An Update in Thromboembolism and Anticoagulation

David Garcia, MD

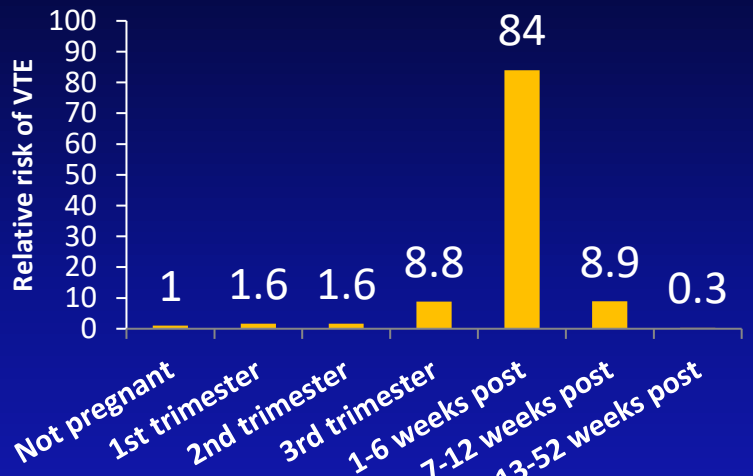
September 2024

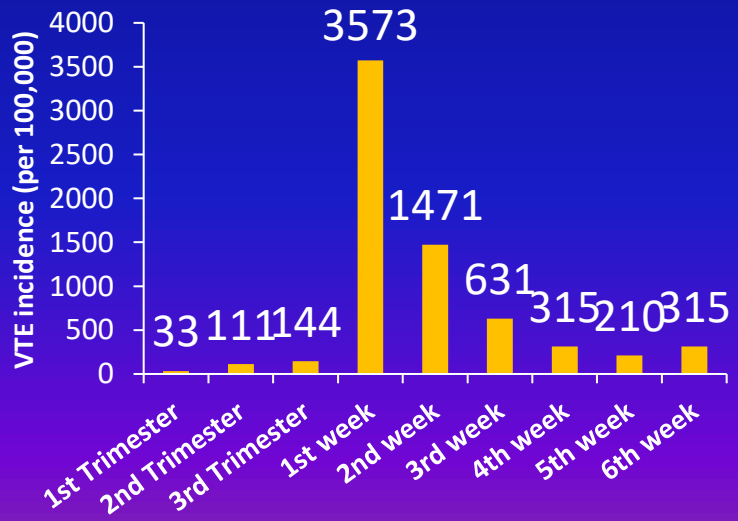
Outline

- Pregnancy
- Cancer
- Duration issues
  - Thrombophilia testing
  - Low-dose Fxa inhibitors
- Anticoagulation ‘failure’
- ‘Reversal’, procedures, lab measurements
- HIT
- Arterial thrombosis

Epidemiology of VTE in pregnancy

- Incidence of VTE– 0.76 to 1.72 per 1000 pregnancies
- Incidence of fatal PE- 1.1-1.5 per 100,000 deliveries
- VTE increases with age
  - < 20- 1.47 per 1000 deliveries
  - 20-29 years- 1.63
  - 30-39 years- 1.93
  - 40 + years- 2.75





Marik and Plante N Engl J Med 2008;James AH, et al. Am J Obstet Gyne 2006; Heit J et al. Ann Intern Med 2005; Pomp ER et al. J Thromb Haemost 2008

Antepartum PRIMARY Prophylaxis*

- AT deficiency + FH
- Homozygous FVL or PG** mutation +/- FH
- “Combined thrombophilias” +/- FH

*All are “conditional suggestions”
**Prothrombin gene

BATES et al. Blood Advances. 2018 Nov 27;2(22):3317-3359.

Postpartum PRIMARY Prophylaxis

- "Combined thrombophilias" +/- FH
- Homozygous for PG or FVL mutation +/- FH
- AT*, proC, proS deficiency + FH
- *Suggests against* for
  - FH + heterozygous FVL or PG mutation

*Strong recommendation

BATES et al. Blood Advances 2018 Nov 27;2(22):3317-3359.

Women with prior VTE not on AC therapy (secondary prophylaxis)

- Unprovoked or estrogen-associated
  - Antepartum *and* Postpartum LMWH
- Provoked (e.g. after surgery)
  - Postpartum LMWH

BATES et al. Blood Advances. 2018 Nov 27;2(22):3317-3359.

Initial VTE Treatment

- Anticoagulation
  - Unfractionated heparin
    - Bolus 80 U/kg IV
    - Infusion 18 U/kg/h adjusted to aPTT 50-80 seconds
  - LMWH
    - Dalteparin 200 IU/kg sc qday
    - Enoxaparin 1 mg/kg sc q12h
  - Fondaparinux 5-10 mg sc qday (depends on weight)
  - Rivaroxaban 15 mg PO BID x 21 days, then 20 mg QD
  - Apixaban 10 mg PO BID x 7 days, then 5 mg PO BID

Initial VTE Treatment

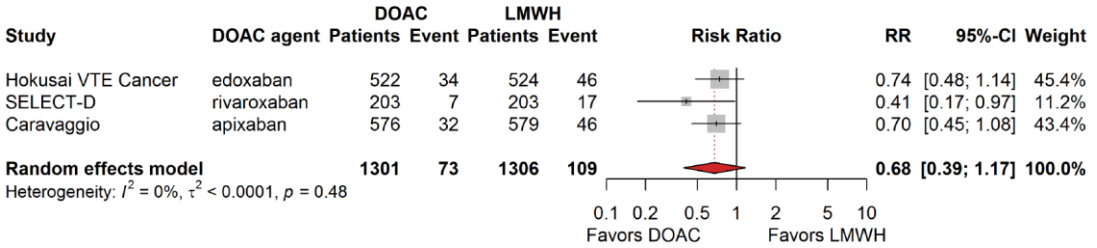
- Anticoagulation
  - Warfarin (must overlap with parenteral agent for minimum 4-5 days)
  - Dabigatran 150 mg po BID – after 5-day heparin “lead-in”
  - Edoxaban 60 mg PO QD - after 5-day heparin “lead-in”
- Other
  - ~~Vena caval filter (retrievable or permanent)~~*
  - ~~Pharmacomechnical Thrombolysis~~*
  - ~~Elastic compression stockings~~

*rare exceptions

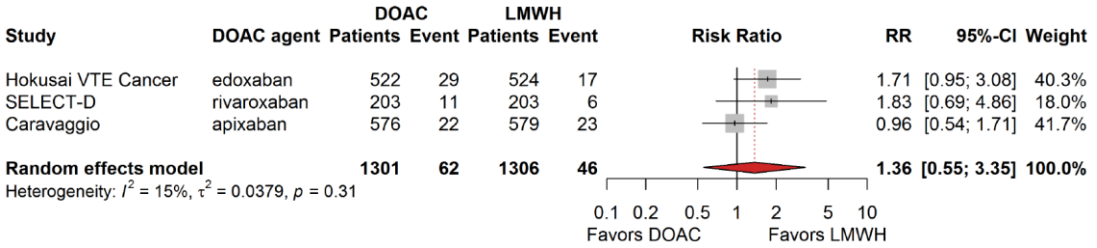
Cancer-associated VTE

Pooled Analysis of Oral FXa inhibitors vs. LMWH

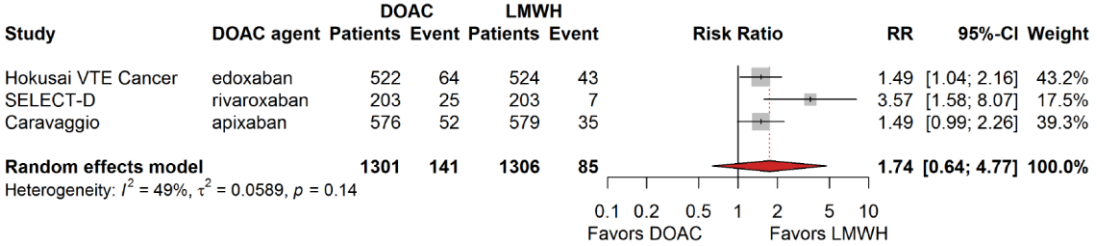
Recurrent VTE



Major bleeding



Clinically relevant non-major bleeding



Mulder F et al. *Blood*. 2020; blood.2020005819.

Can we use DOACs in patients with gastrointestinal cancer?

- 2018 ISTH Guidance Statement:

- Suggest the use of specific DOACs (edoxaban, [apixaban] and rivaroxaban) for cancer patients with an acute diagnosis of VTE, a low risk of bleeding, and no drug–drug interactions with current systemic therapy.

- We suggest the use of LMWHs for cancer patients with an acute diagnosis of VTE and a high risk of bleeding, including patients with luminal gastrointestinal cancers with an intact primary, patients with cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis, or colitis. Edoxaban, [apixaban] and rivaroxaban are acceptable alternatives if there are no drug–drug interactions with current systemic therapy.

* Khorana A, et al, *JTH* 2018

ASH: Treatment of Patients with Active Cancer

- The panel suggests DOACs (apixaban, edoxaban, or rivaroxaban) over LMWH.
- The panel suggests DOACs (apixaban, edoxaban, or rivaroxaban) over VKAs.
- The panel suggests LMWH over VKAs.

Lyman et al Blood Advances 2021. 5 (4): 927–974.

Duration of AC after VTE

Thrombophilia - Why test?

- **Because the results will influence the intensity of anticoagulation**
  - **No evidence in any setting**
- **Because the results will influence the duration of anticoagulation**
  - **Rare circumstances**
- **Because it might influence future decisions for the patient or their family**
  - **Very selected patients/scenarios**
- **Curiosity**
  - **A legitimate reason IF the patient is fully aware of the implications**
- **Because the results will influence the choice of anticoagulant**
  - **"Triple-positive" Antiphospholipid syndrome**
- **Because we can or we didn't bother to think about it**
  - **The most frequent reason, unfortunately**

Important APS Papers

Criteria

2023 ACR/EULAR antiphospholipid syndrome classification criteria

Medha Barbhaiya ,[1] Stephane Zuily ,[2] Ray Naden,[3] Alison Hendry,[4] Florian Manneville,[5] Mary-Carmen Amigo,[6] Zahir Amoura,[7] Danieli Andrade ,[8] Laura Andreoli ,[9] Bahar Artim-Esen,[10] Tatsuya Atsumi,[11] Tadej Avcin,[12] Michael H Belmont ,[13] Maria Laura Bertolaccini,[14] D Ware Branch,[15] Graziela Carvalheiras,[16] Alessandro Casini,[17] Ricard Cervera,[18] Hannah Cohen,[19] Nathalie Costedoat-Chalumeau ,[20] Mark Crowther,[21] Guilherme de Jesús ,[22] Aurelien Delluc,[23] Sheetal Desai,[24] Maria De Sancho,[25] Katrien M Devreese,[26,27] Reyhan Diz-Kucukkaya,[28] Ali Duarte-García ,[29] Camille Frances,[30] David Garcia,[31] Jean-Christophe Gris ,[32] Natasha Jordan,[33] Rebecca K Leaf,[34] Nina Kello ,[35]

Ann Rheum Dis. 2023 Aug 28;ard-2023-224609. doi: 10.1136/ard-2023-224609. Online ahead of print.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 81, NO. 1, 2023

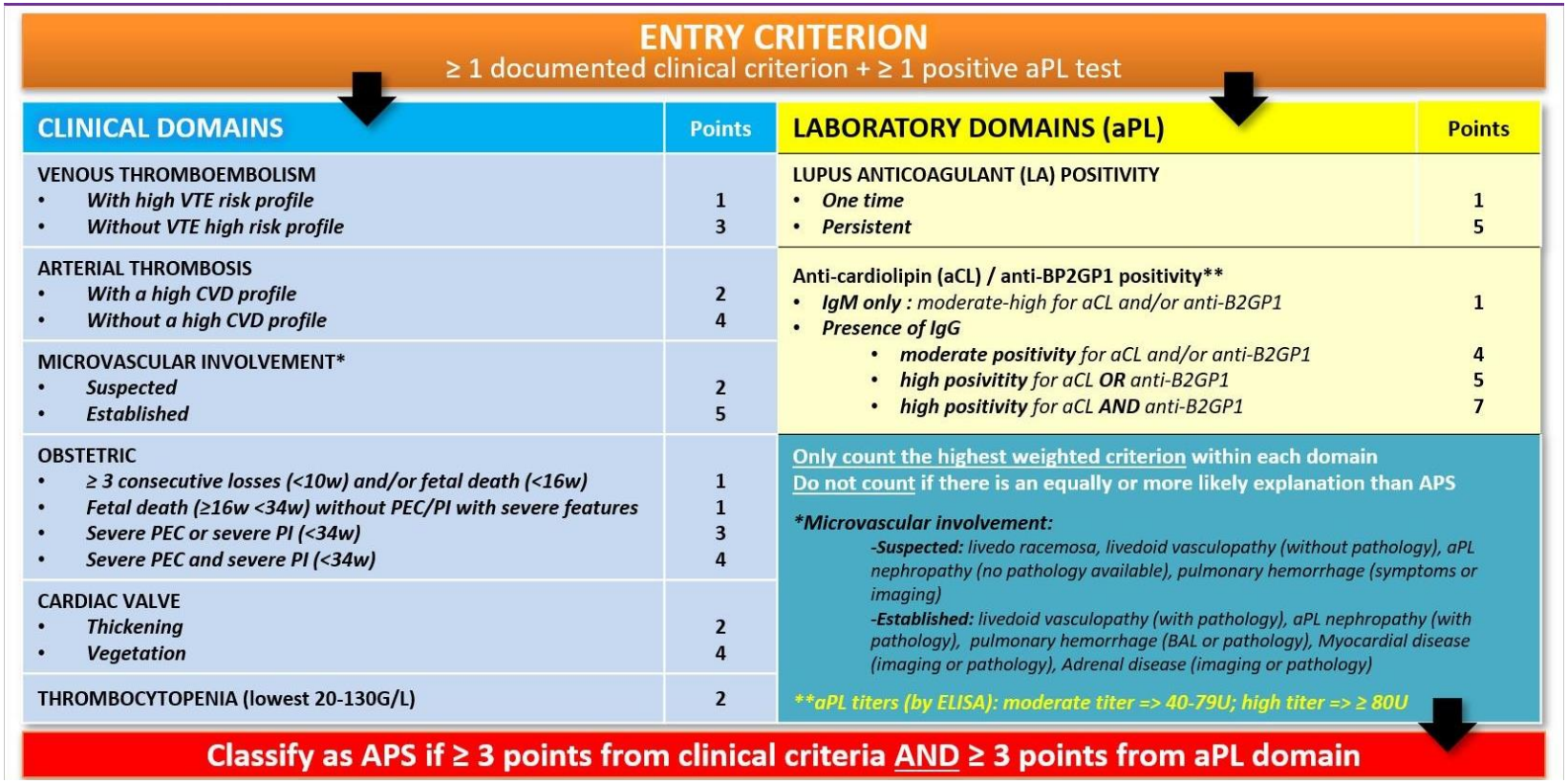
Direct Oral Anticoagulants vs Vitamin K Antagonists in Patients With Antiphospholipid Syndromes

Meta-Analysis of Randomized Trials

Candrika D. Khairani, MD, MMSc,[a,*] Antoine Bejjani, MD,[a,*] Gregory Piazza, MD, MS,[a,b] David Jimenez, MD, PhD,[c] Manuel Monreal, MD, PhD,[d] Saurav Chatterjee, MD,[e] Vittorio Pengo, MD,[f] Scott C. Woller, MD,[g,h] Josefina Cortes-Hernandez, MD, PhD,[i] Jean M. Connors, MD,[j] Yogendra Kanthi, MD,[k,l] Harlan M. Krumholz, MD, SM,[m,n,o] Saskia Middeldorp, MD, PhD,[p] Anna Falanga, MD,[q,r] Mary Cushman, MD, MSc,[s,t] Samuel Z. Goldhaber, MD,[a,b] David A. Garcia, MD,[u] Behnood Bikdeli, MD, MS[a,b,m,v]

J Am Coll Cardiol. 2023;81:16–30

Proposed APS Classification Criteria



ENTRY CRITERION
≥ 1 documented clinical criterion + ≥ 1 positive aPL test

CLINICAL DOMAINS	Points
VENOUS THROMBOEMBOLISM	
• *With high VTE risk profile*	1
• *Without VTE high risk profile*	3
ARTERIAL THROMBOSIS	
• *With a high CVD profile*	2
• *Without a high CVD profile*	4
MICROVASCULAR INVOLVEMENT*	
• *Suspected*	2
• *Established*	5
OBSTETRIC	
• *≥ 3 consecutive losses (<10w) and/or fetal death (<16w)*	1
• *Fetal death (≥16w <34w) without PEC/PI with severe features*	1
• *Severe PEC or severe PI (<34w)*	3
• *Severe PEC and severe PI (<34w)*	4
CARDIAC VALVE	
• *Thickening*	2
• *Vegetation*	4
THROMBOCYTOPENIA (lowest 20-130G/L)	2

LABORATORY DOMAINS (aPL)	Points
LUPUS ANTICOAGULANT (LA) POSITIVITY	
• *One time*	1
• *Persistent*	5
Anti-cardiolipin (aCL) / anti-BP2GP1 positivity**	
• ***IgM only :*** *moderate-high for aCL and/or anti-B2GP1*	1
• ***Presence of IgG***	
◦ ***moderate positivity*** *for aCL and/or anti-B2GP1*	4
◦ ***high posivitity*** *for aCL* ***OR*** *anti-B2GP1*	5
◦ ***high positivity*** *for aCL* ***AND*** *anti-B2GP1*	7

Only count the highest weighted criterion within each domain
Do not count if there is an equally or more likely explanation than APS

**Microvascular involvement:*
*-**Suspected:** livedo racemosa, livedoid vasculopathy (without pathology), aPL nephropathy (no pathology available), pulmonary hemorrhage (symptoms or imaging)*
*-**Established:** livedoid vasculopathy (with pathology), aPL nephropathy (with pathology), pulmonary hemorrhage (BAL or pathology), Myocardial disease (imaging or pathology), Adrenal disease (imaging or pathology)*

***aPL titers (by ELISA): moderate titer => 40-79U; high titer => ≥ 80U*

Classify as APS if ≥ 3 points from clinical criteria AND ≥ 3 points from aPL domain

Barbhaiya et al. Arthritis and Rheumatology. 2023 Oct;75(10):1687-1702.

Proposed APS Classification Criteria

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CARDIAC VALVE	
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Microvascular involvement:

-Suspected: *livedo racemosa, livedoid vasculopathy (without pathology), aPL nephropathy (no pathology available), pulmonary hemorrhage (symptoms or imaging)*

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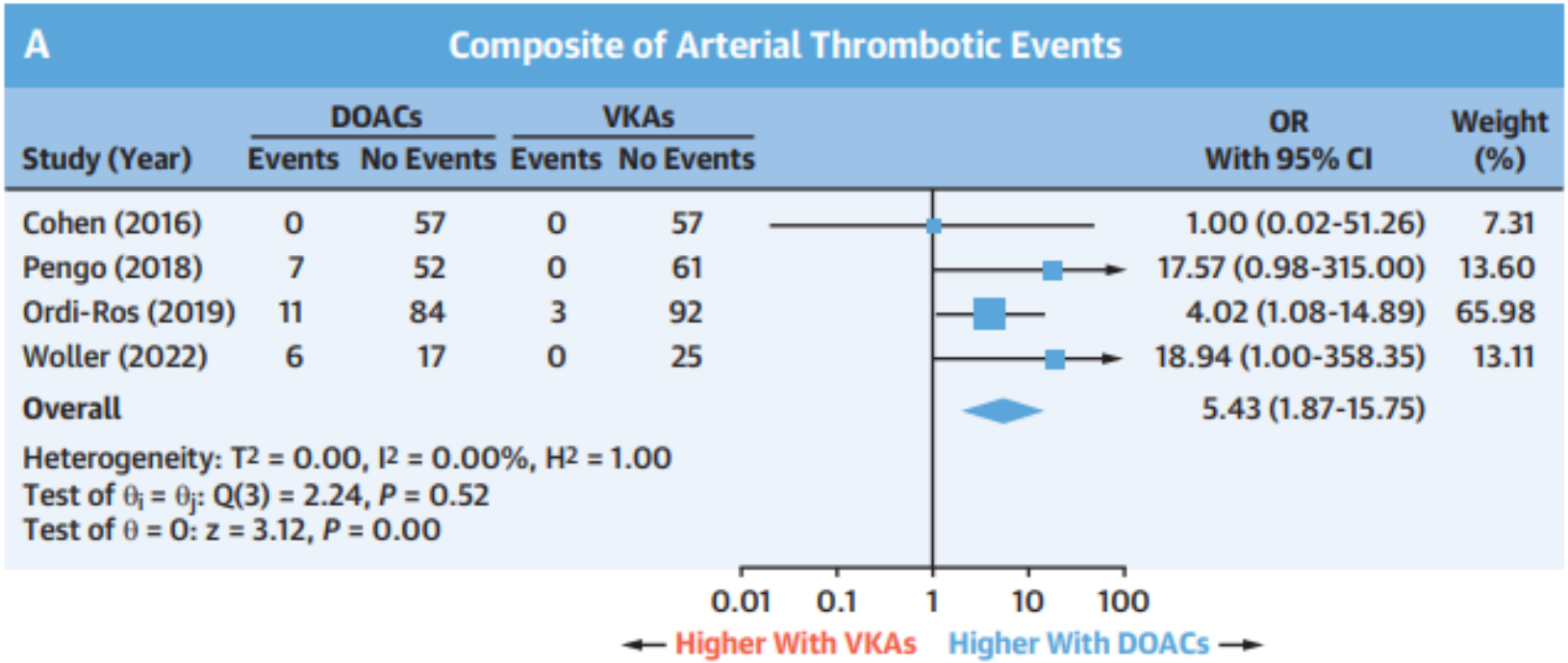
Barbhaiya et al. Arthritis and Rheumatology. 2023 Oct;75(10):1687-1702.

FXa inhibitor vs. warfarin in APS



J Am Coll Cardiol. 2023;81:16–30

Thrombophilia: Summary

- Antiphospholipid antibody testing could change treatment and is probably appropriate for many patients with unprovoked VTE
  - if/when d/c therapy contemplated
  - if clinical features suggest APS (mild thrombocytopenia, livedo reticularis, late pregnancy loss)

- More comprehensive thrombophilia testing *may* be indicated in some patients but most often the results will not change management

- Special situations
  - Splanchnic vein thrombosis: consider JAK2 V617F mutation and PNH testing

A Suggested Approach

Treat Proximal DVT or PE (unprovoked*) *at least* 3 months

- Ensure the patient is up-to-date on age-appropriate cancer screening and perform careful physical exam and review of systems.
- Discuss risks/benefits of extended therapy with all patients; re-evaluate periodically.
- Encourage extended therapy for patients who:
  - are male
  - have had previous VTE
  - had PE (rather than DVT) as their index event
  - have poor cardiopulmonary reserve
  - have low risk of AC-related bleeding (see next slide)
- Test patients for antiphospholipid syndrome before permanently discontinuing.
- Consider d-dimer testing in women if other factors equivocal**

*Kearon C et al. J Thromb Haemost. 2016 Jul;14(7):1480-3.
**Kearon C et al. J Thromb Haemost. 2019 Jul;17(7):1144-1152.

Factors Associated with Increased Major Bleeding Risk

Table 1: The VTE-BLEED score.

Factor	Score
Active cancer[a]	2
Male with uncontrolled arterial hypertension[b]	1
Anaemia[c]	1.5
History of bleeding[d]	1.5
Age ≥60 years old	1.5
Renal dysfunction[e]	1.5
Classification of patients with the VTE-BLEED score	
Low bleeding risk	Total score <2
High bleeding risk	Total score ≥2

Klok et al. Thromb Haemost 2017; 117: 1164–1170

Long-term (secondary) VTE Prevention

Trial Name	Drug	Year Published (or presented)	Comparator	VTE Prevented per 1,000/yr vs. comparator	*Extra* Major Bleeds per 1,000/yr vs. comparator
EINSTEIN CHOICE†	Riva (10 QD)	2010	ASA	> 20	Fewer than 10
RE-SONATE*	Dabi (150 BID)	2012	placebo	> 50	Approximately 10
AMPLIFY** Extension	Apix (2.5 BID)	2013	placebo	> 50	Fewer than 10?

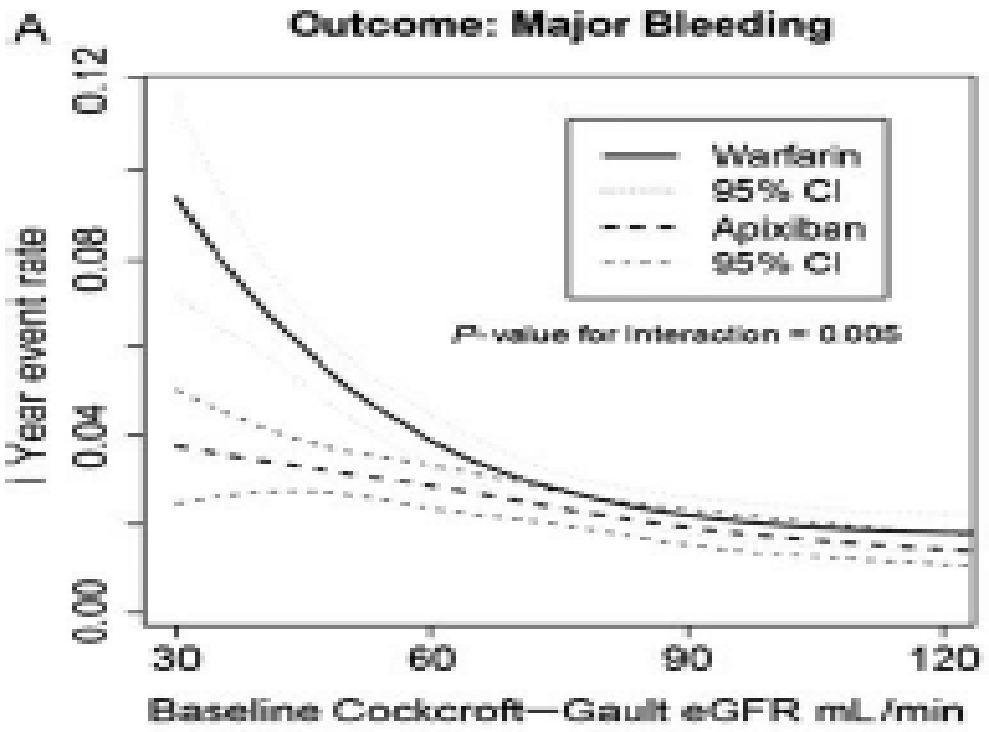
† Weitz et al. NEJM 2017; 376:1211-1222.
* Schulman et al. NEJM 2013; 368:709-18.
** Agnelli et al. NEJM 2013 Feb 21;368(8):709-18

Do NOT Prescribe DOACs For Patients Who:

- Are likely to skip doses
- ? Weigh more than ____ kg* (?)
- Take medicines likely to interact
- Are “triple positive” for APLA
- Cannot afford them
- Have mech. prosthetic heart valves

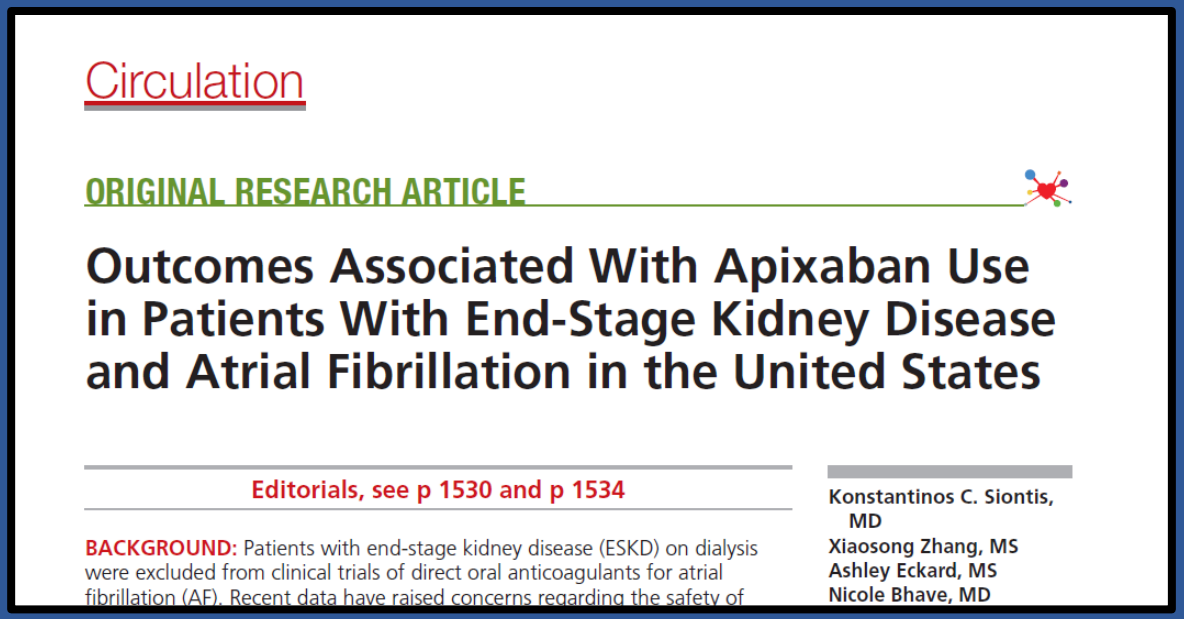
*see Wang, T.F. Blood. 2020 Mar 19;135(12):904-911.
AND
*Martin, K. J Thromb Haemost. 2021 Aug;19(8):1874-1882.

Risk of Anticoagulant-associated Major Bleeding Increases with Lower GFR



Hohnloser et al. Eur Heart J. 2012 Nov;33(22):2821-30

Apixaban vs. warfarin in ESRD: cohort study of approx, 9,400 Medicare beneficiaries



Circulation

ORIGINAL RESEARCH ARTICLE

Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States

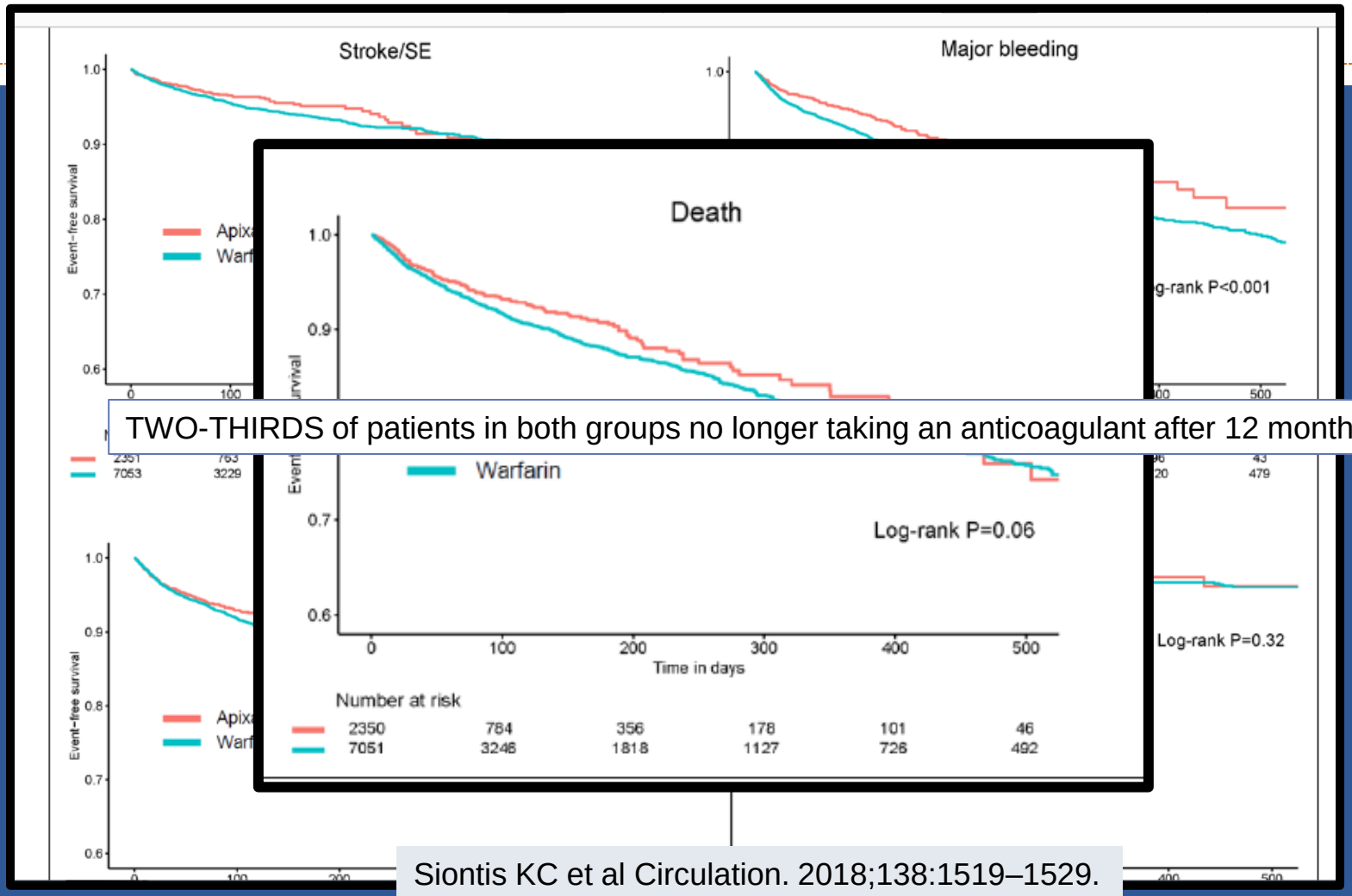
Editorials, see p 1530 and p 1534

BACKGROUND: Patients with end-stage kidney disease (ESKD) on dialysis were excluded from clinical trials of direct oral anticoagulants for atrial fibrillation (AF). Recent data have raised concerns regarding the safety of

Konstantinos C. Siontis, MD
Xiaosong Zhang, MS
Ashley Eckard, MS
Nicole Bhave, MD

Time period: 2010-2015

Siontis KC et al Circulation. 2018;138:1519–1529.



TWO-THIRDS of patients in both groups no longer taking an anticoagulant after 12 months!

Siontis KC et al Circulation. 2018;138:1519–1529.

For moderate renal impairment see: Harel et al. J Am Soc Nephrol 25: 431–442, 2014

Warfarin Reversal

INR	Response
INR 5-9	Hold warfarin 1-2 days, follow INR, consider vit K 1-2.5 mg PO
INR > 9	Hold warfarin, follow INR, consider vit K 2.5-5 mg PO
Serious bleeding	Hold warfarin, follow INR, give IV vit K 5-10 mg + Kcentra (4-factor PCC) – dose depends on INR

PCC = prothrombin complex concentrate (contains large amounts of all vit K dependent clotting factors).

Holbrooke et al. Chest. Feb 2012.

Anticoagulation Reversal

Anticoagulant	Reversal	Additional considerations
Unfractionated Heparin (Half-life ~ 60 min)	Protamine 1 mg/100 units UFH Infuse slowly (< 5mg/min)	Max dose = 50 mg Risk of anaphylaxis
LMWH (Half-life 3.5-7 hrs)	Within 8 hrs: Protamine 1mg/1mg Enoxaparin More than 8 hrs: Protamine 0.5mg/mg Enox	Max dose = 50 mg Risk of anaphylaxis
Fondaparinux (Half-life 17-21 hrs)	FVIIa 90 mcg/kg IV or FEIBA 50-100 u/kg	Risk of thromboembolic events
Dabigatran	1. Idarucizumab 5 gm IV 2. Hemodialysis	
Rivaroxaban or apixaban or edoxaban	1. Kcentra 2000 units IV *or* 2. FEIBA 3. Andexanet alpha	Risk of thromboembolic events

ORIGINAL ARTICLE

Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

Authors: Stuart J. Connolly, M.D., Mukul Sharma, M.D., Alexander T. Cohen, M.D., Andrew M. Demchuk, M.D., Anna Członkowska, M.D., Arne G. Lindgren, M.D., Carlos A. Molina, M.D., +34, for the ANNEXA-I Investigators* Author Info & Affiliations

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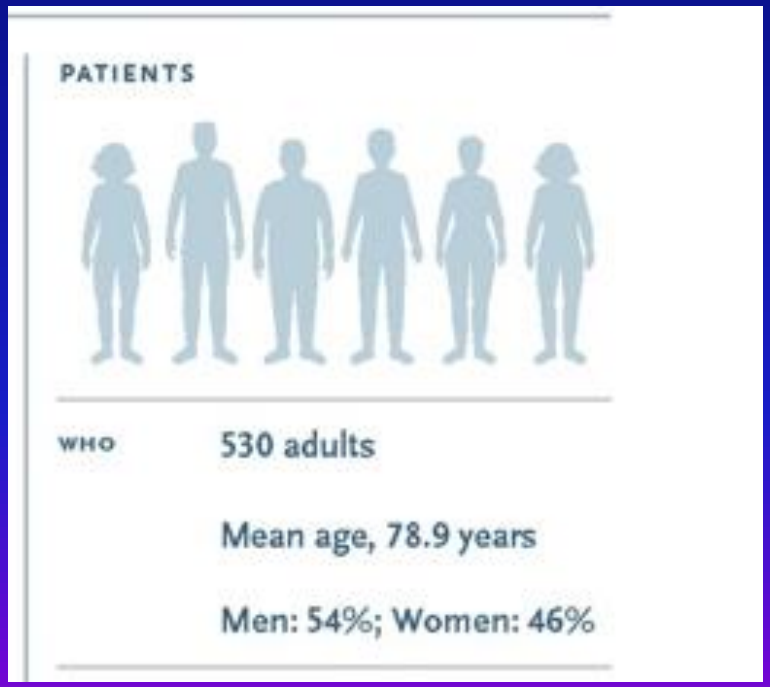
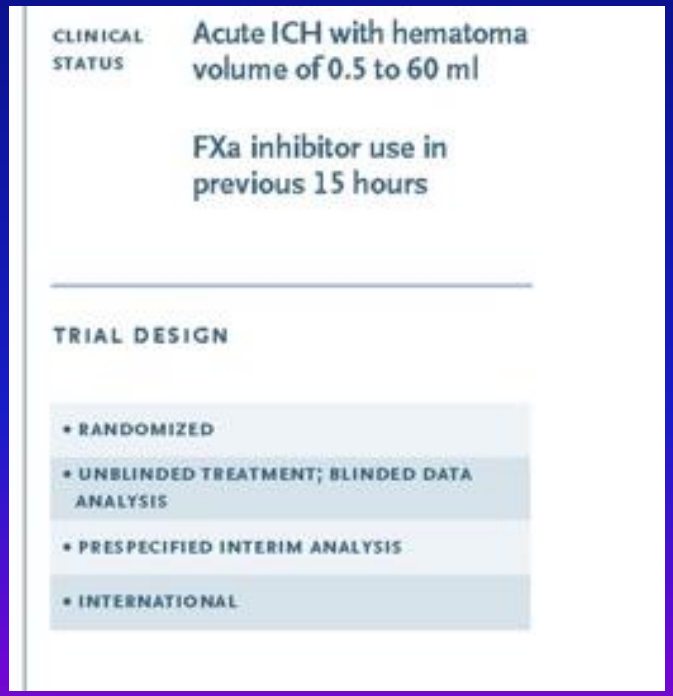
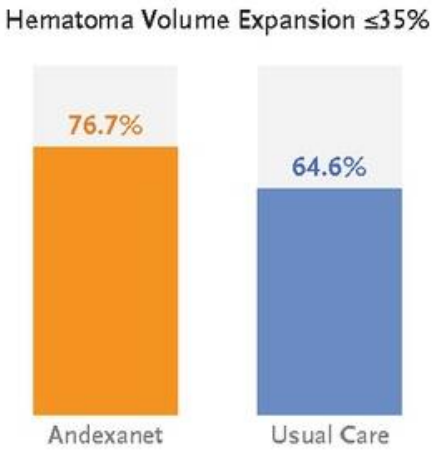


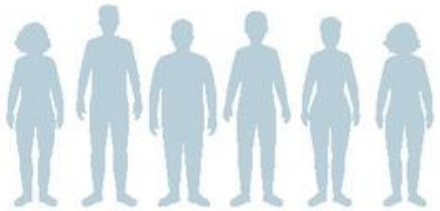


RESULTS

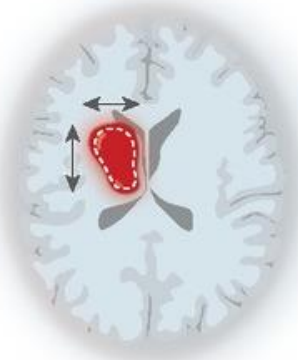
Hemostatic efficacy occurred more often in the andexanet group than in the usual-care group. The difference between treatment groups appeared to be driven by differences in hematoma volume expansion, given that the results for the two other components of the primary end point did not differ appreciably between the groups.

Thrombotic events, including ischemic stroke, were more common in the andexanet group.





Most of the patients who met the criteria for hemostatic efficacy had **≤20% expansion of hematoma volume,** defined by the trial as "excellent" efficacy.



≤20%
expansion of hematoma volume

Disability outcomes on the modified Rankin scale were **similar in the two groups.**

N Engl J Med 2024;390:1745-1755

Table 3. Thrombotic Events and Deaths at 30 Days.*

Event	Andexanet (N=263)	Usual Care (N=267)	Increase per 100 Patients (95% CI)†	P Value†
	no. of patients (%)		*percentage points*	
≥1 Thrombotic event	27 (10.3)	15 (5.6)	4.6 (0.1 to 9.2)	0.048
Transient ischemic attack	0	0	—	
Ischemic stroke	17 (6.5)	4 (1.5)	5.0 (1.5 to 8.8)	
Myocardial infarction	11 (4.2)	4 (1.5)	2.7 (–0.2 to 6.1)	
Deep-vein thrombosis	1 (0.4)	2 (0.7)	–0.4 (–2.4 to 1.5)	
Pulmonary embolism	1 (0.4)	6 (2.2)	–1.9 (–4.5 to 0.2)	
Arterial systemic embolism	3 (1.1)	2 (0.7)	0.4 (–1.7 to 2.7)	
Death	73 (27.8)	68 (25.5)	2.5 (–5.0 to 10.0)	0.51

* The safety analysis is based on the intention-to-treat extended population (all patients, including those who were enrolled after the database lock for the interim analysis but before the trial was stopped).

† In the analysis of the number of patients with at least one thrombotic event, the increase with andexanet per 100 patients is estimated from the between-group difference, the 95% confidence interval is a Wald confidence interval, and the P value is derived from a chi-square test. In the analysis of death at 30 days, the estimated increase with andexanet per 100 patients, the 95% confidence interval, and the P value were calculated with the use of a Cochran–Mantel–Haenszel test stratified according to the time from symptom onset to the performance of the baseline imaging scan (<180 or ≥180 minutes). For the specific thrombotic events, the unconditional exact confidence intervals based on the Farrington–Manning relative risk score are given.

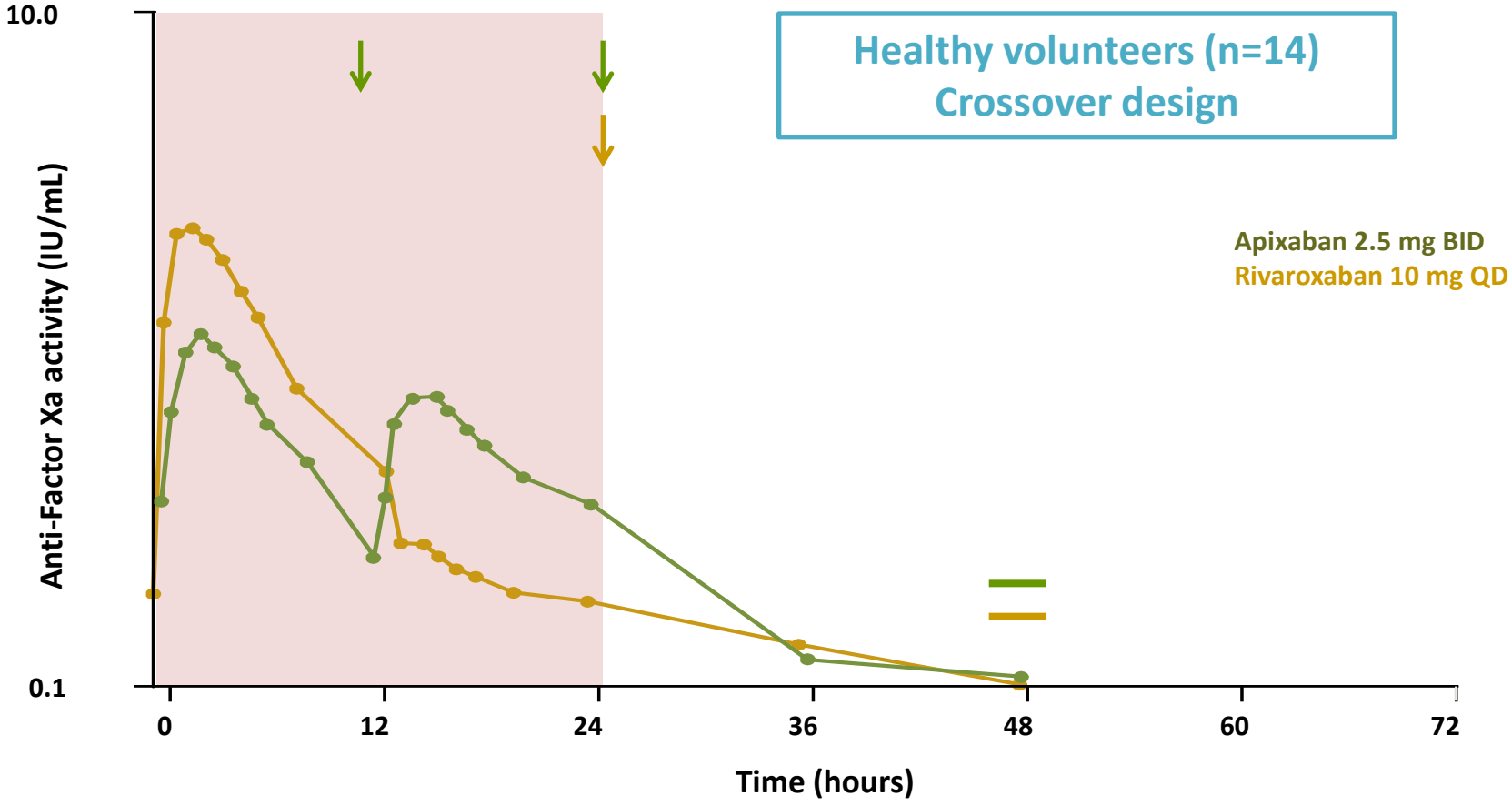
N Engl J Med 2024;390:1745-1755

How Emergent is the need to Reverse?

- *Critical to discuss risk of delay…*

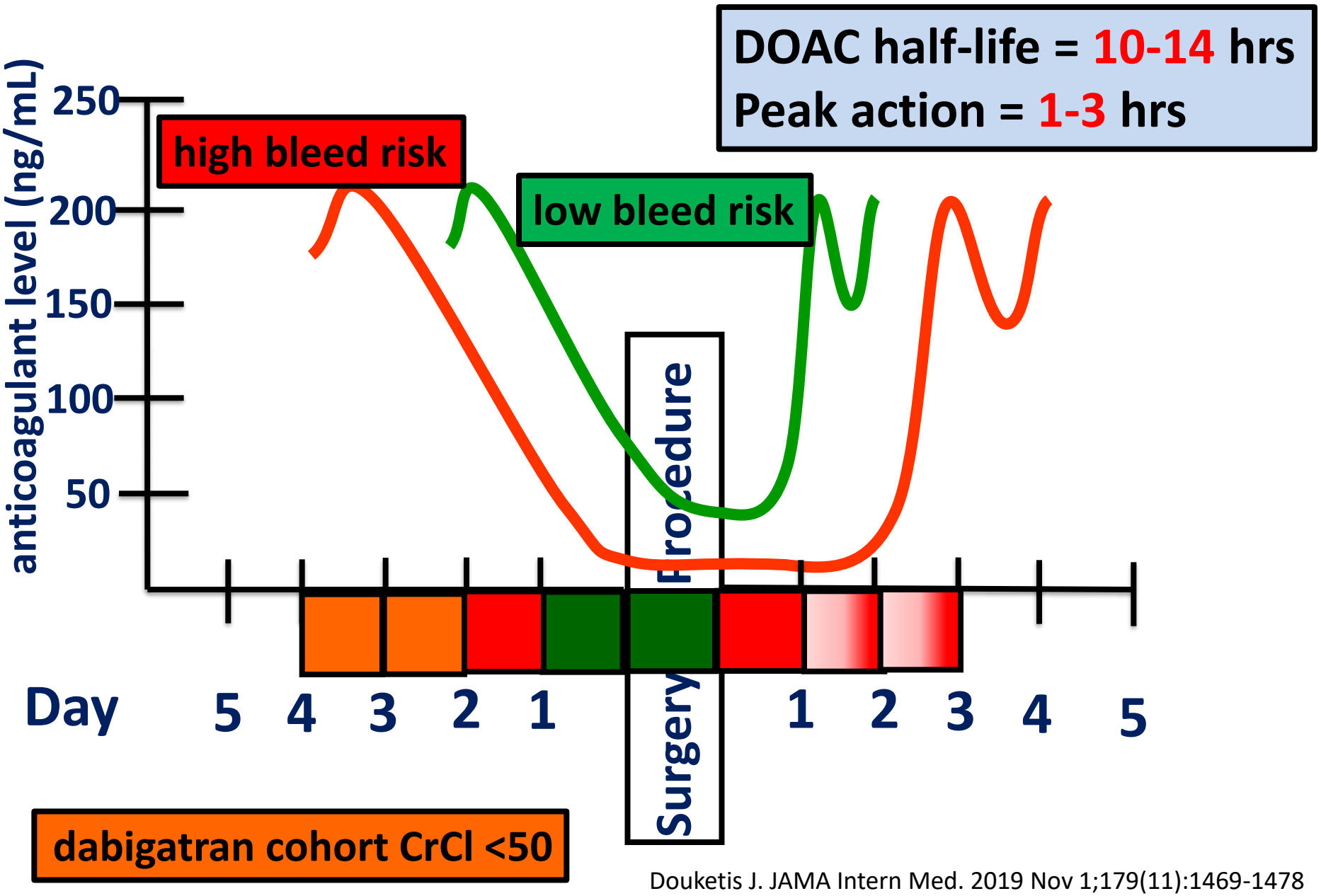
- *Drug effect will dissipate quickly*
- *“Prohemostatic” interventions carry risk*

Pharmacodynamics of apixaban and rivaroxaban



Frost et al. *J Thromb Haemost* 2011;9(Suppl 2): ISTH abstract no. P-WE-159.

DOACs: Perioperative Management



Douketis J. JAMA Intern Med. 2019 Nov 1;179(11):1469-1478

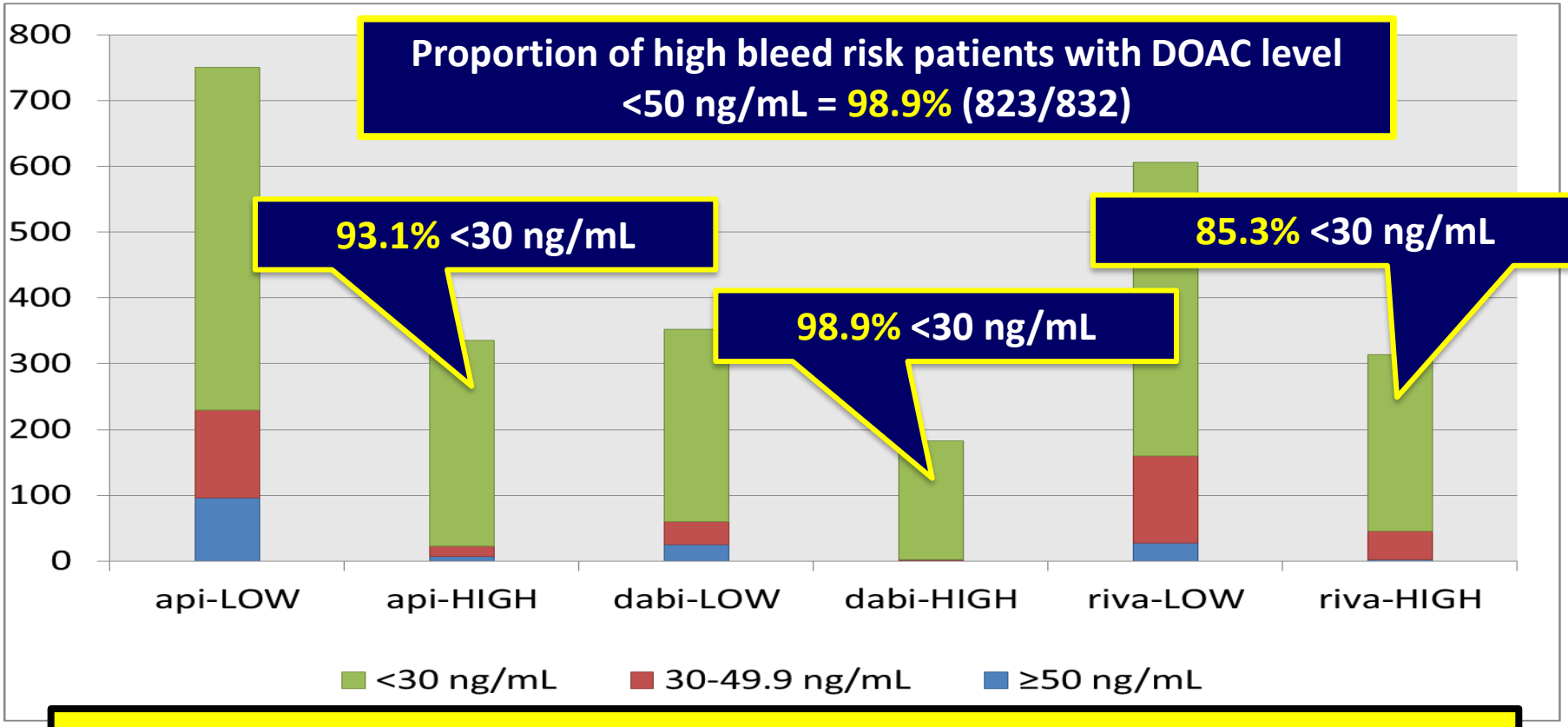
Results: Primary Outcomes (ITT Analysis)

Outcome (%, 95% CI) (expected)	Cohort		
	Apixaban *n=1257*	Dabigatran *n=668*	Rivaroxaban *n=1082*
*Arterial thromboembo-lism (0.5%)	0.16 (0-0.48) *n=2*	0.60 (0-1.33) *n=4*	0.37 (0-0.82) *n=4*
**Major bleeding (1.0%)	1.35 (0-2.00) *n=17*	0.90 (0-1.73) *n=6*	1.85 (0-2.65) *n=20*

*Ischemic stroke, TIA, systemic embolism, **ISTH definition

Douketis J. JAMA Intern Med. 2019 Nov 1;179(11):1469-1478

Results: Residual Preoperative DOAC Levels



DOAC levels measured in 2,541 (85%) patients

Douketis J. JAMA Intern Med. 2019 Nov 1;179(11):1469-1478

Lab Measurement for DOACs

- DOACs can (but do not always) prolong “traditional” clotting times (PTT or PT)

- Thrombin time (TT) is very sensitive to (even low concentrations of) dabigatran – a normal thrombin time excludes dabigatran

Best tests for DOACs

- Dabigatran: dilute thrombin time (*calibrated for dabigatran*)

- FXa inhibitors: anti-Xa assay (*calibrated for a particular DOAC*)
  - mPT (at UWMC and HMC) also sensitive

- "expected" trough: ~ 50 – 150 ng/mL
- "expected" peak: 150 – 250 ng/mL

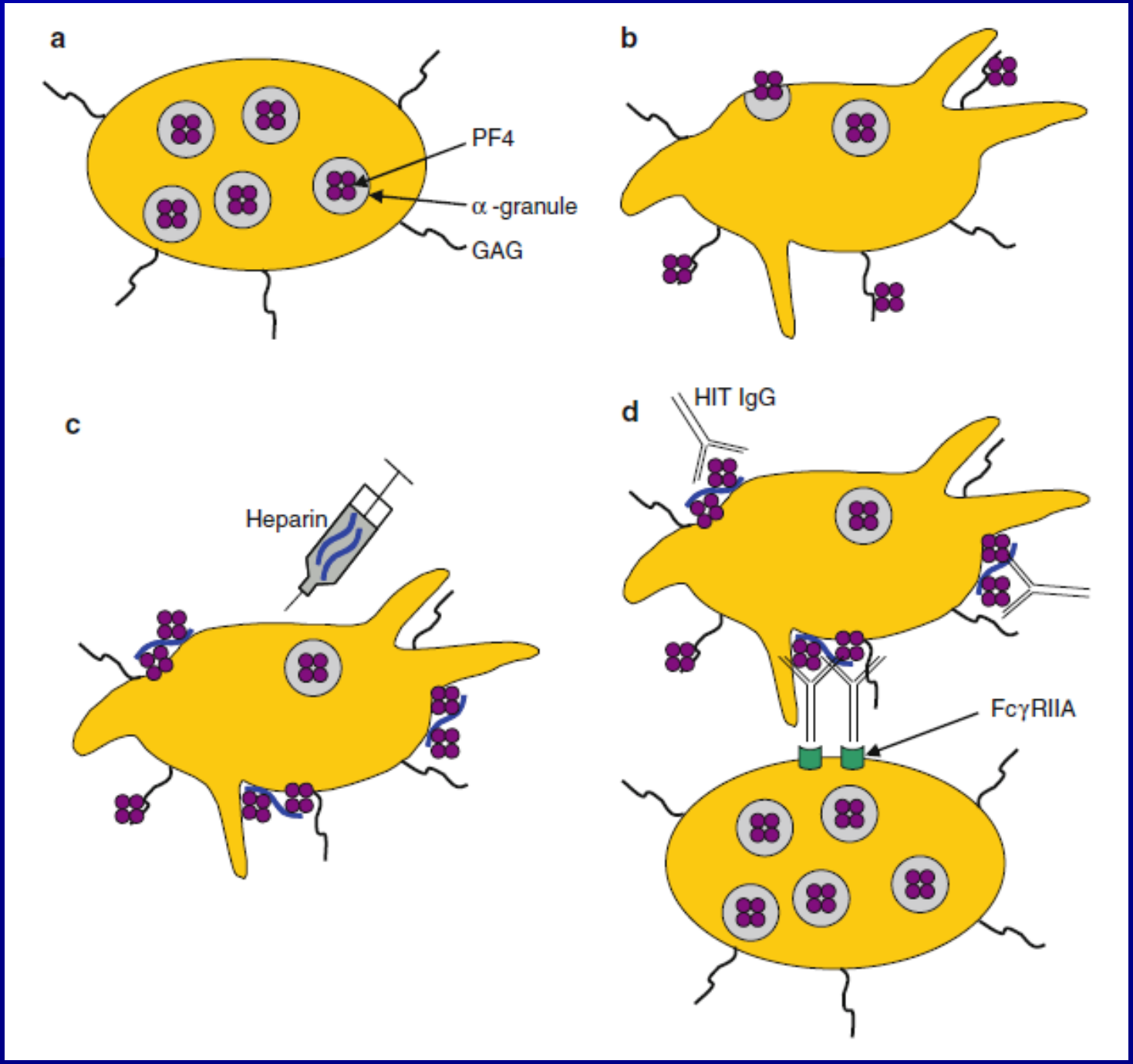
Samuelson et al. Chest. 2017 51(1):127-138.

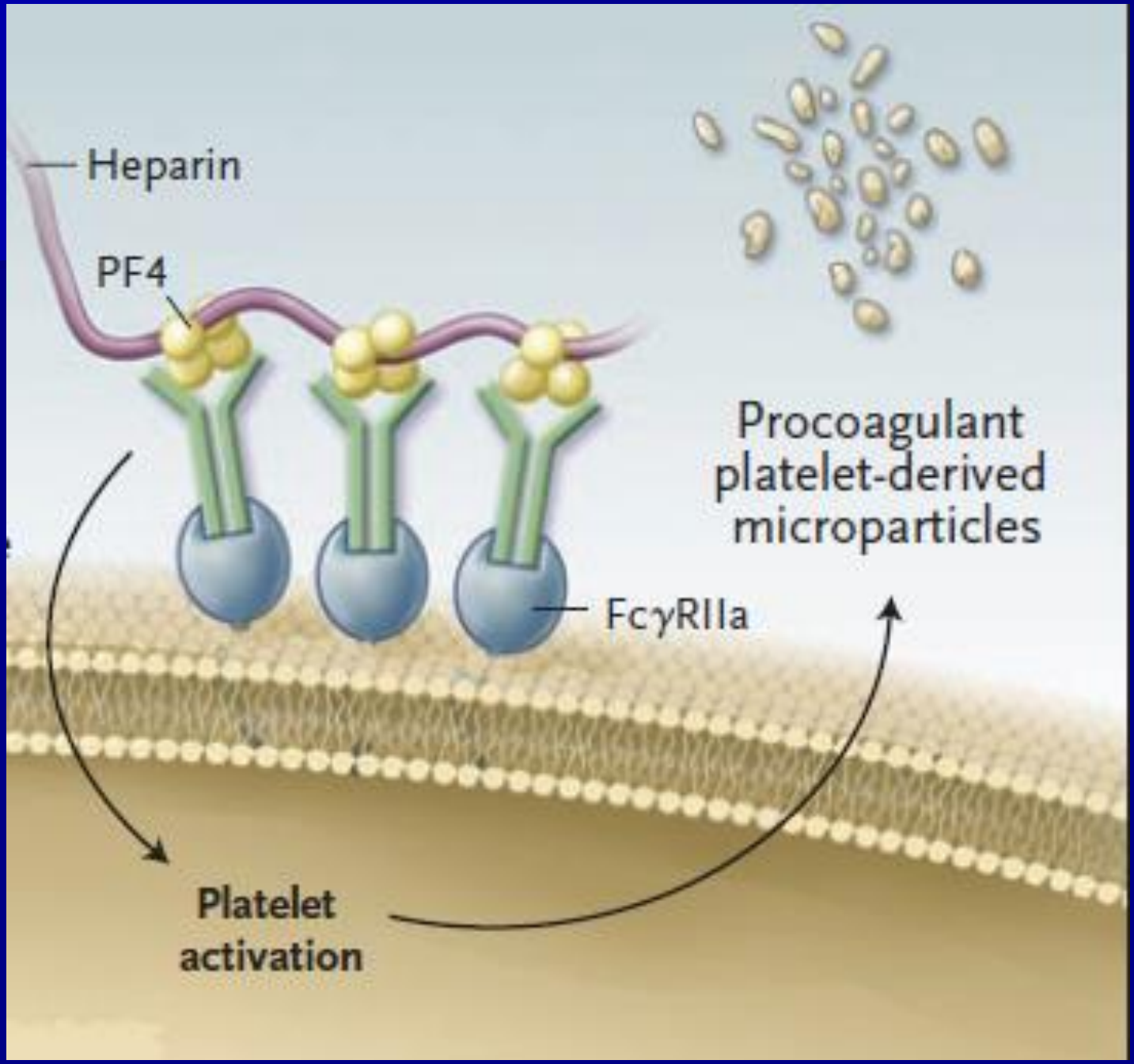
“Recurrent VTE” on anticoagulation

Question the diagnosis! Interview the patient re: adherence. Look up INR results, interview radiologists and compare images (old vs. new)

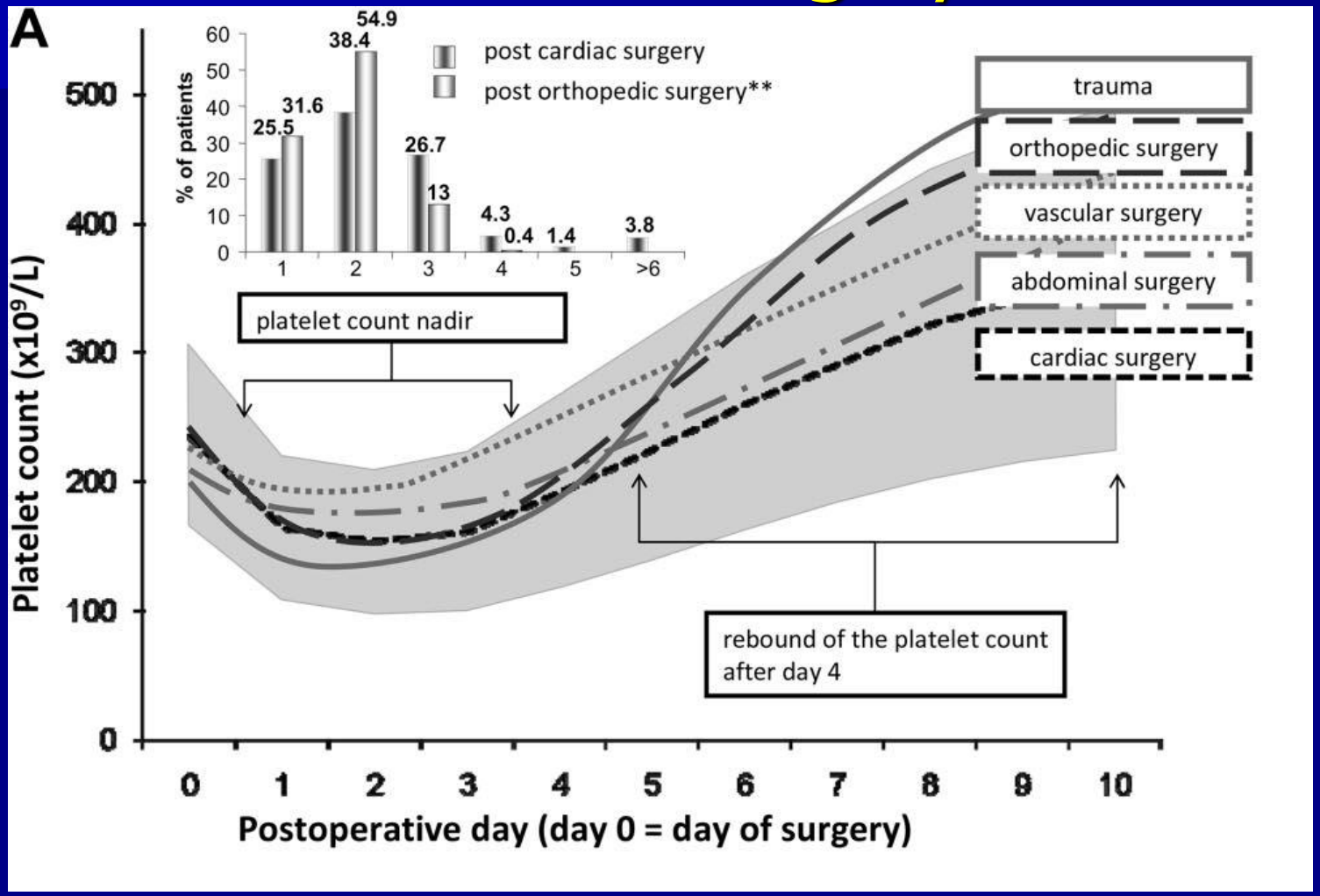
Clinical Scenario	Management
Therapeutic AC	On VKA- consider LMWH or fondaparinux or rivaroxaban On LMWH- empiric 25% dose escalation or fondaparinux or rivaroxaban
Anatomic Compression	Relieve compression, reinstitute AC
Underlying Cancer	Switch to LMWH
Heparin-induced thrombocytopenia	DTI or fondaparinux
Antiphospholipid syndrome	Higher INR target (3-4) or alternative anticoagulation (LMWH, fonda)

Recommended paper: Schulman S. Blood. 2017 Jun 22;129(25):3285-3293.


a
PF4
α -granule
GAG
b
c
Heparin
d
HIT IgG
FcγRIIA

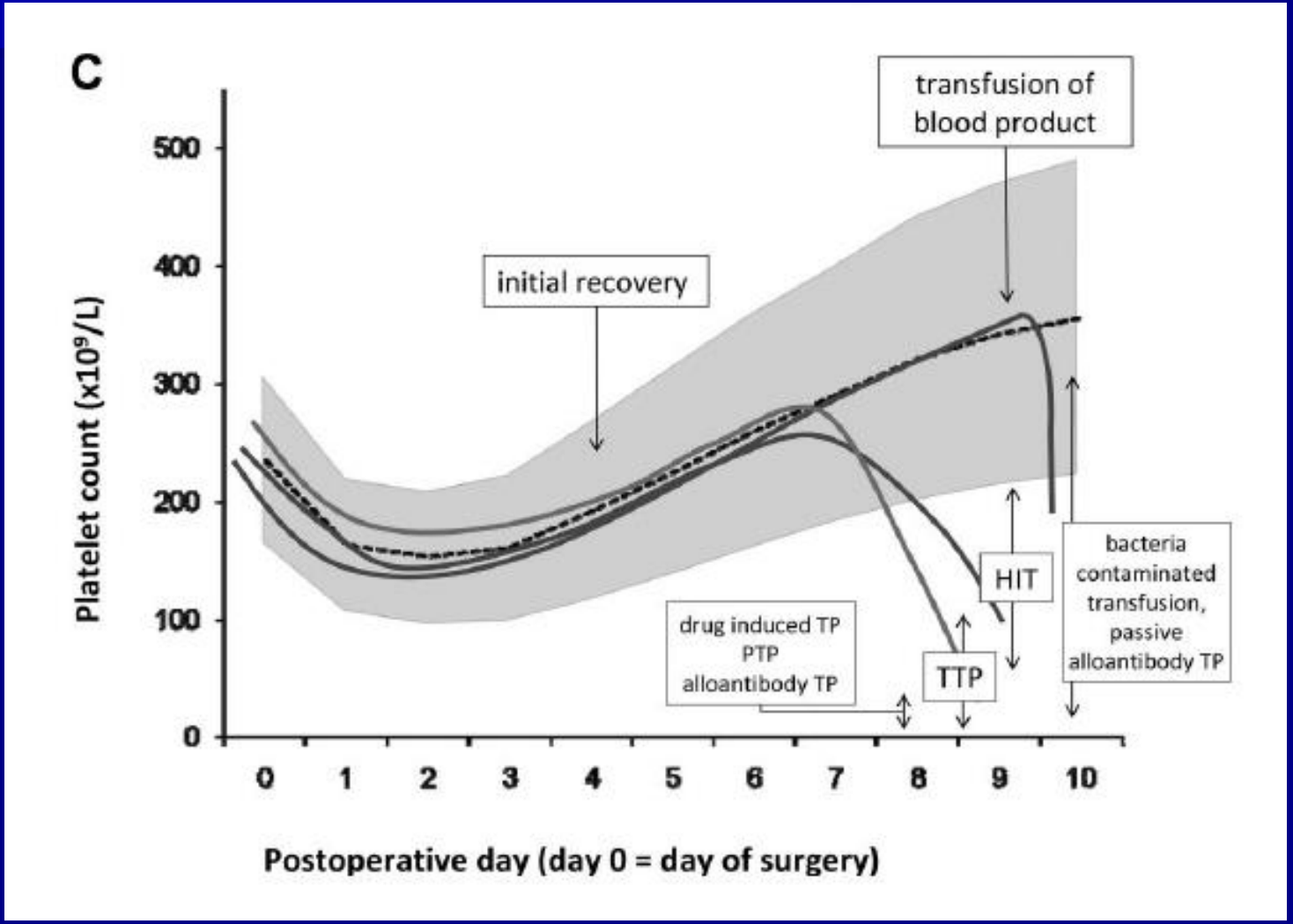

Heparin
PF4
Procoagulant
platelet-derived
microparticles
FcγRIIa
Platelet
activation

Thrombocytopenia is Common After Surgery



Greinacher A, et al. *ASH Education Book 2010*

Typical Timing of HIT After Cardiac Surgery



The Pre-Test Probability (PTP) of HIT Can Be Estimated Using the "4Ts"

The Four " T's"	2points	1point	0points
Thrombocytopenia	50% ↓ Nadir 20-100	30-50% ↓ Nadir 10-19	<30% ↓ Nadir<10
Timing of ↓ plt (relative to heparin)	5-10d or <1d reexposure	Other	<5d No reexposure
Thrombosis	Proven	Recurrent or suspected	None
eTiology of ↓ plt	No other cause	Possible other	Other probable

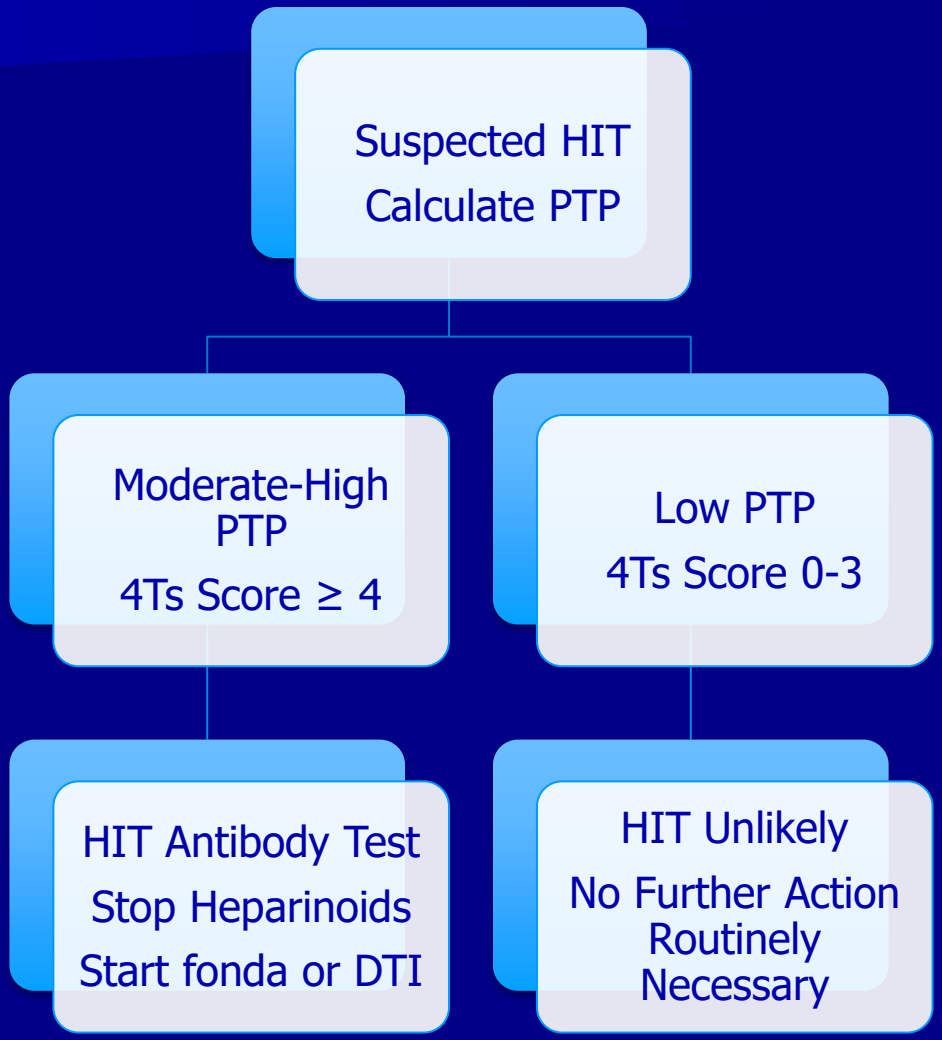
Total Score: 0-3 = Low Pre-Test Probability

4-5 = Moderate Pre-Test Probability

6-8 = High Pre-Test Probability

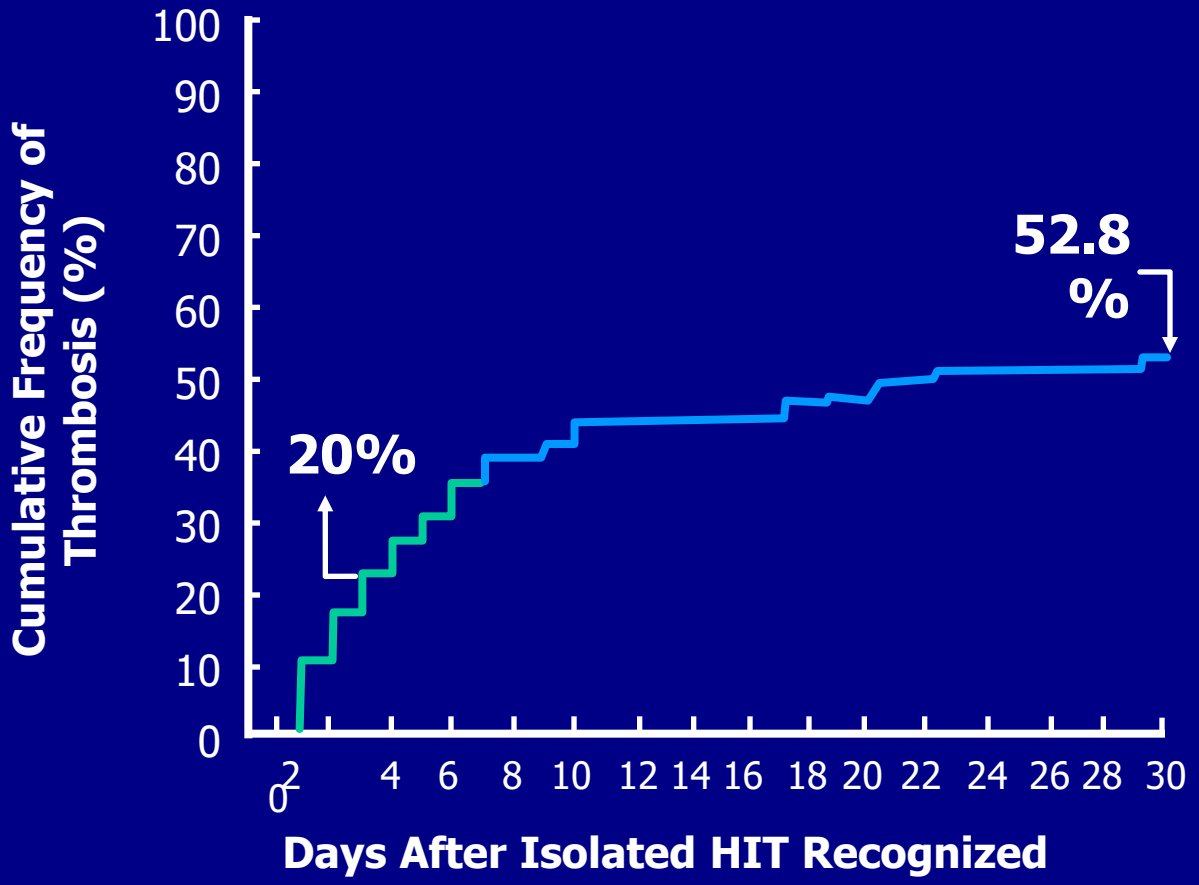
Lo et al. JTH 2006;4:759-65
Gruel et al. Curr Opin Pulm Med 2008;14:397-402

Simplified, Diagnostic Algorithm When Initially Considering HIT



Risk of Thrombosis in Patients With HIT

Stopping heparin is important, but not enough to prevent TEC



Warkentin and Kelton. *Am J Med* 1996;101

Laboratory Testing in HIT

Test	Advantages	Disadvantages
SRA*	Sensitivity: high Specificity: high	Technically demanding Not readily available
ELISA	Sensitivity: high Technically easy	Specificity: low (false positives common)
PEA*	Sens & Spec comp to SRA	Uses flow cytometry & donor platelets

* Determines whether “plt-activating” Abs are present

What About Arterial Thrombosis?

- Most of the inherited deficiencies (Pro C/S, FVL, AT, etc.) have *not* been associated with an increased risk of arterial thrombosis.
- Look for cardiac source (TEE, event monitor for AF)
- Look for vasculitis or other vessel wall problem
- Tests that *might* be helpful [might impact management decisions]
  - HCY
  - Antiphospholipid antibodies
  - PNH, JAK-2 V617F

Moll, S. "How I Treat": Patients with Unexplained Arterial Thrombsosis Blood (2020) 2020 Jun 25:blood.2019000820. doi: 10.1182/blood.2019000820.

Questions ?