An Update in Thromboembolism

David A. Garcia, MD

September 2020

Declaration of Interest

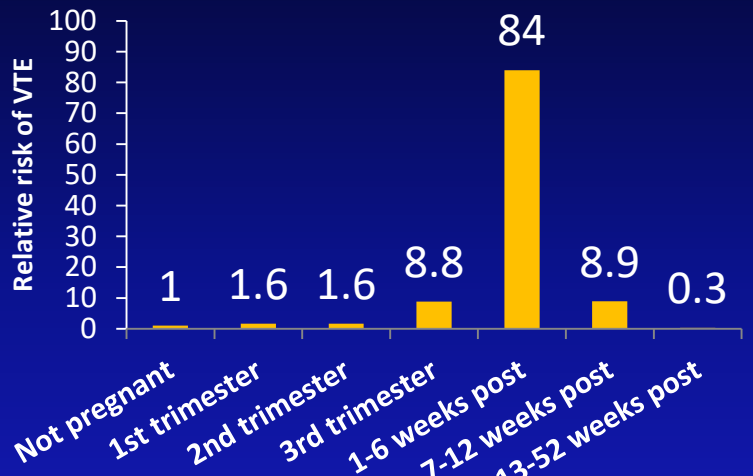
- Research funding
  - Incyte

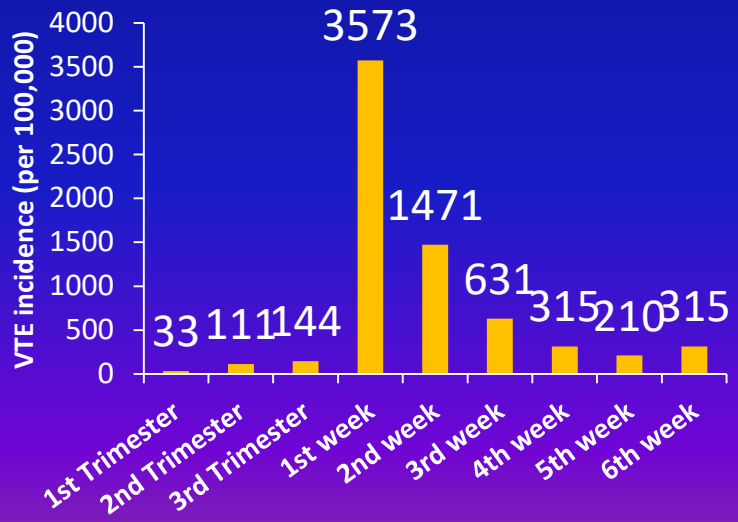
Outline

- Risks/mechanisms
- Pregnancy
- Cancer
- New acute treatment options
- Duration issues
  - Thrombophilia testing
  - Aspirin, target-specific oral agents
- Catheters
- Anticoagulation ‘failure’
- ‘Reversal’

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

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. 2018 Nov 27;2(22):3317-3359.

Women with prior VTE not on AC therapy

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

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~~

Thrombolysis for ilio-femoral clot:

Vedantham et al. N Engl J Med. 2017 Dec 7;377(23):2240-2252

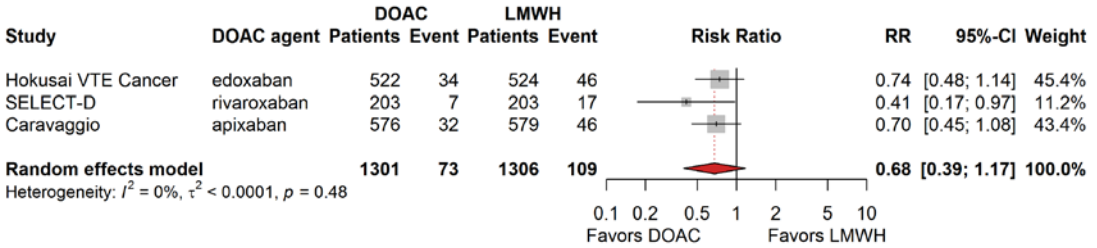
Table 3. Binary Trial Outcomes.

Outcome	Pharmacomechanical-Thrombolysis Group (N=336)	Control Group (N=355)	Risk Ratio (95% CI)	P Value
	number of patients (percent)			
Post-thrombotic syndrome between 6 and 24 mo*				
Ulcer at any follow-up assessment	12 (4)	17 (5)		
Villalta score ≥5 without ulcer	144 (43)	154 (43)		
Late endovascular procedure only	1 (<1)	0		
Total	157 (47)	171 (48)	0.96 (0.82–1.11)†	0.56
Post-thrombotic syndrome according to follow-up visit‡				
At 6 mo	78/291 (27)	113/285 (40)	0.68 (0.53–0.86)	
At 12 mo	92/272 (34)	88/258 (34)	0.99 (0.78–1.26)	
At 18 mo	85/245 (35)	76/222 (34)	1.01 (0.79–1.30)	
At 24 mo	79/258 (31)	86/239 (36)	0.85 (0.66–1.09)	
Major non–post-thrombotic syndrome treatment failure	4 (1)	7 (2)	0.58 (0.17–1.98)§	0.38¶
Any treatment failure‖	158 (47)	176 (50)	0.94 (0.80–1.09)†	0.39¶
Moderate-to-severe post-thrombotic syndrome**	60 (18)	84 (24)	0.73 (0.54–0.98)†	0.04¶
Major bleeding††				
First 10 days	6 (1.7)	1 (0.3)	6.18 (0.78–49.2)§	0.049
Total over 24 mo	19 (5.7)	13 (3.7)	1.52 (0.76–3.01)§	0.23
Any bleeding				
First 10 days	15 (4)	6 (2)	2.64 (1.04–6.68)§	0.03

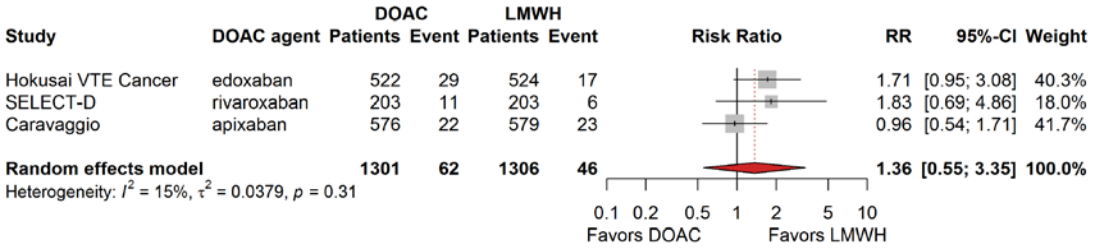
Also see: Haig et al Lancet Haematol 2016;3:e64-e71

Pooled Analysis of DOAC Trial Results Using Homogenized Endpoint Definitions

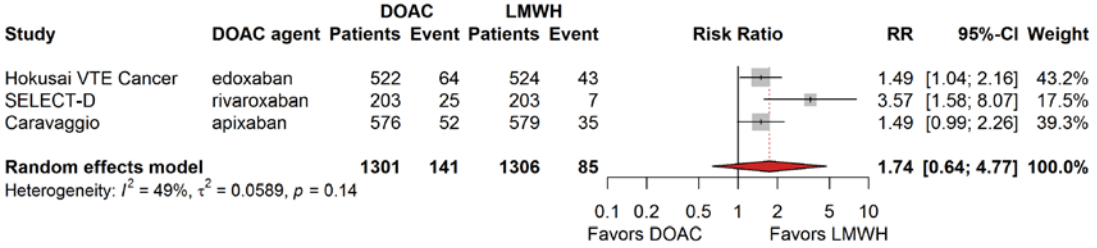
Recurrent VTE



Major bleeding



Clinically relevant non-major bleeding



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

DOAC Trial Baseline Characteristics for the Treatment of Cancer-Associated VTE

	HOKUSAI-VTE CANCER		SELECT-D		ADAM-VTE		CARAVAGGIO	
	Edoxaban (n=522)	Dalteparin (n=524)	Rivaroxaban (n=203)	Dalteparin (n=203)	Apixaban (n=150)	Dalteparin (n=150)	Apixaban (n=576)	Dalteparin (n=579)
Age, years	64.3 ± 11.0	63.7 ± 11.7	67[†]	67[†]	64	64	67.2±11.3	67.2±10.9
Male sex, %	53.1	50.2	57	48	48	49	50.7	47.7
Metastatic disease, %	52.5	53.4	58	58	65[‡]	66[‡]	67.5*	68.4*
Active chemo, %	71.6[‖]	73.1[‖]	81	85	74	74	85.6[‖]	85.8[‖]
GI tumors, %								
Colorectal	15.9	15.1	27	23	12.2	19.6	21.0	19.5
Upper	6.3	4.0	7[§]	12[§]	4.8	2.7	4.0	5.4
Pancreatic or hepatobiliary	9.4	7.6	10[¶]	6.4[¶]	15.6	16.2	7.6	7.4
ECOG PS, %								
0	29.7	28.2	29	30	40.0	41.3	32.3	29.4
1	46.6	46.9	44	47	46.7	50.7	48.8	47.8
2	23.6	23.7	26	21	13.3	8.0	18.9	22.8
Qualifying VTE diagnosis, %								
PE ± DVT	62.8	62.8	–	–	56	51	52.8	57.7
DVT only	37.2	37.2	–	–	37	35	47.2	42.3
Symptomatic DVT or PE	68.0	67.0	47	48	–	–	79.9	80.3
Incidental DVT or PE	32.0	33.0	53	52	–	–	20.1	19.7

*Recurrent locally advanced or metastatic disease. [†]Median age. [‡]Distant metastases. [§]Includes gastric and esophageal/gastroesophageal cancers. [‖]Includes any anticancer drug therapy (cytotoxic, hormonal, targeted, or immunomodulatory), radiotherapy, surgery, or a combination of these therapies. [¶]Includes pancreatic and gallbladder cancers.
DOAC=direct-acting oral anticoagulant; DVT=deep vein thrombosis; ECOG PS=Eastern Cooperative Oncology Group performance status; GI=gastrointestinal; NR=not reported; PE=pulmonary embolism; VKA=vitamin K antagonist; VTE=venous thromboembolism.

DOAC Trial Results for the Treatment of Cancer-Associated VTE

	HOKUSAI-VTE CANCER Edoxaban	SELECT-D Rivaroxaban	ADAM-VTE Apixaban	CARAVAGGIO Apixaban
Randomized patient numbers	1050	406	300	1170
Trial duration, months	12	6	6	6
Primary endpoint	Composite of recurrent VTE or ISTH major bleeding	Recurrent VTE	ISTH major bleeding	Recurrent VTE
VTE recurrence				
Oral agent (O)	7.9%	4%	0.7%	5.6%
Dalteparin (D)	11.3%	11%	6.3%	7.9%
HR (95% CI); O vs D	0.71 (0.48-1.06)	0.43 (0.19-0.99)↓	0.099 (0.013-0.78)	0.63 (0.37-1.07)
Major bleeding				
Oral agent	6.9%	6%	0%	3.8%
Dalteparin	4.0%	4%	1.4%	4.0%
HR (95% CI); O vs D	1.77 (1.03-3.04) ↑	1.83 (0.68-4.96)	NE	0.82 (0.40-1.69)
Fatal bleeding				
Oral agent	0%	0.5%	0%	0%
Dalteparin	0.2%	0.5%	0%	0.3%
HR (95% CI); O vs D	NR	NR	NE	NR
Major GI bleeding				
Oral agent	3.8%	3.9%	0%	1.9%
Dalteparin	1.1%	2.0%	0%	1.7%
HR (95% CI); O vs D	NR	NR	NE	1.05 (0.44-2.50)
CRNM Bleeding				
Oral agent	14.6%	13%	6.2%	9.0%
Dalteparin	11.1%	4%	4.2%	6.0%
HR (95% CI); O vs D	1.38 (0.98-1.94)	NR	NR	1.42 (0.88-2.30)

Yellow highlights denote statistically significant results.

Can we use DOACs in patients with gastrointestinal cancer?

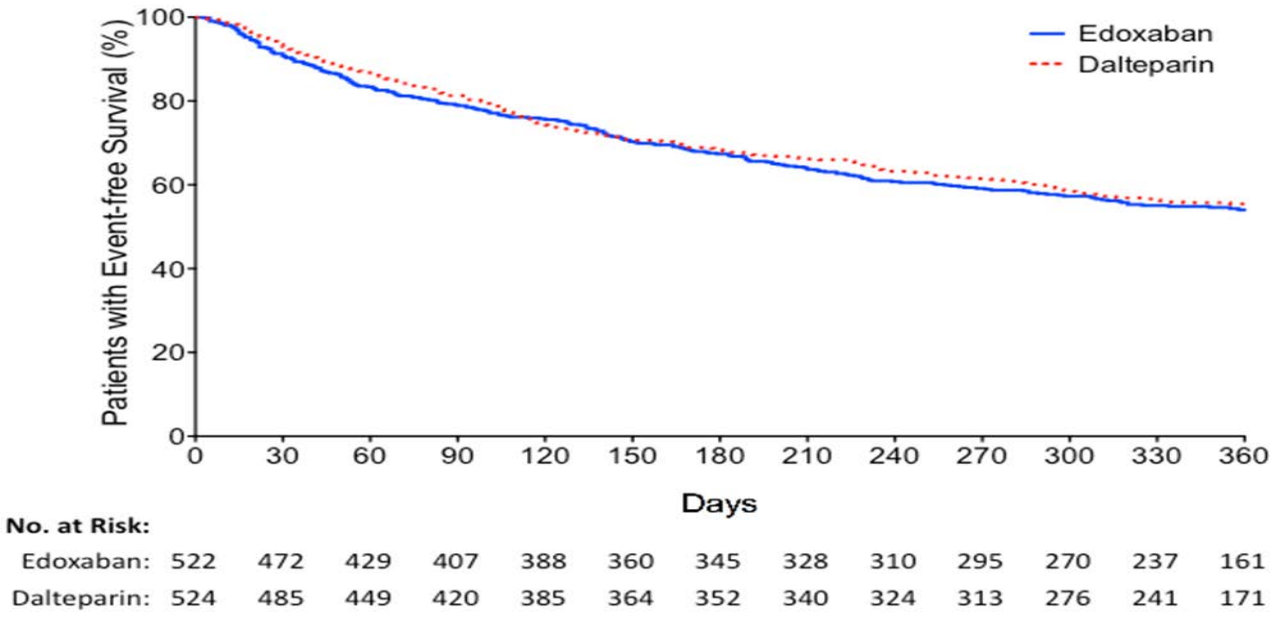
- 2018 ISTH Guidance Statement:

- We suggest the use of specific DOACs (edoxaban 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 and rivaroxaban are acceptable alternatives if there are no drug–drug interactions with current systemic therapy.

* Khorana A, et al, *JTH* 2018

Event-free Survival
Freedom from Recurrent VTE, Major Bleeding and Death



Raskob G et al. *N Engl J Med*. 2018 Feb 15;378(7):615-624.

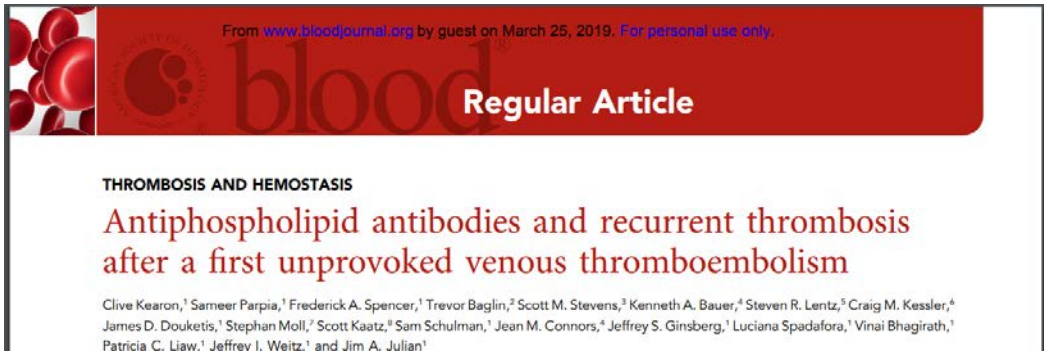
Duration of AC after VTE

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**
  - **Little evidence, except for specific circumstances**
- **Because it might influence future decisions for the patient or their family**
  - **Selected patients**
- **Curiosity**
  - **A legitimate reason IF the patient is fully aware of the implications**

- **Because we can or we didn't bother to think about it**
  - **The most frequent reason, unfortunately**

Important APS Papers



blood

Regular Article

THROMBOSIS AND HEMOSTASIS

Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism

Clive Kearon,[1] Sameer Parpia,[1] Frederick A. Spencer,[1] Trevor Baglin,[2] Scott M. Stevens,[3] Kenneth A. Bauer,[4] Steven R. Lentz,[5] Craig M. Kessler,[6] James D. Douketis,[1] Stephan Moll,[7] Scott Kaatz,[8] Sam Schulman,[1] Jean M. Connors,[4] Jeffrey S. Ginsberg,[1] Luciana Spadafora,[1] Vinai Bhagirath,[1] Patricia C. Liaw,[1] Jeffrey I. Weitz,[1] and Jim A. Julian[1]

2018;131(19):2151-2160

blood

Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

Vittorio Pengo,[1] Gentian Denas,[1] Giacomo Zoppellaro,[1] Seena Padayattil Jose,[1] Ariela Hoxha,[2] Amelia Ruffatti,[2] Laura Andreoli,[3] Angela Tincani,[3] Caterina Cenci,[4] Domenico Prisco,[4] Tiziana Fierro,[5] Paolo Gresele,[5] Arturo Cafolla,[6] Valeria De Micheli,[7] Angelo Ghirarduzzi,[8] Alberto Tosetto,[9] Anna Falanga,[10] Ida Martinelli,[11] Sophie Testa,[12] Doris Barcellona,[13] Maria Gerosa,[14] and Alessandra Banzato[1]

2018;132(13):1365-1371


Annals of Internal Medicine

ORIGINAL RESEARCH

Rivaroxaban Versus Vitamin K Antagonist in Antiphospholipid Syndrome

A Randomized Noninferiority Trial

Josep Ordi-Ros, MD, PhD; Luis Sáez-Comet, MD, PhD; Mercedes Pérez-Conesa, MD; Xavier Vidal, MD, PhD; Antoni Riera-Mestre, MD, PhD; Antoni Castro-Salomó, MD, PhD; Jordi Cuquet-Pedragosa, MD; Vera Ortiz-Santamaria, MD; Montserrat Mauri-Plana, MD, PhD; Cristina Solé, PhD; and Josefina Cortés-Hernández, MD, PhD

2019;171:685-694

Thrombophilia: Summary

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

- More comprehensive testing may be indicated with strong family history

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

- For most patients, *don't do it*.

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.
- 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.

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

You Have Decided to "Extend" Antithrombotic Tx

- What are the options besides warfarin?

Comparison of the DOAC Agents

- Dabigatran
  - Direct thrombin inhibitor
  - Taken twice daily (150 mg)
  - 5 days of parenteral (LMWH) treatment needed
- Rivaroxaban
  - Direct FXa inhibitor
  - 15 mg twice daily for 3 wks, then 20 mg **once daily**
  - Can be used as monotherapy
- Apixaban
  - Direct FXa inhibitor
  - 10 mg twice daily for seven days; then 5 mg **BID**
  - Can be used as monotherapy
- Edoxaban
  - Direct FXa inhibitor
  - Daily (60 mg; or 30 mg for renal impairment or low weight)
  - 5 days parenteral (LMWH) treatment needed

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?

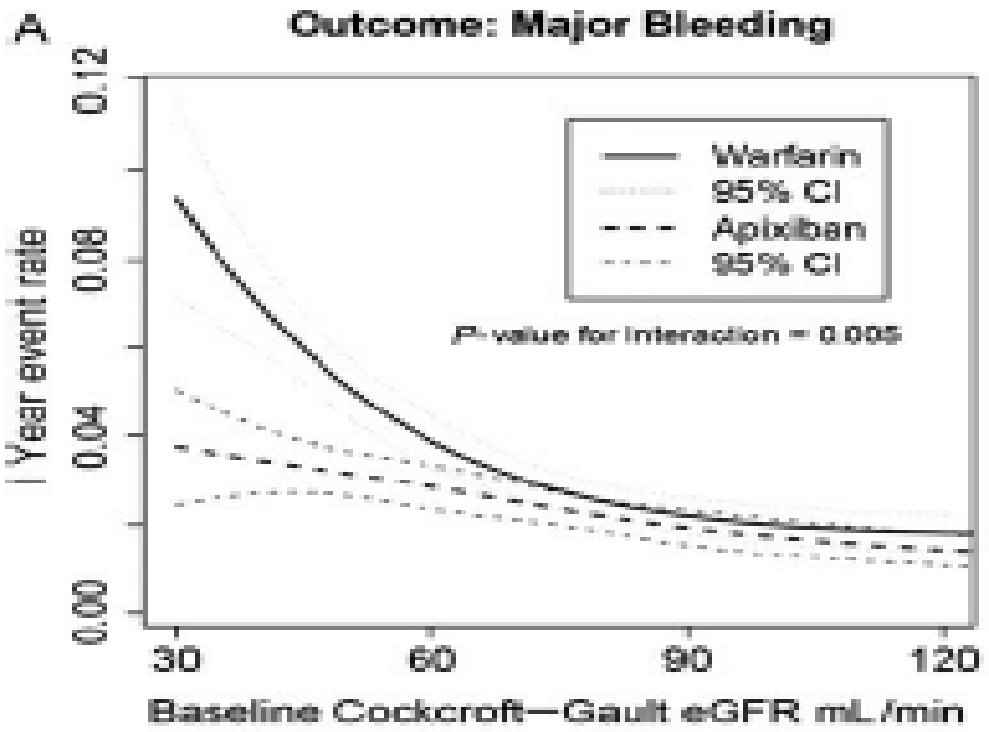
† Weitz et al. NEJM 2017; 376:1211-1222.
* Schulman et al. NEJM 2013; 368:709-18.
** Agnelli et al. NEJM 2013 Feb 21;368(8):709-18

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 APL
- Cannot afford them

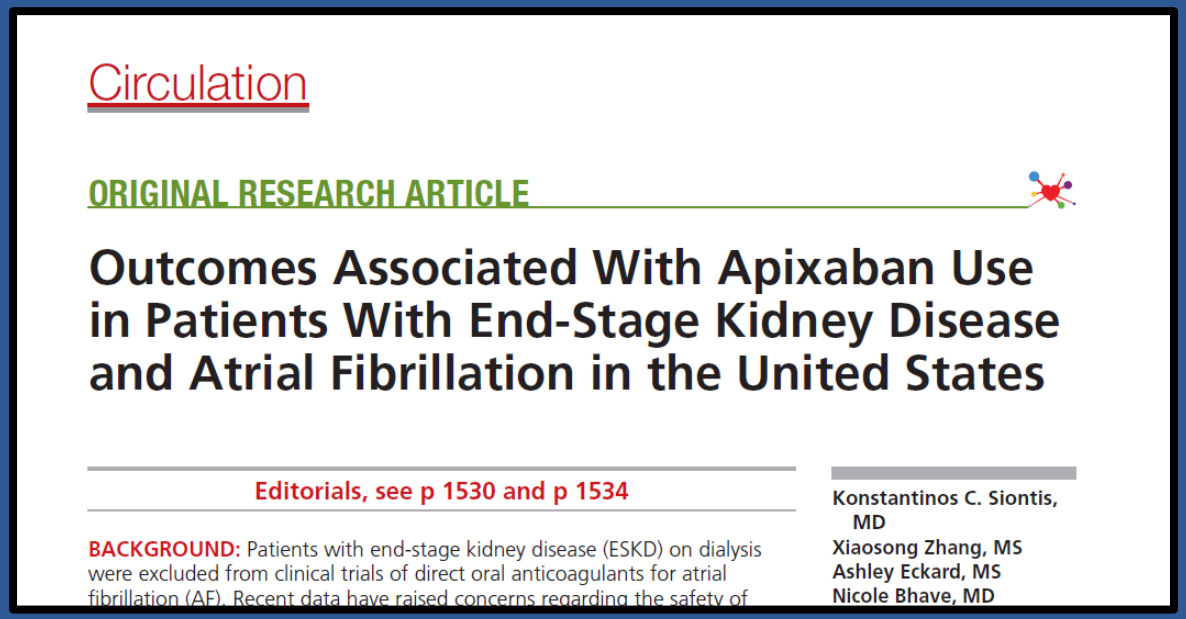
*see Wang, T.F. Blood. 2020 Mar 19;135(12):904-911.

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

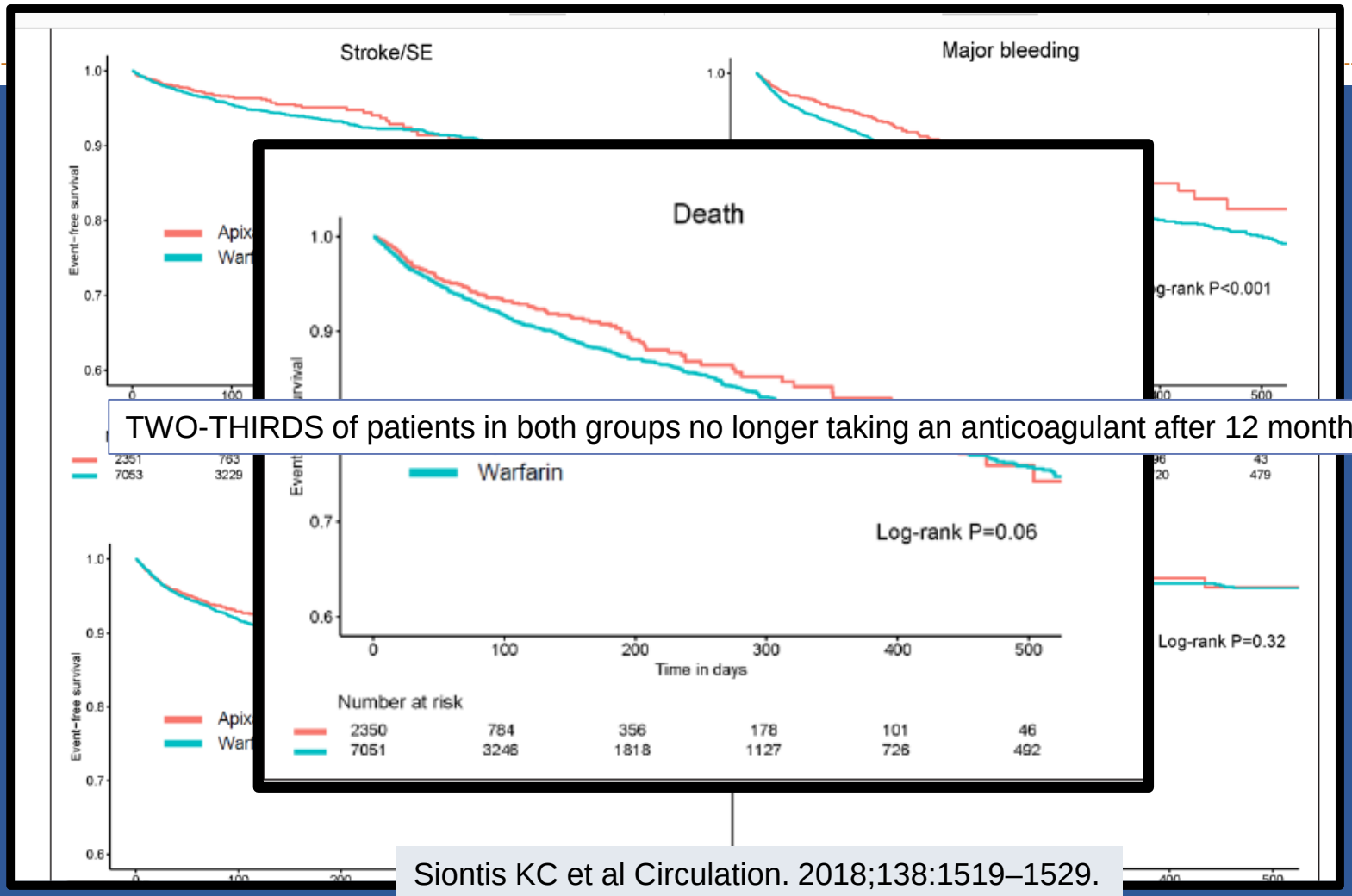
Editorials, see p 1530 and p 1534

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

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

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

New 2018 ASH Clinical Practice Guidelines on Venous Thromboembolism:

What You Should Know

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

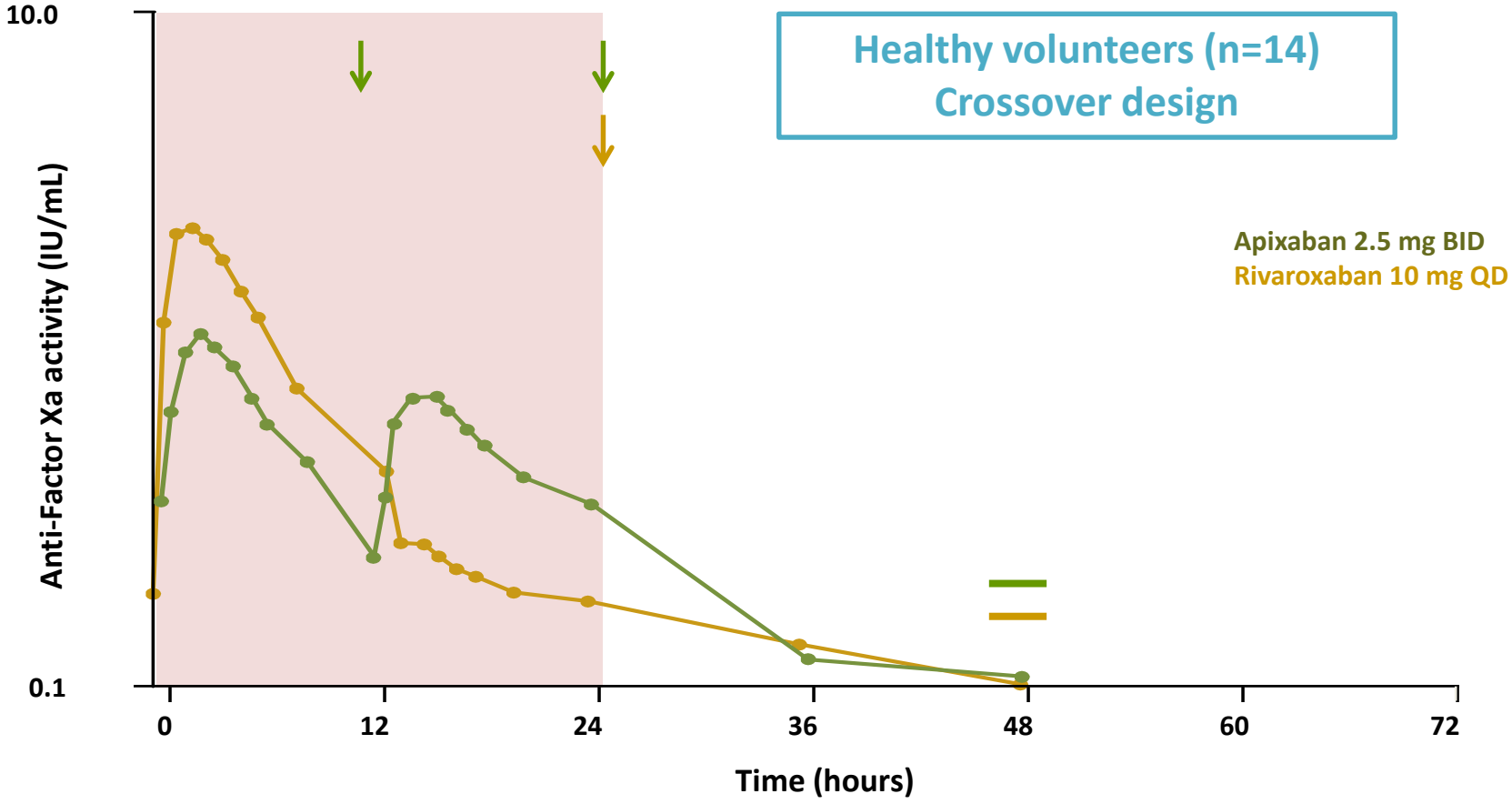
Anticoagulation Reversal

- Key papers:
  - **Pollack et al. N Engl J Med 2017;377:431-41**
    - **(idaucizumab for dabigatran)**
  - **Connolly et al. N Engl J Med. 2019 Feb 7. [Epub ahead of print]**
    - **(andexanet alpha for FXa inhibitors)**
  - **Piran S, et al. Blood Adv. 2019 Jan 22; 3(2): 158–167.**
    - **(4-factor PCC for FXa inhibitors)**

How Emergent is the need to Reverse?

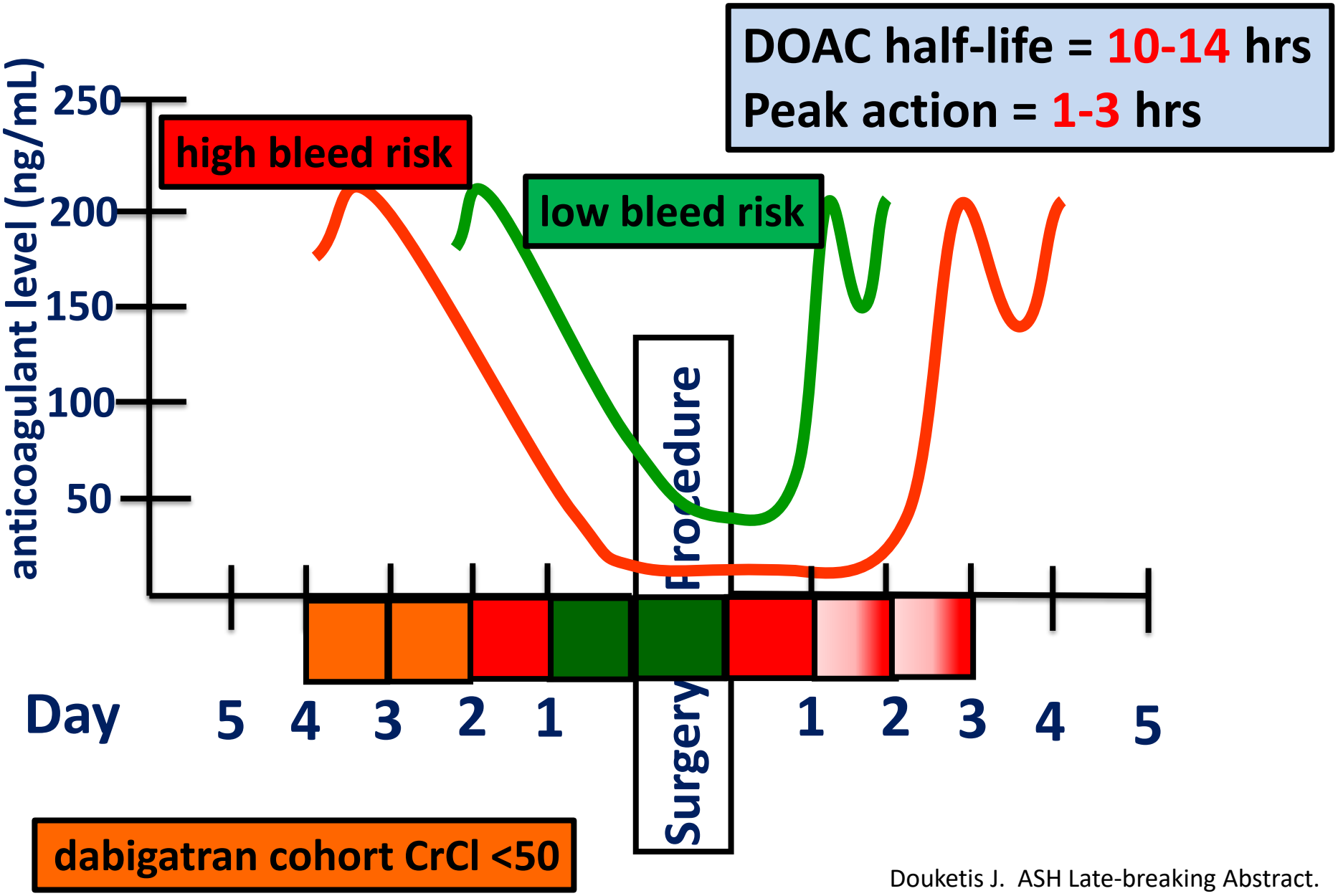
- *Critical to discuss risk of delay*
  - *Because:*
- *Drug effect will dissipate quickly*
- *"Prohemostatic" interventions carry risk*

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. ASH Late-breaking Abstract.

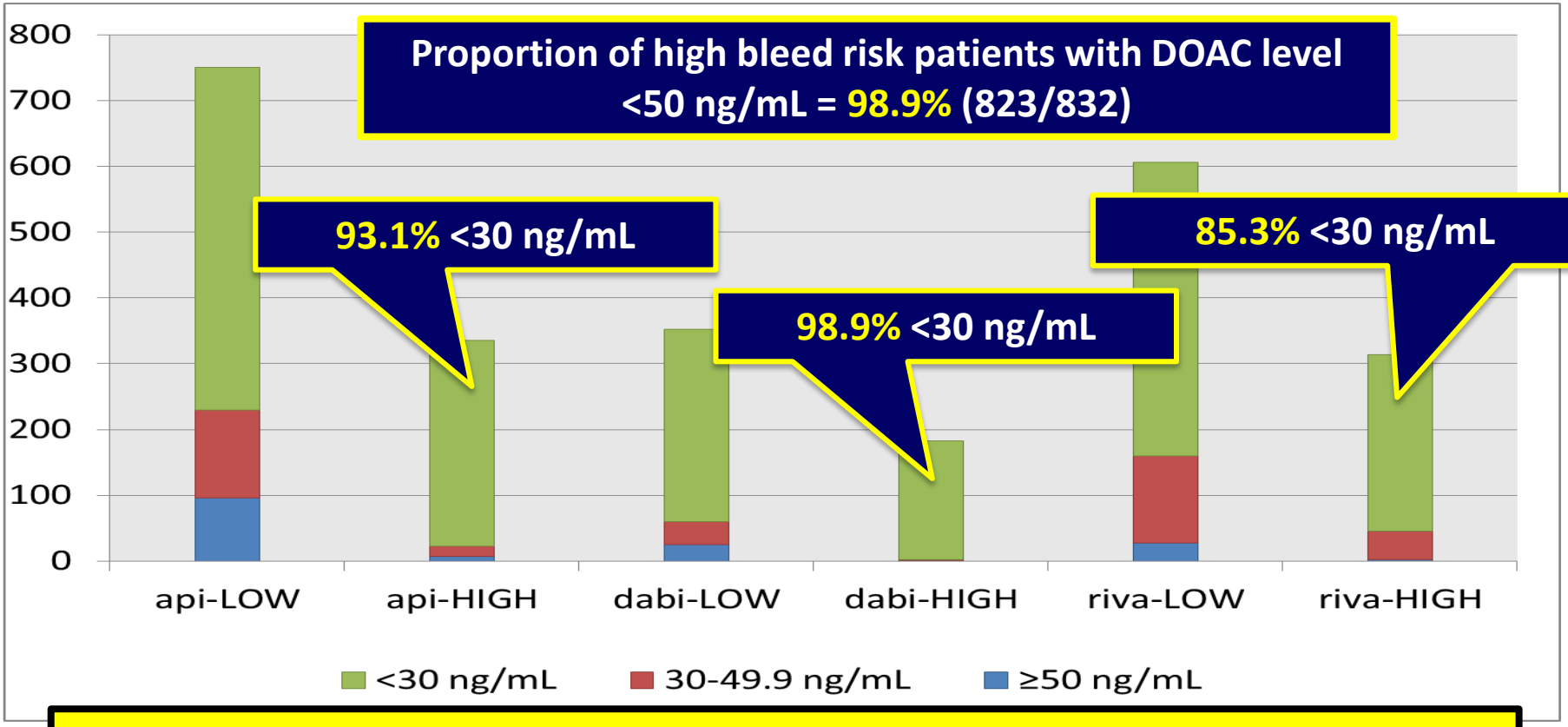
Results: Primary Outcomes (ITT Analysis)

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. ASH Late-breaking Abstract.

Results: Residual Preoperative DOAC Levels



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

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 ng/mL
- "expected" peak: 150 – 250 ng/mL

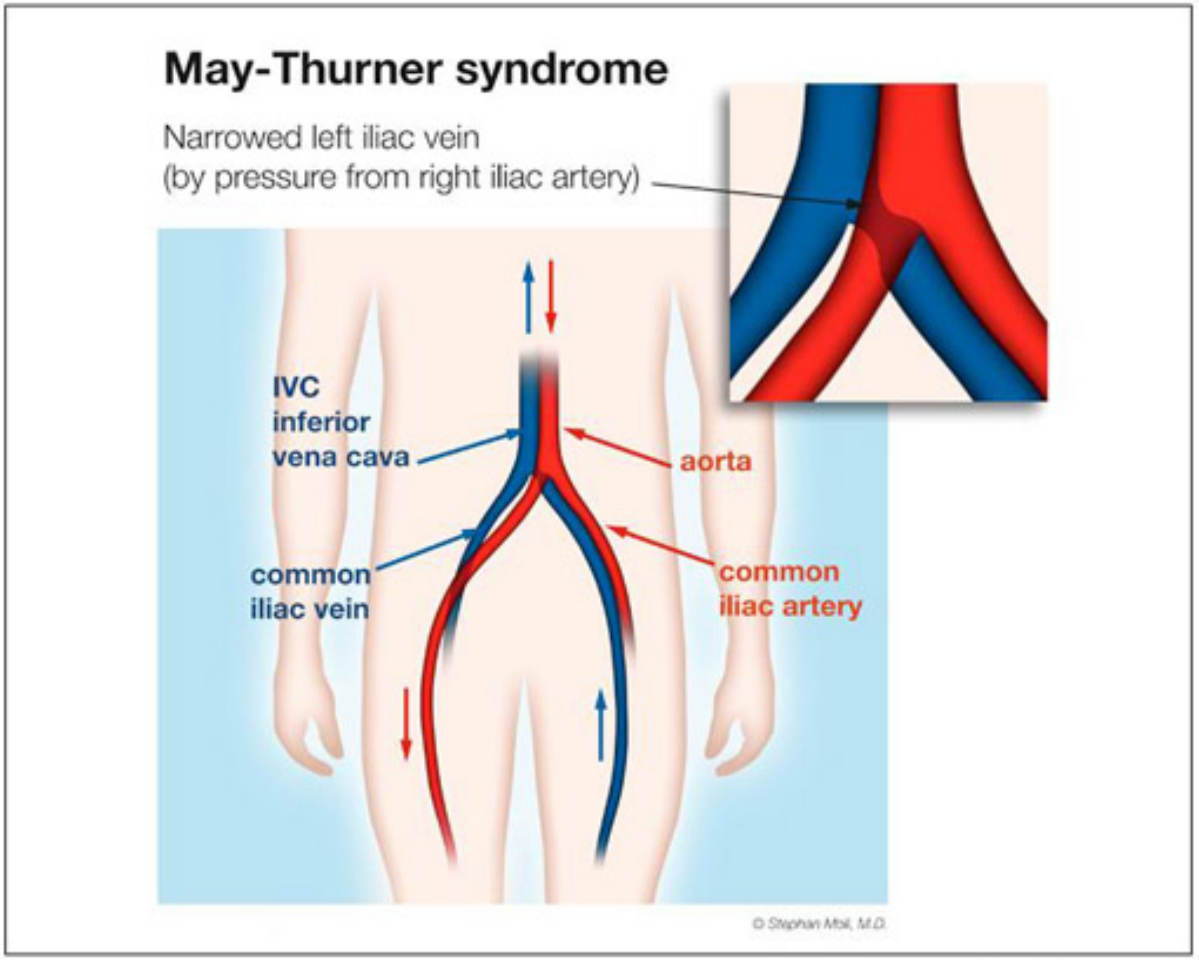
Samuelson et al. Chest. 2017 51(1):127-138.

“Recurrent VTE” on anticoagulation

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

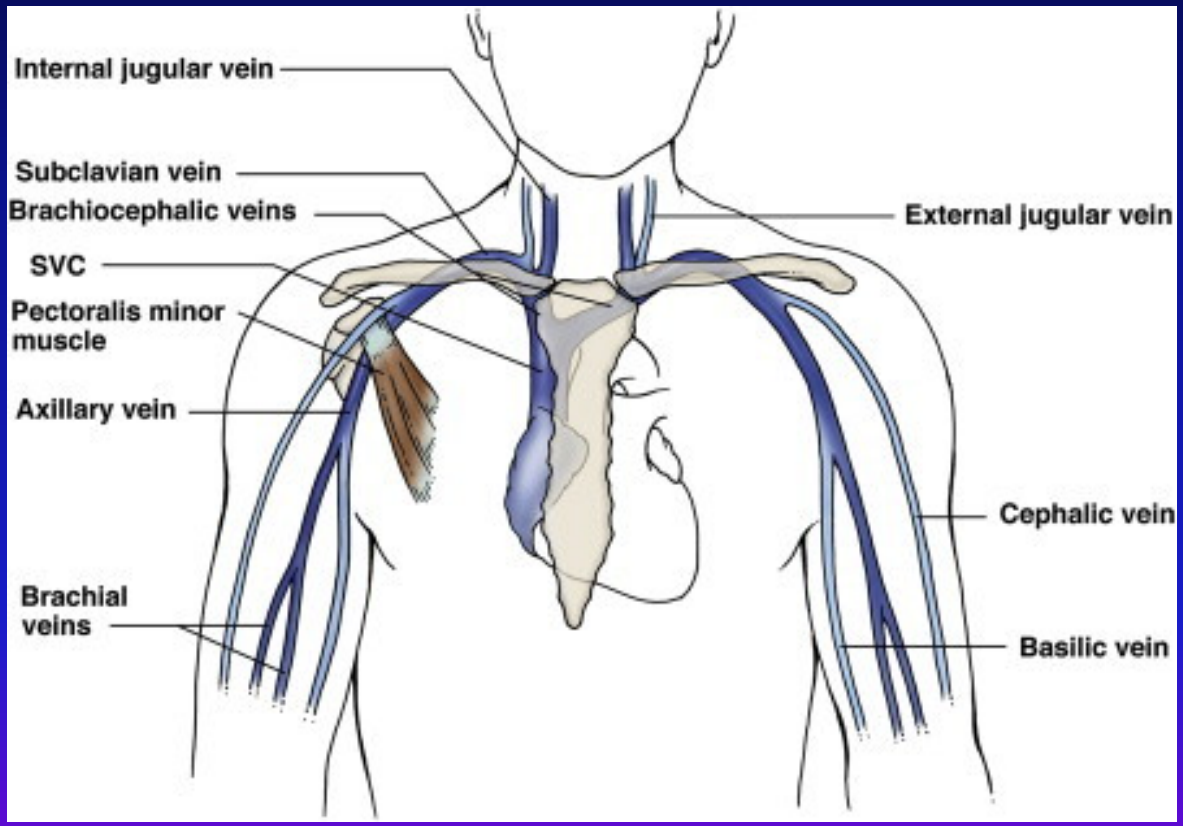
Clinical Scenario	Management
Therapeutic AC	On VKA- consider LMWH or fondaparinux or rivaroxaban On LMWH- empiric 25% dose escalation or fondaparinux or rivaroxaban
Anatomic Compression	Relieve compression, reinstitute AC
Underlying Cancer	Switch to LMWH
Heparin-induced thrombocytopenia	DTI or fondaparinux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

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



Graphic assistance: Jeff Harrison, Wilmington, N.C.

Thoracic Outlet Syndrome



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
- Look for vasculitis or other vessel wall problem
- Tests that *might* be helpful [might impact management decisions]
  - HCY
  - Antiphospholipid antibodies
  - PNH, JAK-2

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