếu tố V Leiden đồng hợp tử hoặc thiếu hụt protein C, S, antithrombin), khuyến cáo điều trị chống đông mở rộng/kéo dài liều đầy đủ và đánh giá lại định kỳ (I-C).

67. BN HKTM sâu và hội chứng kháng phospholipid có 3 xét nghiệm dương tính hoặc có tiền sử huyết khối động mạch hoặc mạch máu nhỏ, KHÔNG khuyến cáo dùng DOAC (III-B).

68. BN HKTM sâu và 3 xét nghiệm hội chứng kháng phospholipid đều dương tính, nên điều trị chống đông kháng vitamin K với INR mục tiêu 2-3 (IIa-B).

69. BN HKTM sâu và bệnh lý tăng đông nguy cơ cao, khuyến cáo theo dõi lâu dài bởi 1 chuyên gia về bệnh lý tăng đông (I-C).

Stavros K. Kakkos et al. European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. *Eur J Vasc Endovasc Surg* (2021) 61, 9-82

BIẾN CỐ CHẢY MÁU

Chảy máu khi dùng DOACs/NOACs điều trị NVAF

Meta-Analysis of NOACs vs Warfarin

Efficacy

Result	Risk Ratio	95% CI	*P* Value
Stroke/SEE	0.81	0.73, 0.91	< .0001
Ischemic stroke	0.92	0.83, 1.02	.10
Hemorrhagic stroke	0.49	0.38, 0.64	< .0001
MI	0.97	0.78, 1.20	.77
All-cause mortality	0.90	0.85, 0.95	.0003

Safety

Result	Risk Ratio	95% CI	*P* Value
Major bleeding	0.86	0.73, 1.00	.06
ICH	0.48	0.39, 0.59	< .0001
GI bleeding	1.25	1.01, 1.55	.043

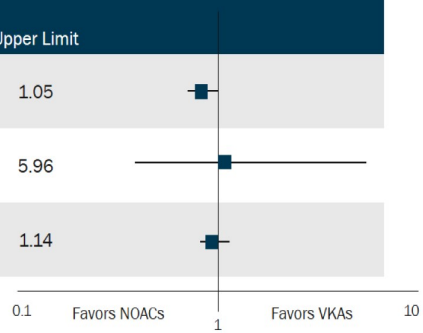
Ruff CT, et al. *Lancet*. 2014;383:955-962.

So với VKA, NOACs tăng 25 % nguy cơ chảy máu tiêu hoá (!)

Chảy máu khi dùng DOACs/NOACs điều trị VTE

DOACs vs Warfarin for VTE
Efficacy

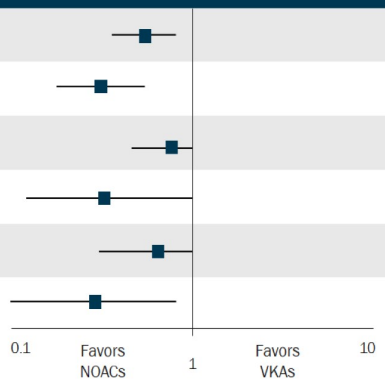
Outcome	RR	Lower Limit	Upper Limit
Recurrent VTE	0.88	0.74	1.05
Fatal PE	1.02	0.39	5.96
Overall mortality	0.97	0.83	1.14



van der Hulle T, et al. *J Thromb Haemost*. 2014;12:320-328.

DOACs vs Warfarin for VTE
Safety

Outcome	RR	Lower Limit	Upper Limit
Major bleeding	0.60	0.41	0.88
Nonfatal bleeding at a critical site	0.36	0.23	0.62
CRNM bleeding	0.76	0.58	0.99
Nonfatal intracranial bleeding	0.39	0.16	0.94
Major GI bleeding	0.68	0.36	1.30
Fatal bleeding	0.36	0.15	0.87



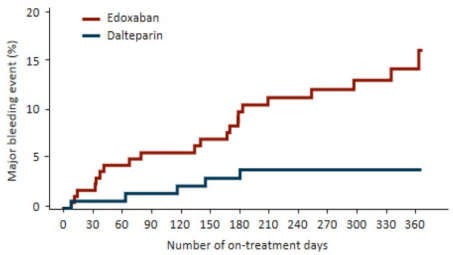
van der Hulle T, et al. *J Thromb Haemost*. 2014;12:320-328.

- **Các kết cục về hiệu quả tương đương.**
- **Các kết cục về an toàn (chảy máu) tốt hơn, *trừ chảy máu tiêu hoá nặng*.**

Chảy máu khi dùng DOACs/NOACs điều trị CAT

Hokusai-VTE-Cancer
Major Bleeding Events in GI Cancer

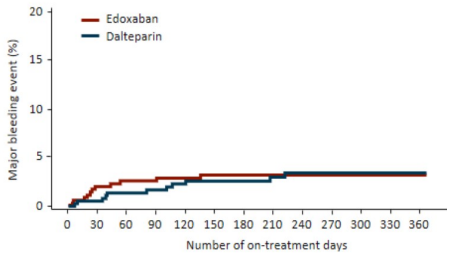
Patients With GI Cancer



Number at risk

Edoxaban	165	134	121	108	97	89	79	70	64	59	48	38	28
Dalteparin	140	123	116	108	94	89	79	67	60	54	48	40	25

Patients With Non-GI Cancer



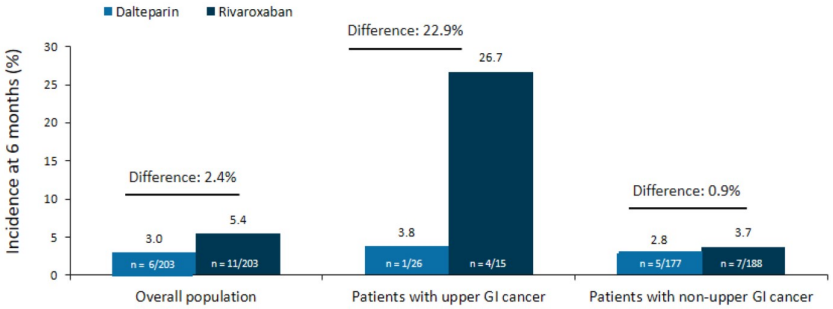
Number at risk

Edoxaban	357	315	284	271	255	234	220	190	179	171	144	123	88
Dalteparin	384	347	305	278	254	236	216	151	138	131	108	95	63

Kraaijpoel N, et al. *Thromb Haemost.* 2018;118:1439-1449.

SELECT-D
Major Bleeding Events in Upper GI Cancer

Incidence of major bleeding events in SELECT-D



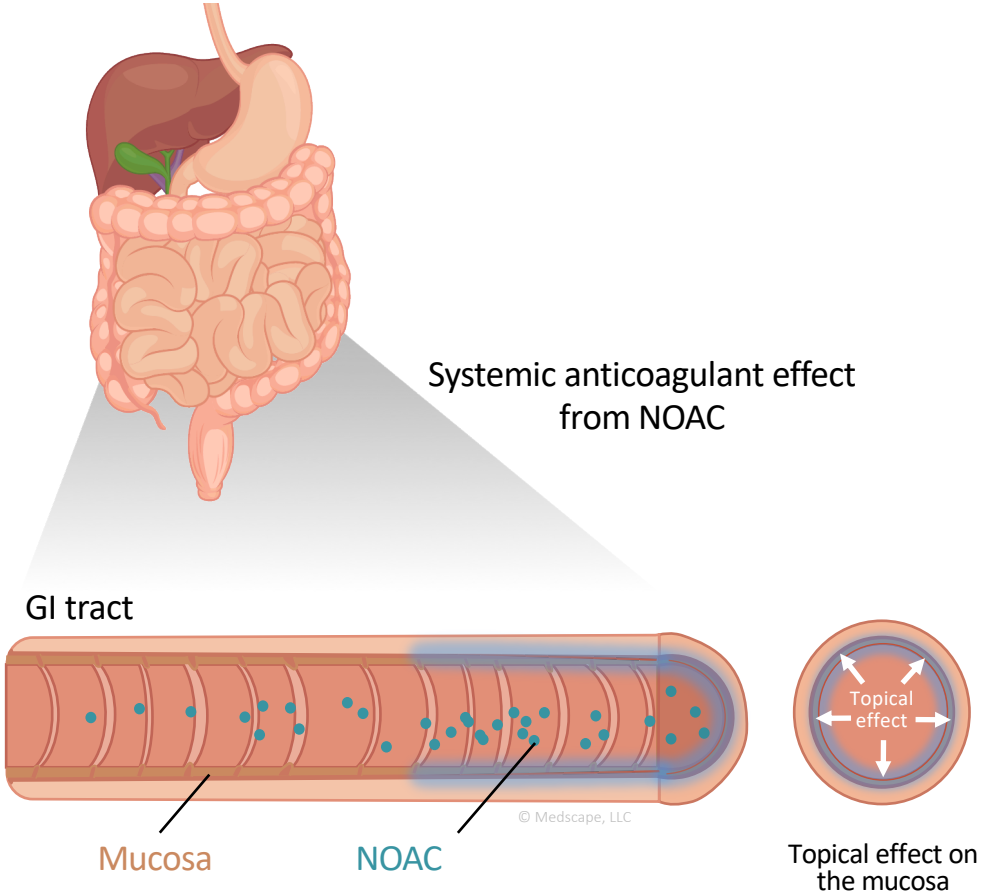
Equivalent results for CARAVAGGIO are currently unavailable but publication expected.
Results show percentage of patients with an event in the 'at risk' population. Upper GI cancer included esophageal, gastroesophageal, and gastric primary tumor types.
Young AM, et al. *J Clin Oncol.* 2018:36:2017-2023.

Randomized Trials in CAT

Study	Drug	GI Cancer, %	Recurrent VTE, %	Major Bleeding, %	CRNM Bleeding, %	All-Cause Mortality, %
Hokusai-VTE Cancer[a] (2018)	Edoxaban, n = 522	6.3	7.9	6.9	14.6	39.5
	Dalteparin, n = 524	4.0	11.3	4.0	11.1	36.6
SELECT-D[b] (2018)	Rivaroxaban, n = 203	3.0	3.9	5.4	12.3	NR
	Dalteparin, n = 203	2.0	8.9	3.0	3.4	NR
ADAM VTE[c] (2019)	Apixaban, n = 145	4.8	0.7	0	6.2	16.0
	Dalteparin, n = 142	2.7	6.3	1.4	6.3	11.0
Caravaggio[d] (2020)	Apixaban n, = 576	4.0	5.6	3.8	12.2	23.4
	Dalteparin n, = 597	5.4	7.9	4.0	9.7	26.4
Trends With NOACs			↓ ~30%	↑ ~30%*		↔

*Major bleeding occurred predominantly in patients with cancer in the GI tract.
a. Raskob GE, et al. *N Engl J Med.* 2018;378:615-624; b. Young AM, et al. *J Clin Oncol.* 2018;36:2017-2023; c. McBane RD 2nd, et al. *J Thromb Haemost.* 2020;18:411-421; d. Agnelli G, et al. *N Engl J Med.* 2020;382:1599-1607.

Chảy máu tiêu hoá là gót chân Achilles của DOACs/NOACs?



Incomplete absorption (topical anticoagulant effect)

Direct caustic effect (eg, tartaric acid in dabigatran)

Inhibition of mucosal healing

Cheung KS, et al. *World J Gastroenterol*. 2017;23:1954-1963.

DOACs/NOACs vs VKA ở BN rung nhĩ cao tuổi bị suy yếu: nghiên cứu FRAIL AF (ESC 2023)

- **Tiêu chuẩn nhận bệnh:**

- Tuổi ≥ 75.

- Đang điều trị VKA vì rung nhĩ ở 1 trong 8 trung tâm ở Hà Lan.

- Điểm đánh giá suy yếu **Groningen Frailty Indicator (GFI) ≥3.**

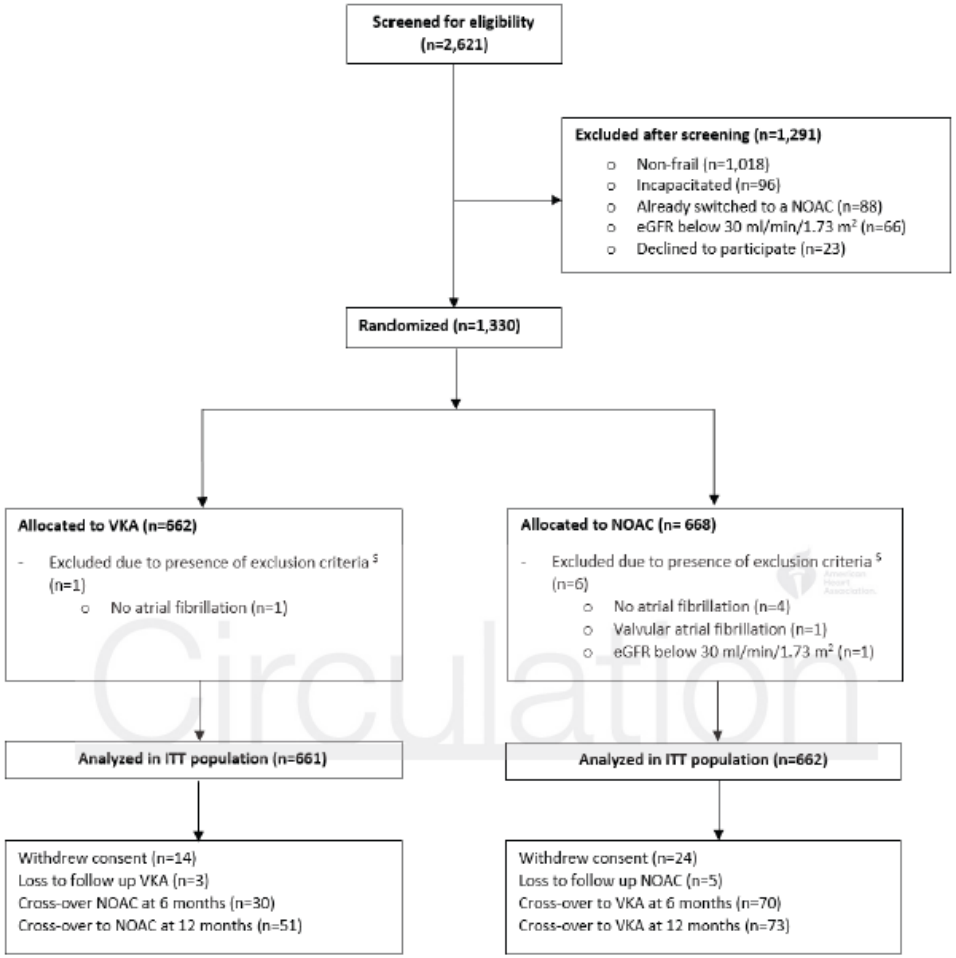
- Đồng ý chuyển từ điều trị VKA sang NOAC.

- **Tiêu chuẩn loại trừ:**

- Rung nhĩ do bệnh van tim (van cơ học và/hoặc HHL khít).

- MLCT ước tính < 30 mL/phút/1,73 m2.

- Tham gia 1 chương trình nghiên cứu khác và/hoặc không sẵn sàng hoặc không thể đăng ký ICF.



10.1161/CIRCULATIONAHA.123.066485

Kết quả nghiên cứu

Variable	Switch to NOAC		Continue with VKA		
	No. (%)	No. of events / 100 patient-yr (95% CI)	No. (%)	No. of events / 100 patient-yr (95% CI)	Hazard Ratio (95% CI)
Primary outcome					
Major or CRNM bleeding	101 (15.3%)	17.8 (14.5-21.6)	62 (9.4%)	10.5 (8.0-13.4)	1.69 (1.23-2.32)
Secondary outcomes					
Bleeding outcomes separately					
Major bleeding	24 (3.6%)	3.9 (2.5-5.9)	16 (2.4%)	2.6 (1.5-4.2)	1.52 (0.81-2.87)
CRNM bleeding	84 (12.7%)	14.6 (11.7-18.1)	49 (7.4%)	8.2 (6.1-10.9)	1.77 (1.24-2.52)
TE events	16 (2.4%)	2.6 (1.5-4.3)	13 (2.0%)	2.1 (1.1-3.6)	1.26 (0.60-2.61)
Composite of TE events plus major or CRNM bleeding	115 (17.4%)	20.6 (17.0-24.7)	73 (11.0%)	12.4 (9.8-15.6)	1.65 (1.23-2.21)
Composite of ischemic and hemorrhagic stroke	14 (2.1%)	2.3 (1.3-3.8)	11 (1.7%)	1.8 (0.9-3.2)	1.30 (0.59-2.87)
All-cause mortality	44 (6.7%)	7.1 (5.2-9.5)	46 (7.0%)	7.4 (5.4-9.8)	0.96 (0.64-1.45)

10.1161/CIRCULATIONAHA.123.066485

TƯƠNG TÁC THUỐC

Có phải là vấn đề cần quan tâm?

- **HOKUSAI VTE Cancer:** *dùng Edoxaban liều giảm (30 mg/ngày)* nếu điều trị thuốc ức chế P-glycoprotein mạnh.
- **SELECT-D:** dùng cùng chất ức chế hoặc hoạt hoá P450 3A4 hoặc P-glycoprotein mạnh là tiêu chuẩn loại trừ.
- **ADAM VTE:** Dùng cùng chất hoạt hoá CYP 3A4 mạnh là tiêu chuẩn loại trừ. *Dùng Apixaban liều giảm (2,5 mg x 2 lần/ngày)* nếu dùng chất ức chế CYP 3A4 và/hoặc P-glycoprotein mạnh.

Drug-Drug Interactions

- NOACs and warfarin are substrates of key metabolic and transport pathways
- Some DDIs are well documented; clinical relevance of many potential DDIs is unknown
  - Unknowns are further complicated by polytherapy

Anticoagulants as Substrates for Major Pathways

Anticoagulant	CYP3A4 (metabolic)	P-gp (transport)	Other CYP metabolizing enzymes (2C9, 2C19, 2C8, 2C18, 1A2)
LMWH	No	No	No
VKAs	Major	No/minor	All (major: CYP2C9)
Apixaban	Major	Major	Minor: 1A2, 2C8, 2C9, 2C19
Edoxaban	Minor	Major	No
Rivaroxaban	Major	Major	No
Dabigatran	No	Moderate	No

Fitzgerald JL, Howes LG. *Drug Saf*. 2016;39:841-845.

Drug-Drug Interactions
Inducers and Inhibitors of CYP3A4 and P-gp

Inhibitors of CYP3A4 and/or P-gp may increase risk of bleeding on NOACs

Chemotherapies	CYP3A4	P-gp
Doxurubicin	↓	
Topotecan	↓	
Vinblastine	↓	
Mitotane	↑	
Venetoclax		↓

Supportive care	CYP3A4	P-gp
Aprepitant	↓	
Methylprednisolone	↓	
Dexamethasone	↑	↑

Kinase inhibitors	CYP3A4	P-gp
Afatinib		↓
Alectinib		↓
Ceritinib	↓	
Crizotinib	↓	
Dasatinib	↓	
Ibrutinib		↓
Idelalisib	↓	↓
Imatinib	↓	
Lapatinib	↓	↓
Nilotinib	↓	↓
Osimertinib	↓	
Vemurafenib	↑	↓
Lenvatinib	↑	↑

Short NJ, Connors JM. *Oncologist*. 2014;19:82-93.

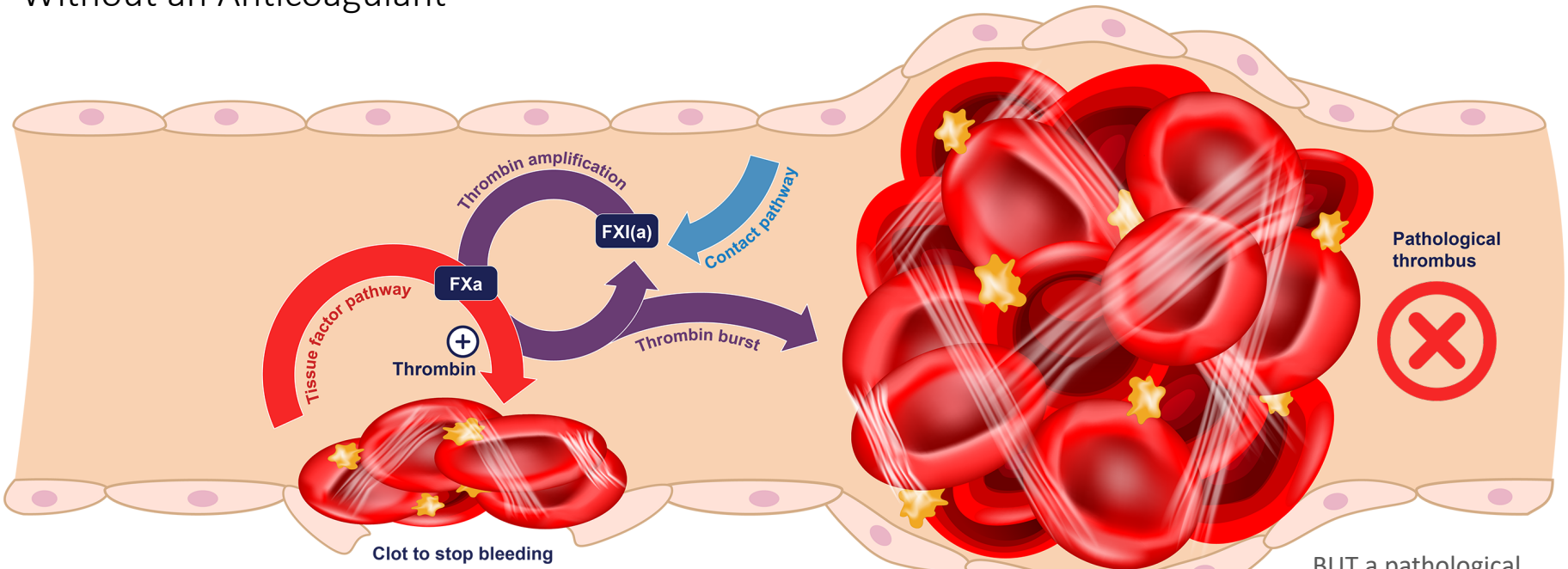
KẾT LUẬN

- Hiện tại, NOACs/DOACs đã trở thành "tiêu chuẩn" trong điều trị các bệnh lý liên quan đến huyết khối.
- Tuy nhiên, ***trong 1 số bệnh cảnh lâm sàng cụ thể, NOACs/DOACs có thể liên quan đến tăng nguy cơ tắc mạch (động mạch/đột quỵ…) hoặc chảy máu (đường tiêu hoá…).***
- **Cá thể hoá điều trị luôn cần thiết.**
- Nguyên tắc điều trị thuốc chống đông: **Đúng chỉ định – Đúng liều dùng – Đảm bảo tuân trị & theo dõi cẩn thận.**

Newcomers & the game is not over…

Normal Physiology

Without an Anticoagulant



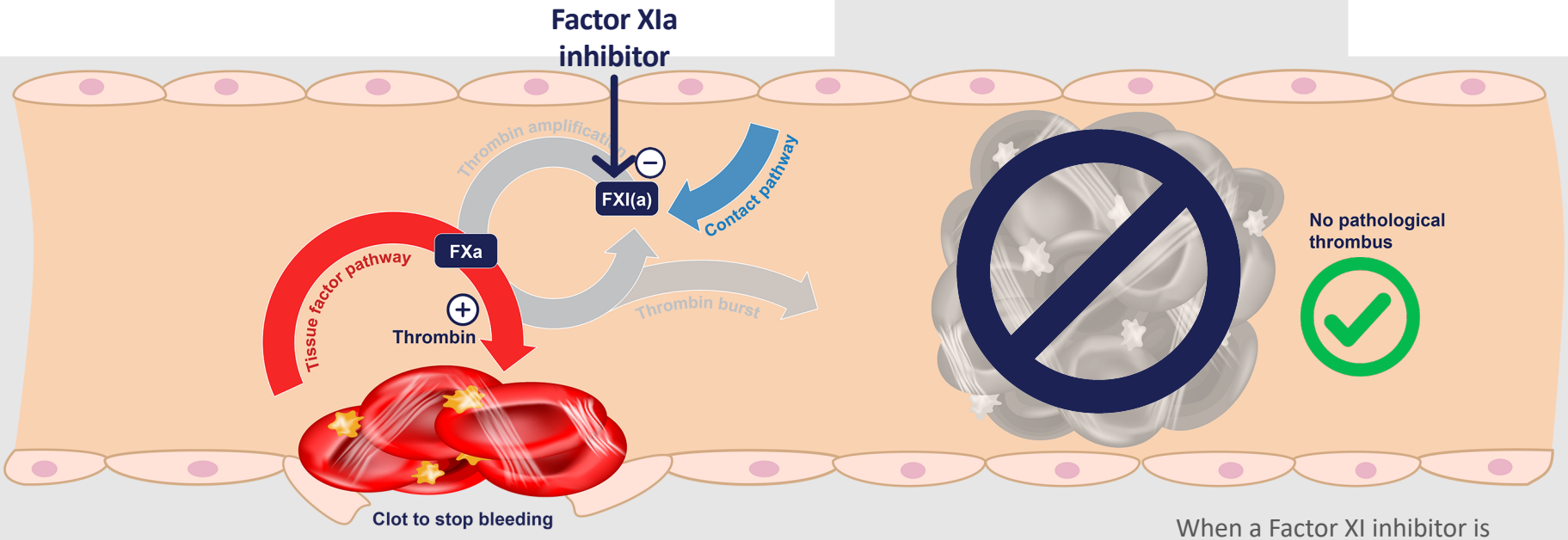
When no anticoagulant is used, a clot is formed to stop the bleeding—

BUT a pathological thrombus could also be created.

Newcomers & the game is not over…

With a Factor XIa Inhibitor

Hypothesis: Uncoupling Hemostasis & Thrombosis



AND the tissue factor pathway still produces thrombin, which allows beneficial blood clots to form to stop bleeding.

When a Factor XI inhibitor is used, thrombin amplification is inhibited, which prevents pathologic thrombi—

Newcomers & the game is not over…

PACIFIC Program

Concerted evaluation across phase 2 programs

PACIFIC AF

Atrial fibrillation
20mg asundexian
50mg asundexian
apixaban

~750 patients randomized
Results at ACC 2022

PACIFIC AMI

Acute myocardial infarction
10mg asundexian
20mg asundexian
50mg asundexian
placebo

+ dual antiplatelet therapy

~ 1600 patients randomized
Results at ESC 2022

PACIFIC STROKE

Non-cardioembolic ischemic stroke
10mg asundexian
20mg asundexian
50mg asundexian
placebo

+ single or dual antiplatelet therapy

~ 1800 patients randomized
Results at ESC 2022

Less bleeding with asundexian 20 or 50 mg QD than with apixaban in patients with AF[1]

- One coordinated IDMC
- One blinded CEC with uniform process

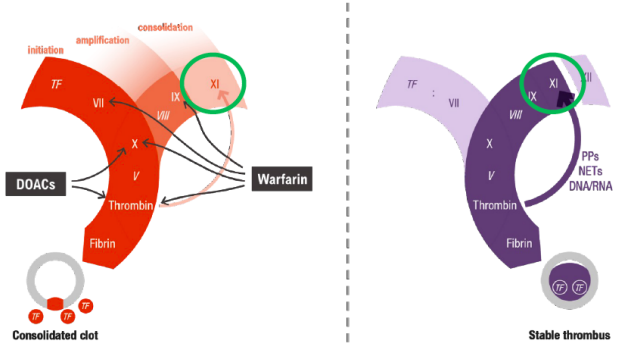
[1]Piccini JP, et al. Lancet 2022; 399: 1383–90

Newcomers & the game is not over…

Factor XI Inhibition

Potential to Uncouple

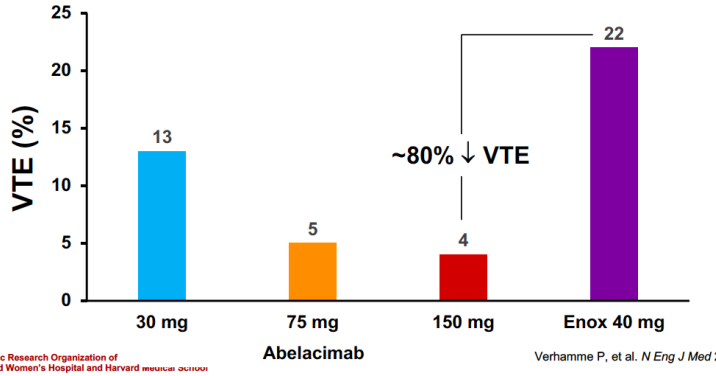
Hemostasis from **Thrombosis**



Hsu C, et al. *J Am Coll Cardiol* 2021;78:625-631

Abelacimab for Prevention of Venous Thromboembolism

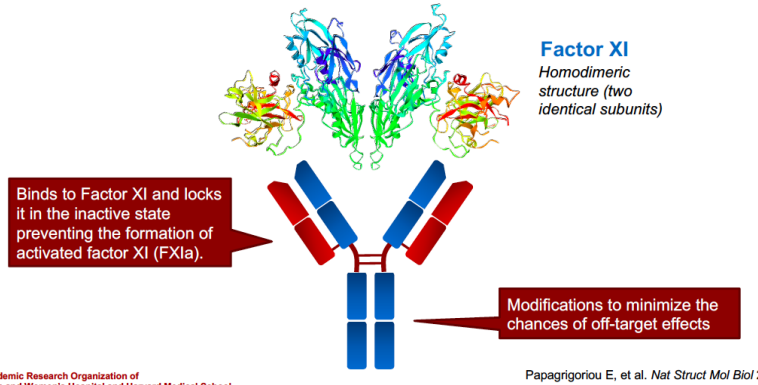
Phase 2, Open-Label, RCT in 400 Patients After Total Knee Placement



Verhamme P, et al. *N Eng J Med* 2021;385:609-617

Abelacimab

Highly selective, fully human monoclonal antibody



Papagrigoriou E, et al. *Nat Struct Mol Biol* 2006;13:557-558

Bleeding Endpoints

AZALEA TIMI 71

Endpoint (ISTH Definition)	Riva 20 mg (N=430) Incidence Rate	Abelacimab 150 mg (N=427) Incidence Rate	HR (95% CI)	P Value	Abelacimab 90 mg (N=425) Incidence Rate	HR (95% CI)	P-Value
Major + CRNM Bleeding	8.1	2.7	0.33 (0.19-0.55)	<0.001	1.9	0.23 (0.13-0.42)	<0.001
Major Bleeding	3.7	1.0	0.26 (0.11-0.61)	0.002	0.7	0.19 (0.07-0.50)	<0.001
GI Bleeding	2.1	0.1	0.07 (0.01-0.50)	0.008	0.1	0.07 (0.01-0.51)	0.009
ICH	0.6	0.3	0.50 (0.09-2.72)	0.42	0.6	1.03 (0.26-4.10)	0.97
CRNM Bleeding	4.6	1.8	0.39 (0.21-0.75)	0.004	1.1	0.25 (0.11-0.54)	<0.001

Incidence rates per 100 Pt-years

On-Treatment Population
Based on final DMC Datacut

XIN TRÂN TRỌNG CẢM ƠN!