POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

MALATTIE TROMBOTICHE
Trombosi e Cancro

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DICHIARAZIONE

Anna Falanga

- Partecipazione ad Advisory Board **(Sanofi, Bayer)**
- Speaker a Simposi sponsorizzati (**Sanofi, Bayer, Leo Pharma, Pfizer, BMS, Novartis**)

Education sessions:

- Thrombosis and anticoagulation: clinical considerations in selected populations
- Thrombosis prevention and treatment

Scientific program:

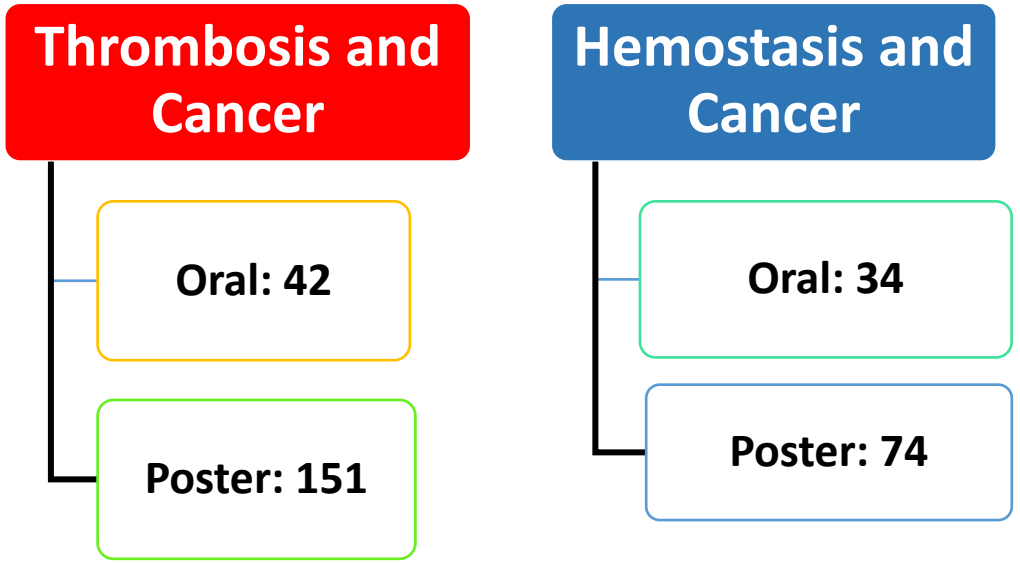
- New therapeutic targets for thrombosis that do not cause bleeding

Special symposium:

- Special symposium on the basic science of hemostasis and thrombosis

Special-interest session:

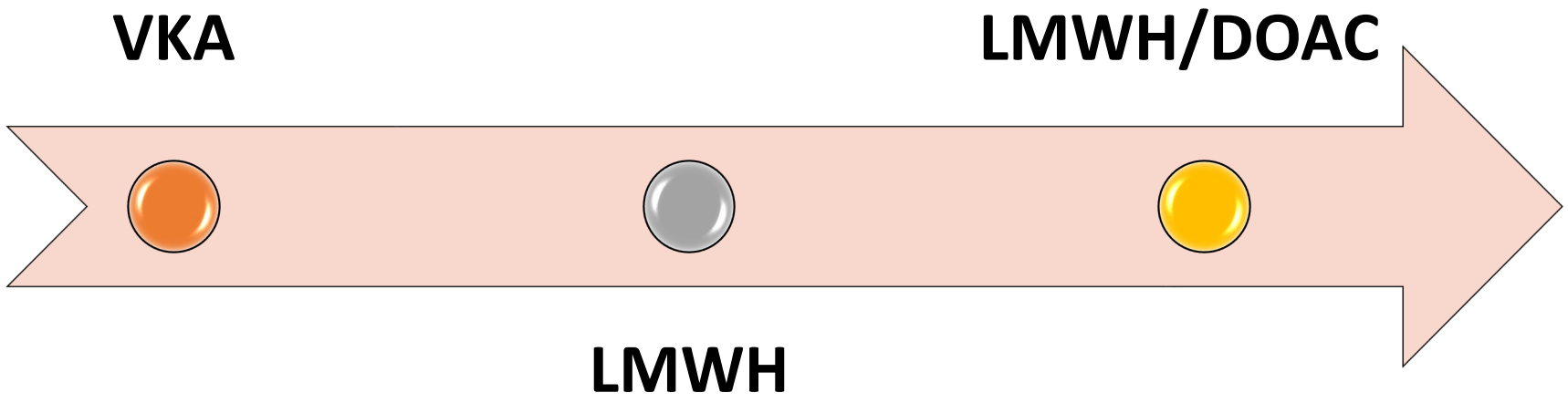
ASH guidelines on VTE: prevention and treatment in patients with cancer



Thrombosis Treatment

FXI and FXII inhibitors to prevent or treat thromboembolism

Cancer-associated thrombosis (CAT) treatment evolution



VKA = Vitamin K antagonist; LMWH = Low Molecular weight heparins; DOACs = Direct Oral Anticoagulants

Oggi sono disponibili molteplici opzioni per il trattamento del TEV nei pazienti con tumore

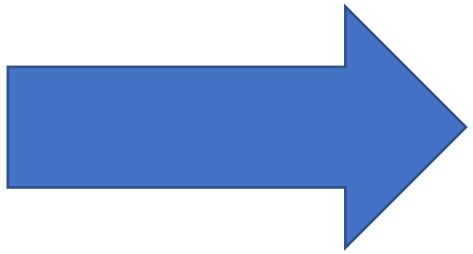
- EBPM per più di 3 mesi
- EBPM per alcuni giorni seguite da DOAC
- EBPM per alcuni giorni in sovrapposizione con AVK
- DOAC fin dall'inizio

Issues remain with current anticoagulant strategies

Specifically, the risk of bleeding remains relevant

In particular in:

- Cancer patients
- Elderly patients with comorbidities
- Patients with renal or liver insufficiency
- Patients with history of bleeding or major bleeding risk factors
- Patients requiring concomitant antiplatelet treatment



SEARCH FOR NEW ANTICOAGULANTS

FXI and FXII inhibitors to prevent or treat thromboembolism

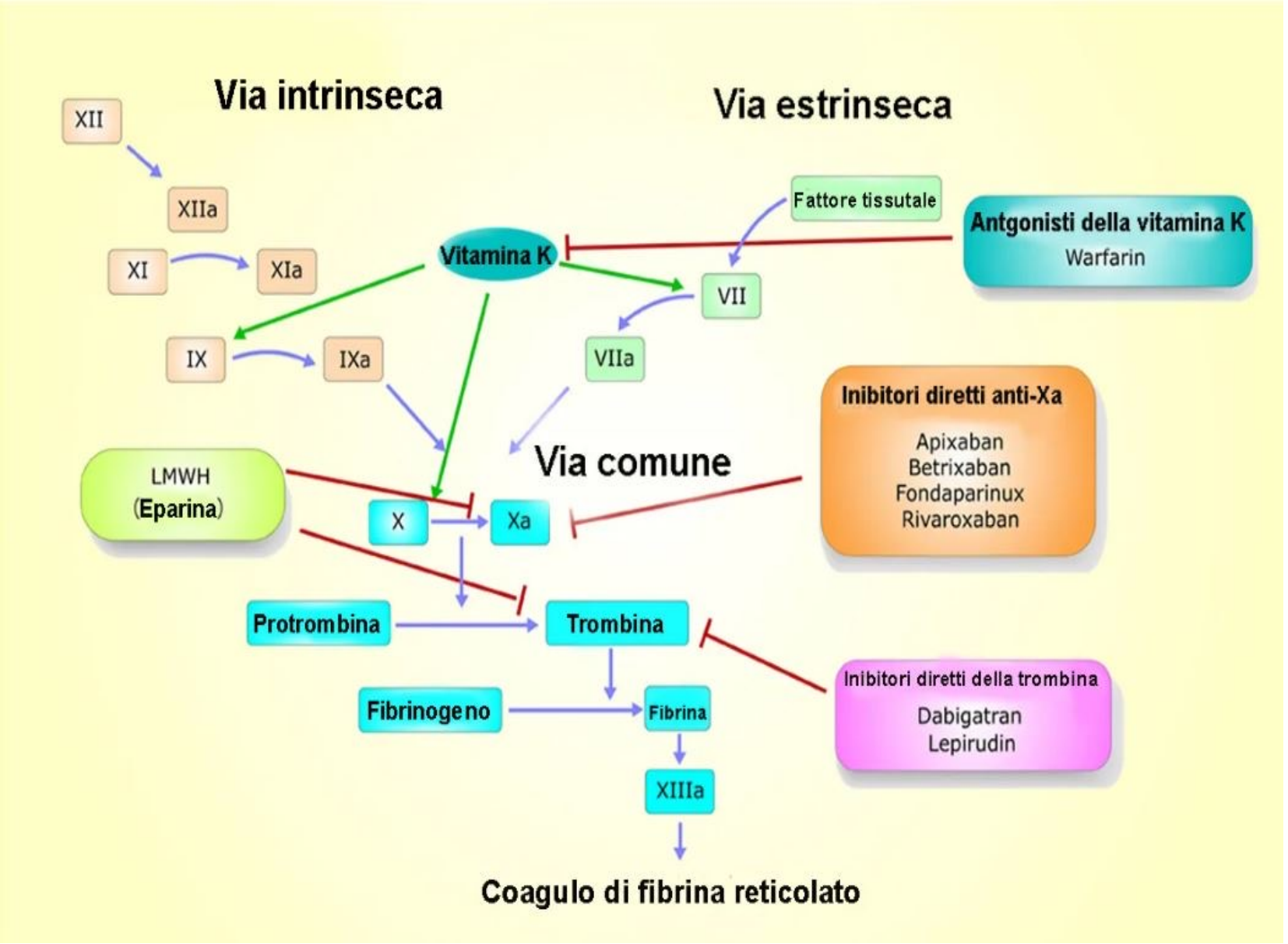
Available anticoagulants target either multiple coagulation factors (AVK) or individual proteins of the extrinsic (anti-TF) or common pathways (DOACs)

The **contact pathway** has a limited role in initiating physiologic *in vivo* coagulation and it contributes to thrombosis more than to hemostasis. Therefore, it is an attractive target for the development of anticoagulant with an enhanced <u>safety</u> profile.

FXI and FXII have received attention as **potential targets:**

- FXI inhibition does not promote bleeding; and FXI deficiency confers protection from thrombotic events

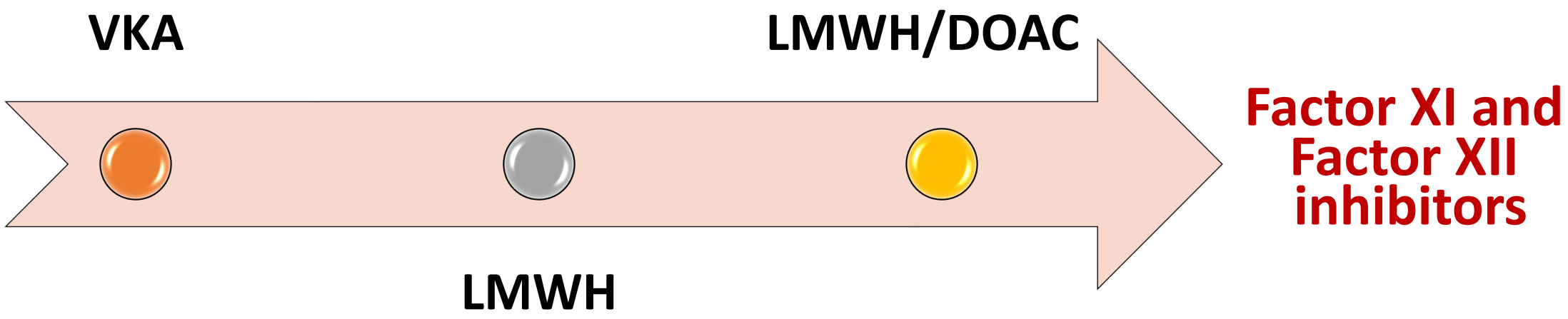
- Due to its properties, **FXII** may be targeted in disease conditions where downstream proinflammatory and prothrombotic cascades are dysregulated



Strategies to target FXI or FXII

Strategy	Mechanism of action	Route of administration	Onset of action	Half-life	Administration frequency	Renal excretion	Metabolism of CYP	Potential for food and drug interactions
Antisense oligonucleotides (ASO)	Reduce hepatic synthesis of FXI or FXII	Subcutaneous	Slow (weeks)	Long (weeks)	Once weekly to once monthly	No	No	No
DNA Aptamers	Bind FXI or FXII and block specific macromolecular interactions	Intravenous or subcutaneous	Rapid (minutes to hours)	Short (minutes to hours)	Daily	No	No	No
Antibodies (Abelacimab, Osocimab, Xisomab, Garadacimab)	Bind FXI or FXII and block activation or activity	Intravenous or subcutaneous	Rapid (hours)	Long (days to weeks)	Once monthly	No	No	No
Small molecules (Milvexian, Asundexian)	Active site-directed inhibitor of FXI	Oral	Rapid (minutes to hours)	Short (8.3-13.8 hours)	Once or twice daily	Yes, <20%	Yes	Yes

Cancer-associated thrombosis (CAT) treatment: Next?



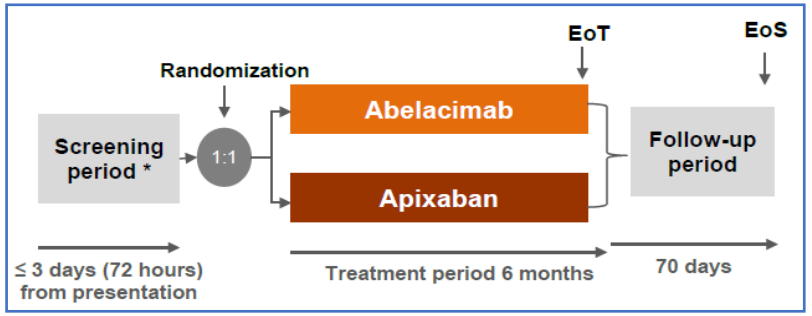
VKA = Vitamin K antagonist; LMWH = Low Molecular weight heparins; DOACs = Direct Oral Anticoagulants

FXI inhibitors: Two new RCTs

- Abelacimab: monoclonal antibody inhibiting (active) FXI.
- Phase 3 trials, enrolling ~2,700 patients:

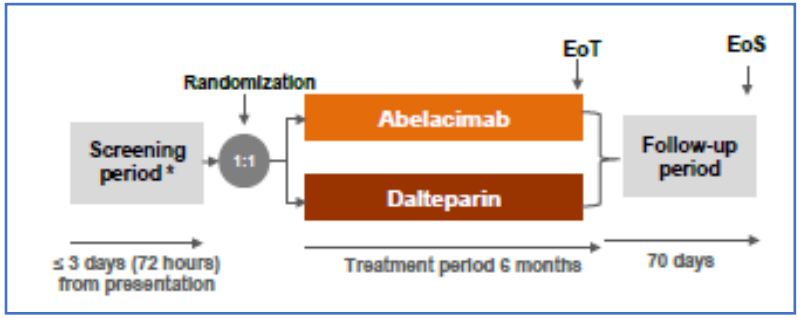
1. ASTER open-label randomized trial

Abelacimab* *vs* apixaban (indication DOAC)



2. MAGNOLIA open-label randomized trial

Abelacimab* *vs* dalteparin (contraindication DOAC)

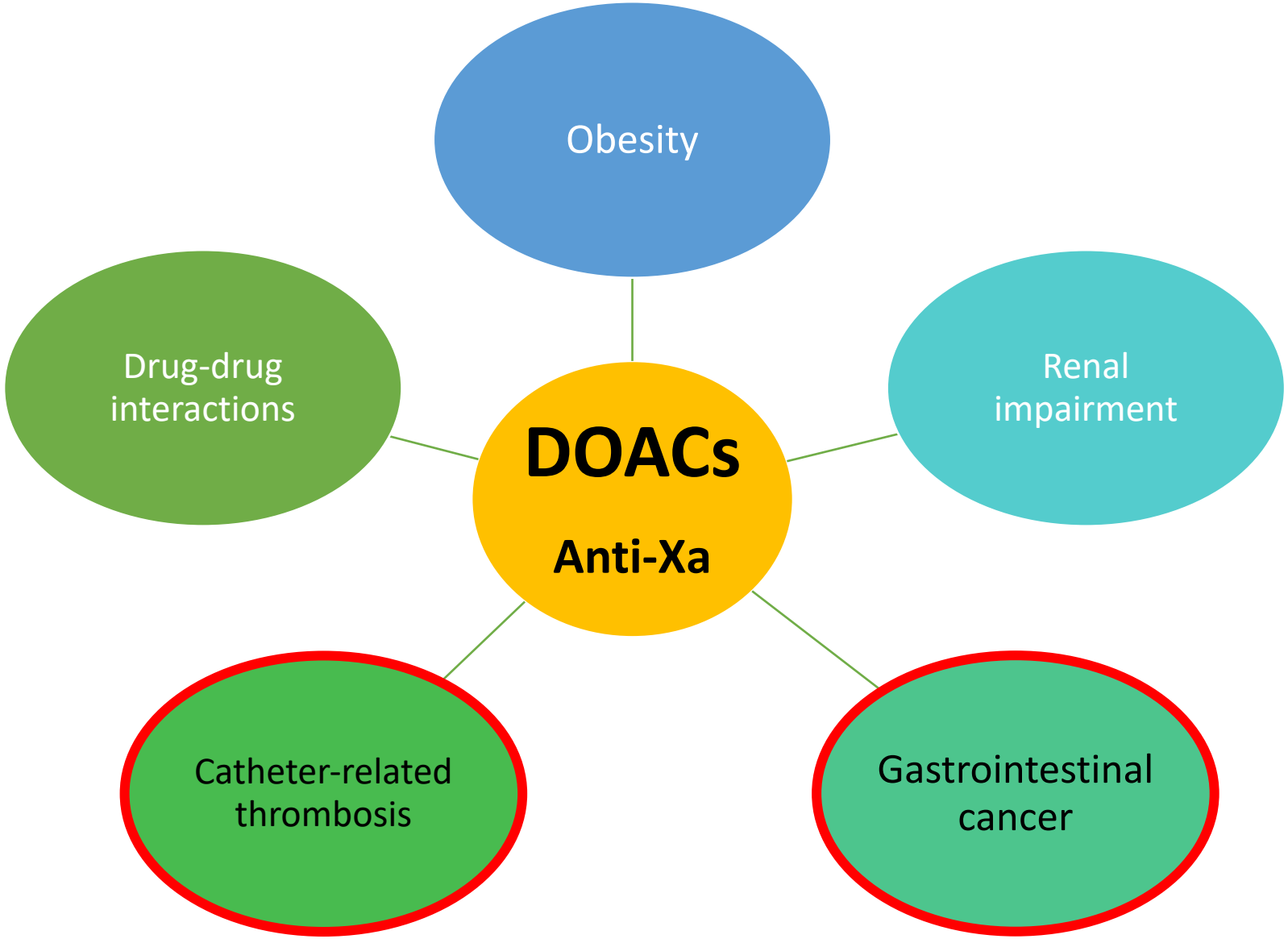


*abelacimab 150 mg iv, 1 monthly administration

Thrombosis Prevention and Treatment

The most 5 frequently asked questions about Xa inhibitors (DOAC anti-Xa)

Commonly asked questions about oral FXa inhibitors



Wang, Carrier, ASH, 2022

Catheter-related thrombosis

Study	N	Anticoagulant	Recurrent VTE	Total bleeding
Catheter study (Kovacs et al, JTH 2007)	74	LMWH -> VKA	0%	4.7% (3/74) ▪ 3 MB
Catheter 2 study (Davies et al, Thromb Res 2018)	70	Rivaroxaban	1.4% (1/70)	12.9% (9/70) ▪ 7 MB (10%) ▪ 4 CRNMB
Catheter 3 study (This ASH) (Kovacs et al. #517 Oral session, 11 Dec 2022)	70	Dalteparin x 7 days -> Apixaban	1.4% (1/70)	8.6% (6/70) ▪ 2 MB ▪ 4 CRNMB

- CVC-related thrombosis is common, with an overall rate of symptomatic VTE of 6.8% (95% CI 5.5-8.3%)
- Thromboprophylaxis is not a standard practice; a RCT assessing the efficacy and safety of Rivaroxaban for primary prevention of VTE in patients with cancer and CVC is ongoing (NCT05029063)
- **Tailoring of anticoagulant** for the management of CVC-related thrombosis **in cancer patients is individualized** as for proximal lower extremity DVT and PE based on patient characteristics, type of cancer and anticancer treatment

Wang, Carrier, ASH, 2022

Gastrointestinal cancer

Bleeding outcomes in the gastrointestinal cancer subgroup in randomized controlled trials comparing DOACs with dalteparin for acute cancer-associated VTE

Trials	Hokusai-VTE Cancer[34]	Select-D[35]	ADAM-VTE[32]	Caravaggio[31]	CASTA-DIVA[33]
Total N	1046	406	300	1155	158
DOACs	Edoxaban	Rivaroxaban	Apixaban	Apixaban	Rivaroxaban
GI cancer	305 (29.2)	177 (43.6)	105 (35)	375 (32.5)	46 (29.1)
Upper GI cancer	54 (5.2)	41 (10.1)	11 (3.7)	54 (4.7)	3 (1.9)
Major bleeding (DOAC vs dalteparin)	21/165 (12.7) vs 5/140 (3.6) HR 4.0 (95% CI, 1.5–10.6)	8/91 (8.8) vs 5/86 (5.8)	0/48 (0) vs 0/57 (0)	9/188 (4.8) vs 9/187 (4.8)	NR
CRNMB (DOAC vs dalteparin)	NR	7/91 (7.7) vs 1/86 (1.2)	NR	19/188 (10.1) vs 7/187 (3.7)	NR

Values are presented as number (%) unless otherwise indicated.
CRNMB, clinically relevant nonmajor bleeding; NR, not reported.

- Identifying patients at higher risk of bleeding complications might be helpful to tailor anticoagulation in patients with cancer-associated VTE
- **ASH2021 Guidelines: avoid DOACs in patients with unresected luminal GI cancers due to the higher risk of GI bleeding**

Wang, Carrier, ASH, 2022

DOACs (anti-Xa) for the treatment of cancer-associated VTE: Key studies

	Sample size (N)	Study design	DOAC	Comparator	Primary outcome	Treatment duration
Hokusai VTE Cancer[1]	1,050	Randomised, open-label, non-inferiority trial	Edoxaban	Dalteparin	Composite of recurrent VTE and/or major bleeding	6–12 months
SELECT-D[2]	406	Randomised, open-label, pilot	Rivaroxaban	Dalteparin	Recurrent VTE	6 months*
CARAVAGGIO[3]	1,170	Randomised, open-label, blinded endpoint (PROBE), non-inferiority	Apixaban	Dalteparin	Recurrent VTE	6 months

**A second random assignment for a further 6 months' treatment in this study was closed based on a recommendation from the DSMC.*
DSMC, Data and Safety Monitoring Committee; PROBE, prospective, randomised, open-label with blind endpoint evaluation.

As of May 5th 2022, DOACs do not have an approved label for its use in the treatment of cancer-associated deep vein thrombosis

1. Raskob GE, et al. *N Engl J Med* 2018;378:615–24; 2. Young AM, et al. *J Clin Oncol* 2018;36:2017–23; 3. Agnelli G, et al. N Engl J Med 2020;382:1599–607

Thrombosis and Anticoagulation in cancer patients

OPEN ISSUES:

- **There are no head-to-head studies to directly compare safety of the different DOACs anti-Xa**
- The impact of thrombocytopenia on management of anticoagulation
- The bleeding risk of anticoagulation in brain tumors (primary or metastases)

Rivaroxaban vs Apixaban for treatment of Ca-VTE: a head-to-head analysis of the US cohort of the observational study in Ca-VTE for rivaroxaban (H2H-OSCAR-US)

Aim: to evaluate the effectiveness and safety of rivaroxaban vs apixaban for the treatment of Ca-VTE in routine practice

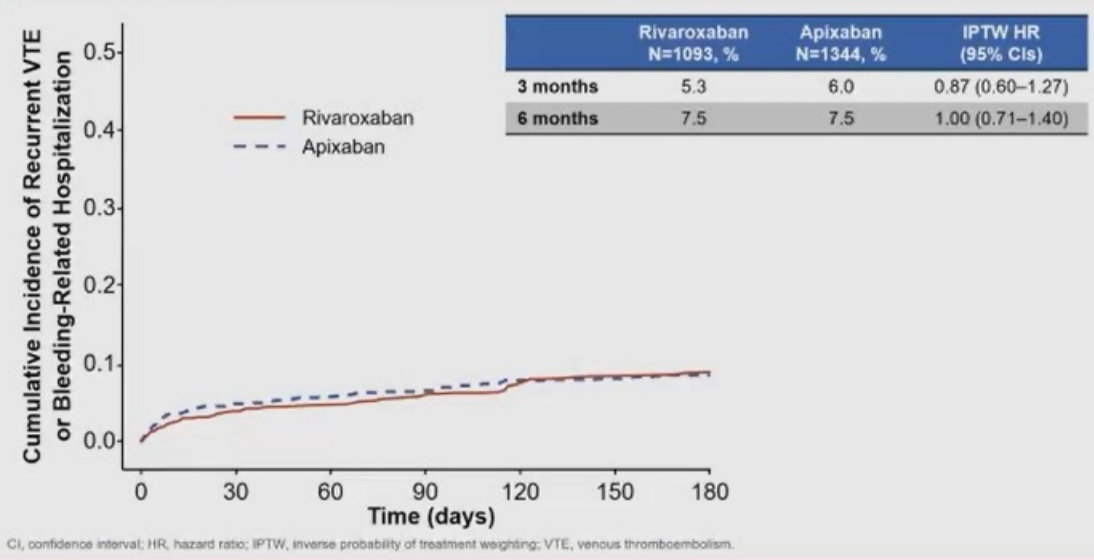
#522 Snow Caroti et al. _ Oral presentation

Primary outcome: composite of recurrent VTE or any bleeding resulting in hospitalization at 3 months

Study cohorts: 1,093 Rivaroxaban vs 1,344 Apixaban

Studio retrospettivo, dati della vita reale, dai registri US dal 2013 al 2020

The primary outcome was comparable in patients treated with rivaroxaban or apixaban at 3 months

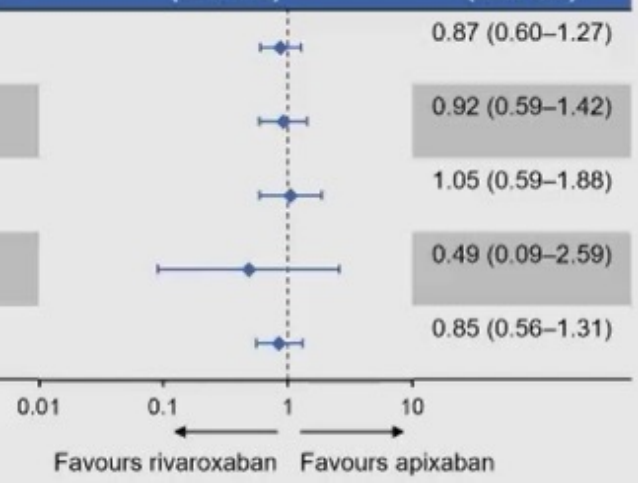


	Rivaroxaban N=1093, %	Apixaban N=1344, %	IPTW HR (95% CIs)
3 months	5.3	6.0	0.87 (0.60–1.27)
6 months	7.5	7.5	1.00 (0.71–1.40)

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; VTE, venous thromboembolism.

Patients treated with rivaroxaban or apixaban had comparable effectiveness and safety outcomes at 3 months (IPTW= inverse probability of treatment weighting)

	Rivaroxaban N=1093, %	Apixaban N=1344, %	IPTW-HR* (95% CIs)
Recurrent VTE or bleeding related hospitalization	5.3	6.0	0.87 (0.60–1.27)
Recurrent VTE	3.8	4.2	0.92 (0.59–1.42)
Bleeding related hospitalization	2.4	2.3	1.05 (0.59–1.88)
Critical organ bleed	0.2	0.4	0.49 (0.09–2.59)
Recurrent VTE or critical organ bleed	3.8	4.5	0.85 (0.56–1.31)



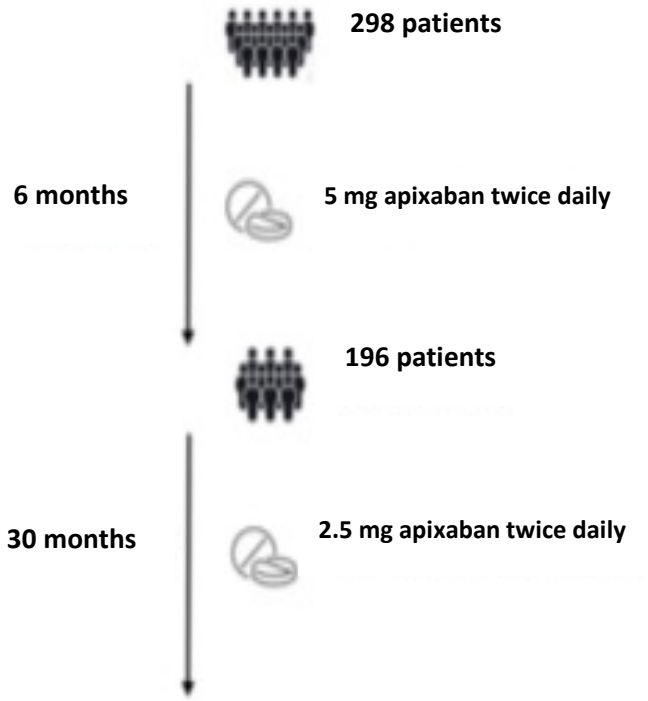
- Among patients with active cancers excluding esophageal, gastric, unresected colorectal, bladder, non-cerebral CNS cancers and leukemia, and experiencing acute VTE, **rivaroxaban was associated with similar effectiveness and safety as apixaban at 3-months**
- Prescribers should consider patient preference, adherence, and other patient specific factors when choosing optimal anticoagulation therapy

Bleedings in cancer patients treated with apixaban for VTE

Aim: to investigate risk factors for bleedings and to find out if reducing the dose of apixaban influenced bleedings

#2508 Hussaini et al._ Poster presentation

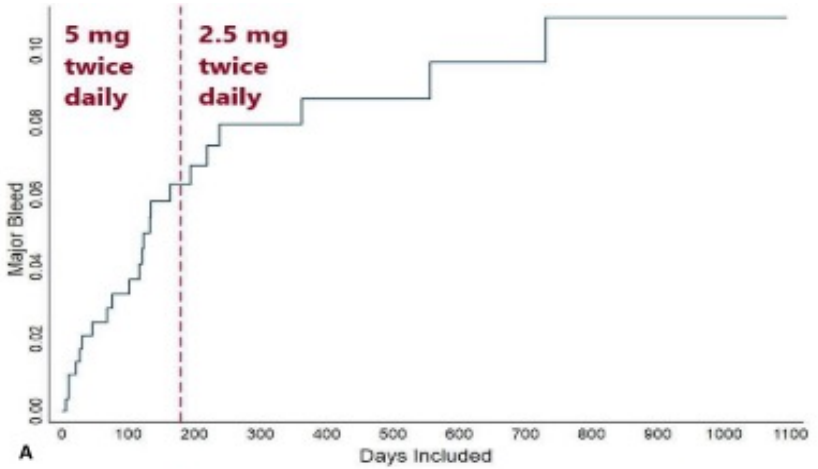
The **CAP study** was a prospective, single-arm, interventional study conducted in Norway to assess the efficacy and safety of apixaban as a treatment for cancer-associated VTE



- Bleeding risk factors
- Bleedings in low dose apixaban

- Risk factors for bleeding were advanced age, low BMI, low Hb during 6 months of apixaban 5mg twice daily
- No risk factors were associated with bleeding during the 30 months of apixaban 2.5mg twice daily
- Resected luminal GI cancer had low risk of bleeding
- **The frequency of major bleeding events was higher in full-dose period compared to the low-dose period, but the frequency of CRNMB was not influenced by the reduction in apixaban dose**

Major bleeding



Clinically relevant non major bleeding

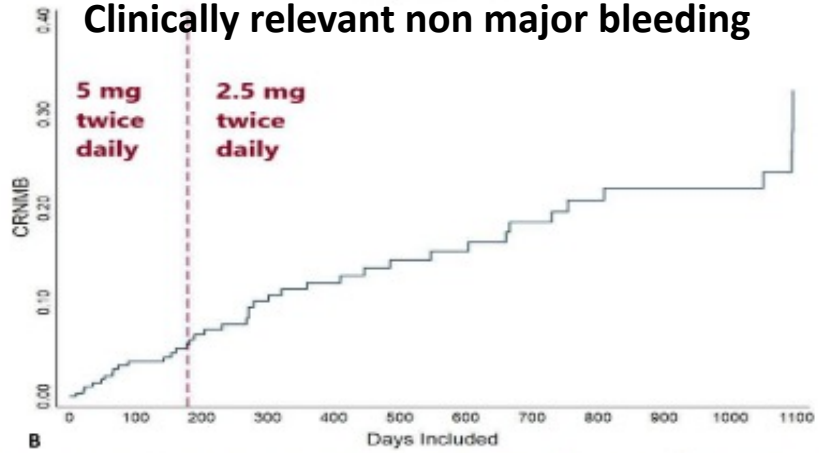


Figure 1 Cumulative percentage of patients with major bleeding (A) and CRNMB (B).

Thrombosis and Anticoagulation in cancer patients

OPEN ISSUES:

- There are no head-to-head studies to directly compare safety of the different DOACs anti-Xa
- **The impact of thrombocytopenia on management of anticoagulation**
- **The bleeding risk of anticoagulation in brain tumors (primary or metastases)**

Impact of thrombocytopenia on bleeding and recurrent thrombosis in cancer associated thrombosis: a post-hoc analysis of Hokusai VTE cancer study

Aim: to investigate the impact of platelet count on bleeding and recurrent thrombosis
N=**1045 patients on anticoagulant therapy** (median age 65 years, 52% male) VTE: *63% PE; 37% DVT*

#2504 Otasevic et al._ Poster presentation

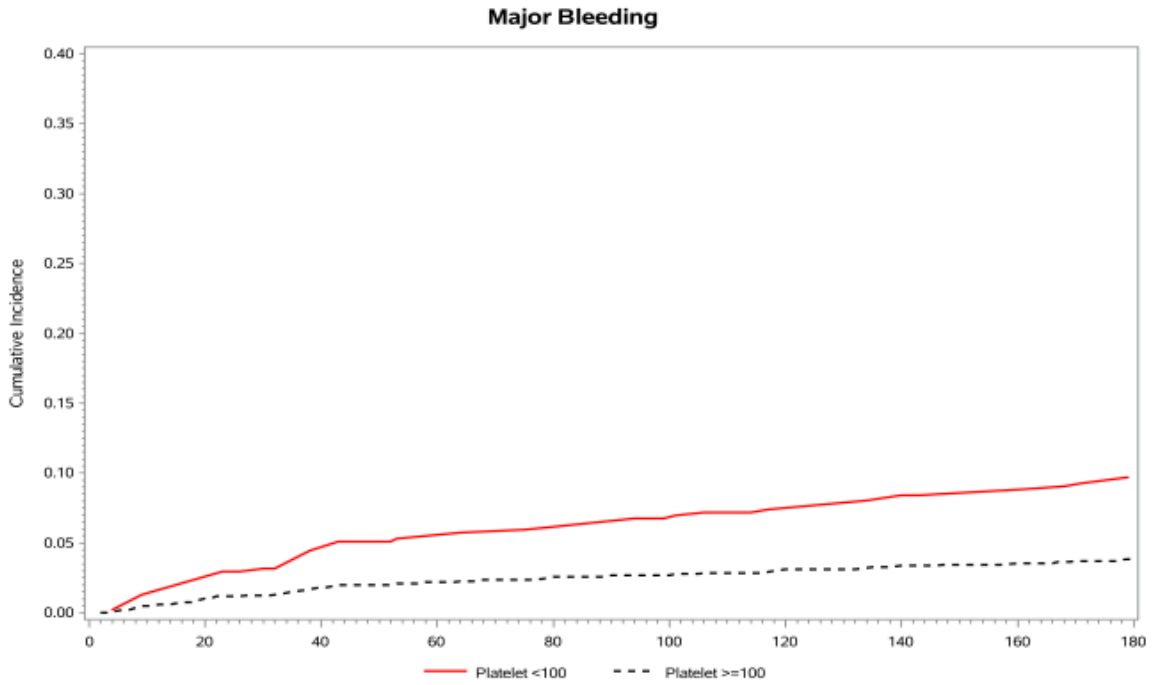
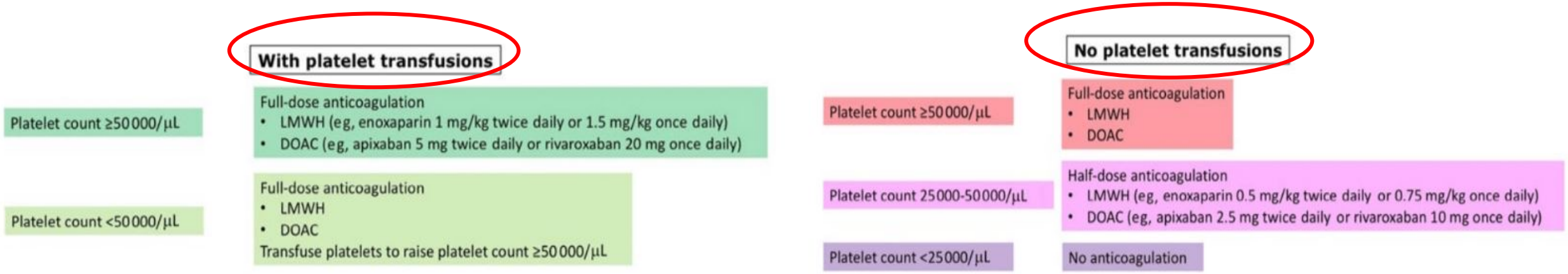


Fig 1: Cumulative incidence of major hemorrhage in patients with baseline platelet count >100,000/µL (broken blue) and baseline platelet count ≤100,000/µL (red)

Cumulative incidence of major bleeding at 180 days was higher (8.9%) in patients with platelet count <100,000/ µL compared to 3.9% in those higher than 100,000/µL

- **Thrombocytopenia (≤ 100,000/uL) was associated with an increased risk of major bleeding by two-fold (8.9 *vs* 3.9%)**
- **No difference in the risk of recurrent thrombosis was detected**
- It is important to recognize even mild thrombocytopenia as an important risk factor for bleeding in patients being anticoagulated for CAT

How to manage anticoagulation therapy in patients with CAT and thrombocytopenia?



TROVE study is the first multicenter, observational, prospective study to compare 2 strategies:

1. Full anticoagulation with platelet transfusion

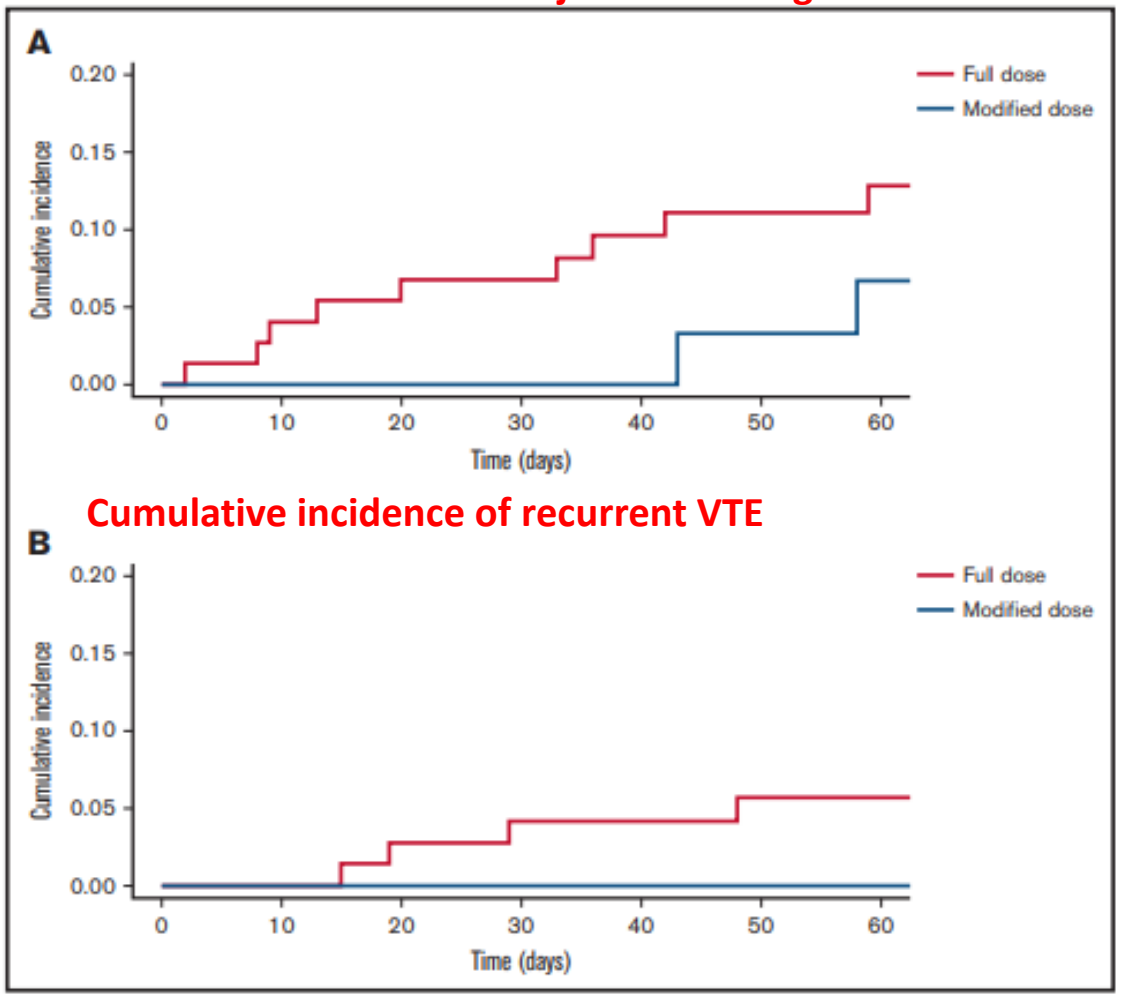
2. Dose-modified anticoagulation based on platelet count, without platelet transfusion;

No anticoagulation with platelets <25,000/µL

Goshua, ASH, 2022

TROVE study

Cumulative incidence of major hemorrhage



Cumulative incidence of recurrent VTE

Patients treated with full-dose anticoagulation and platelet transfusions **compared** to those treated with dose-modified anticoagulation without platelet transfusions

had higher **risk of recurrent venous thromboembolism and major bleeding**

Lack of randomization for treatment allocation and differences in some baseline characteristics among groups

Carney BJ et al. Blood Adv 2021

Thrombosis and Anticoagulation in cancer patients

OPEN ISSUES:

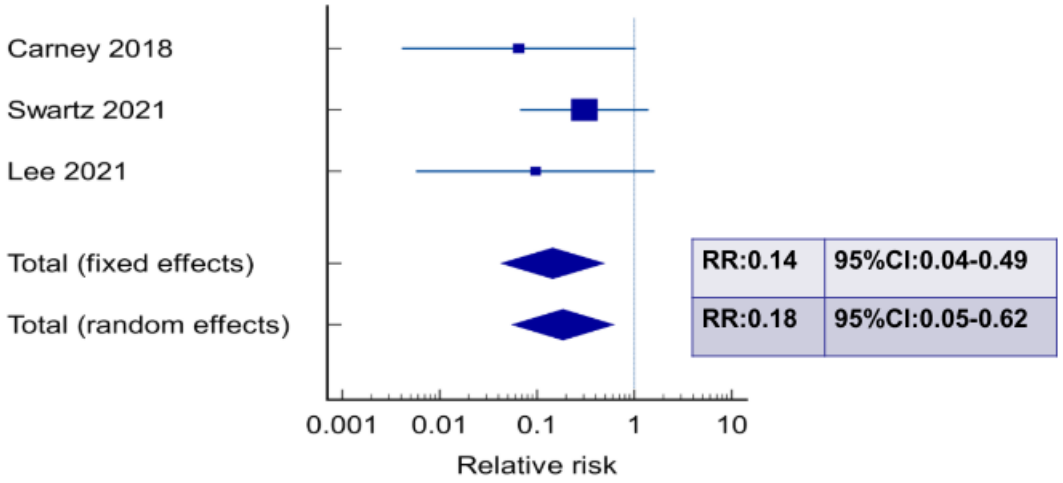
- There are no head-to-head studies to directly compare safety of the different DOACs anti-Xa
- The impact of thrombocytopenia on management of anticoagulation
- **The bleeding risk of anticoagulation in brain tumors (primary or metastases)**

Risk of Intracranial Hemorrhage with DOACs vs LMWH in primary and secondary brain cancers: an up-to-date meta-analysis of comparative studies

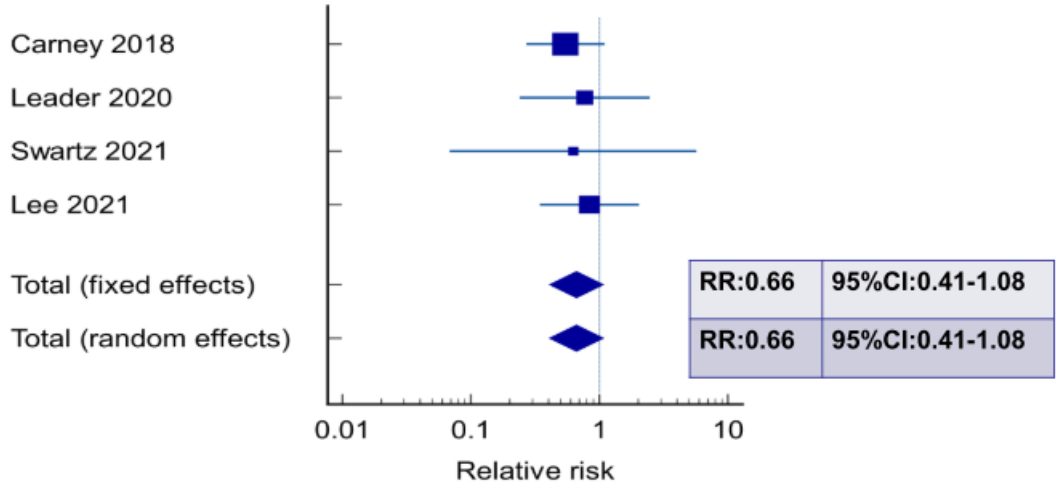
#2505 Haddad et al._ Poster presentation

Aim: a meta-analysis conducted to compare the relative risk (RR) of ICH of DOACs to that of LMWH in patients with brain cancers
Four retrospective comparative studies with a total of **488 patients** were included

Primary brain cancer RR of all ICH: DOACs vs LMWH



Metastatic brain cancer RR of all ICH: DOACs vs LMWH



- This is the first meta-analysis to show that **DOACs are associated with lower relative risk of all ICH compared to LMWH in patients with primary and metastatic brain cancers**
- In the absence of randomized clinical trials, it represents the most compelling data supporting the use of DOACs to treat thromboembolic events in these patient populations

Antiplatelet medications and intracranial hemorrhage in patients with primary brain tumors

#1198 Ma et al._ Poster presentation

A retrospective matched cohort study

Aim: to investigate whether patients with primary brain tumors receiving antiplatelet medications had an increased risk of ICH compared to a matched cohort. Patients treated with antiplatelet medications (aspirin and P2Y12 inhibitors) were matched with patients not receiving these agents.

Table 1: Characteristics of ICH events

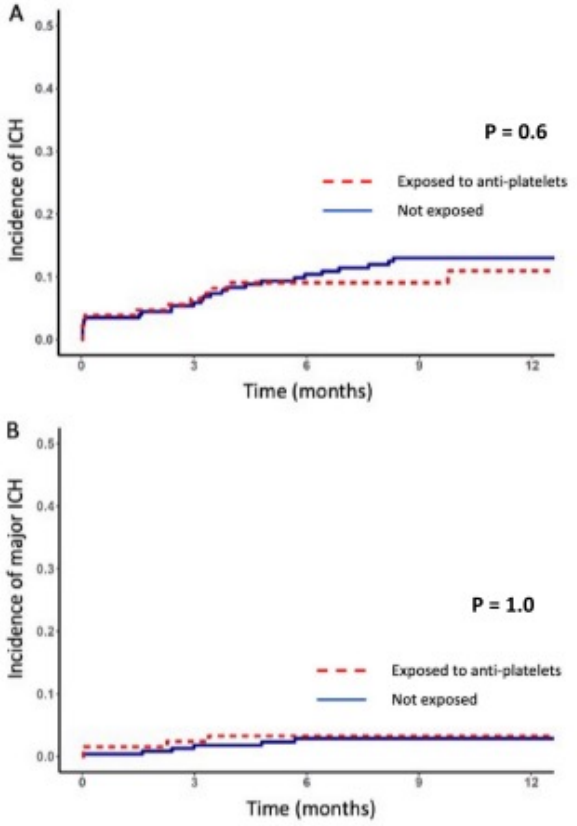
387 total patients

	Total (n = 55)	Antiplatelet (n = 18)	Control (n = 37)
ICH Category (%)			
Major	14 (25.5)	5 (27.8)	9 (24.3)
Measurable	19 (34.5)	5 (27.8)	14 (37.8)
Trace	17 (30.9)	8 (44.4)	9 (24.3)
Location of bleed			
Intraparenchymal	36 (65.5)	11 (61.1)	25 (67.6)
Subdural	12 (21.8)	4 (22.2)	8 (21.6)
Intraventricular	6 (10.9)	3 (16.7)	3 (8.1)
Subarachnoid	1 (1.8)	0 (0.0)	1 (2.7)
Presence of symptoms	13 (23.6)	5 (27.8)	8 (21.6)
ICH volume, mean +/- SD	10 +/- 20.5	12.5 +/- 23.7	8.9 +/- 19.4
Anticoagulation exposure	32 (58.2)	13 (72.2)	19 (51.4)

Table 2: Univariable Fine-Gray competing risk regression for impact of anticoagulation exposure on the development of ICH

Anticoagulation	Hazard ratio (95% CI)	P-value
All ICH		
Both vs. Neither	1.92 (0.95 – 3.88)	0.07
Antiplatelet only vs. Neither	0.50 (0.18 – 1.35)	0.17
Anticoagulation only vs. Neither	1.56 (0.82 – 2.96)	0.17
Major ICH		
Both vs. Neither	2.51 (0.35 – 17.76)	0.36
Antiplatelet only vs. Neither	2.80 (0.46 – 17.04)	0.26
Anticoagulation only vs. Neither	5.03 (1.05 – 24.04)	**0.04**

Figure 1: Cumulative incidence of ICH at 1 year. Figure 1A depicts all ICH events and figure 1B depicts major ICH events.



- **Antiplatelet medications are not associated with an increased incidence of ICH in patients with primary brain tumors**
- A non-statistically significant increase in risk of ICH with combined antiplatelet and anticoagulation exposure is shown

GRAZIE!