Recent advances in the management of thrombotic complications associated with cancer

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Learning objectives

Discuss indications for anticoagulation prophylaxis in cancer patients

Discuss role of direct oral anticoagulants and low-molecular weight heparin in treatment of cancer associated venous thromboembolism

Cancer and thrombosis
The problem

- The reported incidence of cancer associated venous thrombosis varies widely between studies (1.6% to 6%)
- 4-7 x higher risk of Venous Thromboembolism (VTE)
- 3 x higher risk of recurrent VTE
- 2 x higher risk of bleeding with anticoagulation
- Thromboembolism is a leading cause of death for patients with malignancy

Mahajan A, et. al. The incidence of cancer-associated thrombosis is increasing over time. Blood Adv. 2022 Jan 11;6(1):307-320 PMID: 34649273

Mechanisms of thrombosis in cancer
What causes the problem

Extracellular vesicles may contain Tissue Factor

Neutrophil extracellular traps

Inflammatory cytokines - TNFα, IL -1β, IL6, VEGF

Extracellular microRNAs

PAI -1

Hisada Y, Mackman N. Mechanisms of cancer-associated thrombosis. Res Pract Thromb Haemost. 2023 Mar 15;7(3):100123. PMID: 37122533

Risk factors

Cancer type (highest risk pancreatic, brain, stomach, lung) and cancer genetics (e.g. Jak2 V617F mutation)

Cancer stage (risk higher in advanced stages) and grade

Type of treatment (e.g. lenalidomide, asparaginase)

Underlying comorbidities including prior history of venous thromboembolism, thrombophilia carrier

The Khorana risk score

Who will develop chemotherapy associated venous thromboembolism?

Association of venous thromboembolism with multiple variables was characterized in:

Derivation cohort consisted of 2701 cancer outpatient from a prospective observational study

Risk model derived and validated in an independent cohort of 1365 patients from the same study

Khorana AA, et.al. Development and validation of a predictive model for chemotherapy-associated thrombosis.
Blood. 2008 May 15;111(10):4902-7 PMID: 18216292

The Khorana risk score

Who will develop chemotherapy associated venous thromboembolism?

Patient's Characteristics	**Risk score**
Site of cancer	
-Very high risk (stomach, pancreas)	2
-High risk (lung, lymphoma, gyn, GU)	1
Prechemotherapy platelet count ≥ 350 $x10^9$/L	1
Prechemotherapy Hgb < 10 g/dL or use of Red Cell growth factors	1
Pre-chemo WBC count >11 $x10^9$/L	1
BMI ≥ 35 kg/m2	1

Risk of short-term VTE

0 = low risk	0.3-0.8%
1-2= intermediate risk	1.8-2.0%
>2 = high risk	6.7-7.1%

Khorana AA, et.al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008 May 15;111(10):4902-7 PMID:18216292

Other Prediction Models for Venous thromboembolism in Cancer Patients

- Protecht score = Khorana + chemotherapeutic agents (cisplatin, carboplatin and gemcitabine)

- Vienna Cancer and Thrombosis Study (CATS) score = Khorana + d-dimer and soluble P-selectin

- New Austrian prediction model = based on tumor-site category and d-dimer biomarker

Verso M, et. al. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score.
Intern Emerg Med. 2012 Jun;7(3):291-2. PMID: 22547369.

Ay C, et. al., Prediction of venous thromboembolism in cancer patients.
Blood. 2010 Dec 9;116(24):5377-82 PMID: 20829374.

Pabinger I, et. al. A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts.
Lancet Haematol. 2018 Jul;5(7):e289-e298 PMID: 29885940

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer

Gary H. Lyman,[1,2,*] Marc Carrier,[3,*] Cihan Ay,[4] Marcello Di Nisio,[5] Lisa K. Hicks,[6] Alok A. Khorana,[7] Andrew D. Leavitt,[8,9] Agnes Y. Y. Lee,[10,11] Fergus Macbeth,[12] Rebecca L. Morgan,[13] Simon Noble,[14] Elizabeth A. Sexton,[15] David Stenehjem,[16] Wojtek Wiercioch,[13] Lara A. Kahale,[17,†] and Pablo Alonso-Coello[18,†]

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Lyman GH, et. Al. Blood Adv. 2021 Feb 23;5(4):927-974. Erratum in: Blood Adv. 2021 Apr 13;5(7):1953.

Thrombosis Prophylaxis Recommendations in Hospitalized Cancer patients

- For **hospitalized medical** patients with cancer:
  Use thromboprophylaxis during hospitalization
  LWWH over UFH
  Pharmacological prophylaxis over mechanical prophylaxis
- For **patients with cancer undergoing surgery**:
  In pts with low bleeding risk – pharmacologic prophylaxis
  In pts with high bleeding risk – mechanical prophylaxis
  In pts with high thrombosis risk but without high bleeding risk –both mechanical and pharmacologic prophylaxis

Lyman GH, et. al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021 Feb 23;5(4):927-974. PMID: 33570602.

Prevention of clots in ambulatory cancer patients

Cassini trial — Xarelto 10 mg daily vs placebo

VTE rates	Xarelto 6%	vs 8.8% placebo
Major bleeding rates	Xarelto 2%	vs 1% placebo

Khorana AA, Soff GA, et. al. CASSINI Investigators. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N Engl J Med. 2019 Feb 21;380(8):720-728. PMID: 30786186.

Prevention of clots in ambulatory cancer patients

Avert trial	Apixaban 2.5 mg bid vs placebo
VTE rates	Apixaban 4.2% vs 10.2% placebo
Major bleeding rates	Apixaban 3.5% vs 1.8% placebo

Carrier M, Abou-Nassar K, et. al. AVERT Investigators. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. N Engl J Med. 2019 Feb 21;380(8):711-719PMID: 30511879.

Thromboprophylaxis in ambulatory cancer patients

No thromboprophylaxis in low-risk patients

Thromboprophylaxis in high-risk patients

ASH suggests
ISTH suggests
ASCO may be offered
NCCN consider

Lyman GH, et. al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021 Feb 23;5(4):927-974. PMID: 33570602

Streiff MB, Abutalib SA, Farge D, Murphy M, Connors JM, Piazza G. Update on Guidelines for the Management of Cancer-Associated Thrombosis. Oncologist. 2021 Jan;26(1):e24-e40 PMID: 33275332

Treatment of cancer-associated Venous thromboembolism

It used to be low-molecular weight heparin…

CLOT trial

Recurrent VTE: 15.7 % warfarin vs 7.9 % dalteparin

Major Bleeding: 6% warfarin vs 4% dalteparin

CATCH trial

Recurrent VTE: 10% warfarin vs 6.9% tinzaparin

Major Bleeding: 2.7% warfarin vs 2.4% tinzaparin

Lee AY Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer.
N Engl J Med. 2003 Jul 10;349(2):146-53 PMID: 12853587.

Lee AYY CATCH Investigators. Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial.
JAMA. 2015 Aug 18;314(7):677-686 PMID: 26284719.

Direct oral Anticoagulants in the management of cancer patients with venous thromboembolism

Edoxaban

Recurrent VTE:
7.9% edoxaban vs 11.3% dalteparin

Major bleeding:
6.9% edoxaban group vs 4.0 % dalteparin group

Raskob GE, et. al. Hokusai VTE Cancer Investigators. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med. 2018 Feb 15;378(7):615-624 PMID: 29231094.

Direct oral Anticoagulants in the management of cancer patients with venous thromboembolism

Rivaroxaban

Recurrent VTE: 4% rivaroxaban vs 11% dalteparin

Major bleeding: 6% rivaroxaban vs 4% dalteparin

Young AM, et. al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D).
J Clin Oncol. 2018 Jul 10;36(20):2017-2023 PMID: 29746227.

Direct oral Anticoagulants in the management of cancer patients with venous thromboembolism

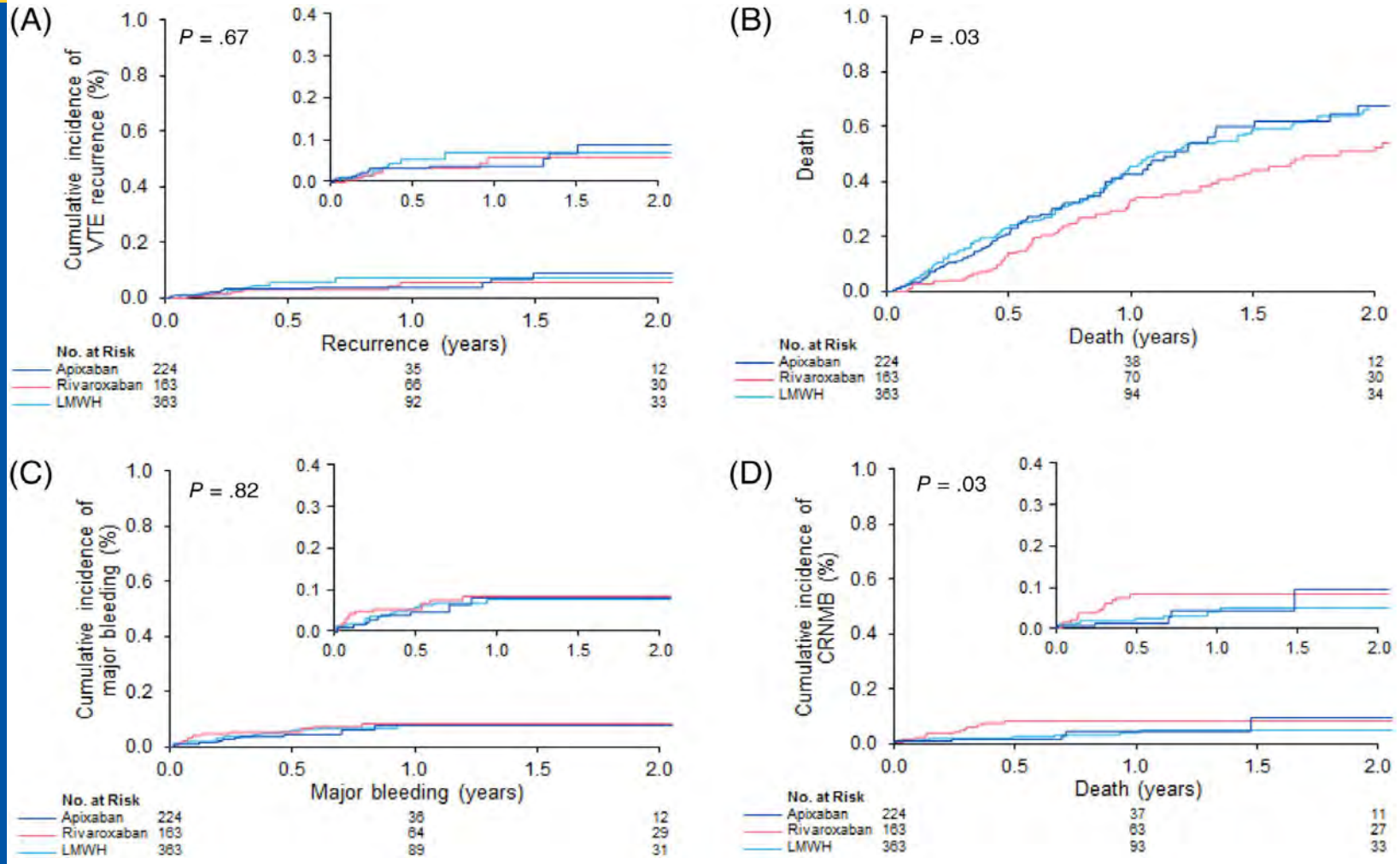
Apixaban

Recurrent VTE: 5.6% apixaban vs 7.9 % dalteparin

Major bleeding: 3.8% apixaban vs 4.0% dalteparin

Agnelli G, et. al. Caravaggio Investigators. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer.
N Engl J Med. 2020 Apr 23;382(17):1599-1607 PMID: 32223112.

Comparison of apixaban to rivaroxaban and enoxaparin in acute cancer-associated venous thromboembolism



Consecutive patients treated with apixaban, rivaroxaban, or enoxaparin at Mayo Thrombophilia Clinic (March 1, 2013 to January 31, 2018)

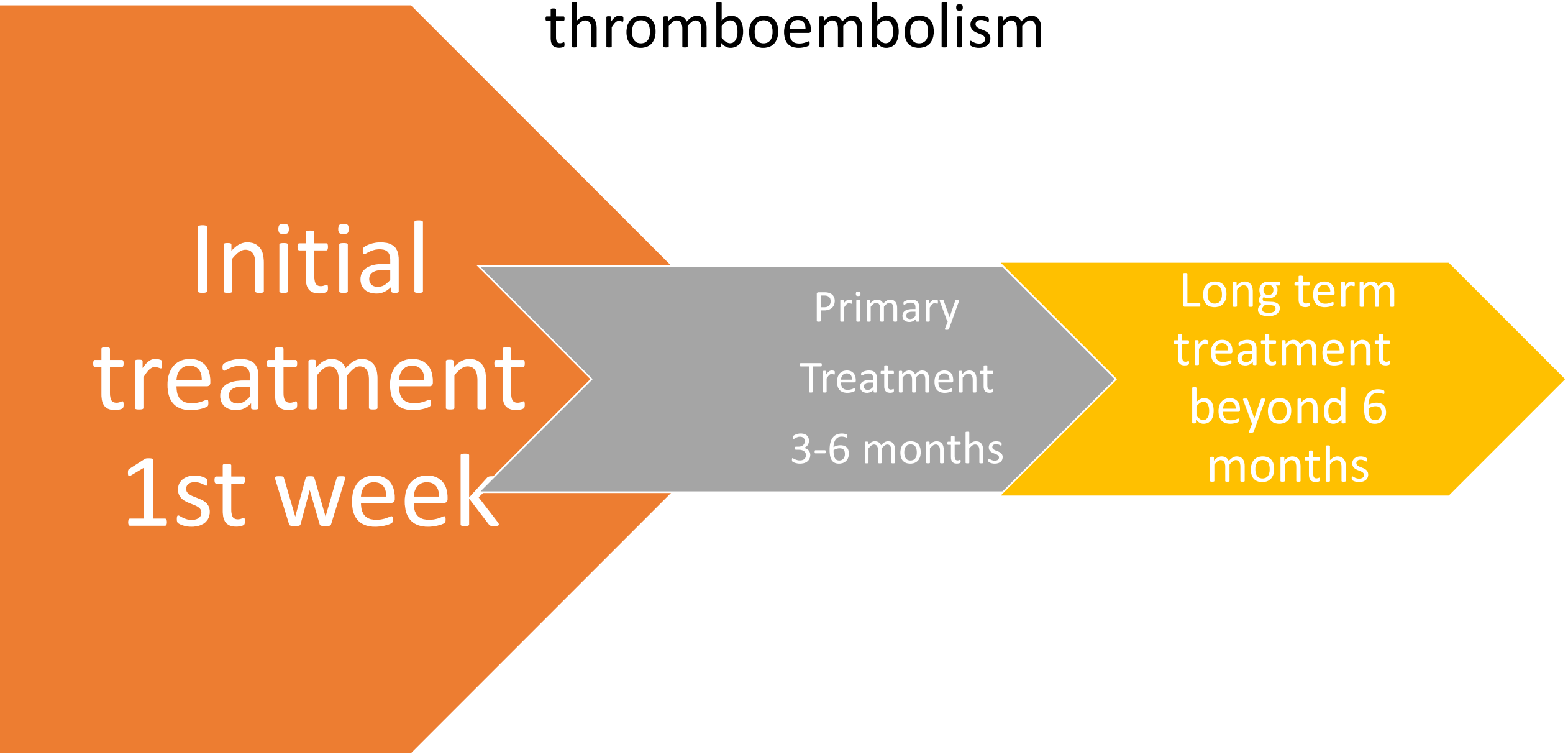
There were 750 patients treated for acute Ca-VTE with apixaban (n = 224), rivaroxaban (n = 163), and enoxaparin (n = 363) within 14 days of diagnosis and for at least 3 months, or until study event.

Recurrence of VTE and major bleeding were similar in apixaban, rivaroxaban, and enoxaparin groups. Rivaroxaban was associated with higher CRNMB but lower mortality compared to apixaban and enoxaparin.

Wysokinski WE, et. al., Am J Hematol. 2019 Nov;94(11):1185-1192 PMID: 31378995

Treatment of cancer-associated Venous thromboembolism

Treatment of cancer-associated Venous thromboembolism



Initial treatment in patients with cancer diagnosed with venous thromboembolism

- Direct oral anticoagulant such as Apixaban, Edoxaban or Xarelto or LMWH
- LMWH favored over unfractionated heparin (except in severe renal failure)
- Caution with DOACs in patients with gastrointestinal cancers

Lyman GH, et. al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021 Feb 23;5(4):927-974. PMID: 33570602

Treatment of cancer-associated Venous thromboembolism

Short and long-term treatment of cancer associated venous thromboembolism

- Direct oral anticoagulant such as Apixaban, Edoxaban or Rivaroxaban is preferred over LMWH

- Continue treatment beyond 6 months in patients with active cancer

Lyman GH, et. al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer.
Blood Adv. 2021 Feb 23;5(4):927-974. PMID: 33570602

Treatment of cancer-associated Venous thromboembolism

Influence of primary cancer site on clinical outcomes of anticoagulation for associated venous thromboembolism

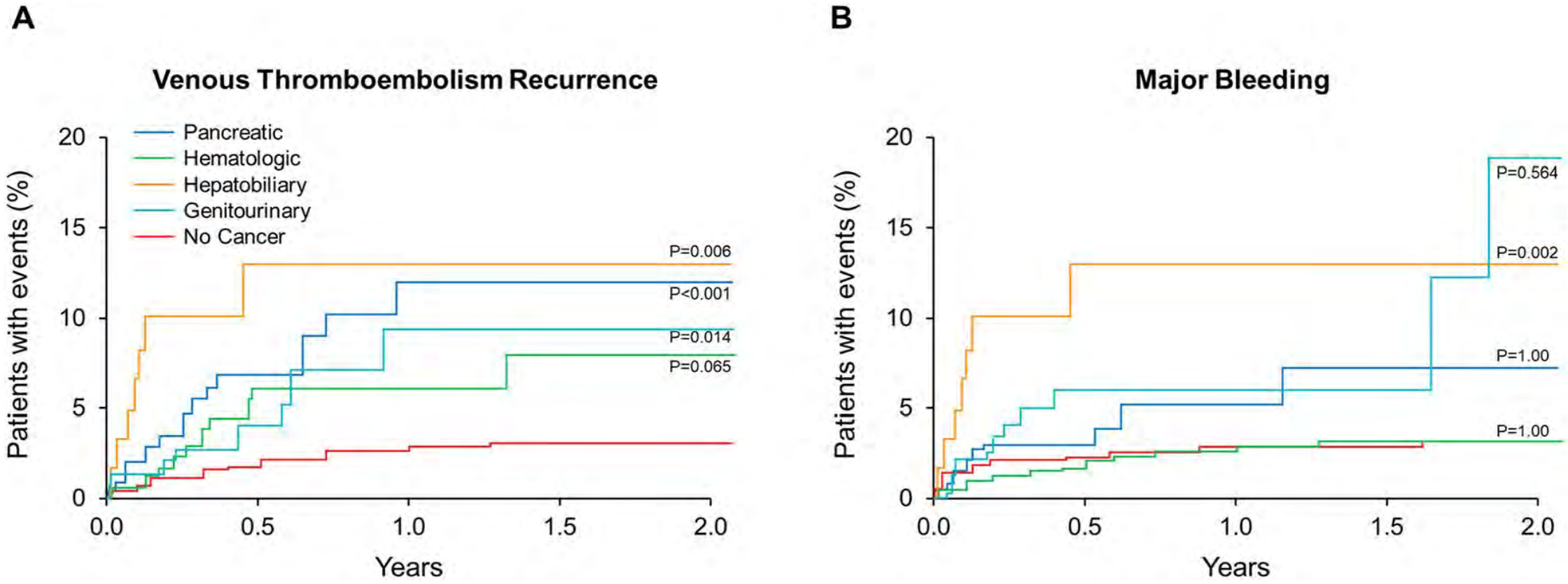
Patients with acute venous thromboembolism (VTE) enrolled between 03/01/2013 and 04/30/2021 were followed prospectively to assess VTE recurrence, major bleeding (MB), clinically relevant non-major bleeding (CRNMB), and death

patients with Ca-VTE n=1702 (45.3 %)
gastrointestinal (*n* = 340)
pancreatic (*n* = 223)
hematologic (*n* = 188)
genitourinary (*n* = 163)
lung (*n* = 139), ovarian (*n* = 109,
breast (*n* = 97), renal (*n* = 75)
prostate (*n* = 73)
hepatobiliary (*n* = 70)
brain (*n* = 57)
other cancers (*n* = 168)

patients without VTE without cancer (n=2057)

Wysokinski WE, et. al.
Thromb Res. 2023 Jan;221:37-44 PMID: 36463701.

Influence of primary cancer site on clinical outcomes of anticoagulation for associated venous thromboembolism



Wysokinski WE, Thromb Res. 2023 Jan;221:37-44 PMID: 36463701.

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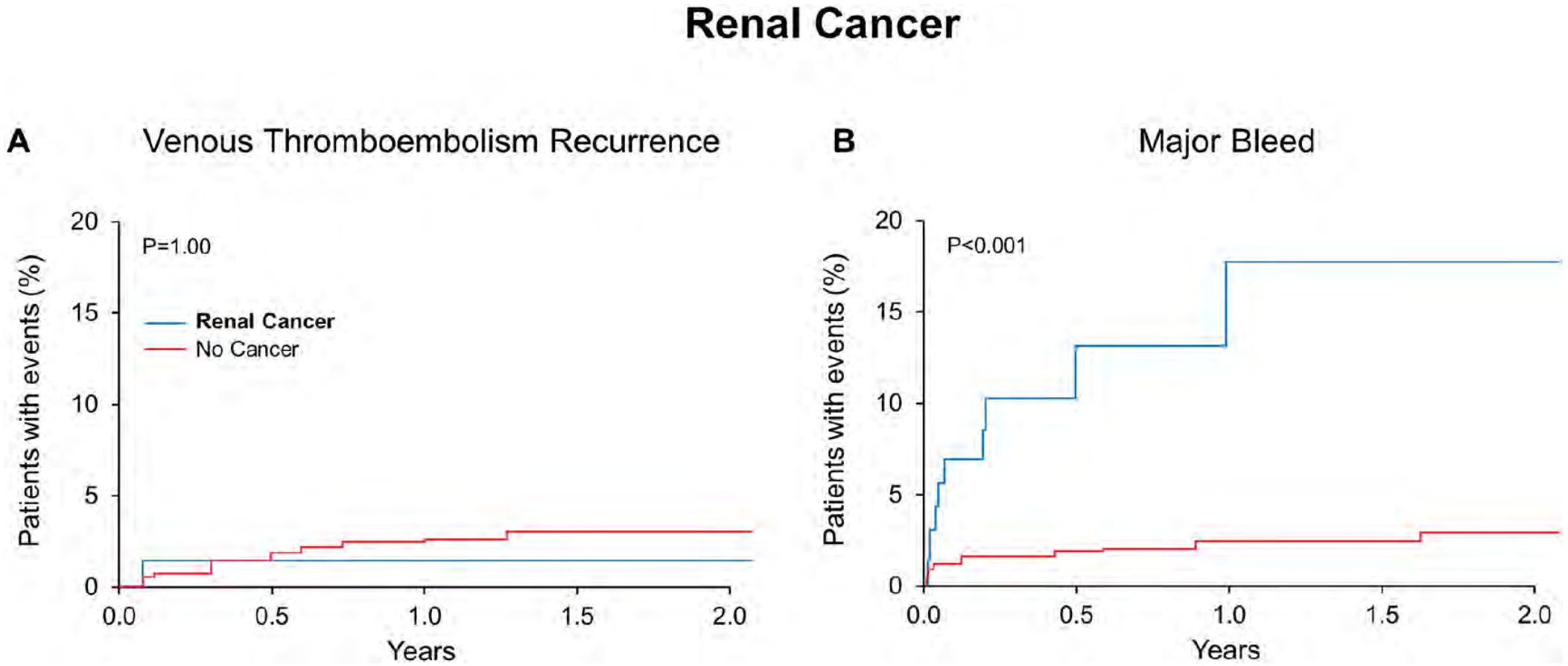


Wysokinski WE, Thromb Res. 2023 Jan;221:37-44 PMID: 36463701.

Influence of primary cancer site on clinical outcomes of anticoagulation for associated venous thromboembolism

Patients with hepatobiliary, pancreatic, genitourinary, and hematologic cancers had higher VTE recurrence rates, while major bleeding rates were not statistically different compared to patients without cancer.

Renal cancer patients, on the other hand, had a much higher rate of major bleeding but a similar VTE recurrence rate compared to non-cancer-VTE patients.

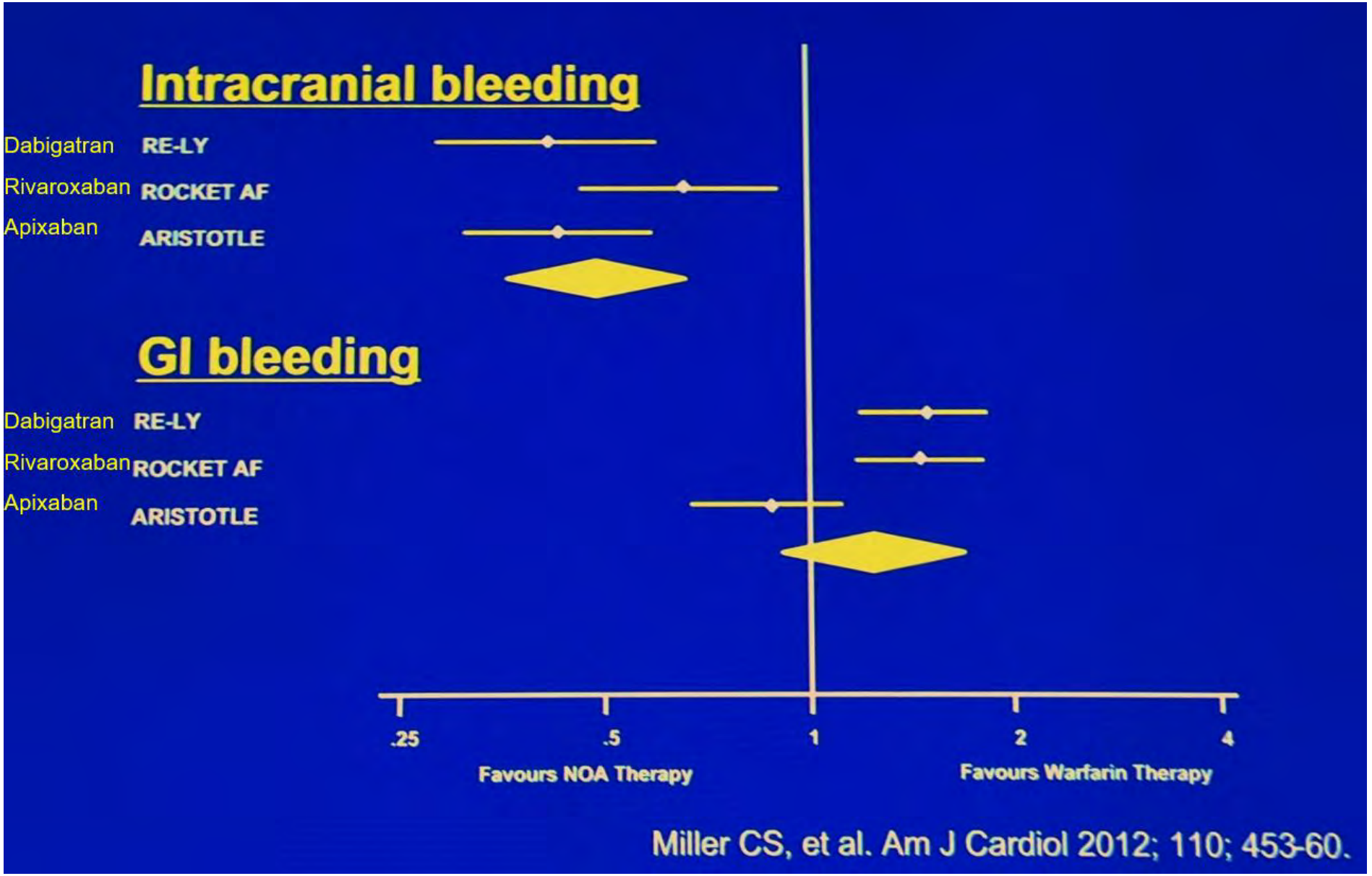
The lung, ovarian, gastrointestinal, breast, and prostate cancer groups showed VTE recurrence and MB rates that were not different from those of non-cancer-VTE.

A higher proportion of major bleeding versus VTE recurrence was observed in patients with renal, lung, hepatobiliary, gastrointestinal, ovarian, prostate, and “other cancers”, while patients with pancreatic, hematologic, genitourinary, and breast cancers had proportionally higher VTE recurrence than major bleeding.

These findings raise the possibility that modification of anticoagulation intensity and duration relative to specific cancer location may positively influence outcomes.

Wysokinski WE, Thromb Res. 2023 Jan;221:37-44 PMID: 36463701.

Direct oral anticoagulants compared with vitamin K inhibitor for stroke prevention in A-fib
Intracranial hemorrhage and gastrointestinal bleeding comparison

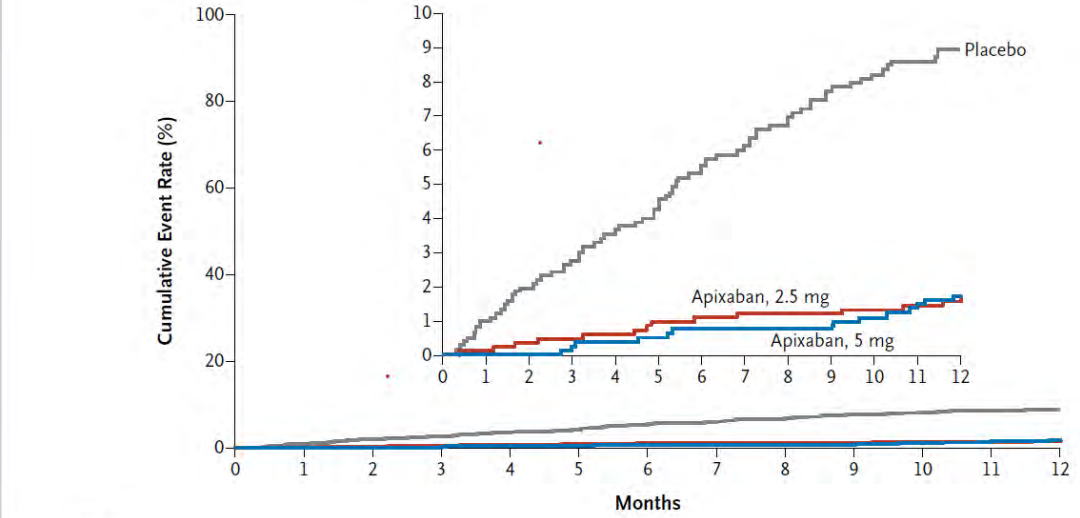


What about dose intensity of long-term anticoagulation in cancer patients with venous thromboembolism?

Reduced or low-dose direct oral anticoagulants have been studied in randomized controlled trials for the extended prevention of venous thromboembolism after 6 months of treatment at full, therapeutic doses

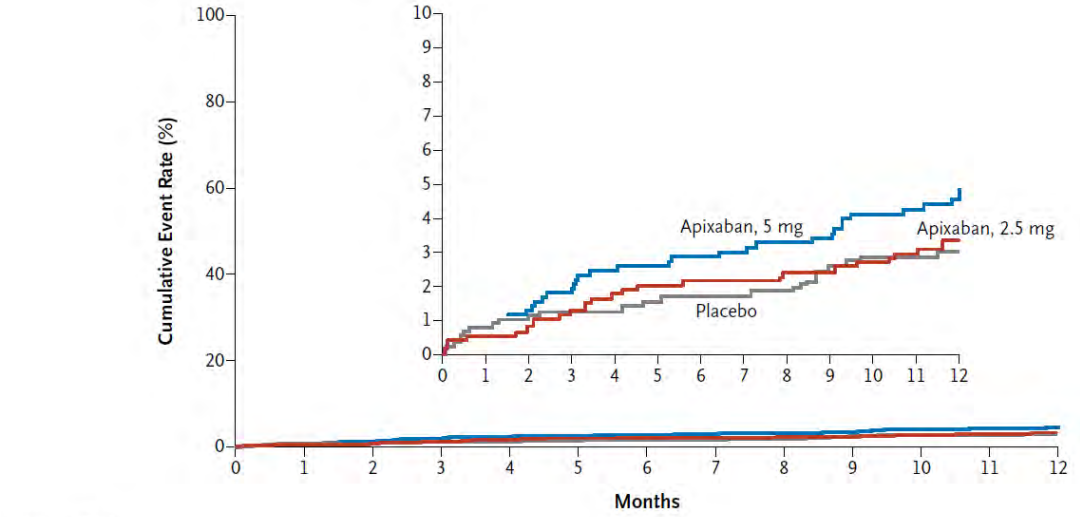
Apixaban for extended treatment of venous thromboembolism

Symptomatic recurrent VTE or VTE-related death



No. at Risk					
Apixaban, 2.5 mg	840	836	825	818	533
Apixaban, 5 mg	813	807	799	791	513
Placebo	826	796	768	743	471

Major or clinically relevant nonmajor bleeding



No. at Risk					
Apixaban, 2.5 mg	840	786	759	737	354
Apixaban, 5 mg	811	751	716	689	331
Placebo	823	749	687	651	298

After 6 months of therapeutic anticoagulation patients were randomized to:

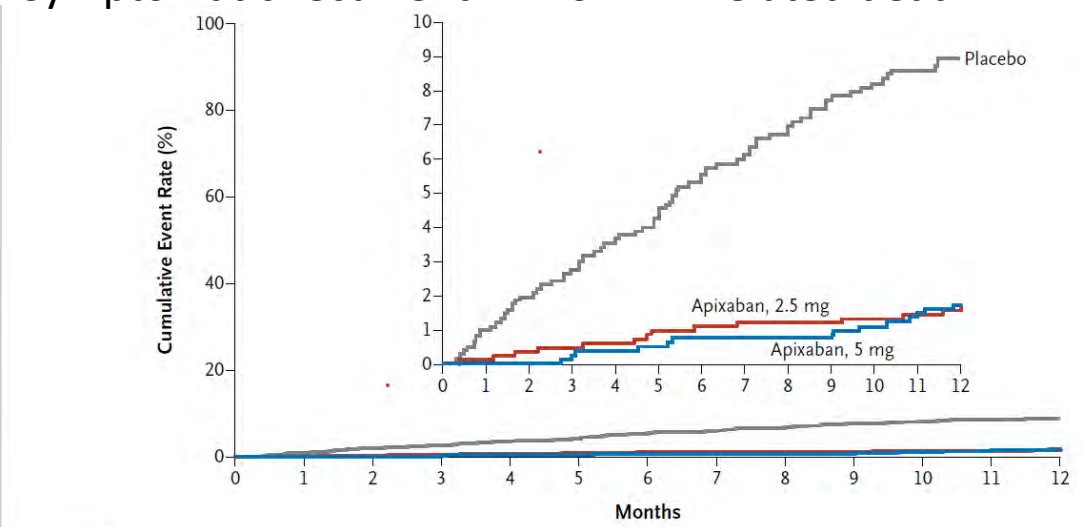
Continue full-dose therapeutic apixaban 5 mg orally twice daily

Continue prophylactic dose apixaban 2.5 mg orally twice daily

Placebo

Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI; AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013 Feb 21;368(8):699-708. doi: 10.1056/NEJMoa1207541. Epub 2012 Dec 8. PMID: 23216615.

Symptomatic recurrent VTE or VTE-related death



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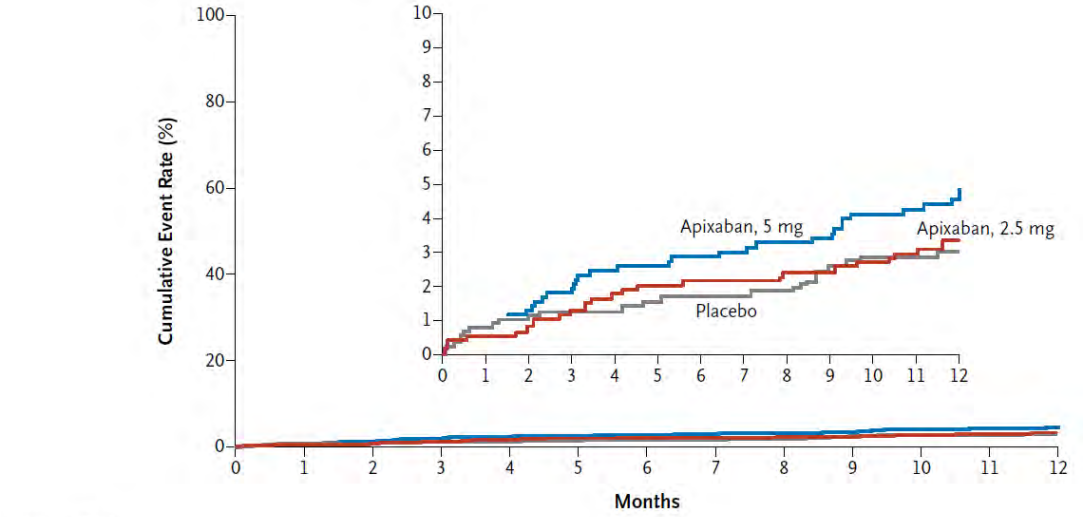

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Exclusion Medical History and Concurrent Diseases

a) Subjects with a provoked index event without the existence of a persistent risk factor for recurrence as described in the eligibility checklist.

b) More than 12 months of anticoagulation planned for the most recent DVT or PE (index event).

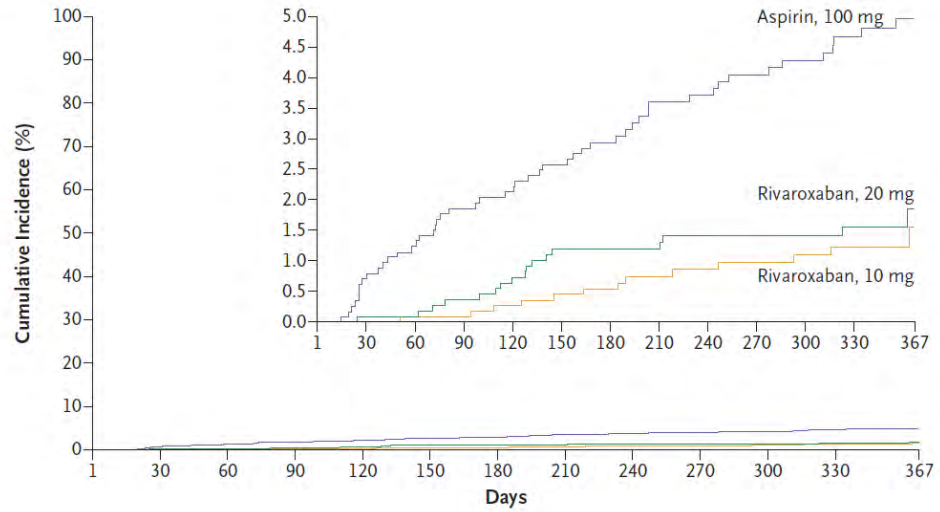
c) Subjects with indications for long-term treatment with a VKA, such as: • Mechanical valve • Atrial fibrillation or atrial flutter with moderate to high risk of systemic thromboembolism • Multiple episodes of unprovoked DVT or PE • Documented anti-phospholipid antibodies, anti-thrombin III deficiency, protein C deficiency, protein S deficiency, homozygous factor V Leiden, or homozygous prothrombin gene mutation.

d) Subjects with cancer who will be treated indefinitely with anticoagulation therapy.

Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI; AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013 Feb 21;368(8):699-708. doi: 10.1056/NEJMoa1207541. Epub 2012 Dec 8. PMID: 23216615.

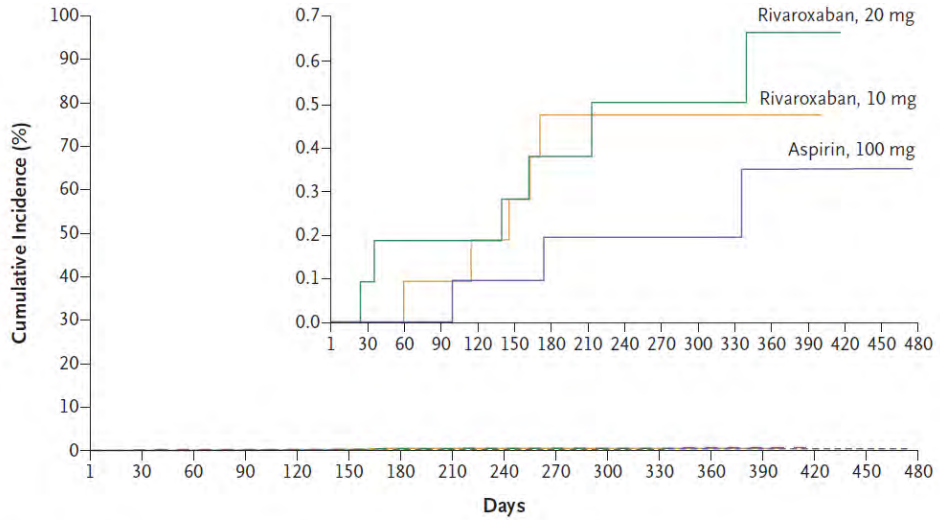
Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

Fatal or nonfatal venous thromboembolism



No. at Risk													
Rivaroxaban, 20 mg	1107	1102	1095	1090	1084	1079	997	876	872	860	794	718	0
Rivaroxaban, 10 mg	1126	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
Aspirin, 100 mg	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

Major bleeding



No. at Risk																
Rivaroxaban, 20 mg	1107	1081	1063	1048	1036	1024	963	818	801	780	712	642	449	10	0	0	0
Rivaroxaban, 10 mg	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469	8	0	0	0
Aspirin, 100 mg	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445	5	2	2	0

After 6 months of therapeutic anticoagulation patients were randomized to:

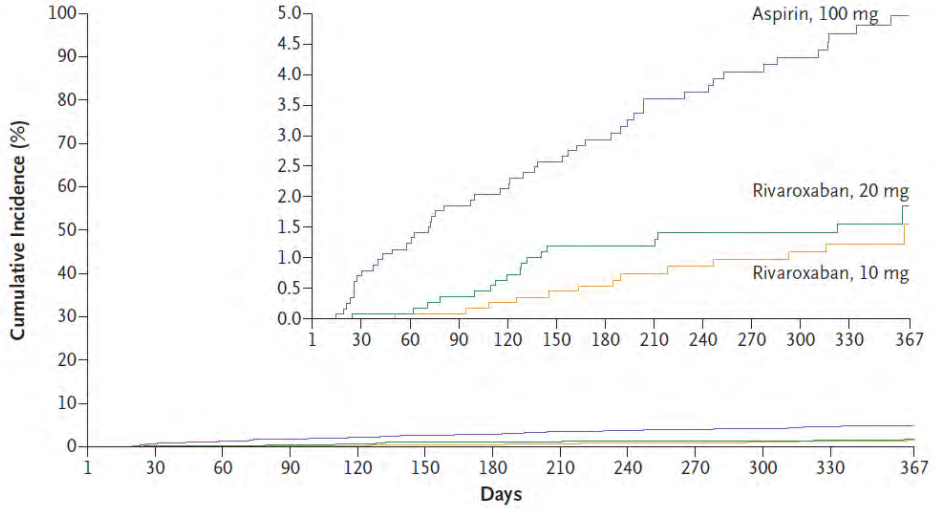
Continue full-dose therapeutic rivaroxaban 20 mg orally daily

Continue maintenance dose rivaroxaban 10 mg orally daily

Discontinue rivaroxaban and start baby aspirin orally daily

Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Freitas MCS, Holberg G, Kakkar AK, Haskell L, van Bellen B, Pap AF, Berkowitz SD, Verhamme P, Wells PS, Prandoni P; EINSTEIN CHOICE Investigators. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. N Engl J Med. 2017 Mar 30;376(13):1211-1222. doi: 10.1056/NEJMoa1700518. Epub 2017 Mar 18. PMID: 28316279.

Fatal or nonfatal venous thromboembolism



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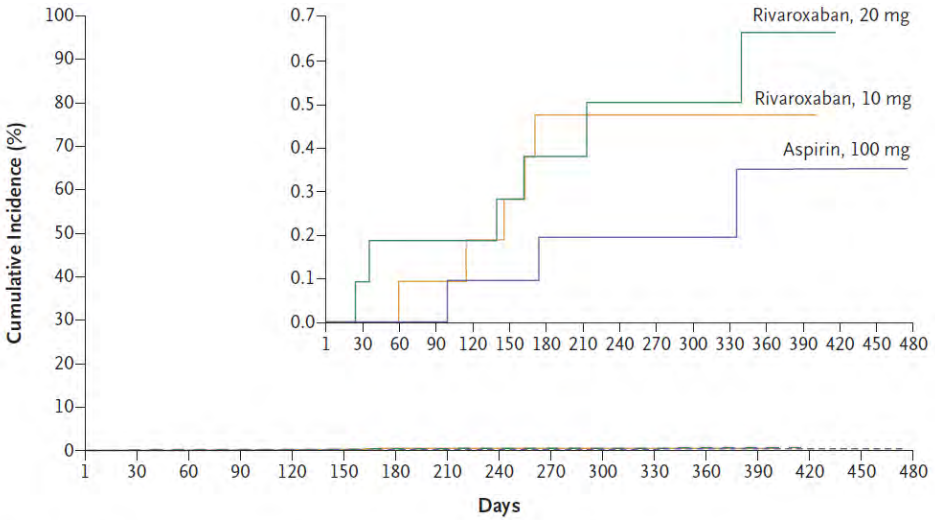
Aspirin, 100 mg	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

Major bleeding



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Rivaroxaban, 10 mg	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469	8	0	0	0
Aspirin, 100 mg	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445	5	2	2	0

Characteristic	Rivaroxaban		Aspirin
	20 mg (N=1107)	10 mg (N=1127)	100 mg (N=1131)
Male sex — no. (%)	602 (54.4)	620 (55.0)	643 (56.9)
Age — yr			
Mean ±SD	57.9±14.7	58.8±14.7	58.8±14.7
Median (IQR)	59.0 (48.0–69.0)	60.0 (48.0–69.0)	60.0 (48.0–69.0)
Weight — no. (%)			
<70 kg	276 (24.9)	283 (25.1)	277 (24.5)
70 to ≤90 kg	471 (42.5)	480 (42.6)	508 (44.9)
>90 kg	360 (32.5)	364 (32.3)	346 (30.6)
Body-mass index†			
<30	712 (64.3)	751 (66.6)	756 (66.8)
≥30	394 (35.6)	376 (33.4)	375 (33.2)
Missing data	1 (0.1)	0	0
Creatinine clearance — no. (%)			
<30 ml/min	1 (0.1)	2 (0.2)	1 (0.1)
30 to <50 ml/min	40 (3.6)	49 (4.3)	63 (5.6)
50 to <80 ml/min	279 (25.2)	302 (26.8)	277 (24.5)
≥80 ml/min	787 (71.1)	774 (68.7)	790 (69.8)
Index event — no. (%)			
Isolated deep-vein thrombosis	565 (51.0)	565 (50.1)	577 (51.0)
Isolated pulmonary embolism	381 (34.4)	381 (33.8)	366 (32.4)
Both deep-vein thrombosis and pulmonary embolism	155 (14.0)	179 (15.9)	181 (16.0)
Index event asymptomatic or unconfirmed	6 (0.5)	2 (0.2)	7 (0.6)
Classification of index venous thromboembolism — no. (%)			
Provoked	666 (60.2)	647 (57.4)	663 (58.6)
Unprovoked	441 (39.8)	480 (42.6)	468 (41.4)
Hormonal therapy — no. (%)			
Estrogens	8 (0.7)	6 (0.5)	8 (0.7)
Progestins	29 (2.6)	30 (2.7)	30 (2.7)
Known thrombophilia — no. (%)	79 (7.1)	74 (6.6)	70 (6.2)
Previous venous thromboembolism — no. (%)	198 (17.9)	197 (17.5)	194 (17.2)
Active cancer — no. (%)	25 (2.3)	27 (2.4)	37 (3.3)
Median duration of study-drug administration (IQR) — days	349 (189–362)	353 (190–362)	350 (186–362)
Individual intended study duration — no. (%)			
6 mo	206 (18.6)	209 (18.5)	212 (18.7)
9 to <12 mo	229 (20.7)	240 (21.3)	238 (21.0)
12 mo	672 (60.7)	678 (60.2)	681 (60.2)

Active cancer patients between 2-3% on each arm

Weitz JI, et. Al. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. N Engl J Med. 2017 Mar 30;376(13):1211-1222.

Extended full dose versus low-dose direct oral anticoagulants (DOAC) in cancer patients.

Consecutive patients with VTE were identified using the Mayo Clinic VTE registry from March 1, 2013 to December 31, 2021.

148 patients (115 (78%) on apixaban and 33(22%) on rivaroxaban) were identified in the low dose DOAC and 3060 patients in the full-dose anticoagulation group.

Low-dose DOAC prescription was more likely in patients with pulmonary embolism alone or in combination with DVT.

Patients transitioned to low-dose DOAC had similar age, sex and weight compared to the full dose anticoagulation group.

The mean time to start of a low-dose DOAC was 5.4 months.

Vlazny DT, et. al. Poster #1276 presented at American Society of Hematology meeting December 2023

Extended full dose versus low-dose direct oral anticoagulants (DOAC) in cancer patients.

There was no significant difference in venous thromboembolism recurrence or death on different DOAC doses.

Apixaban continue to be the dominant DOAC used in the low-dose group

Most cancer patients on low-dose DOAC had lymphoma, prostate, melanoma, ovarian or breast cancer.

Vlazny DT, et. al. Poster #1276 presented at American Society of Hematology meeting December 2023

Additional considerations in the treatment of cancer associated venous thromboembolism

- In patients with cancer should you treat with anticoagulation:
  - Incidental PE **YES**
  - Subsegmental PE **YES**
  - Visceral/splanchnic vein thrombosis **YES** though observation is also an option

For patients with cancer and recurrent VTE despite receiving therapeutic LMWH consider increasing the LMWH dose to a supratherapeutic level

- IVC filter is not recommended for prevention in recurrent VTE

Lyman GH, et. al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021 Feb 23;5(4):927-974. PMID: 33570602

Additional considerations in the treatment of cancer associated venous thromboembolism

Should you keep central venous catheter (CVC) in patients with cancer and CVC-related clot ? **YES**

Continue therapeutic anticoagulation while the central venous catheter is in place.

Continue therapeutic anticoagulation for 3 months after central venous catheter is removed.

Consider thrombectomy/thrombolysis in patients with limb-threatening thrombosis and low risk of bleeding

Lyman GH, et. al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021 Feb 23;5(4):927-974. PMID: 33570602

Wall C, Moore J, Thachil J. Catheter-related thrombosis: A practical approach. J Intensive Care Soc. 2016 May;17(2):160-167PMID: 28979481

Rajasekhar A, Streiff MB. How I treat central venous access device-related upper extremity deep vein thrombosis. Blood. 2017 May 18;129(20):2727-2736 PMID: 28373261.

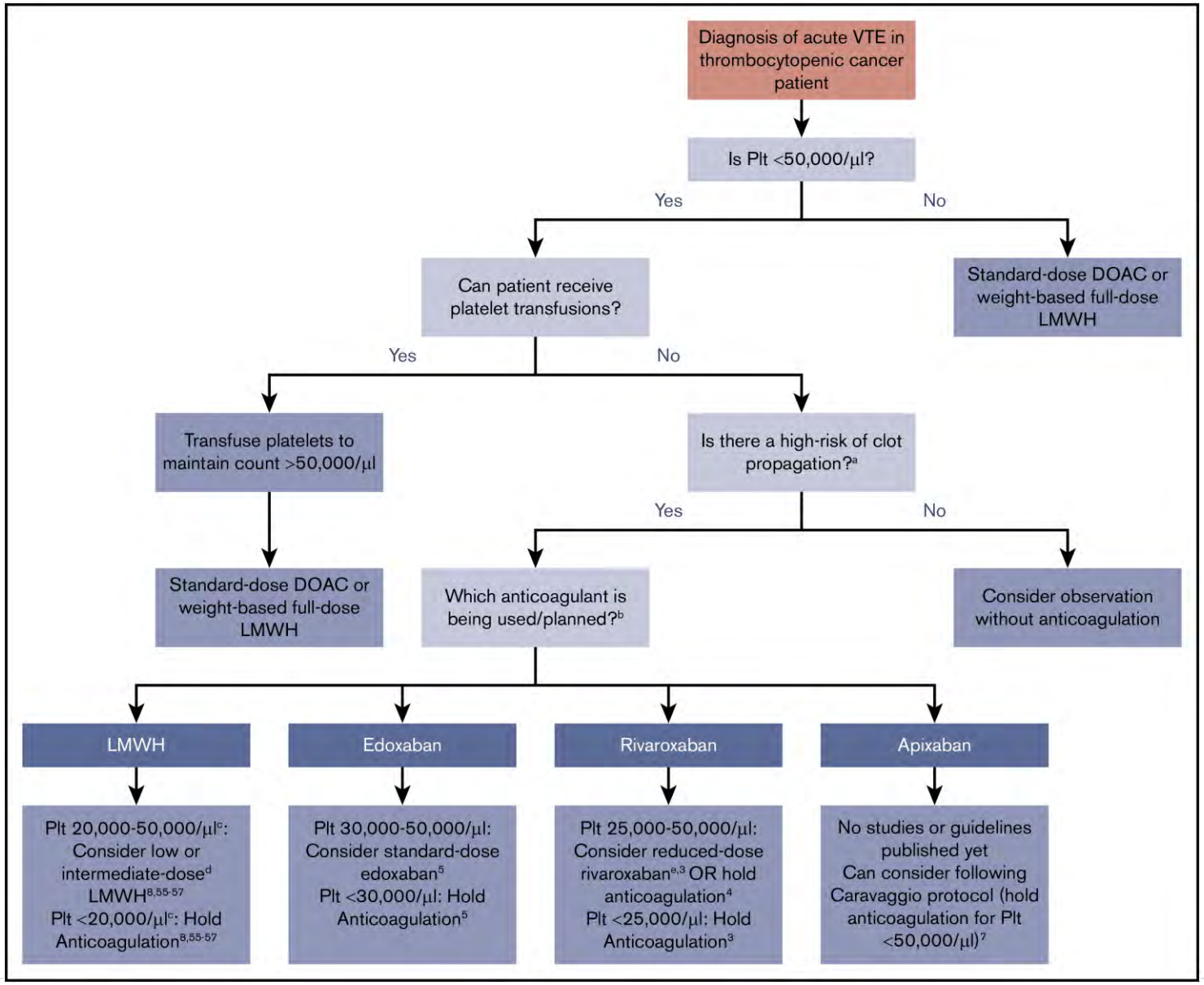
Managing anticoagulation in thrombocytopenic patients with malignancy

Cut off plt count 50k/uL for therapeutic anticoagulation

Consider intermediate or prophylactic anticoagulation with plt count 20-50 k/uL

Consider timing of acute clot (< 3 months vs >3 months), type of tumor and treatment

Managing anticoagulation in thrombocytopenic patients with malignancy



Al-Samkari H, Connors JM. Hematology Am Soc Hematol Educ Program. 2019 Dec 6;2019(1):71-79 PMID: 31808892

Anticoagulant/cancer therapy drug to drug interactions

	Metabolic pathway	Drug	Indication
Strong effect	CYP3A4/5 inhibition	Imatinib, dasatinib	CML
	P-gp inhibition	Cabozantinib	Kidney cancer
	CYP3A4/5 induction	Enzalutamide	Prostate cancer
Moderate effect	CYP3A4/5 inhibition	Pazopanib	Kidney cancer
	P-gp inhibition	Abemaciclib	Breast cancer
	CYP3A4/5, P-gp inhibition	Crizotinib	NSCLC
	CYP3A4/5, P-gp induction	Dabrafenib Brigatinib	Melanoma and NSCLC NSCLC

Strong CYP 3A4/5 inhibitors may increase the AUC of substrates five-fold or more.

Strong inducers may decrease the AUC of substrates by 80% or more

Grange C, et. al. Anti-coagulant Treatment of Cancer-Associated Thrombosis in Frail Patients. Impact of Frailties on the Management of Drug-Drug Interactions. Clin Pharmacokinet. 2023 Nov;62(11):1523-1531 PMID: 37824026

Anticoagulation management with direct oral anticoagulants in patients with cancer associated venous thromboembolism and renal insufficiency

Renal elimination varies between anti-Xa DOACs: 50% for edoxaban, 36% for rivaroxaban and 27% for apixaban

Bleeding is more common in patients with higher anti- Xa DOACs peak levels.

In patients with intermediate clearance between 30 and 49 ml/min, anti-Xa DOACs are relatively well tolerated without dose adjustment.

Full doses of anti-Xa DOACs are contraindicated by European recommendations when creatinine clearance is below 30 ml/min for rivaroxaban and edoxaban, or 25 ml/min for apixaban.

On the contrary, the US Food and Drug Administration (FDA) allows apixaban use up to 15 ml/min in VTE.

Studies are still ongoing, and efforts to detect drug–drug interactions must be maintained given the risk of drugs accumulation.

Grange C, et. al. Anti-coagulant Treatment of Cancer-Associated Thrombosis in Frail Patients Impact of Frailties on the Management of Drug-Drug Interactions. Clin Pharmacokinet. 2023 Nov;62(11):1523-1531 PMID: 37824026

Rivaroxaban and Apixaban anti-Xa chromogenic assay

Table. **Plasma Concentrations of Rivaroxaban in Patient Populations Studied(1)**

Patient population/clinical setting	**Rivaroxaban dose**	**C-min (ng/mL)*** trough plasma concentration (predose)	**C-max (ng/mL)** peak plasma concentration** (postdose)
VTE prevention after total hip replacement surgery	10 mg once daily	9 (1-38)	125 (91-196)
DVT treatment (continued treatment)	20 mg once daily	26 (6-87)	270 (189-419)
Stroke prevention in patients with non-valvular AF (CR-CL > or =50 mL/min)	20 mg once daily	44 (12-137)	249 (184-343)
Stroke prevention in patients with non-valvular AF (CR-CL 30-49 mL/min)	15 mg once daily	57 (18-136)	229 (178-313)
Secondary prevention in patients with acute coronary syndrome	2.5 mg twice daily	17 (6-37)	46 (28-70)

Median (5th-95th percentile)

Table. **Predicted Apixaban Steady-State Exposure Concentrations(1)**

Dosage	**Apixaban C-min (ng/mL)** trough plasma concentration (predose)	**Apixaban C-max (ng/mL)** peak plasma concentration (2-4 hours postdose)
Prevention of VTE: elective hip or knee replacement surgery		
2.5 mg twice daily	51 (23-109)	77 (41-146)
Prevention of stroke and systemic embolism: NVAF		
2.5 mg twice daily	79 (34-162)	123 (69-221)
5 mg twice daily	103 (41-230)	171 (91-321)
Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTE)		
2.5 mg twice daily	32 (11-90)	67 (30-153)
5 mg twice daily	63 (22-177)	132 (59-302)
10 mg twice daily	120 (41-335)	251 (111-572)

Median (5th-95th percentile)

*** Therapeutic reference ranges have not been established***

These are “on-therapy” levels

Phase 3 clinical trials with factor XI inhibitors in patients with cancer associated venous thromboembolism

The phase 3 trials with FXI inhibitors in VTE are focused on abelacimab, which is being tested against apixaban or dalteparin in patients with cancer-associated VTE.

Abelacimab is a fully humanized monoclonal antibody that binds to FXI with high affinity and locks it in the zymogen confirmation, preventing its activation by FXIIa and thrombin.

It has been evaluated in 3 phase I human studies and 2 phase II studies and is found to be safe and promising.

The pharmacokinetics and pharmacodynamic models obtained from phase I/II studies showed that abelacimab has a half-life of approximately 20 days.

Intravenous administration produces rapid and dose-dependent inhibition of FXI.

No infusions were stopped due to hypersensitivity reactions and no anti-drug antibodies were detected.

Wang TF, Treatment of Cancer-Associated Thrombosis: Recent Advances, Unmet Needs, and Future Direction. Oncologist. 2023 Jul 5;28(7):555-564 PMID: 37171998

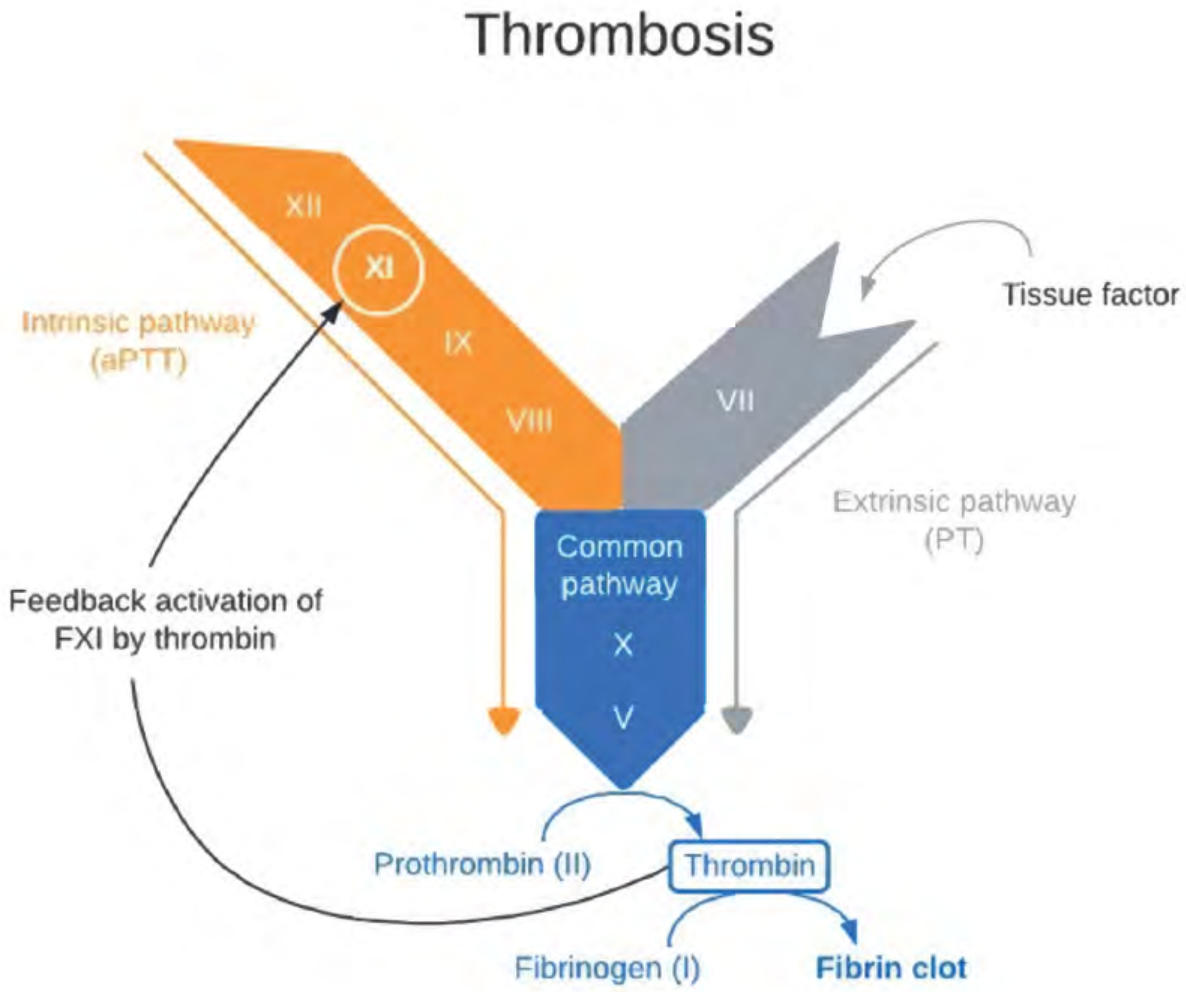
Phase 3 clinical trials with factor XI inhibitors in patients with cancer associated venous thromboembolism

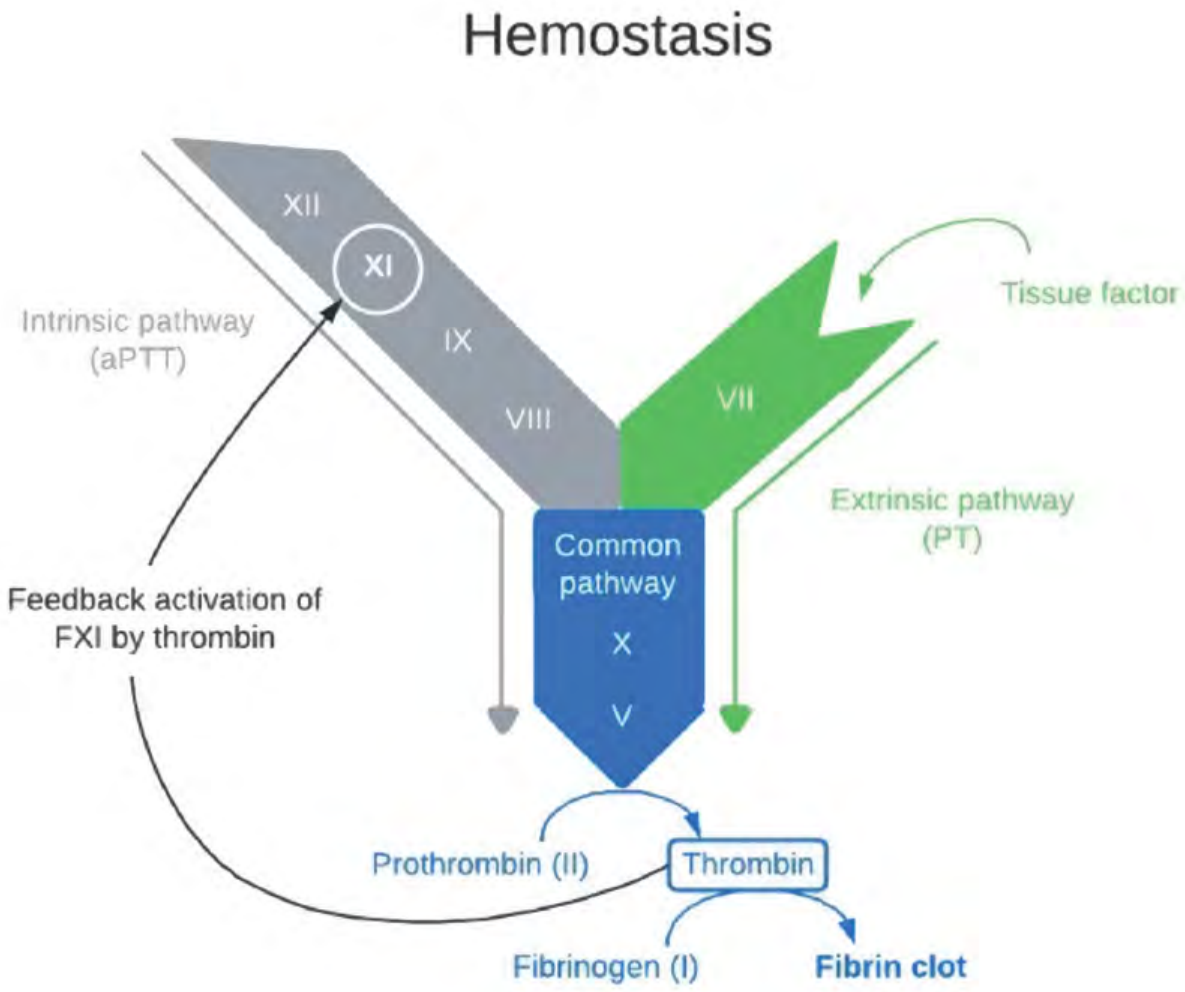
The phase 3 trials with FXI inhibitors in VTE are focused on abelacimab, which is being tested against apixaban or dalteparin in patients with cancer-associated VTE.

ASTER (a study comparing abelacimab to apixaban in the treatment of cancer-associated VTE) is a trial that compares abelacimab (150 mg intravenously followed by 150 mg subcutaneously once a month) with apixaban (10 mg BID for 7 days, then 5 mg BID) in 1655 patients with cancer-associated VTE who can take apixaban (https://www.clinicaltrials.gov; NCT05171049)

MAGNOLIA (a study comparing abelacimab to dalteparin in the treatment of gastrointestinal/genitourinary cancer-associated VTE) is a trial that compares abelacimab (at the same dose as in ASTER) with dalteparin (200 units/kg QD for the first month, then 175 units/kg QD) in 1020 patients with gastrointestinal/genitourinary cancer-associated VTE who have a high risk of bleeding (https://www.clinicaltrials.gov; NCT05171075)

Factor XI inhibitors have the potential of being safer than direct oral anticoagulants as the intrinsic pathway is probably dispensable for normal hemostasis but is likely a major contributor of pathological thrombosis





Wang TF, Treatment of Cancer-Associated Thrombosis: Recent Advances, Unmet Needs, and Future Direction. Oncologist. 2023 Jul 5;28(7):555-564 PMID: 37171998

Questions?

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