POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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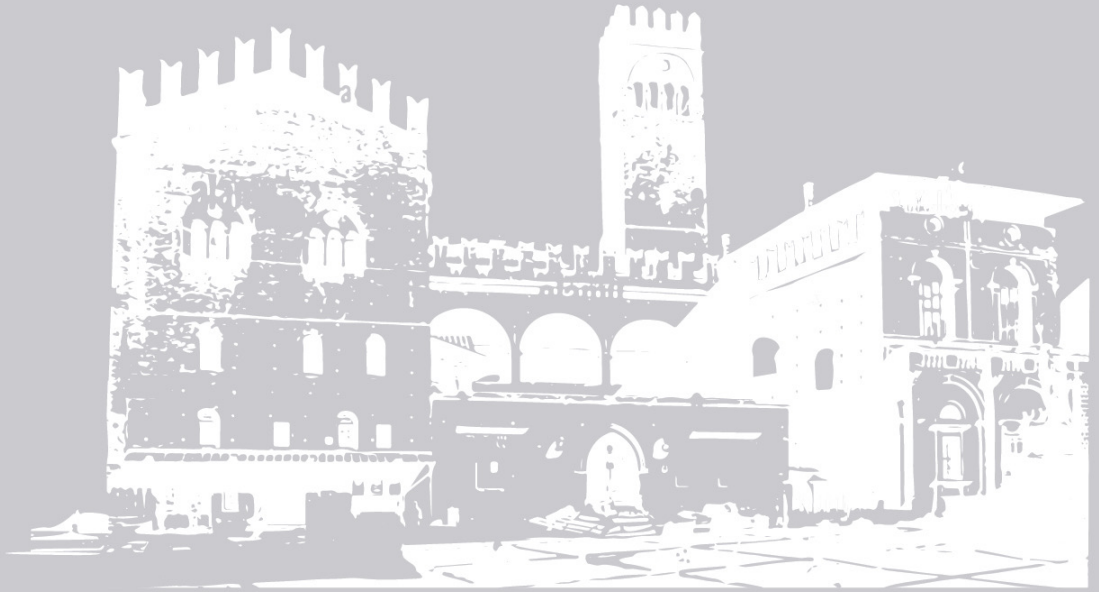

Elena Rossi

Thrombophilia…and beyond

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Disclosures of Name Surname

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No disclosures							

AGENDA

- *Hormones and thrombophilia*
- *News in Hereditary Thrombophilia*
  - *Protein S Deficiency*
  - *Double Heterozigosity*
  - *Factor VIII*
- *Cancer and thrombosis*
- *DOAC use*
- *Reversal therapy*

Sex Hormones, Contraceptives, and Thrombotic Risk: Where Are We Now?

Monday, December 9, 2024: 2:45 PM-4:00 PM

Saskia Middeldorp
Radboud University,
Nijmegen, Netherlands

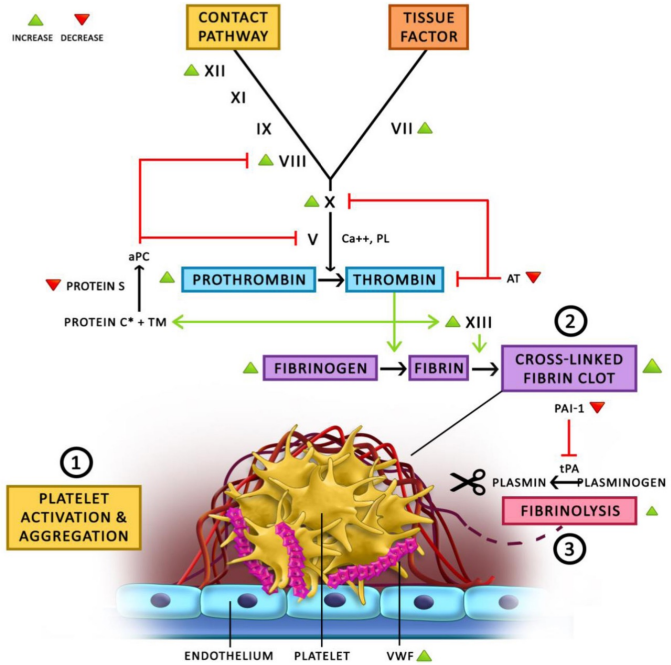
Leslie Skeith
University of Calgary,
Calgary, AB, Canada

Joseph J. Shatzel,
Oregon Health & Science University,
Portland, OR, USA

Thrombotick risk and contraceptive choices – role of thrombophilia

The thrombogenicity of CHCs is due, at least in part, to the combination of multiple changes seen in the clotting factor levels and the vasculature. CHCs increase procoagulant factors (prothrombin, factor VII, VIII, X, and fibrinogen) and decrease anticoagulant factors (protein S and antithrombin).

CHCs also affect fibrinolysis by decreasing levels of plasminogen activator inhibitor (PAI −1) and increasing levels of tissue plasminogen activator (tPA).



Skeith L et al. Blood 2024
Abou-Ismail MY et al, Thromb Res 2020

Thrombotick risk and contraceptive choices – role of thrombophilia

Table 1. VTE risk by hormonal type

Hormonal type	Example agents	Baseline risk in nonusers	Adjusted RR (95%)	Absolute risk
Combined hormonal contraceptives				
COCs[a]		1.9–3.7/10 000 PY[29,30]	Overall: 3.5 (2.9–4.3)[32]	-
First generation	EE[b]/norethindrone	1.9–3.7/10 000 PY[29,30]	3.2 (2.0–5.1)[32]	3.7–16.1/10 000 PY[29]
Second generation	EE/LNG EE/norgestrel	1.9–3.7/10 000 PY[29,30]	2.92 (2.23–3.81)[29]	5–8/10 000 PY[29]
Third generation	EE/desogestrel; EE/gestodene	1.9–3.7/10 000 PY[29,30]	6.61 (5.60–7.80)[29]	9–12/10,000 PY[29]
Fourth generation/unclassified	EE/drosperinone; EE/cytoproterone acetate	1.9–3.7/10 000 PY[29,30]	6.37 (5.43–7.47)[29]	7–9/10 000 PY[29]
Transdermal patch	EE/norelgestromin; EE/LNG	2.1/10 000 PY[35]	7.9 (3.5–17.7)[35]	9.7/10 000 exposure y[35]
Vaginal ring	EE/etonogestrel; EE/nestorone	2.1/10 000 PY[35]	6.5 (4.7–8.9)[35]	7.8/10 000 exposure y[35]
Progestin-only contraceptives				
IUS	LNG	25–29y: 2.4/10 000 PY[63]	0.6 (0.2–1.5)[37]	1.4/10 000 PY[c]
Low-dose POP (<5 mg)	Norethindrone; desogestrel; drosperinone	25–29y: 2.4/10 000 PY[63]	0.9 (0.6–1.5)[37]	2.2/10 000 PY[c]
High-dose POP for menstrual bleeding (>5–30 mg)	Norethindrone acetate; medroxyprogesterone acetate	25–29y: 2.4/10 000 PY[63] 45–49y: 5.4/10 000 PY[63]	5.3 (1.5–18.7)[40] 5.92 (1.16–30.1)[41]	25–29y: 12.7/10 000 PY[c] 45–49y: 28.6/10 000 PY[c]
Injectable DMPA	Medroxyprogesterone acetate	25–29y: 2.4/10 000 PY	2.7 (1.3–5.5)[37]	6.5/10 000 PY[c]
Subdermal implant	Etonogestrel; LNG	2.1/10 000 PY	1.4 (0.6–3.4)[35]	1.7/10 000 exposure y[35]

Skeith L et al. Blood 2024

Thrombotick risk and contraceptive choices – role of thrombophilia

Table 4. Estimated number needed to test to prevent VTE when not taking combined oral contraceptives

Thrombophilia	Risk on COC per year, %	Risk difference per 100 women	Number not taking COCs to prevent 1 VTE	Number of relatives to be tested
Family history of VTE				
General population, no family history	0.08	0.03	3333	None
General population, family history	0.04	0.06	1667	None
Relatives with FVL or PGM	0.5	0.3	333	666
Relatives with AT, PC, or PS deficiency	4.3	3.6	28	56

Table adapted with permission from Middeldorp,[50] which includes data based on family studies and a general population risk based on a baseline VTE risk in young women of 0.01% per year, an RR of VTE by use of COC of 4, and an RR of 2 for VTE by having a positive family history.

Skeith L et al. Blood 2024; Middeldorp S et al. Blood Adv. 2023.

Thrombotick risk and contraceptive choices – role of thrombophilia

ASH guidelines for management of venous thromboembolism: thrombophilia testing (2023)

For women from the general population who are considering using COCs, the ASH guideline panel recommends not performing thrombophilia testing to guide the use of COCs.

For women with a family history of VTE and unknown or low risk thrombophilia (FVL or PGM) thrombophilia status in the family who are considering using COCs, the ASH guideline panel suggests not testing for hereditary thrombophilia to guide the use of COCs.

For women with a family history of VTE and known high-risk thrombophilia (AT, PC, or PS deficiency), the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests ***avoidance of COCs for women with high-risk thrombophilia.***

Centres for Disease Control and Prevention Medical Eligibility Criteria (2024)

Family history (1st- degree relative):
No restriction for LNG IUD, implant, DMPA, POP; for CHC advantages generally outweigh theoretical or proven risks.

For known thrombogenic mutations:
For LNG IUD, Implant, POP advantages generally outweigh theoretical or proven risks; DMPA theoretical or proven risks usually outweigh advantages; CHC unacceptable health risk.

Skeith L et al. Blood 2024; Middeldorp S et al. Blood Adv. 2023; Cohen MK et al. MMWR Recomm Rep. 2024.

Thrombotick risk and contraceptive choices – antiphospholipid antibodies

EULAR recommendations (2017)

Women with SLE should be counselled about the use of effective contraceptive measures (oral contraceptives, subcutaneous implants, IUD), based on their disease activity and thrombotic risk (particularly aPL status). IUD can be offered to all the patients with SLE and/or APS free of any gynaecological contraindication (1/A).

In patients with stable/inactive SLE and negative aPL, combined hormonal contraceptives can be considered (1/A).

In women with positive aPL with or without definite APS, hormonal contraception (with progesterone only) must be carefully weighed against the risk of thrombosis (2/B).

Centres for Disease Control and Prevention Medical Eligibility Criteria (2024)

SLE with positive (or unknown) aPLs:
For LNG IUD, Implant, POP advantages generally outweigh theoretical or proven risks; DMPA theoretical or proven risks usually outweigh advantages; CHC unacceptable health risk.

Skeith L et al. Blood 2024; Andreoli L et al, Ann Rheum Dis 2017; Cohen MK et al. MMWR Recomm Rep. 2024.

Hormone-related thrombosis – the role of thrombophilia

Clinical contest	*VTE risk recurrence*
Women who stopped anticoagulants	5.3% after 1 year 9.1% after 3 years
Women with a first hormonal-contraceptive-related VTE who stopped anticoagulant and contraceptives	1.2-1.3 %pt-y
Women with a first VTE who stopped anticoagulants and after started contraceptives	4.8. %pt-y (COCs) 1.5 %pt-y (none COCs)
Women and men with a provoked VTE by a non surgical risk factor who stopped anticoagulants	4.2 %pt-y
	Bleeding risk
Women and men with unprovoked VTE and long-term DOAC treatment	1.1 %pt-y
Women and men with unprovoked VTE after stopping anticoagulants	0.4 %pt-y

Scheres LJJ and Middeldorp S, Blood 2024;

Hormone-related thrombosis – the role of thrombophilia

All women with a previous hormone-related VTE are at substantial risk during future pregnancy, and thromboprophylaxis through out pregnancy and the post partum period is recommended.

Hormone use or pregnancy/postpartum related events seem to be intermediately strong risk factors with respect to the risk of recurrent VTE. Risk assessment is crucial for identifying women at high risk of VTE recurrence, for whom continuing anticoagulation treatment might be beneficial. To this end the recently published ASH Guideline on Thrombophilia Testing has suggested ***a strategy based on thrombophilia testing.***

Table 5. Suggested thrombophilia testing in hormone-related VTE: who, why, when, what and how to test?

Who	Why	When	What	How[c]		
VTE associated with combined oral contraceptives	Strategy[b] to guide the decision to stop or continue anticoagulant therapy after primary treatment phase; indefinite anticoagulant treatment for patients with thrombophilia is suggested.	Only test when, after shared decision-making, the result impacts the decision to stop or continue anticoagulation therapy.	Thrombophilia panel: • factor V Leiden mutation • prothrombin *G20210A* mutation • PC deficiency • PS deficiency • AT deficiency • antiphospholipid antibodies (LAC, anti-ß2-glycoprotein-I IgG and IgM antibodies, anticardiolipin IgG and IgM antibodies)	If on DOAC: • can influence LAC/PC/PS[d]/AT results • briefly interrupt or temporally switch to LMWH and test at anticoagulant trough	If on VKA: • can influence LAC/PS/PC results • switch to LMWH and test at anticoagulant trough	If on LMWH: test at anticoagulant trough
VTE provoked by pregnancy or 3-month postpartum period						
VTE associated with assisted reproductive technology[a]						
VTE associated with hormone replacement therapy[a]						
VTE associated with gender-affirming therapy[a]						

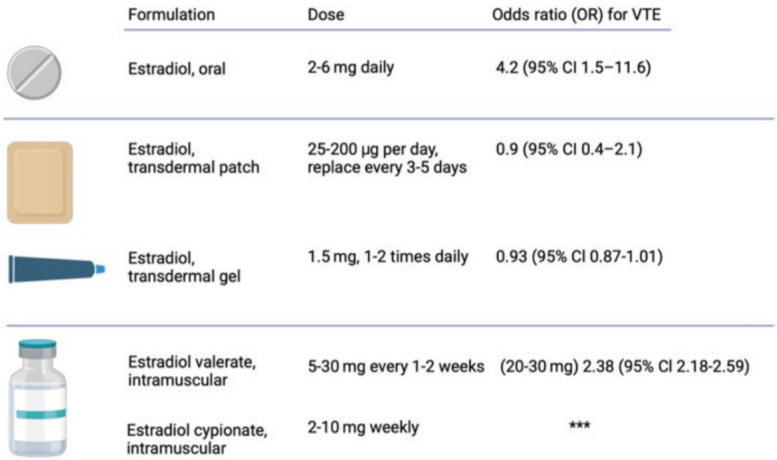
Scheres LJJ and Middeldorp S, Blood 2024;

Gender-affirming hormone therapy (GAHT) - the role of thrombophilia

Underlying thrombophilia and hypercoagulable blood disorders have been well documented to increase VTE events in cisgender women.

While in asymptomatic transgender and gender-diverse individuals screening for thrombophilia is not recommended before starting GAHT, those with known thrombophilia, myeloproliferative neoplasm, or active malignancy should have a comprehensive discussion regarding the risks and benefits of using exogenous estrogen.

The heightened risk of thrombosis associated with these conditions as well as the psychological impact of discontinuing GAHT should be considered.

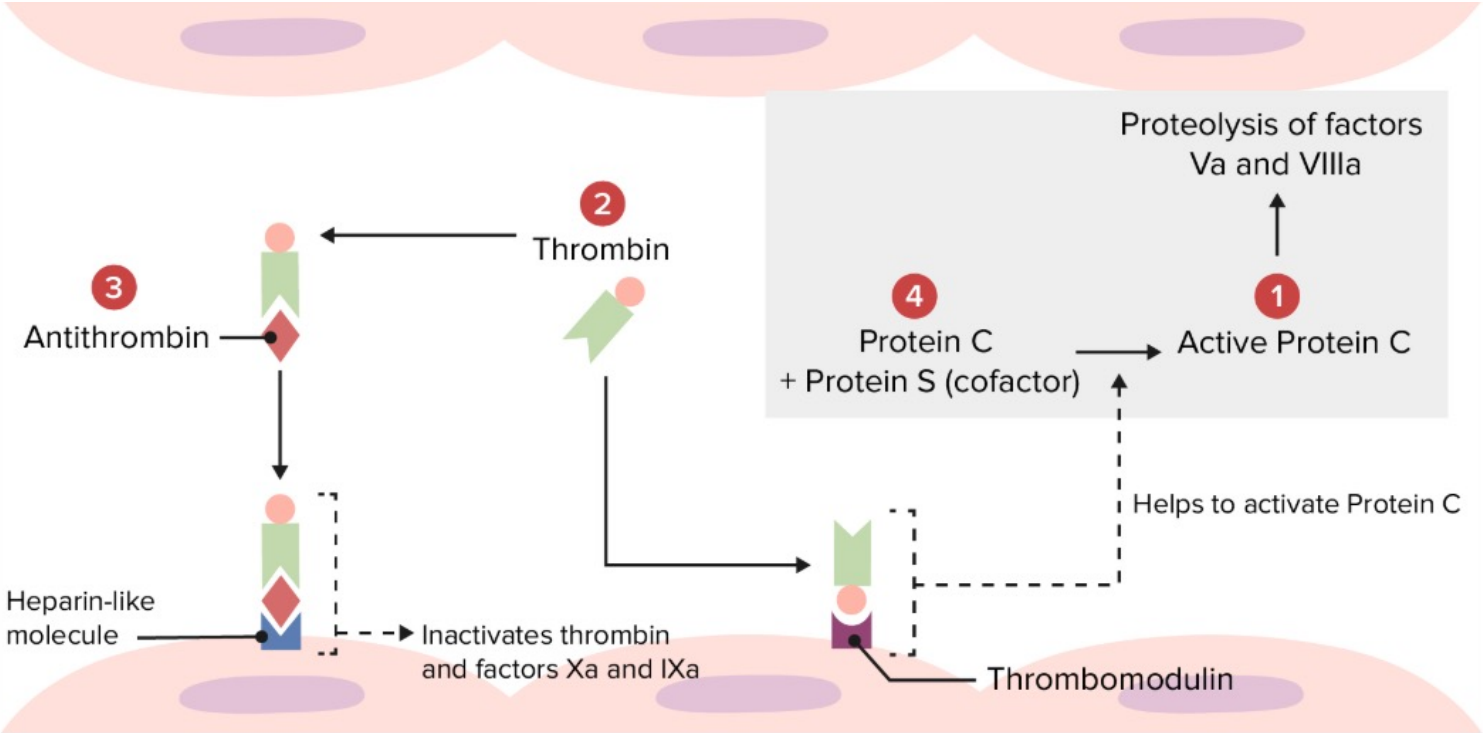


Formulation	Dose	Odds ratio (OR) for VTE
Estradiol, oral	2-6 mg daily	4.2 (95% CI 1.5–11.6)
Estradiol, transdermal patch	25-200 µg per day, replace every 3-5 days	0.9 (95% CI 0.4–2.1)
Estradiol, transdermal gel	1.5 mg, 1-2 times daily	0.93 (95% CI 0.87-1.01)
Estradiol valerate, intramuscular	5-30 mg every 1-2 weeks	(20-30 mg) 2.38 (95% CI 2.18-2.59)
Estradiol cypionate, intramuscular	2-10 mg weekly	***

Recently, the Endocrine Society of America established clinical practice guidelines recommending that serum estradiol levels in those receiving GAHT should not exceed the peak physiological range of 100-200 pg/mL observed in cisgender women.
These guidelines aim to avoid supraphysiological estradiol concentrations, which presumably increase the risk of VTE.

King H et al, Blood 2024

Protein S and Protein C



Effects of Low-Molecular-Weight Heparin on Pregnancy Outcomes in Protein S Deficiency: A Prospective, Randomized Controlled Phase II Clinical

Hereditary thrombophilia (e.g., antithrombin, protein C and protein S(PS) deficiency is associated with a 5-7% risk of VTE during pregnancy.
This study is a prospective, randomized controlled phase II clinical trial to assess whether low-molecular-weight heparin could improve pregnancy outcomes in pregnant patients with PS deficiency.

Eligible pregnant women with PS deciency were randomized 1:1:1 into three groups, each receiving 0.4 ml of enoxaparin daily plus 75 mg of aspirin, 75 mg of aspirin alone, or no intervention until delivery, and 0.4 ml of enoxaparin daily for up to 6 weeks postpartum.

	LMWH+ASA (n=16)	*ASA (N=16)*	*No intervention (n=16)*
Delivery ages	34 yrs (27-41)	35 yrs (29-43)	32 yrs (26-41)
Previuos VTE	2	0	0
Preeclampsia (n)	0	2	1
Pregnancy bleeding (n)	3	3	0
Posta-partum Hemorrhage (n)	2	3	3
Intraoperative hemorrhage (ml)	340.6±264.7	221.8±135.3	284.4±179.5
Born alive child (n)	16	16	14
Preterm births (n)	2	1	0
Apgar score <10 at 1° min	1	0	1

Zang M et al, Blood 2024

Leveraging Population-Scale Multiomic Datasets to Elucidate the Risk of Thrombosis Associated with Protein S (PROS1) Deficiency

Using two biorepositories with paired genetic and phenotypic data: the ***UK Biobank*** (N=426,436) and the ***NIH*** All of Us program (N=204,006), ***rare germline variants*** (MAF <0,1%) ***in protein S*** (PROS1) were selected. At each mutation was assigned an ***in silico functional impact score (FIS***) between 0.0 and 1.0, with higher scores reflecting greater predicted likelihood that a variant results in protein loss of function.

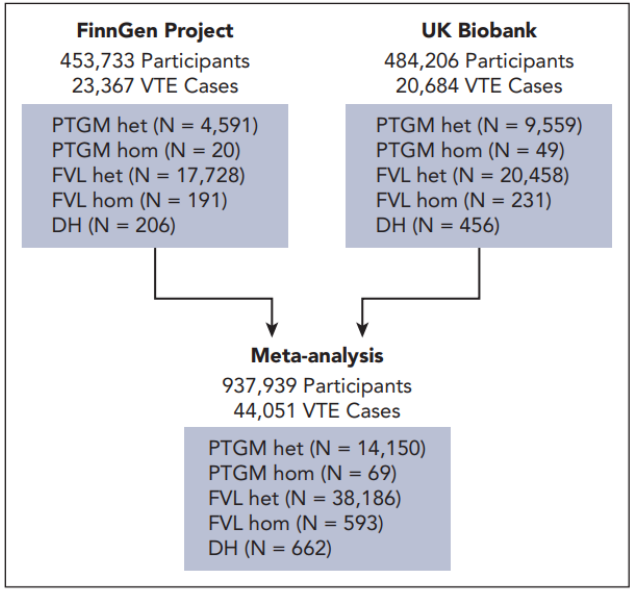
In the UKB, we identied 961 carriers of a PROS1 variant with FIS ≥0.7 (99.8% heterozygous) and 39 carriers of a variant with FIS=1.0 (100.0% heterozygous). ***Plasma PS was signicantly decreased in FIS=1.0*** (mean PS=51.2%, P=0.0003) but not FIS ≥0.7 (mean PS=97.1%, P=0.21) variant carriers. The presence of PROS1 variants (FIS ≥0.7) was signicantly associated with VTE (OR=1.98, 95% CI: 1.55-2.48, $P=1.95x10^{-7}$). Participants with ***FIS=1.0 variants experienced further elevation in VTE risk (OR=14.0, 95% CI: 6.98-27.14, $P=9.09x10^{-11}$).***

This findings were indipendently replicated in the AoU dataset (OR=2.99, 95% CI: 2.13-4.08, P=7.54x10-9 for FIS ≥0.7; OR=13.8, 95% CI: 6.66-28.16, P=8.1x10-11 for FIS =1.0).

Chaudhry SA et al, Blood 2024.

Single- and double-heterozygous carriers of FVLeiden e PTG20210A

Using multidimensional data from the UK Biobank (UKB) and FinnGen biorepositories, authors evaluated the clinical impact of DH carrier status across 937.939 individuals.

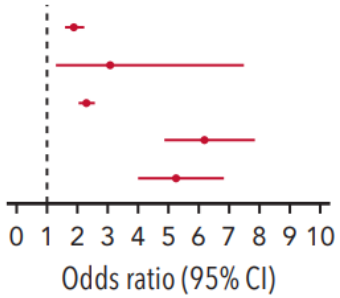


Ryu J et al, Blood 2024.

Single- and double-heterozygous carriers of FVLeiden e PTG20210A

After adjusting for sex, age, and ancestry, we found that DH genotype carriers experienced a significantly elevated risk of VTE compared with individuals who are wild-type for both alleles, but also lower VTE risks were associated with single heterozygosity for PTGM and FVL.

		Carriers/Non-carriers			
Genotype	**Carriers/total (%)**	**Cases**	**Controls**	**OR [95% CI]**	***P* value**
PTGM het	14,150/899,016 (1.5)	1,077/39,271	13,073/845,595	1.86 [1.57 - 2.21]	8.6×10^{-13}
PTGM hom	69/923,052 (<0.01)	7/39,271	62/845,595	3.07 [1.26 - 7.43]	0.014
FVL het	38,186/884,935 (4.3)	3,582/39,271	34,604/845,595	2.28 [2.03 - 2.56]	1.9×10^{-43}
FVL hom	593/885,288 (0.06)	87/39,271	335/845,595	6.19 [4.63 - 7.88]	1.1×10^{-49}
DH	662/885,528 (0.07)	122/39,271	540/845,595	5.24 [4.01 - 6.84]	4.8×10^{-34}



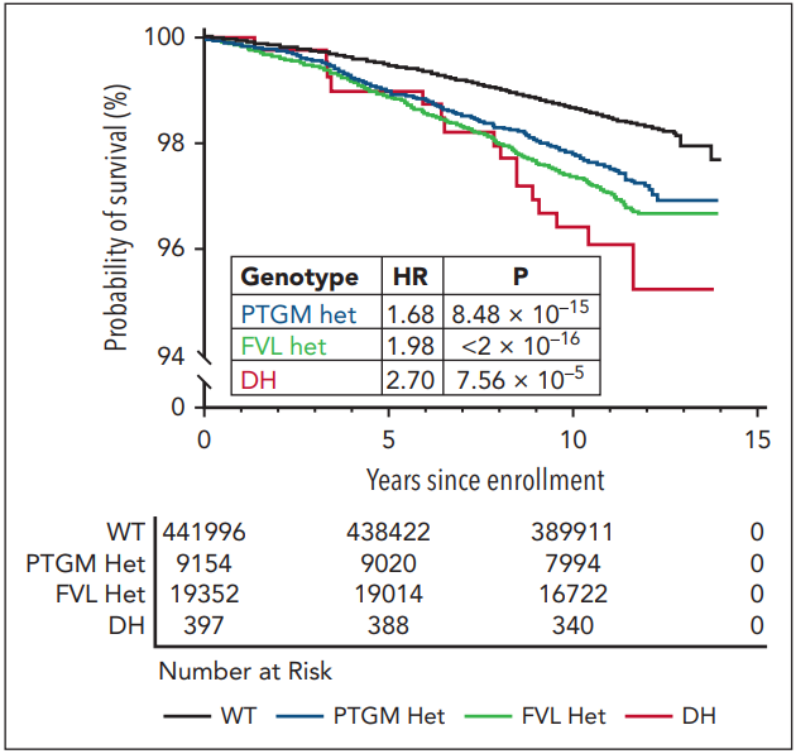
Ryu J et al, Blood 2024.

Single- and double-heterozygous carriers of FVLeiden e PTG20210A

VTE incidence was significantly higher among PTGM individuals, FVL individuals, and DH individuals than among wild-type participants.

Correspondingly, patients homozygous for PTGM (N = 48) and FVL (N = 198) demonstrated an increased risk of incident VTE, although this trend did not achieve significance for PTGM homozygous individuals.

The risk for the 3 subtypes of ***arterial thrombosis*** (MI, CVA, and PAD) was ***not significantly higher in DH*** individuals after adjusting for multiple comparisons.



Ryu J et al, Blood 2024.

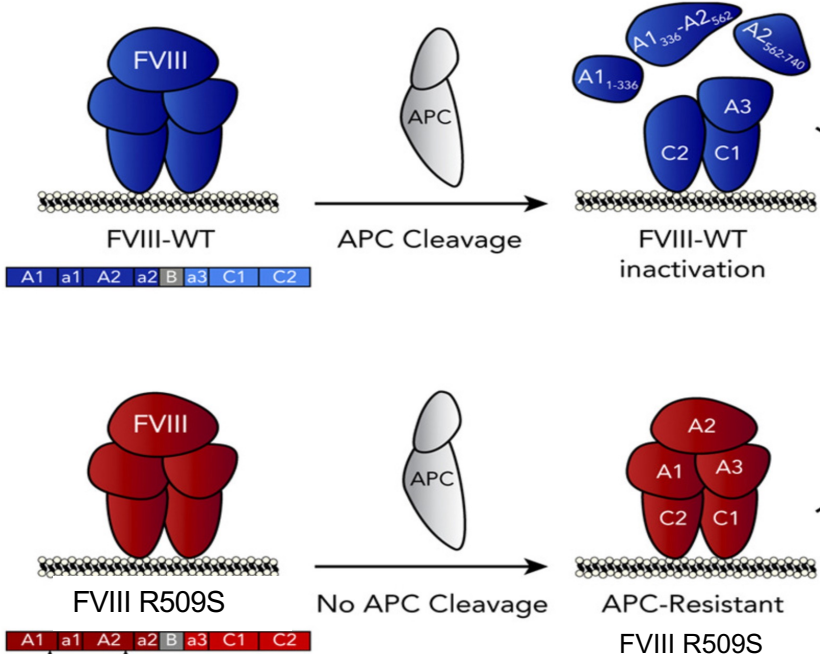
A novel factor VIII mutation

An 18-year-old male presented with recurrent, life-threatening thromboses since birth including arterial (perinatal stroke, splenic infarct) and venous (bilateral lower extremity, mesenteric vein, portal vein and pulmonary emboli). He was found to have markedly elevated factor VIII activity ranging from 300 to 900%.

With WGS, IGV was used to identify an unique exonic point mutation, R590A in Exon 12.

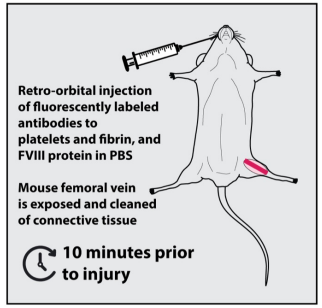
In silico studies suggest that while the mutated FVIIIa has a higher affinity for APC based on scores, it appears to alter the binding site, leading to reduced interactions with APC compared with WT.

The clotting APCR for FVIII showed, in fact, resistance.

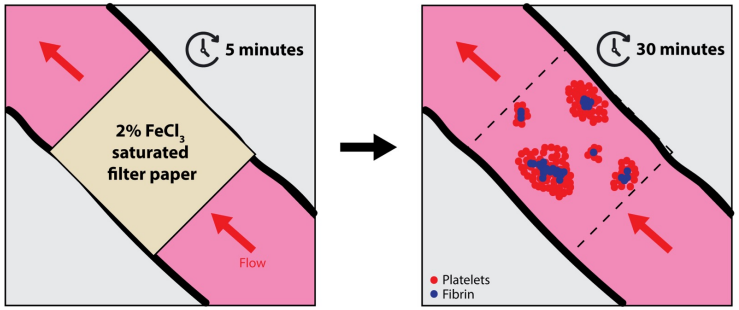


Wischmeyer J et al, Blood 2024.

Factor VIII excess and thrombosis

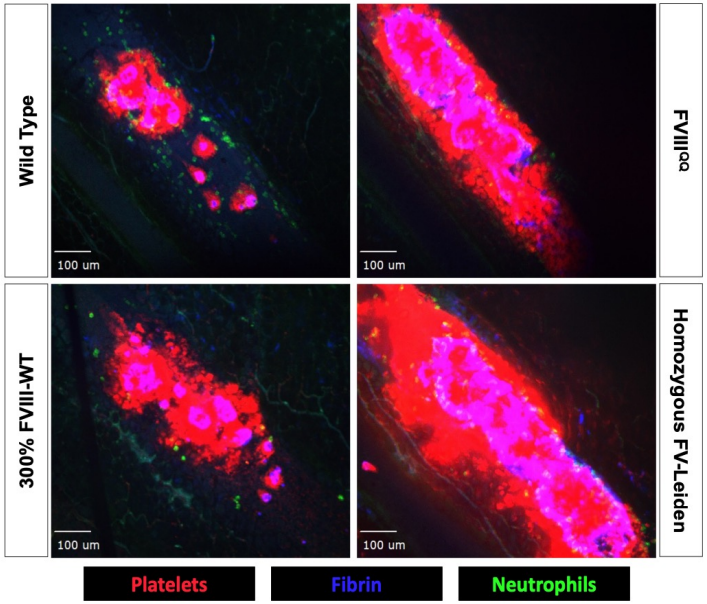


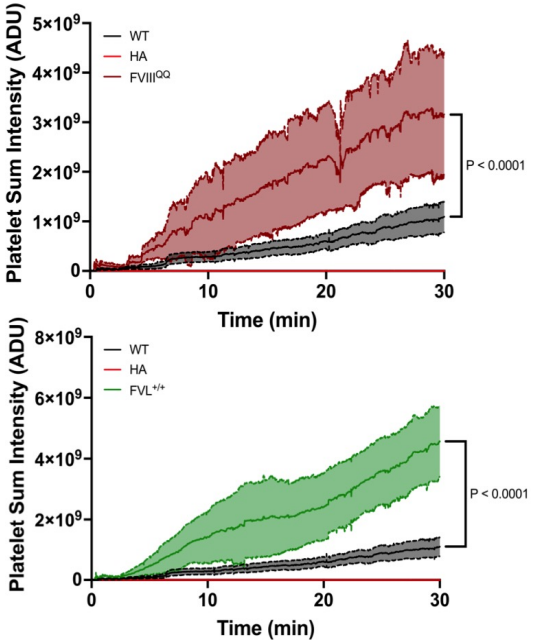
1. **Abs and FVIII protein are administered 10 minutes prior to injury and femoral vein is exposed**
2. **2% ferric chloride-soaked filter paper is applied directly to femoral vein for 5 minutes**
3. **Confocal images are collected for 30 minutes**



Morris J et al, Blood 2024.

Factor VIII excess and thrombosis





FVIIIQQ mice demonstrated a 3.5-fold increase in platelet sum intensity that was significantly increased from that of WT mice ($P < 0.0001$).

Homozygous FV-Leiden (FVL+/+) (green curve) mice were assayed to confirm that observations may correlate with an established prothrombotic risk in mice that similarly probes the APC pathway.
FVL+/+ mice demonstrated a 4.5-fold increase in platelet accumulation that was significantly increased compared to that of WT mice ($P < 0.0001$).

Morris J et al, Blood 2024.

Clonal Hematopoiesis of Indeterminate Potential (CHIP) and thrombosis

The study was conducted using prospective cohorts within the Atherosclerosis Risk in Communities (ARIC) Study, a population-based setting.

	Cohort V2 (n= 10,765)	Cohort V5 (n= 3,980)
Median age	57.3 yrs	75.7 yrs
At least 1 CHIP	1081 (10%)	985 (24.7%)
>1 CHIP	191 (1.7%)	195 (4.9%)

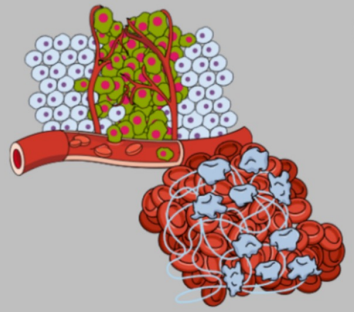
Singularly, DNMT3A and ASXL1 don't significantly correlate with thrombotick risk in both cohort; vice versa TET2 appears statistically associated with an increased thrombotic risk in the V45 cohort (HR 2.21 (1.25-3.91), p=0.007).

VTE number (%)	Cohort V2	Cohort V5
CHIP	12 (1.1%)	44 (4.5%)
Non-CHIP	116 (1.2%)	96 (3.2%)
HR (95%CI)	0.86 (95% CI 0.47-1.56)	**1.45 (95%CI 1.0-2.1)**

Saadatagah S et al, Blood 2024.

Cancer and thrombosis

Cancer-Associated Thrombosis Risk Factors



A Patient related factors

Age
Female gender
Race (e.g. African American)
Prior history of thrombosis
Commorbidities
Obesity

B Cancer related factors

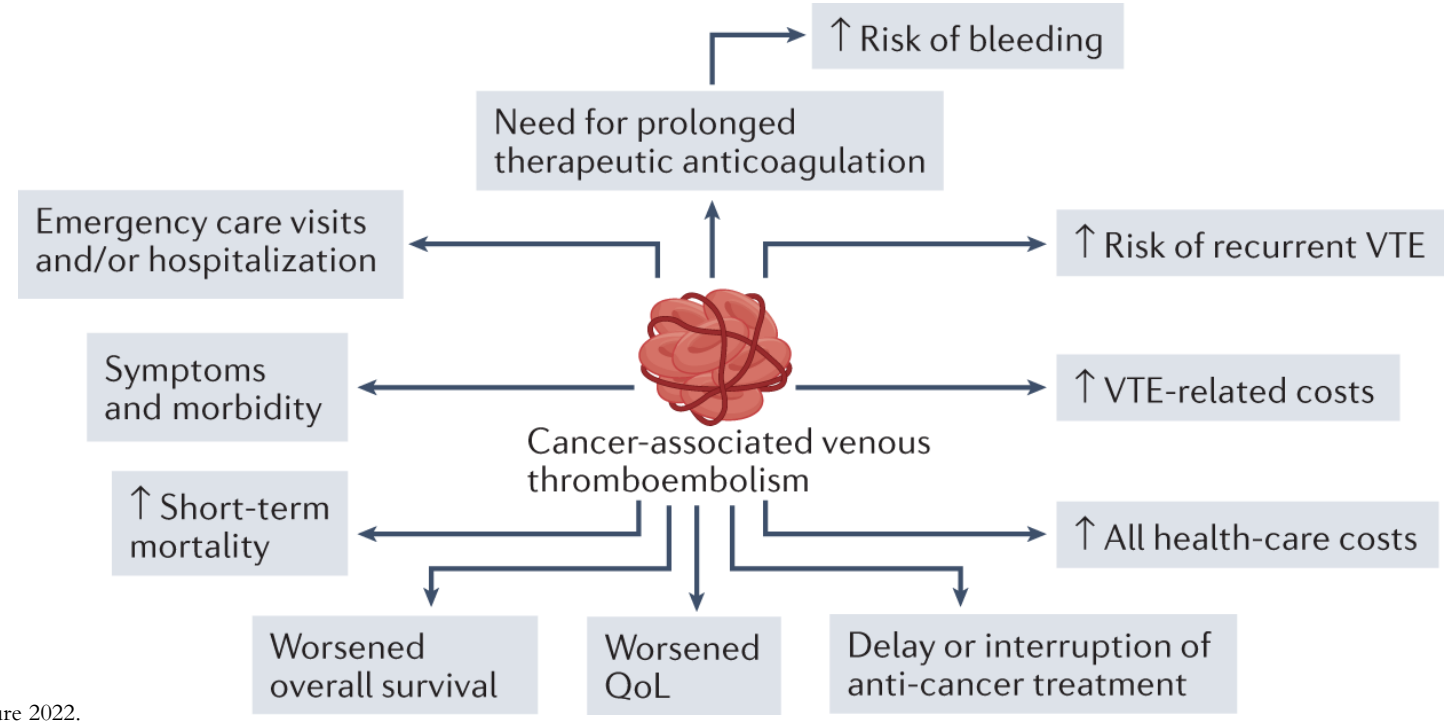
Advanced stage
Metastases
Site
Type (pancreatic, lymphoma, etc.)

C Treatment related factors

Hospitalization
Blood transfusions
Chemotherapy (protein kinase inhibitors, etc.)
Surgery

Tsantes AG et al, Cancers 2024

Cancer and thrombosis



Khorana AA et al, Nature 2022.

Features evaluated at onset of systemic therapy	Risk score
Cancer type (ICD-O-3 code)	
Colorectal & intestinal	+1
Lung, kidney, bladder, testicular, uterine, ovarian, brain, sarcoma, multiple myeloma, aggressive lymphoid malignancy (DLBCL, T/NK, Pre-B/T, ALL)	+2
Esophageal & gastric, pancreas, gallbladder, cholangiocarcinoma	+3
Cancer stage	
Advanced or metastatic (III-IV)	+1
Systemic therapy	
Targeted or endocrine (no chemo/immunotherapy)	-1
Complete blood count	
White blood cell > 11	+1
Hemoglobin < 10	+1
Platelet ≥ 350	+1
Other Predictors	
Body mass index (BMI) ≥ 35	+1
Non-Hispanic Asian Pacific Islander	-1
History of VTE lifetime (ICD code)	+1
History of paralysis lifetime (ICD code)	+1
History of hospitalization > 3d within last 90d	+1

Li A et al, Blood 2024.

Cancer and thrombosis

EHR-CAT risk score was validated using data from Epic Cosmos, a dataset created in collaboration with a community of Epic health systems representing more than 259 million patient records from over 1,548 hospitals.

Data from 304,780 patients were collected in the analytic cohort.

At 6 months after systemic therapy, there were 7% all-cause mortality and 3.6% new VTE.

The 6-month cumulative incidence of VTE was 1.0%, 2.9%, 4.3%, 5.5%, 7.4%, 10.7% for score 0, 1, 2, 3, 4, 5, respectively. The c statistic for EHR-CAT was 0.72 (vs. 0.62 for Khorana score).

Cancer and thrombosis

From the National Inpatient Sample (NIS) Database, 1,233,832 cancer patients were selected (period 2016-2018), and 63,505 (5.1%) of them were diagnosed with acute VTE.

Female patients had a significantly higher incidence of VTE compared to males (5.5% vs. 4.8%; p<0.001). Significant racial disparities in VTE incidence were observed, with black patients having the highest incidence (6.4%), followed by whites (5%), Native Americans and Hispanics (4.9%), and Asians (3.9%).

Regarding cancer subtype, 78.6% (n=970,405) had ***solid malignancies*** and 21.4% (n=263,427) had hematological malignancies. Patients with solid malignancies exhibited a significantly higher incidence of VTE compared to those with hematological malignancies (5.4% vs. 4.1%; p<0.001). Among solid tumors, ***gastrointestinal and lung*** malignancies were the most prevalent, contributing to 28.7% and 25.9% of VTE cases, respectively.

Among hematological malignancies, ***non-Hodgkin lymphoma*** was the most significant contributor, accounting for 42% of VTE cases.

Araji Get al, Blood 2024

Leukemia and thrombosis

In this retrospective analysis of a cohort of patients with newly diagnosed AL in a reference cancer center in ***Brazil,*** between 2009 and 2022, 421 patients were included, 49% diagnosed with AML, 23% with APL, and 28% with ALL.

The 60-day cumulative incidence of thrombosis was 15% (95% CI 12%–18%), with incidence rates of 21%, 11%, and 20% in ALL, AML, and APL, respectively. Most events occurred within the first 30 days (72%), and the remaining cases were detected at disease presentation (24%) or between 30–60 days from diagnosis (4%).

Arterial thrombosis represented 8 out of 69 events, all cerebrovascular and more frequent in APL (32%). Regarding venous thrombosis, the most common sites were the upper limbs (47%), catheter-related events (20%) and lower limbs (13%).

Prophylactic anticoagulation was administered in 15% of patients with thrombosis.

In the ALL subset, 44% of thrombosis occurred after the use of ***asparaginase***. Cerebral Venous Thrombosis (CVT) represented 25% of this subgroup's events.

Carvalho LV et al, Blood 2024

Leukemia and thrombosis

KHORANA SCORE

Variable	Score
Very high-risk tumor (stomach, pancreas)	2
High-risk tumor (lung, gynecologic, genitourinary excluding prostate)	1
Hemoglobin level <100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count >11 × 10^9/L	1
Prechemotherapy platelet count 350 × 10^9/L or greater	1
Body mass index 35 kg/m^2 or greater	1

A score of 0 = low-risk category. A score of 1–2 = intermediate-risk category. A score of >2 = very high-risk category.

SiAML-thrombosis

Scores = (2 x W) + (2 x P) + D

Score <3: lower risk of thrombosis
Score ≥3: higher risk of thrombosis

White blood cell counts (W)
- 0 if ≤15 x 10^9/L
- 1 if >15 x 10^9/L

Platelet counts (P)
- 0 if ≤40 x 10^9/L
- 1 if >40 x 10^9/L

D-dimer (D)
- 0 if ≤7,000 μg FEU/L
- 1 if >7,000 μg FEU/L

Table 1. The ISTH Scoring System for DIC.

Variable	Value	Points
Platelets (K/μL)	>100	0
	50-100	1
	<50	2
INR	<1.3	0
	1.3-1.7	1
	>1.7	2
D-Dimer (ng/mL)	<400	0
	400-4000	2
	>4000	3
Fibrinogen (mg/dL)	>100	0
	<100	1

No statistical association whit thrombosis were found with Khorana score, ISTH-DIC score and SiAML-thrombosis score.
No clinical and laboratory parameters appeared to be associated with thrombotic risk in acute leukemia.

Carvalho LV et al, Blood 2024

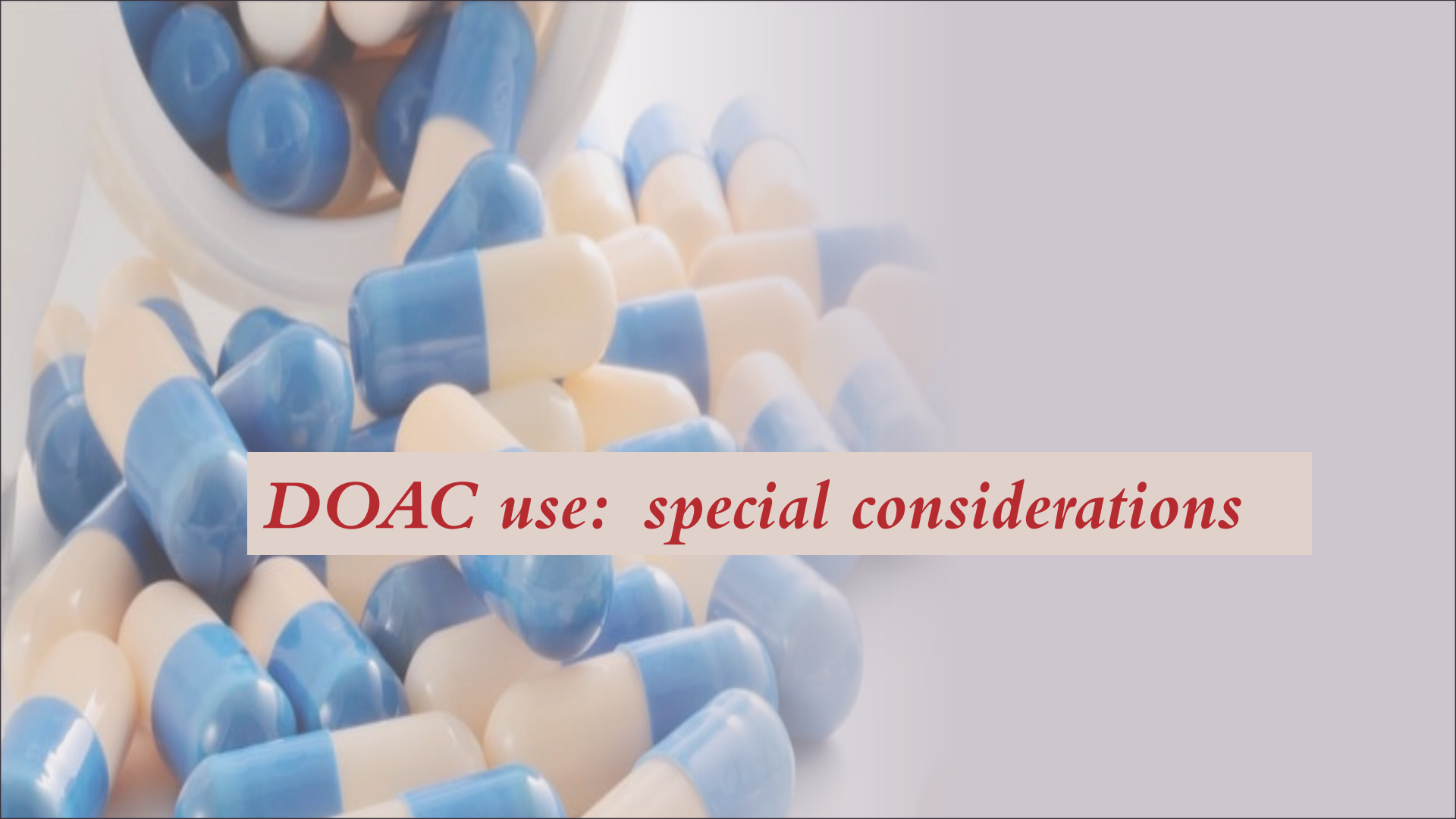
Anticoagulants and cancer-associated thrombosis

12,952 patients with a previous VTE (within 30 days before or six months following cancer diagnosis) were included in the study. After propensity-score matching, 4,641 were included for final analysis with 1,547 in each of DOAC, LMWH, and warfarin treatment groups.

	LMWH	VKA	DOAC (refernce)
Ischemic stroke/TIA (OR)	0.92 (0.79-1.07)	0.91 (0.78-1.06)	/
Median survival (yrs)	9.6 m	11.4 m	10.7 m

The type of anticoagulant did not impact the risk of ATE. Traditional cardiovascular risk factors and systemic anticancer treatment were predictive of ATE among this patient population.

Ma S et al, Blood 2024

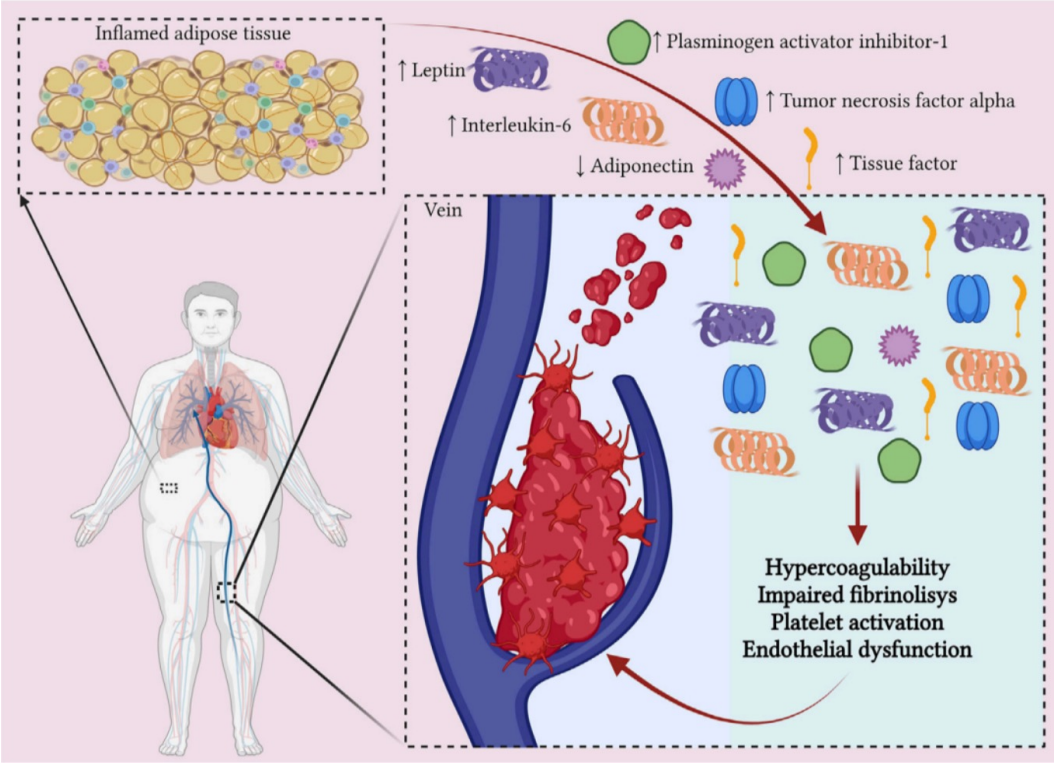


DOAC use: special considerations

Thrombosis and obesity

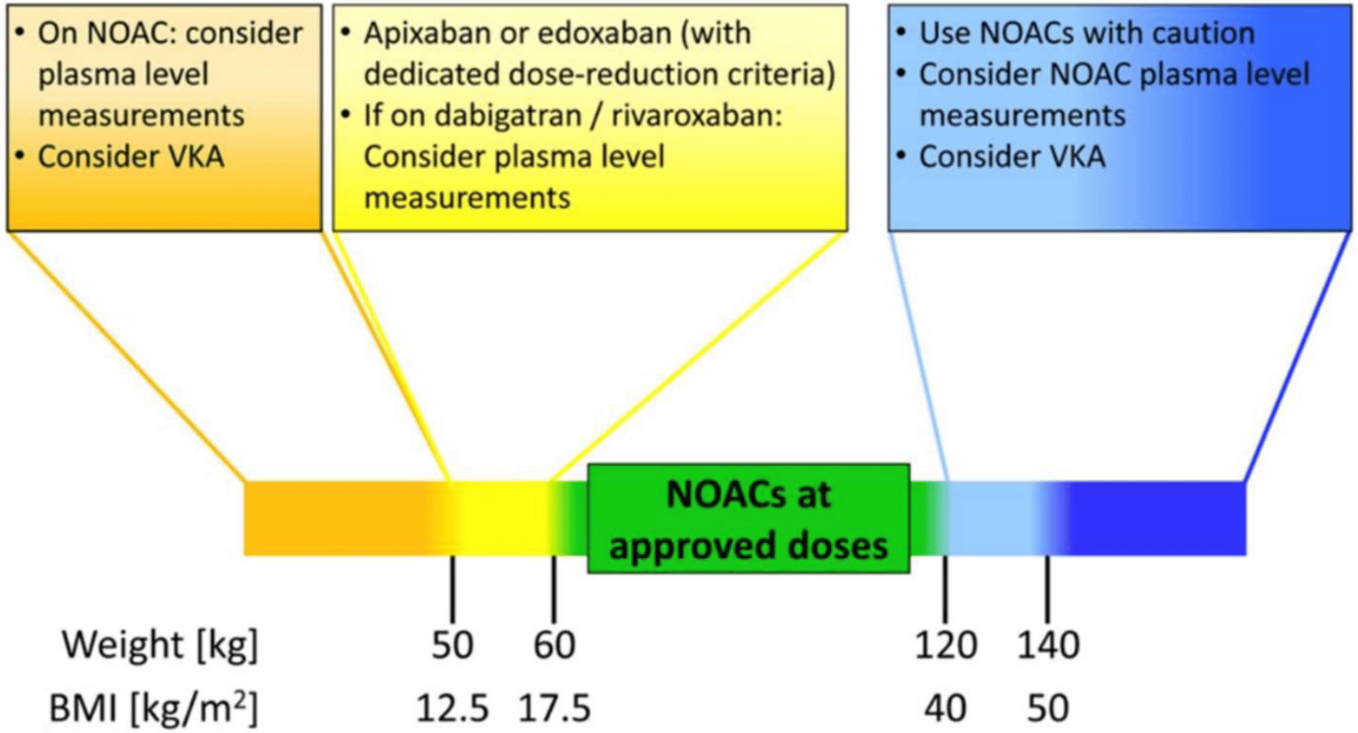
ESC guideline consider obesity a minor risk factor for VTE, although most patients present with additional VTE risk factors, considering the multiple comorbidities associated with obesity.

Several mechanisms increased VTE risk in obesity including a sedentary lifestyle, increased intra-abdominal pressure, diminished blood flow velocity within the lower extremities, as well as inflammatory and metabolic dysregulations that lead to a hypercoagulable state.



Sorodoc V et al, Front Pharmacol 2024

DOACs and obesity



Mocini D et al, JCM 2021

DOACs and obesity

Forty patients with a BMI > 39 kg/m2 and documented acute VTE treated for at least 3 months with therapeutic anticoagulation and after switched to apixaban 2.5 mg bid as extended secondary prophylaxis.

Of evaluable patients, there were ***no recurrent clots*** within one year of the dose reduction. Two patients suffered hemorrhagic complications after dose reduction: One had an acute-on-chronic subdural hematoma on day 168, and another presented with a CSNMB gastrointestinal hemorrhage on day 62, was found to have a large adenoma, and then resumed anticoagulation without further issues.

Characteristics	
BMI (kg/m2)	45.9 ± 5.4
Age	54.4 ± 12.8
Male/female	8/32
Ethnicity	Black 21 Hispanic 7 Caucasic 10 Mixed 2
Previuos VTE	DVT 17 PE ± DVT 23
Concomitant neoplasms	5 (endometrial, breast, JAK2+ essential thrombocythemia, multiple myeloma and B cell lymphoma)

Townsend NW et al, Blood 2024

DOACs and obesity

A propensity-score matching was applied on 187,175 patients on DOAC and 117,487 patients on VKA, resulting in two cohorts of 82,502 morbidly obese patients each. After matching, the demographic characteristics (ethnicity, gender) between the two cohorts were similar.

Event	VKA	DOAC	HR (95%CI)	p
Recurrent VTE	6.89	4.68	0.67 (0.64-0.71)	**0.012**
Incident stroke	9.41	6.09	0.64 (0.61-0.67)	**<0.001**
Mortality rate	9.08	6.65	0.73 (0.70-0.76)	**0.001**
Major bleeding	4.94	3.33	0.67 (0.63-0.71)	**<0.001**
Overall bleeding	13.87	7.49	0.53 (0.51-0.54)	**<0.001**

Akbar AU et al, Blood 2024

Thrombosis and obesity

DIRECT ORAL ANTICOAGULANTS	
GENERAL CHARACTERISTICS	DOACs are preferred over VKAs for VTE management due to their ease of use, efficacy, and safety. Routine monitoring - Not required.
IMPACT OF OBESITY	Their lipophilic properties may increase volume of distribution, potentially lowering plasma concentrations and risking underdosing in morbidly obese patients.
REPORTED FINDINGS	Studies show that DOACs, particularly rivaroxaban and apixaban, are safe and effective for treating and preventing VTE in obese and morbidly obese patients, with outcomes comparable or superior to warfarin. DOACs are associated with comparable or lower rates of VTE recurrence and major bleeding compared to warfarin, especially in patients with severe obesity. Most studies focus on apixaban and rivaroxaban, highlighting their safety and efficacy, while evidence for dabigatran and edoxaban remains limited. Drug-specific peak and trough levels of DOACs should be monitored in this population.

Sorodoc V et al, Front Pharmacol 2024

DOAC level measurement: to do or not to do?

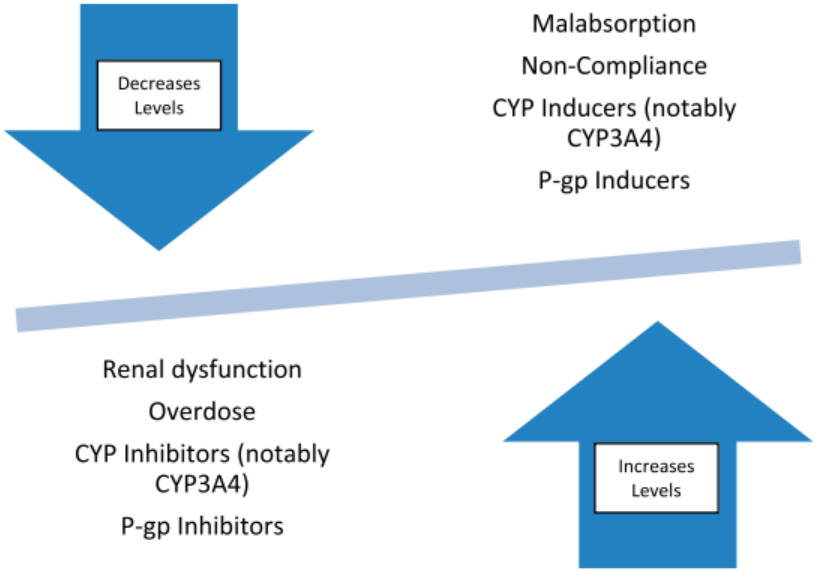


Figure 2. Factors contributing to changes in DOAC drug levels.

Shih AW et al, Blood 2024

DOAC level measurement: to do or not to do?

At University Clinical Hospital of Valencia, the DOAC levels were collected in 300 patients.

The main reasons for requesting levels was extreme weight (40%), drug interactions (20%), and thirdly, advanced chronic kidney disease (CKD) (16%). Other reasons listed by frequency were: urgent surgery or bleeding, thrombosis despite correct dosing, hemorrhagic predisposition, regulated preoperative regimen, high thrombotic risk, CHILD-PUG C cirrhosis, and malabsorption. In 5% of cases, the reason was unknown.

	Low-normal levels	High levels	p
Hemorrhagic event	12%	25%	NS

Martinez C et al, Blood 2024

DOAC level measurement: to do or not to do?

	Patients (n)	*DOAC level (out of range)*	*Event (patients %)*	*p*
Renal function				
- eGFR >50 ml/min	68%	18%	16%	
- eGFR 25-50 ml/min	28%	-	-	
- eGFR <25 ml/min	4%	28%	37%	NS
Concomitant neoplasm				
- Yes	32%	23%	22%	
- No	68%	18%	14%	P<0.05

Therapeutic changes were made in 7% of patients. In 86% of this patients, the reason for the change was levels out of range, resulting in a statistically significant higher percentage of therapeutic changes in patients with levels out of range compared to those with levels within range.

Martinez C et al, Blood 2024

DOAC extended treatment: to reduce or not to reduce?

The RENOVE trial is a randomized study enrolling 2768 patients with a previous VTE event and candidated to an extended treatment.

	Full-dose (n= 1385)		*Reduced-dose (n=1383)*		
	N (%)	5-yrs IR	N (%)	5-yrs IR	p
Recurrences	15 (1.08%)	1.8%	19 (1.37%)	2.2%	NS (for noninferiority)
CRNMB	154 (11.1%)	15.2%	96 (9.94%)	9.9%	-
All-cause death	54 (6,1%)	-	35 (4,3%)	-	-

Couturaud F et al, Blood 2024

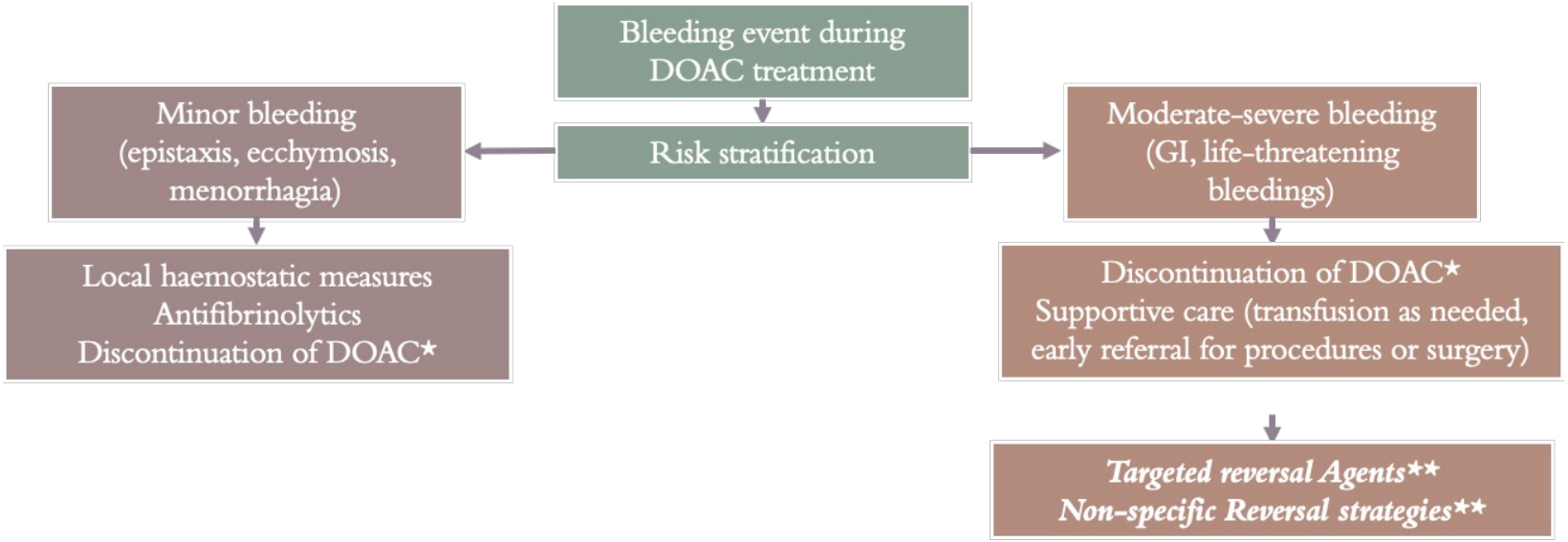
DOAC extended treatment: to reduce or not to reduce?

Among 978 patients who received anticoagulation with API or RIVA after a first VTE, using a propensity-score matching two cohorts were compared: 662 patients with therapeutic dosing to 189 patients on prophylactic dosing.

	Full-dose (n= 662)	*Reduced-dose (n=189)*	
	IR	IR	p
Recurrent PE	1.8	0.3	0.21
Recurrent DVT	1.1	0.3	0.22
Any recurrences	4.1	1.3	0.055
Any bleedings	45.6	40.0	***0.039***
Major bleedings	3.6	1.8	0.067
DEA admissions	17.2	9.1	***0.002***
Hospitalizations	9.0	5.1	***0.011***

Schaefer K J et al, Blood 2024

A practical approach to reversal therapy



★In some of these patients, discontinuation of the DOAC and reinitiation of warfarin may be considered because current literature suggests a higher risk (as high as 25%) of heavy menstrual bleeding if the patient is taking rivaroxaban.

★★consider in patients with severe/life threatening bleeding

Shih AW et al, Blood 2024

A practical approach to reversal therapy

Table 1. Effects of DOACs on coagulation testing and recommended testing

Drug Class	DOAC	Conventional Coagulation Testing			Specialized Coagulation Testing		
		PT	APTT	TT	dTT	ECT/ECA	Anti-Xa Activity
Direct Thrombin Inhibitor	Dabigatran	↑/↔	↑	↑	↑	↑	N/A
Factor Xa Inhibitor	Rivaroxaban	↑/↔	↑/↔	N/A	N/A	N/A	↑
	Apixaban	↑/↔	↑/↔	N/A	N/A	N/A	↑
	Edoxaban	↑/↔	↑/↔	N/A	N/A	N/A	↑

Color key: red, inappropriate testing; yellow, may be useful for excluding clinically relevant drug levels and may approximate drug levels; green, best test available. Adapted from Siegal et al[35] with permission.
↑, increase; ↓, decrease; ↔, no change; N/A, not advised.

Shih AW et al, Blood 2024

A practical approach to reversal therapy

Table 3. Characteristics of DOAC-specific reversal agents

	Ciraparantag	Idarucizumab	Andexanet alfa
Anticoagulants indicated for reversal	Direct thrombin inhibitors, factor Xa inhibitors, heparins	Dabigatran	Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, enoxaparin)
Mechanism of action	Reported to bind anticoagulants via noncovalent hydrogen bonds and charge-charge interactions	Monoclonal antibody fragment to bind dabigatran	Inactive form of factor Xa to bind inhibitors
Suggested administration	Phase 2 study used 100-300 mg single intravenous dose	Total of 5 g given as two 2.5-g 50 mL boluses within 15 minutes of each other	800 mg bolus and 960 mg infusion over 2 h; patients who take apixaban or rivaroxaban more than 7 hours before andexanet administration: 400 mg bolus and 480 mg infusion over 2 hours
Time to onset	Within 10-30 minutes	Within minutes (between vials in REVERSE-AD[31])	Within 2-5 minutes

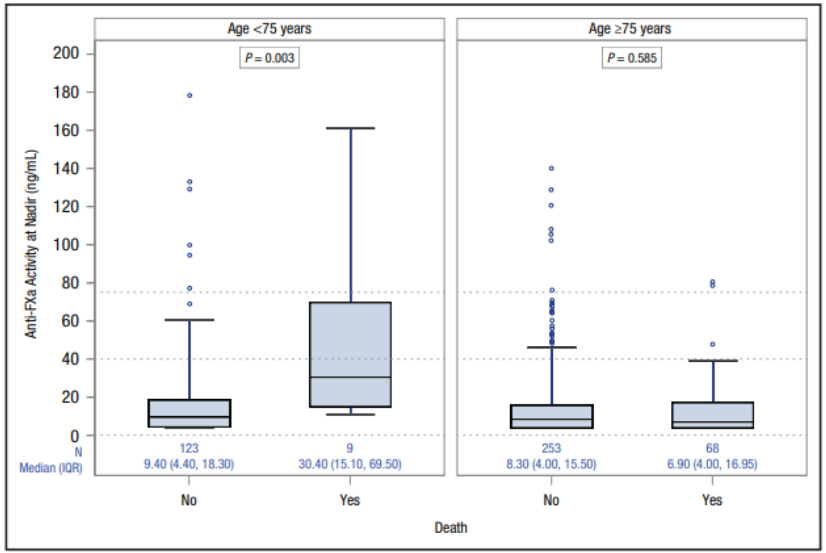
OFF-LABEL USE OF NON-SPECIFIC REVERSAL AGENTS

4PCC 25-50 U/kg depending on severity; Maximum daily dose: 5000 U or
aPCC 50-100 U/kg depending on severity; Maximum daily dose: 200 U/kg

Shih AW et al, Blood 2024

A practical approach to reversal therapy – ANNEXA-4 study

Parameter	Safety population (N=479)	Efficacy population (n=349)
Age, y, mean±SD	77.9±10.7	77.7±10.6
Male sex, n (%)	260 (54.3)	185 (53.0)
White race, n (%)	414 (86.4)	300 (86.0)
Body mass index, kg/m², mean±SD	26.6±5.6	26.6±5.8
Primary indication for anticoagulation, n (%)†		
Atrial fibrillation	389 (81.2)	284 (81.4)
Venous thromboembolism‡	72 (15.0)	51 (14.6)
Other	18 (3.8)	14 (4.0)
Factor Xa inhibitor, n (%)		
Rivaroxaban	176 (36.7)	132 (37.8)
Apixaban	245 (51.1)	172 (49.3)
Edoxaban	36 (7.5)	28 (8.0)
Enoxaparin	22 (4.6)	17 (4.9)
Primary site of bleeding, n (%)		
Gastrointestinal tract	109 (22.8)	78 (22.3)
Central nervous system/ intracranial	331 (69.1)	249 (71.3)
Other	39 (8.1)	22 (6.3)



Overall mortality within 30 days in this study was 15.7%, which is lower than in some cohorts of patients with FXa inhibitor–associated major bleeding. . It is possible that the association between anti-FXa levels and mortality was only seen in younger patients because the signal was confounded by concomitant frailty.

Milling TJ et al, Circulation 2023

A practical approach to reversal therapy – VMX-C001

VMX-C001 is an engineered recombinant ***human coagulation factor X (FX) that is insensitive to inhibition by FXa direct oral anticoagulants (FXa-DOACs)***. Upon administration it bypasses the effect of FXa DOACs and rapidly restores coagulation.

Twenty male monkeys pretreated with Rivaroxaban were anesthetized, the liver was exposed, and a 4 mm diameter/2 mm depth injury was made in the liver using a punch biopsy tool. Thus, they received VMX-C001 IV bolus administration (1.3 mg/kg; N =7 or 0.9 mg/kg; N =7) or placebo (N = 10).

Administration of VMX-C001 reversed the effect of rivaroxaban on bleeding time in both dose groups (1.3 mg/kg: 201 sec, range 123 – 926; 0.9 mg/kg: 239 sec, range 167 – 1133). Additionally, post-injury blood loss was reduced to baseline values in both groups (1.3 mg/kg: 2.3 gr, range 0.5 – 5.3 and 0.9 mg/kg: 2.4 gr, range 1.3 – 8.9).

Verhoef D et al, Blood 2024