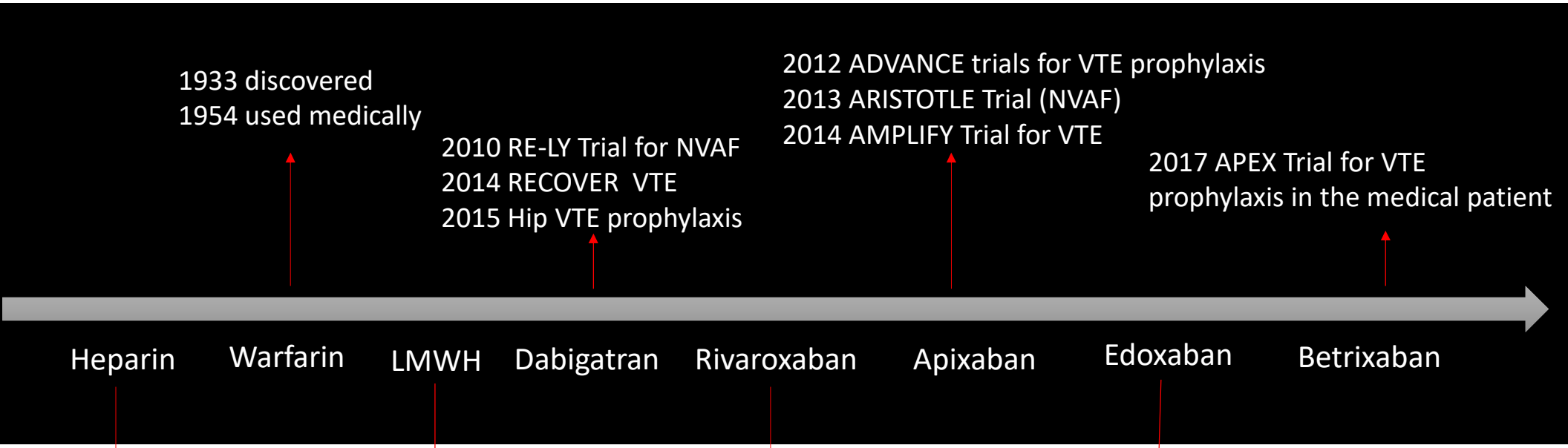
Anticoagulation in 2019

Mo Som, D.O., M.S.



Timeline in Anticoagulant Therapy

The Ideal Anticoagulant

Characteristic	Advantage
Oral administration	Easy to administer
Predictable pharmacokinetics and dose-response relationship	Fixed dose regime; convenience
Rapid onset of action	No need for bridging
Rapid offset of action	Easier to manage bleeding
Wide therapeutic window	Safety
Low, nonspecific plasma protein binding	Reduced risk of drug interaction, dialyzable
Little interaction with food or other drugs	Easy to use, safe
Few adverse events including bleeding complications	Safety
No routine coagulation monitoring required	Easy to use
Available, reliable laboratory method	Easy to assess drug level
Combined/extrarenal elimination route	Useful in severe renal impairment
Appropriate half-life of elimination	Allows once or twice daily admin, yet quick elimination in case of bleeding
Availability of effective and safe antidote	Easy to manage bleeding
Cost-effective	Widespread use

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Savyasa)	Betrixaban (Bevyxxa)
MOA	DTI	Xa	Xa	Xa	Xa
Bioavailability	6-7%	80%	50%	62%	35%
T-Max	1.5 hours	2-4 hours	2-3 hours	1-2 hours	3-4 hours
T 1/2	12-14 hours	9-13 hours	8-15 hours	8-11 hours	19-17 hours
CYP450	No	Yes	Yes	No	No
Renal Clearance	Yes	No	No	No	No
Renal Adjustment	Yes	Yes	No????	Yes	Yes
Antidote	Yes	Yes	Yes	Maybe?	Maybe?

J Am Coll Cardiol Intv 2014;7:1333–51; P&T 2018; 43: 85-88.

Non-Valvular Atrial Fibrillation

Risk Stratifying a Patient with NVAF

- Determining someone's need to be on anticoagulation with NVAF
- Sex Category
  - In the absence of other atrial fibrillation risk factors (CHA2DS2-VASc score of 0 in males and 1 in females) has a lower stroke risk similar to males
  - Excess risk demonstrated with >2 non-sex related stroke risk factors
    - Age > 65 or > 2 non-sex related stroke risk factors

Criteria		Poss. Point
Congestive heart failure Signs/symptoms of heart failure confirmed with objective evidence of cardiac dysfunction	Yes / No	+1
Hypertension Resting BP > 140/90 mmHg on at least 2 occasions or current antihypertensive pharmacologic treatment	Yes / No	+1
Age 75 years or older	Yes / No	+2
Diabetes mellitus Fasting glucose > 125 mg/dL or treatment with oral hypoglycemic agent and/or insulin	Yes / No	+1
Stroke, TIA, or TE Includes any history of cerebral ischemia	Yes / No	+2
Vascular disease Prior MI, peripheral arterial disease, or aortic plaque	Yes / No	+1
Age 65 to 74 years	Yes / No	+1
Sex **C**ategory (female) Female gender confers higher risk	Yes / No	+1

https://clincalc.com/Cardiology/Stroke/CHADSVASC.aspx

2019 AHA Update

COR	LOE	Recommendations
I	A	1. For patients with AF and an elevated CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. Options include: • Warfarin (LOE: A) (S4.1.1-5–S4.1.1-7) • Dabigatran (LOE: B) (S4.1.1-8) • Rivaroxaban (LOE: B) (S4.1.1-9) • Apixaban (LOE: B) (S4.1.1-10), or • Edoxaban (LOE: B-R) (S4.1.1-11) **MODIFIED**: This recommendation has been updated in response to the approval of edoxaban, a new factor Xa inhibitor. More precision in the use of CHA_2DS_2-VASc scores is specified in subsequent recommendations. The LOEs for warfarin, dabigatran, rivaroxaban, and apixaban have not been updated for greater granularity as per the new LOE system. (Section 4.1. in the 2014 AF Guideline) The original text can be found in Section 4.1 of the 2014 AF guideline. Additional information about the comparative effectiveness and bleeding risk of NOACs can be found in Section 4.2.2.2.
	B	
	B	
	B-R	

2019 AHA Update

I	A	**2. NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) (S4.1.1-8–S4.1.1-11).** **NEW**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. When the NOAC trials are considered as a group, the direct thrombin inhibitor and factor Xa inhibitors were at least noninferior and, in some trials, superior to warfarin for preventing stroke and systemic embolism and were associated with lower risks of serious bleeding.

IIa	B	**12. For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA_2DS_2-VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy (S4.1.1-24, S4.1.1-25).** **MODIFIED**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. (Section 4.1. in the 2014 AF Guideline)

Meta Analysis Comparing DOAC's to Warfarin

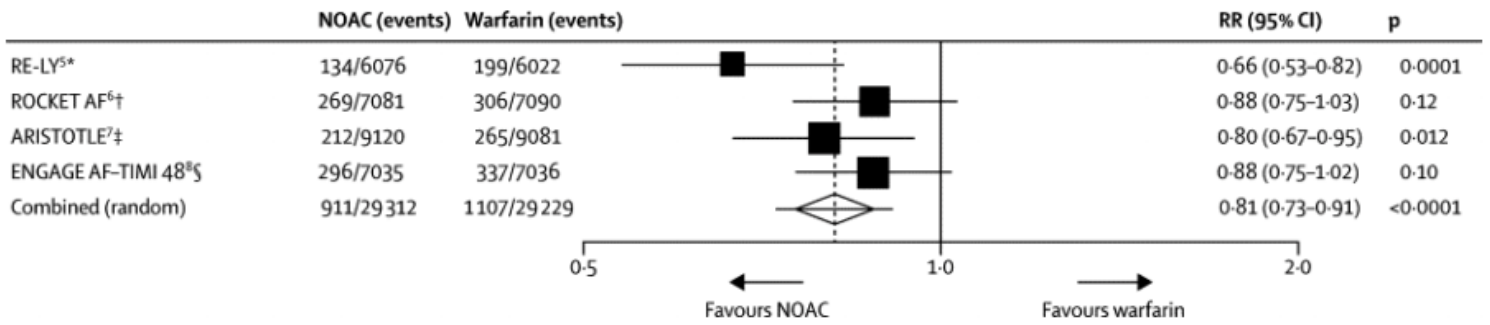


Figure 1. Stroke or systemic embolic eventsData are n/N, unless otherwise indicated. Heterogeneity: I2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban...

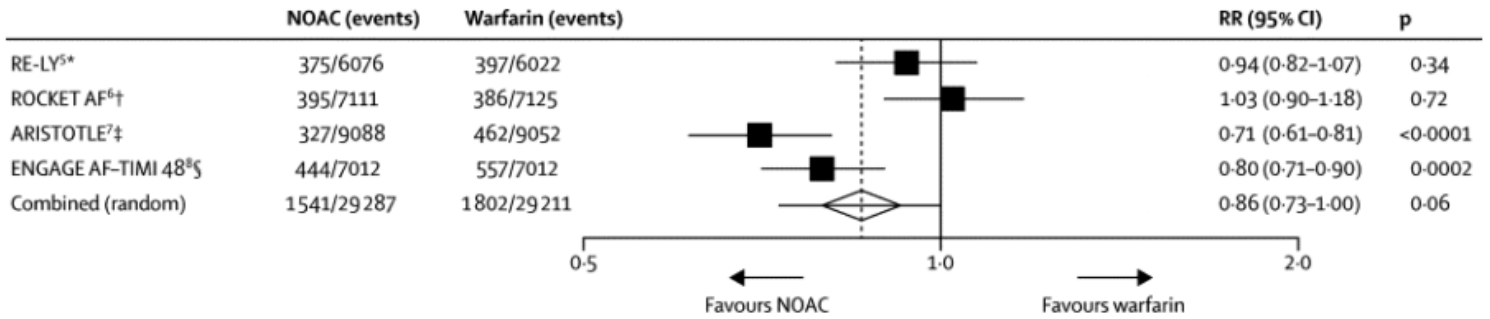


Figure 3. Major bleedingData are n/N, unless otherwise indicated. Heterogeneity: I2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Comparing DOAC Trials for NVAF

	RE-LY[5]			ROCKET-AF[6]		ARISTOTLE[7]		ENGAGE AF-TIMI 48[8]			Combined	
	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)	Warfarin (n=6022)	Rivaroxaban (n=7131)	Warfarin (n=7133)	Apixaban (n=9120)	Warfarin (n=9081)	Edoxaban 60 mg (n=7035)	Edoxaban 30 mg (n=7034)	Warfarin (n=7036)	NOAC (n=42 411)	Warfarin (n=29 272)
Age (years)	71·5 (8·8)	71·4 (8·6)	71·6 (8·6)	73 (65–78)	73 (65–78)	70 (63–76)	70 (63–76)	72 (64–68)	72 (64–78)	72 (64–78)	71·6	71·5
≥75 years	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%	38%	38%
Women	37%	36%	37%	40%	40%	36%	35%	39%	39%	38%	38%	37%
Atrial fibrillation type												
Persistent or permanent	67%	68%	66%	81%	81%	85%	84%	75%	74%	75%	76%	77%
Paroxysmal	33%	32%	34%	18%	18%	15%	16%	25%	26%	25%	24%	22%
CHADS2*	2·2 (1·2)	2·1 (1·1)	2·1 (1·1)	3·5 (0·94)	3·5 (0·95)	2·1 (1·1)	2·1 (1·1)	2·8 (0·97)	2·8 (0·97)	2·8 (0·98)	2·6 (1·0)	2·6 (1·0)
0–1	32%	33%	31%	0	0	34%	34%	<1%	<1%	<1%	17%	17%
2	35%	35%	37%	13%	13%	36%	36%	46%	47%	47%	35%	33%
3–6	33%	33%	32%	87%	87%	30%	30%	54%	53%	53%	48%	50%
Previous stroke or TIA*	20%	20%	20%	55%	55%	19%	18%	28%	29%	28%	29%	30%
Heart failure†	32%	32%	32%	63%	62%	36%	35%	58%	57%	58%	46%	47%
Diabetes	23%	23%	23%	40%	40%	25%	25%	36%	36%	36%	31%	31%
Hypertension	79%	79%	79%	90%	91%	87%	88%	94%	94%	94%	88%	88%
Prior myocardial infarction	17%	17%	16%	17%	18%	15%	14%	11%	12%	12%	15%	15%

Lancet 2014;383:955-62

DOAC Dosing Recommendations in AFib

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Usual Dose	5mg BID	150mg BID	60mg daily (CI if CrCl ≥95 mL/min)*	20mg daily with food
Reduced Dose	2.5mg BID	75mg BID	30mg daily	15mg daily with food
Indications for Reduction	1. If 2 of 3 factors present: Age ≥80 years SCr ≥1.5 mg/dL Weight ≤60 kg 2. Coadministered with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir)	CrCl 15-30 mL/min OR, CrCl 30-50 mL/min with concomitant dronedarone or ketoconazole	CrCl 15-50 mL/min	CrCl ≤50 mL/min
Comments	Those with SCr >2.5 or CrCl <25 mL/min excluded from ARISTOTLE trial†	Those with CrCl <30 mL/min excluded from RE-LY trial†	Those with CrCl <30 mL/min excluded from ENGAGE AF-TIMI 48 trial†	Those with CrCl <30 mL/min excluded from ROCKET-AF trial†
	Consult package inserts for specific use/dosing recommendations with concomitant CYP3A4 and/or P-gp inducers or inhibitors. There are additional drug interactions in which DOACs should be avoided.			

BID: twice daily; SCr: actual serum creatinine; P-gp: P-glycoprotein; CYP3A4: cytochrome P450 3A4; CrCl: creatinine clearance calculated with Cockcroft-Gault equation using actual body weight and actual SCr; CI: contraindicated.

* Contraindicated if CrCl > 95 mL/min due to increased ischemic stroke risk compared to warfarin.

† Use in these situations based on kinetic and dynamic modeling rather than clinical outcomes data.

VTE Prophylaxis in the Orthopedic Patient

ACCP, SIGN, and AAOS guidelines for VTE prophylaxis for patients undergoing elective THR or TKR

Study	Guidelines	Clinical evidence (grade)	Duration of prophylaxis
ACCP (2008[19], 2012[31])	LMWH	1B	At least 10 to 14 days, and up to 35 days
	Low dose UFH	1B	
	VKA	1B	
	Fondaparinux	1B	
	Apixaban	1B	
	Dabigatran	1B	
	Rivaroxaban	1B	
	Aspirin	1B	
	IPCD	1C	
	Preference of LMWH to fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH	2B	
	Preference of LMWH to VKA and aspirin	2C	
SIGN (2010, updated 201516)	LMWH In combination with mechanical prophylaxis Fondaparinux Rivaroxaban Dabigatran	A	Extended prophylaxis (grade A) Optimal duration of extended prophylaxis is unclear
	Aspirin is not recommended as a single pharmacologic agent for VTE prophylaxis	C	–
AAOS (201134)	Use of pharmacologic agents and/or mechanical methods	Moderate	–
	Unclear about which prophylactic strategy (or strategies) is/are optimal or suboptimal. No recommendation for or against specific prophylactics in these patients	Inconclusive	Patients and physicians discuss the duration of prophylaxis (consensus)

Table 3.

ACCP, SIGN, British Orthopaedic Association, and NICE guidelines for VTE prophylaxis for patients undergoing hip fracture surgery

Study	Guidelines		Clinical evidence (grade)	Duration of prophylaxis
ACCP (200819, 201231)	LMWH		1B	At least 10 to 14 days, and up to 35 days
	Low dose UFH		1B	
	VKA		1B	
	Fondaparinux		1B	
	Aspirin		1B	
	IPCD		1C	
	Preference of LMWH to fondaparinux, low dose UFH		2B	
	Preference of LMWH to VKA and aspirin		2C	
SIGN (200974) British Orthopaedic Association (200775)	In combination with mechanical prophylaxis	LMWH	A	4 weeks
		UFH	A	
		Fondaparinux	A	
	Aspirin is not recommended as a single pharmacological agent for VTE prophylaxis		D	–
NICE (201871)	LMWH		–	1 month
	Fondaparinux			

ELSEVIER

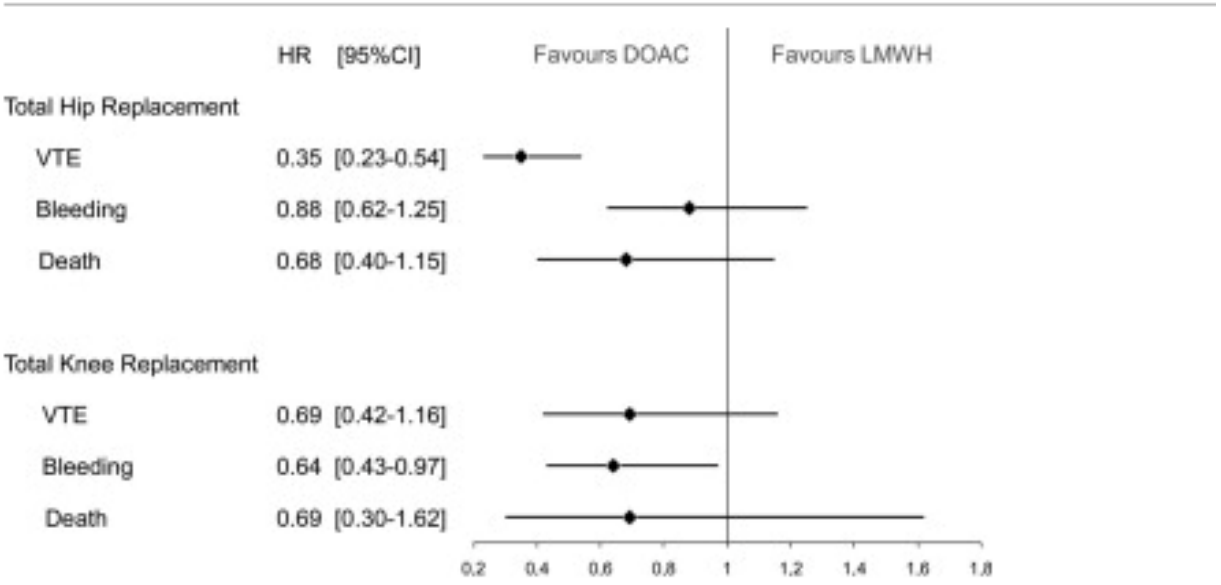
Pharmacological Research
Volume 141, March 2019, Pages 201-207

Comparative effectiveness of direct oral anticoagulants versus low-molecular weight heparins for the prevention of venous thromboembolism after total hip or knee replacement: A nationwide database cohort study

Patrick Blin [a], Charles-Marc Samama [b], Alain Sautet [c], Jacques Benichou [d], Séverine Lignot-Maleyran [a], Stéphanie Lamarque [a], Simon Lorrain [a], Régis Lassalle [a], Cécile Droz-Perroteau [a], Patrick Mismetti [e], Nicholas Moore [a, f]

In A Nutshell

- Nationwide study
  - Low risk of VTE, hospitalized bleeding and death after THR or TKR discharge in patients with VTE prevention in real-life setting, with better benefit-risk profiles of DOAC compared to LMWH, and associated cost savings.



ORIGINAL ARTICLE

Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty

David R. Anderson, M.D., Michael Dunbar, M.D., John Murnaghan, M.D., Susan R. Kahn, M.D., Peter Gross, M.D., Michael Forsythe, M.D., Stephane Pelet, M.D., William Fisher, M.D., Etienne Belzile, M.D., Sean Dolan, M.D., Mark Crowther, M.D., Eric Bohm, M.D., et al.

VTE Prophylaxis in the Medical Patient

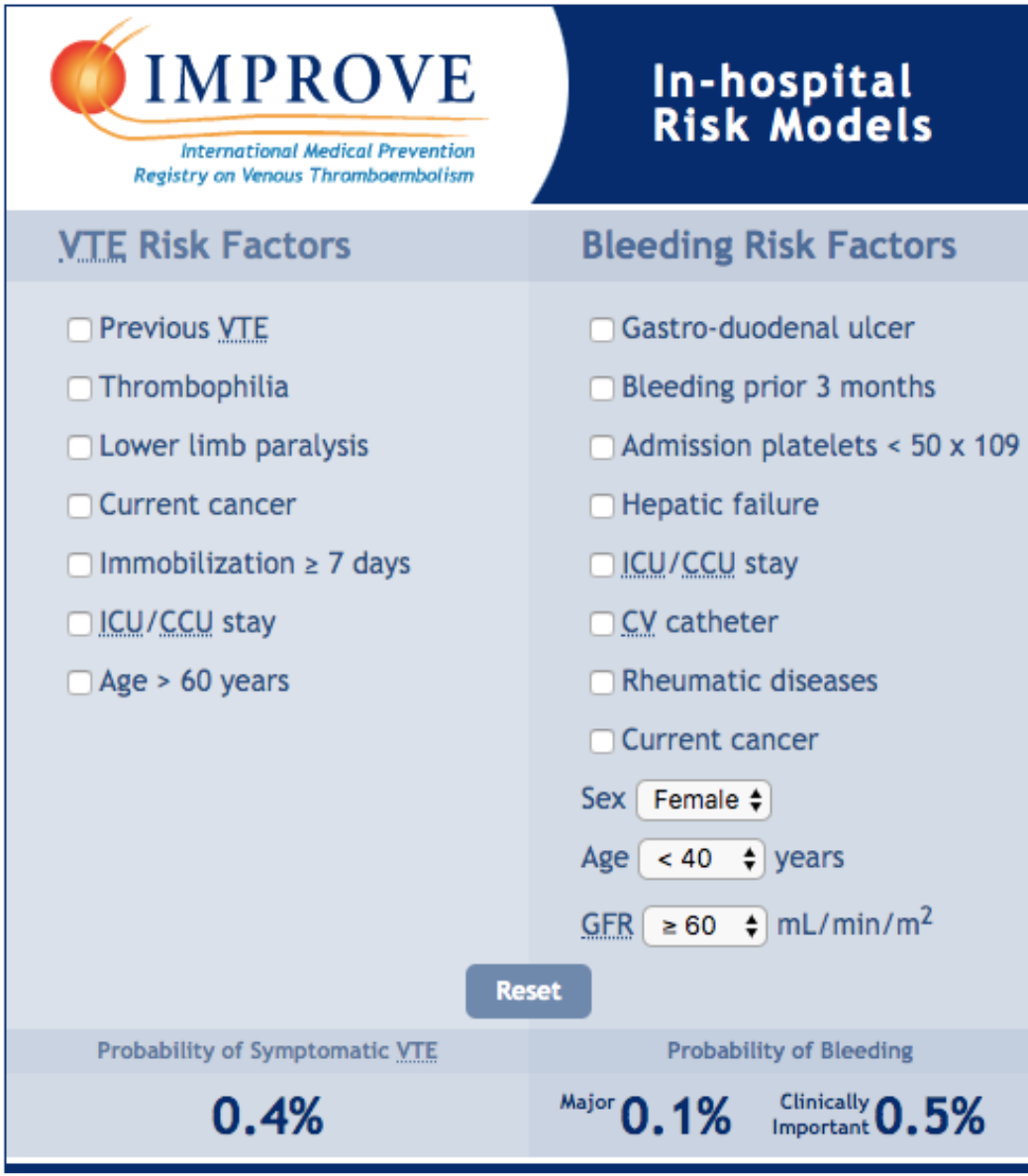
ORIGINAL ARTICLE

Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients

Alexander T. Cohen, M.D., Robert A. Harrington, M.D., Samuel Z. Goldhaber, M.D., Russell D. Hull, M.B., B.S., Brian L. Wiens, Ph.D., Alex Gold, M.D., Adrian F. Hernandez, M.D., and C. Michael Gibson, M.D. for the APEX Investigators*

ACCP 2012 Guidelines
ASH 2018 Guidelines

- **ACCP 2.8.** In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B) .
- **ASH Recommendation 14:**
- In critically ill medical patients, the ASH guideline panel *recommends* inpatient over inpatient plus extended-duration outpatient VTE prophylaxis (strong recommendation, moderate certainty in the evidence of effects)
- **ASH Recommendation 15:**
- In chronically ill medical patients, including nursing home patients, the ASH guideline panel *suggests* not using VTE prophylaxis compared with using any VTE prophylaxis (conditional recommendation, very low certainty in the evidence of effects

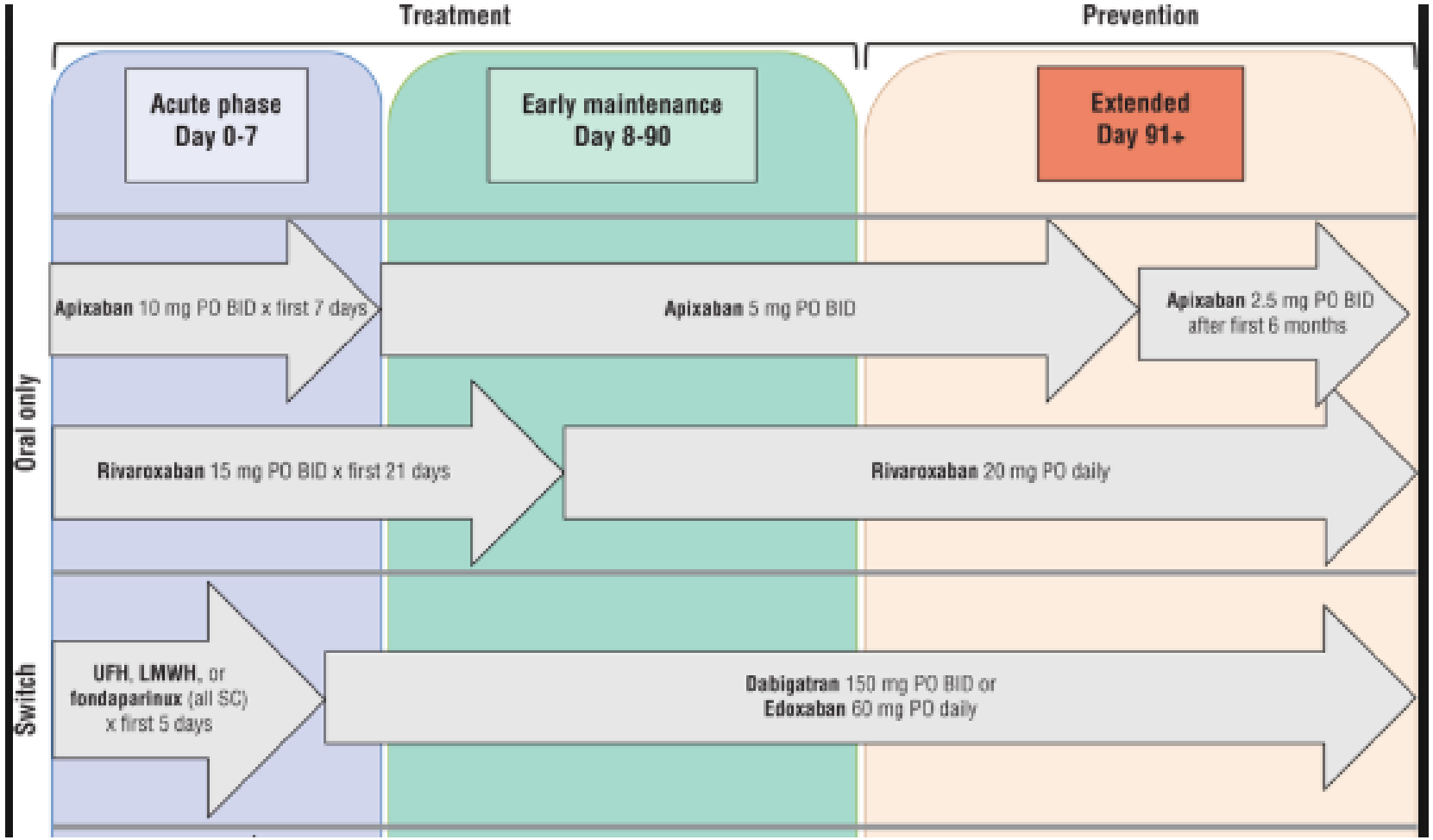


VTE Treatment

Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* 2016;149:315-352.

For VTE without an associated cancer diagnosis, all direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, or edoxaban) are recommended over vitamin K antagonist (VKA) therapy (**all Grade 2B**)

VKA therapy is recommended over low molecular weight heparin in non cancer patients (LMWH; Grade 2C)


Treatment
Prevention
Acute phase
Day 0-7
Early maintenance
Day 8-90
Extended
Day 91+
Oral only
Apixaban 10 mg PO BID x first 7 days
Apixaban 5 mg PO BID
Apixaban 2.5 mg PO BID
after first 6 months
Rivaroxaban 15 mg PO BID x first 21 days
Rivaroxaban 20 mg PO daily
Switch
UFH, LMWH, or
fondaparinux (all SC)
x first 5 days
Dabigatran 150 mg PO BID or
Edoxaban 60 mg PO daily

Study	Treatment	Patients	Recurrent VTE[1]	Major bleeding
RE-COVER, 2009	Dabigatran 150 mg BID vs. VKA	1273/1266	30 (2.4 %) vs. 27 (2.1 %) (HR 1.10; 95 % CI −0.8 to 1.5)	20 (1.6 %) vs. 24 (1.9 %) (HR 0.82; 95 % CI 0.45–1.48)
RE-COVER II, 2014	Dabigatran 150 mg BID vs. VKA	1279/1289	30 (2.3 %) vs. 28 (2.2 %) (HR 1.08; 95 % CI 0.64–1.80)	15 (1.2 %) vs. 22 (1.7 %) (HR 0.69; 95 % CI 0.36–1.32)
EINSTEIN DVT, 2010	Rivaroxaban 15 mg BID X 3 weeks, then 20 mg daily vs. Enoxaparin/VKA	1731/1718	36 (2.1 %) vs. 51 (3.0 %) (HR 0.68; 95 % CI 0.44–1.04)	14 (0.8 %) vs. 20 (1.2 %) (HR 0.65; 95 % CI 0.33–1.30)
EINSTEIN PE, 2012	Rivaroxaban 15 mg BID X 3 weeks, then 20 mg daily vs. Enoxaparin/VKA	2419/2413	50 (2.1 %) vs. 44 (1.8 %) (HR 1.12; 95 % CI 0.75–1.68)	26 (1.1 %) vs. 52 (2.2 %) (HR 0.49; 95 % CI 0.31–0.79)
AMPLIFY, 2013	Apixaban 10 mg BID X 7 days then 5 mg BID vs. Enoxaparin/Warfarin	2609/2635	59 (2.3 % vs. 71 (2.7 %) (RR 0.84; 95 % CI 0.60–1.18)	15 (0.6 %) vs. 49 (1.8 %) (RR 0.31; 95 % CI 0.17–0.55)
HOKUSAI-VTE, 2013	Edoxaban 60 mg daily (or 30 mg daily) vs. warfarin	4118/4122	130 (3.2 %) vs. 146 (3.5 %) (HR 0.89; 95 % CI 0.70–1.13)	56 (1.4 %) vs. 66 (1.6 %) (HR 0.84; 0.59–1.21)

In a Nutshell

- Dabigatran: As effective as warfarin, but higher risk of GI bleeding and ACS?
- Rivaroxaban: As effective as warfarin, but higher risk of GI bleeding > 75 years old
- Apixaban: As effective as warfarin with less bleeding
- Edoxaban: As effective as warfarin with less bleeding

Streiff MB, Agnelli G, Connors JM, et al. Guidance for the treatment of deep vein thrombosis and pulmonary embolism [published correction appears in J Thromb Thrombolysis. 2016 Apr;41(3):548]. *J Thromb Thrombolysis*. 2016;41(1):32–67. doi:10.1007/s11239-015-1317-0

Approved DOAC Dosing for VTE Treatment

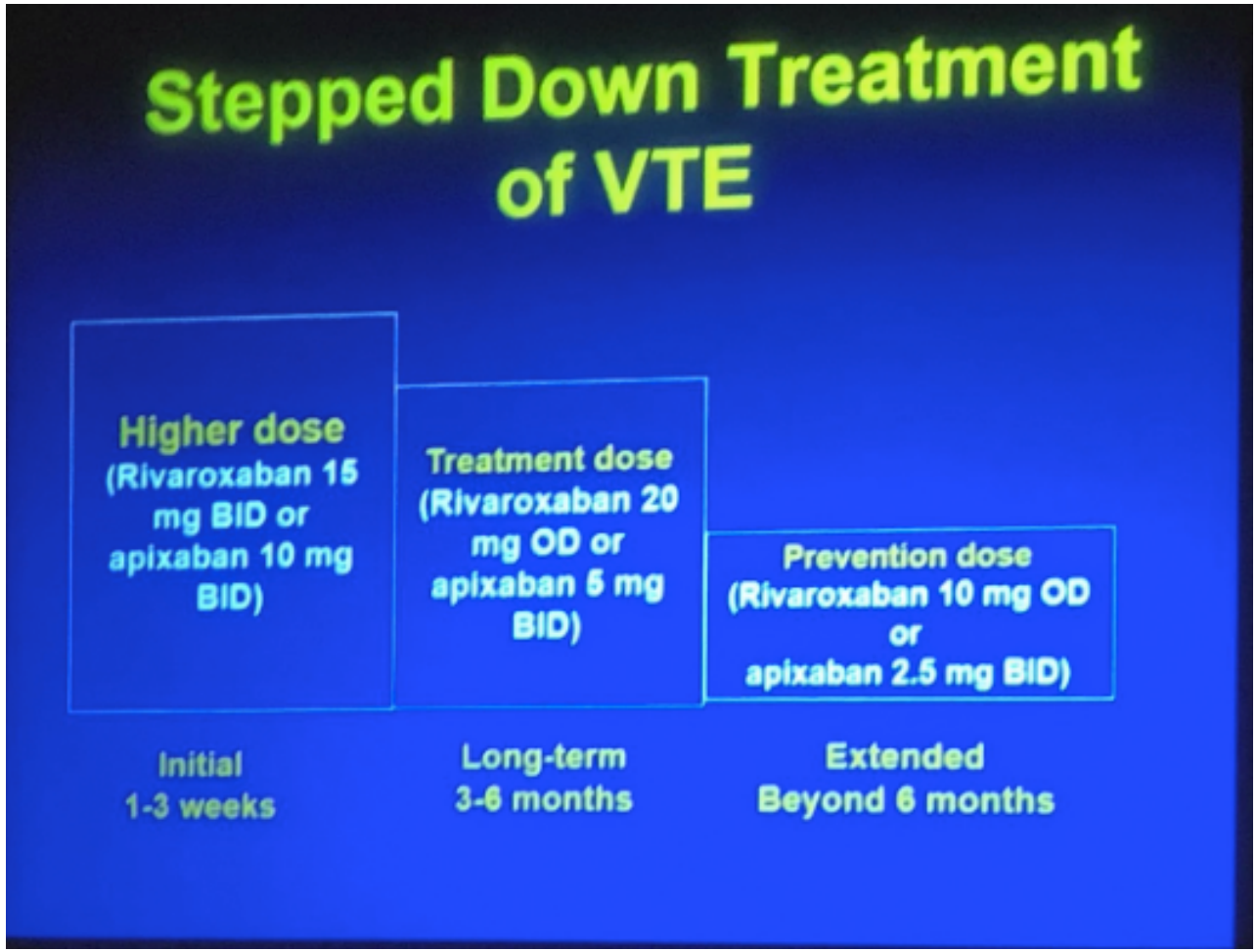
Medication	Dose	Dose Adjustment for Renal Function
Dabigatran*	150 mg twice daily AFTER 5 days of parenteral anticoagulation	Avoid use if CrCl> 30 ml/min
Rivaroxaban**	15 mg twice daily x 21 days followed by 20 mg daily	Avoid use if CrCl> 30 ml/min
Apixaban**	10 mg twice daily x 7days followed by 5 mg twice daily	No dosage adjustment required
Edoxaban*	60 mg daily AFTER 5 days of parenteral anticoagulation	15-50 -ml/min :30 mg once daily

Extending VTE Treatment

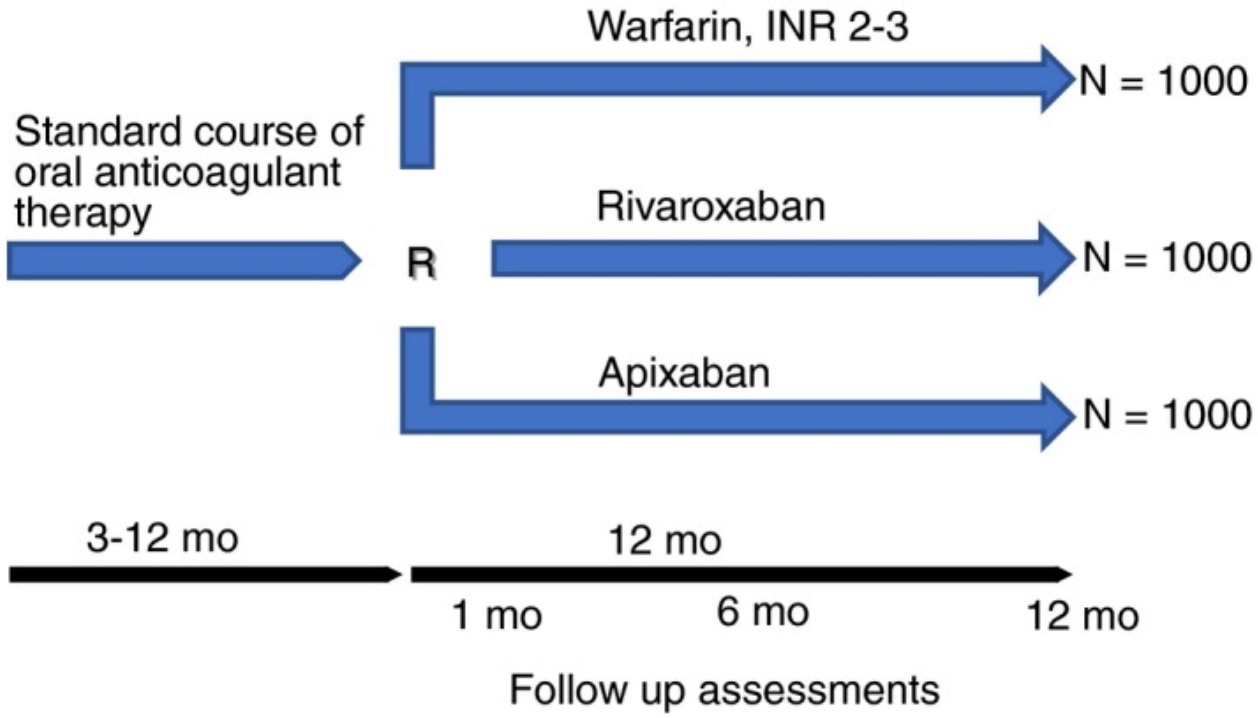
Study	Comparator 1	Comparator 2	Recurrent VTE[a] HR (95% CI)	MB HR (95% CI)	MB/CRNMBHR (95% CI)
RE-MEDY	Dabigatran 150 mg BID	VKA (INR 2-3)	1.44 (0.78-2.64)	0.52 (0.27-1.02)	0.54 (0.41-0.71)
RE-SONATE	Dabigatran 150 mg BID	Placebo	0.08 (0.02-0.25)	Not estimable	2.92 (1.52-5.60)
EINSTEIN-EXT	Rivaroxaban 20 mg daily	Placebo	0.18 (0.09-0.39)	Not estimable	5.19 (2.3-11.7)
EINSTEIN-CHOICE	Rivaroxaban 20 mg daily	ASA 100 mg	0.34 (0.20-0.59)	2.01 (0.50-8.04)	1.59 (0.94-2.69)
EINSTEIN-CHOICE	Rivaroxaban 10 mg daily	ASA 100 mg	0.26 (0.14-0.47)	1.64 (0.39-6.84)	1.16 (0.67-2.03)
AMPLIFY-EXT	Apixaban 5 mg BID	Placebo	Relative risk: 0.20 (0.11-0.34)	Relative risk: 0.25 (0.03-2.24)	Relative risk: 1.62 (0.96-2.73)
AMPLIFY-EXT	Apixaban 2.5 mg BID	Placebo	Relative risk: 0.19 (0.11-0.33)	Relative risk: 0.49 (0.09-2.64)	Relative risk: 1.20 (0.69-2.10)

In a Nutshell

- Dabigatran: Similarly effective as Warfarin with less bleeding
- Rivaroxaban: Superior to placebo with more bleeding
- Apixaban: Superior to placebo


Stepped Down Treatment of VTE
Higher dose (Rivaroxaban 15 mg BID or apixaban 10 mg BID)
Treatment dose (Rivaroxaban 20 mg OD or apixaban 5 mg BID)
Prevention dose (Rivaroxaban 10 mg OD or apixaban 2.5 mg BID)
Initial 1-3 weeks
Long-term 3-6 months
Extended Beyond 6 months

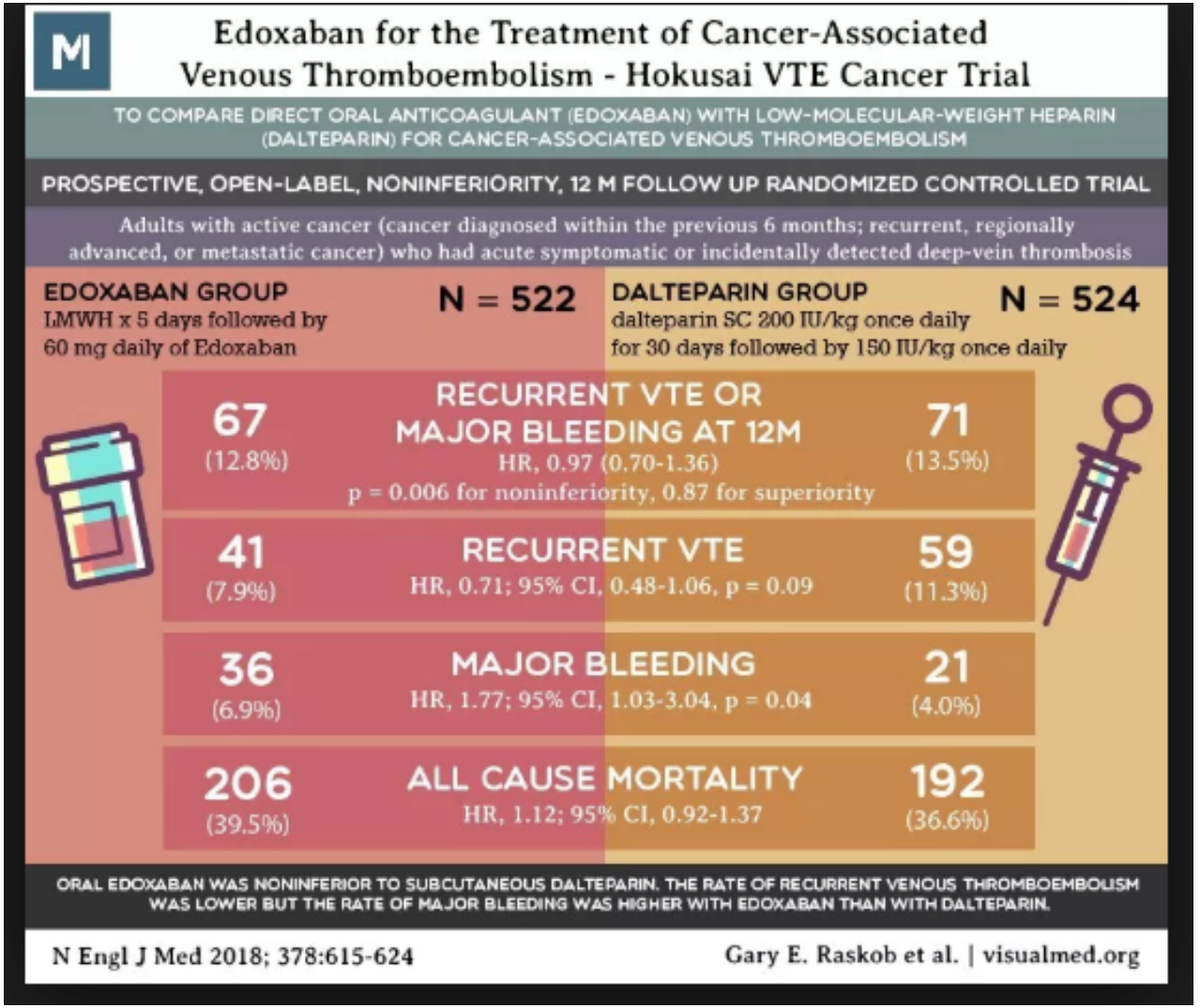
On the Horizon



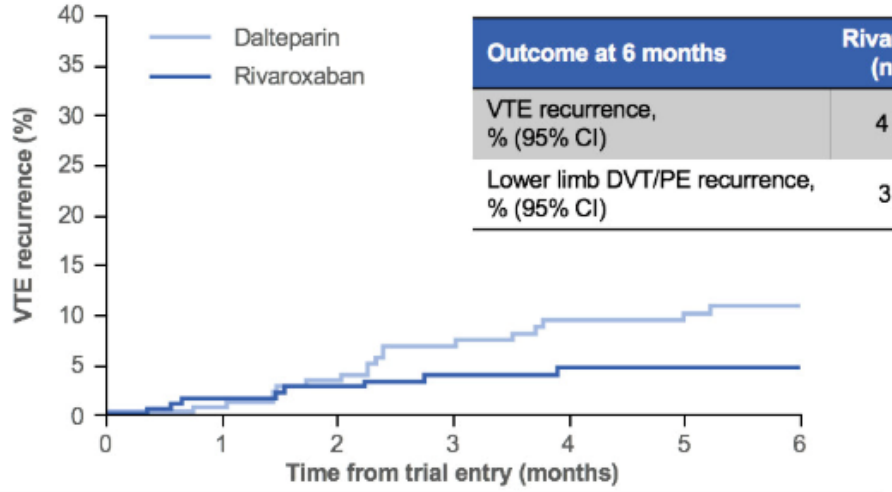
VTE Treatment in the Cancer Patient

Houkasi VTE Cancer Trial

- Edoxaban non-inferior to dalteparin for recurrent VTE at 12 months
- Edoxaban non-inferior to dalteparin in major bleeding at 12 monhts



select-d Primary Outcome: Lower Incidence of VTE Recurrence Events with Rivaroxaban Versus Dalteparin



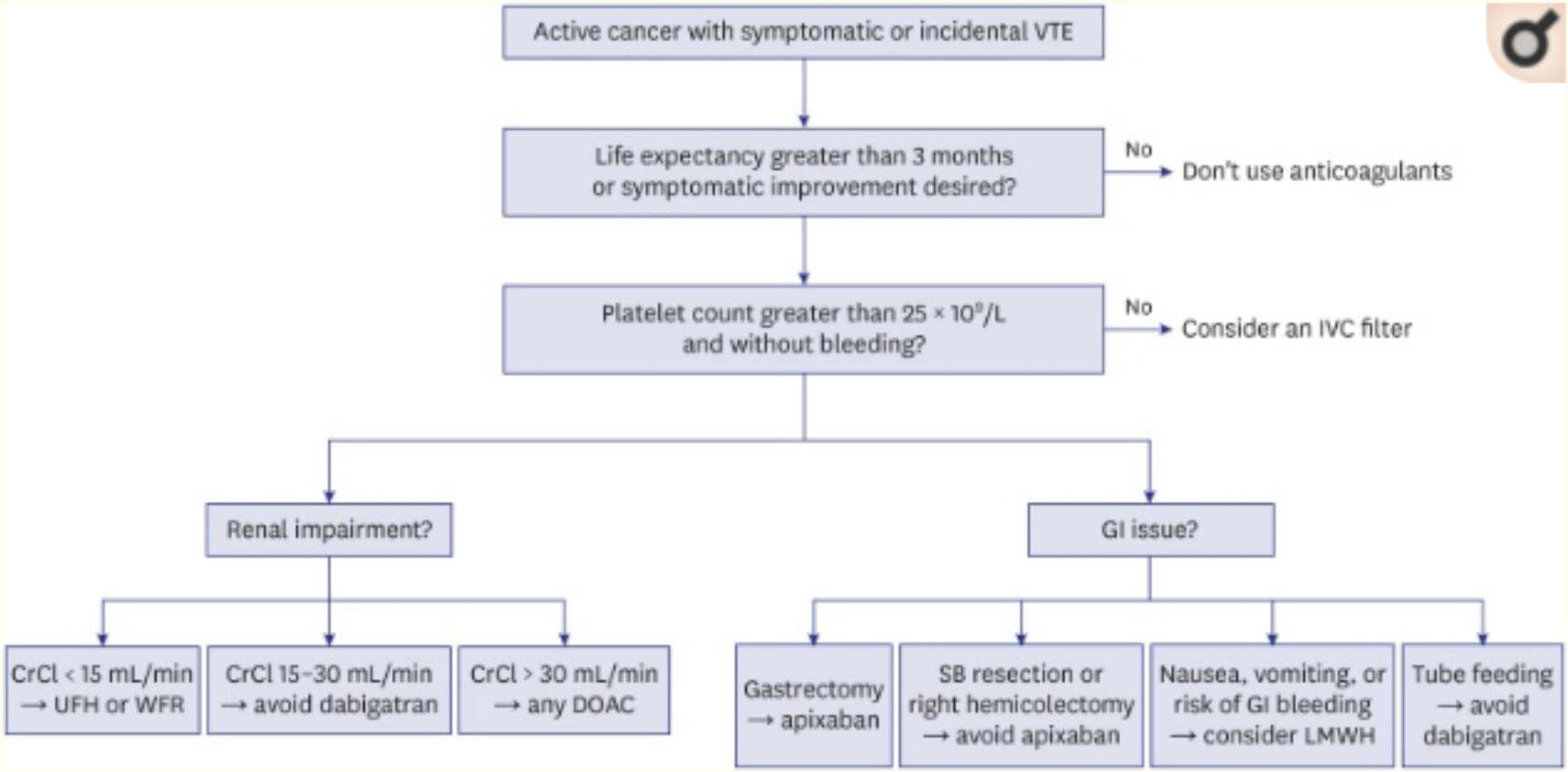
Outcome at 6 months	Rivaroxaban (n=203)	Dalteparin (n=203)
VTE recurrence, % (95% CI)	4 (2–9)	11 (7–16)
Lower limb DVT/PE recurrence, % (95% CI)	3 (1-7)	9 (6-15)

Number at risk				
Dalteparin	203	171	139	115
Rivaroxaban	203	174	149	134

Young A *et al*, ASH 2017: Abstract 625; Available at: http://www.clinicaltrialresults.org/

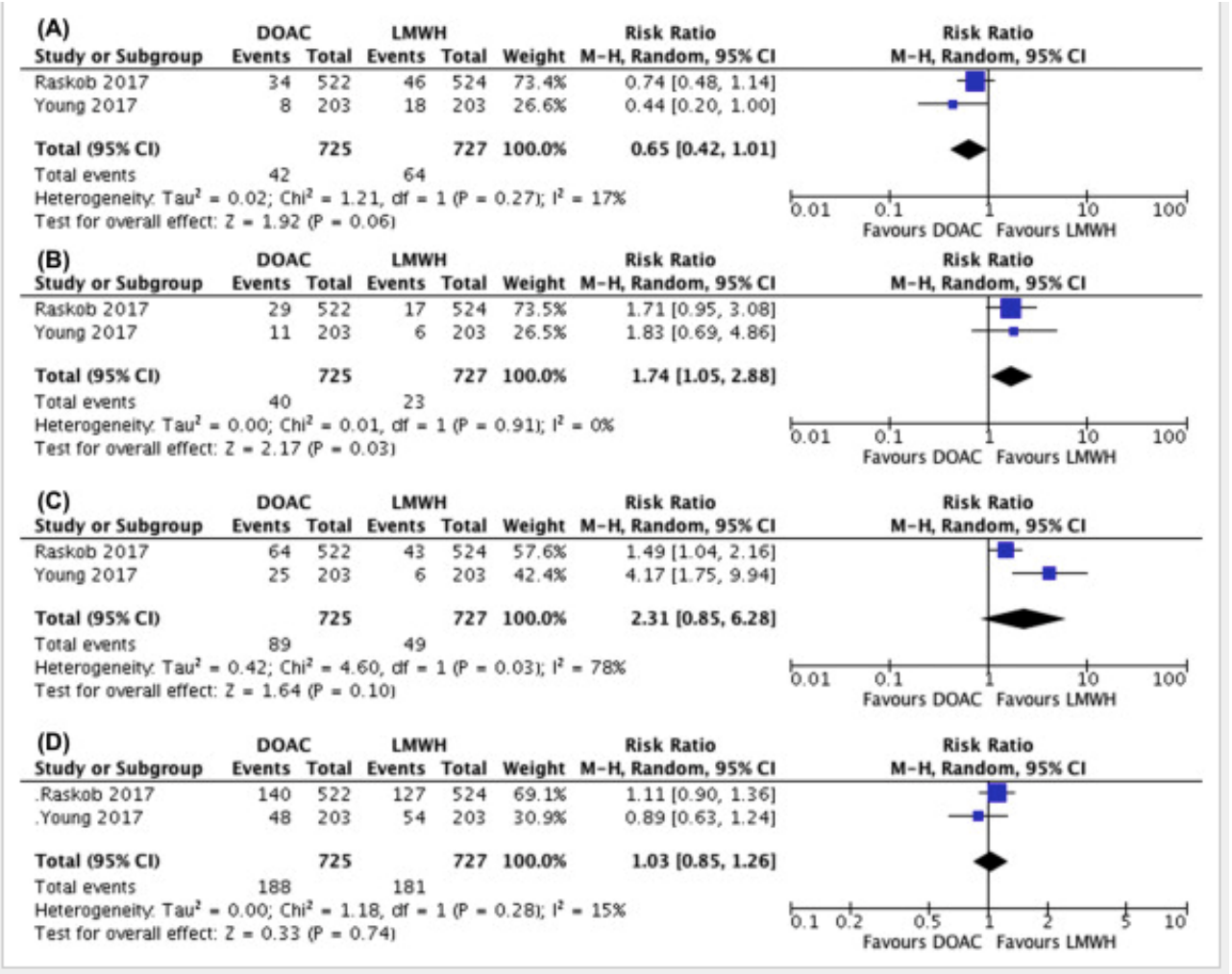
SELECT-D VTE Cancer Trial

- Pilot Trial
- Fewer patients with VTE recurrence at 6 months for the rivaroxaban arm
- Clinically relevant non-major bleeding at 6 months was higher in the rivaroxaban arm


Active cancer with symptomatic or incidental VTE
Life expectancy greater than 3 months or symptomatic improvement desired?
No
Don't use anticoagulants
Platelet count greater than 25 × 10⁹/L and without bleeding?
No
Consider an IVC filter
Renal impairment?
GI issue?
CrCl < 15 mL/min → UFH or WFR
CrCl 15–30 mL/min → avoid dabigatran
CrCl > 30 mL/min → any DOAC
Gastrectomy → apixaban
SB resection or right hemicolectomy → avoid apixaban
Nausea, vomiting, or risk of GI bleeding → consider LMWH
Tube feeding → avoid dabigatran

Meta-Analysis

- (A) VTE recurrence by 6-month
- (B) major bleeding by 6-month,
- (C) clinically relevant non-major bleeding (CRNMB) by 6-month
- (D) overall mortality by 6-month



Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis Li, Ang et al.Thrombosis Research, Volume 173, 158 - 163

Ongoing Trials for CAT and VTE Treatment

Trial (ref)	Sampl (N)	of cancer associated thrombosis (CAT): A systematic review and meta-analysis - Thrombosis Research	DOACs	Comparator	Primary outcome (s)	Treatment duration
CANVAS[39]	940	Randomized, open label	Any DOAC	LMWH or fondaparinux alone or with VKA	VTE recurrence	6 months
CARAVAGGIO	1,126	Randomized, open label, blinded end-point (PROBE), non-inferiority	Apixaban	Dalteparin	VTE recurrence Major bleeding	6 months
CASTA-DIVA[40]	200	Randomized, open label	Rivaroxaban	Dalteparin	VTE recurrence Major bleeding	3 months
ADAM VTE[41]	300	Randomized, open label, superiority	Apixaban	Dalteparin	Major bleeding	6 months
CONKO[42]	450	Randomized, open label	Rivaroxaban	LMWH	Patient-reported treatment satisfaction	3 months

Reduction of MACE

ORIGINAL ARTICLE FREE PREVIEW

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

John W. Eikelboom, M.B., B.S., Stuart J. Connolly, M.D., Jackie Bosch, Ph.D., Gilles R. Dagenais, M.D., Robert G. Hart, M.D., Olga Shestakovska, M.Sc., Rafael Diaz, M.D., Marco Alings, Ph.D., Eva M. Lonn, M.D., Sonia S. Anand, M.D., Petr Widimsky, M.D., Masatsugu Hori, M.D., et al., for the COMPASS Investigators*

Weight Limitations

Why Is this Important?

PACKAGE INSERTS	No Indications with weight > 120 kg and BMI > 40 kg/m2
CHEST GUIDELINES	2018 Chest Presentation in San Antonio states, “DOAC use in the morbidly obese may be safe…and larger studies need to be performed.”
INTERNATIONAL SOCIETY ON THROMBOSIS AND HEMOSTASIS	Suggest against use of the DOACs in patients > 120 kg or BMI > 40 kg/m2

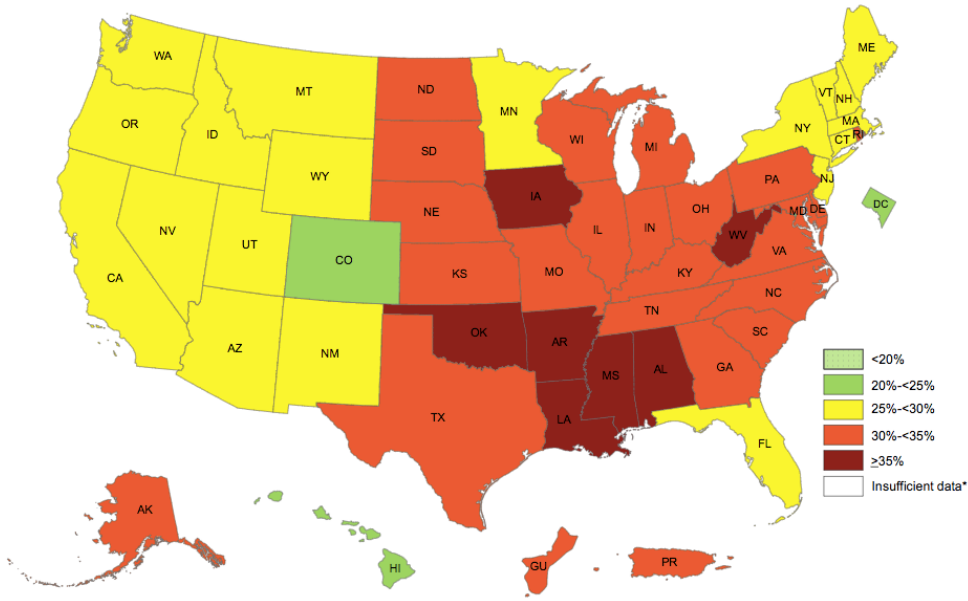


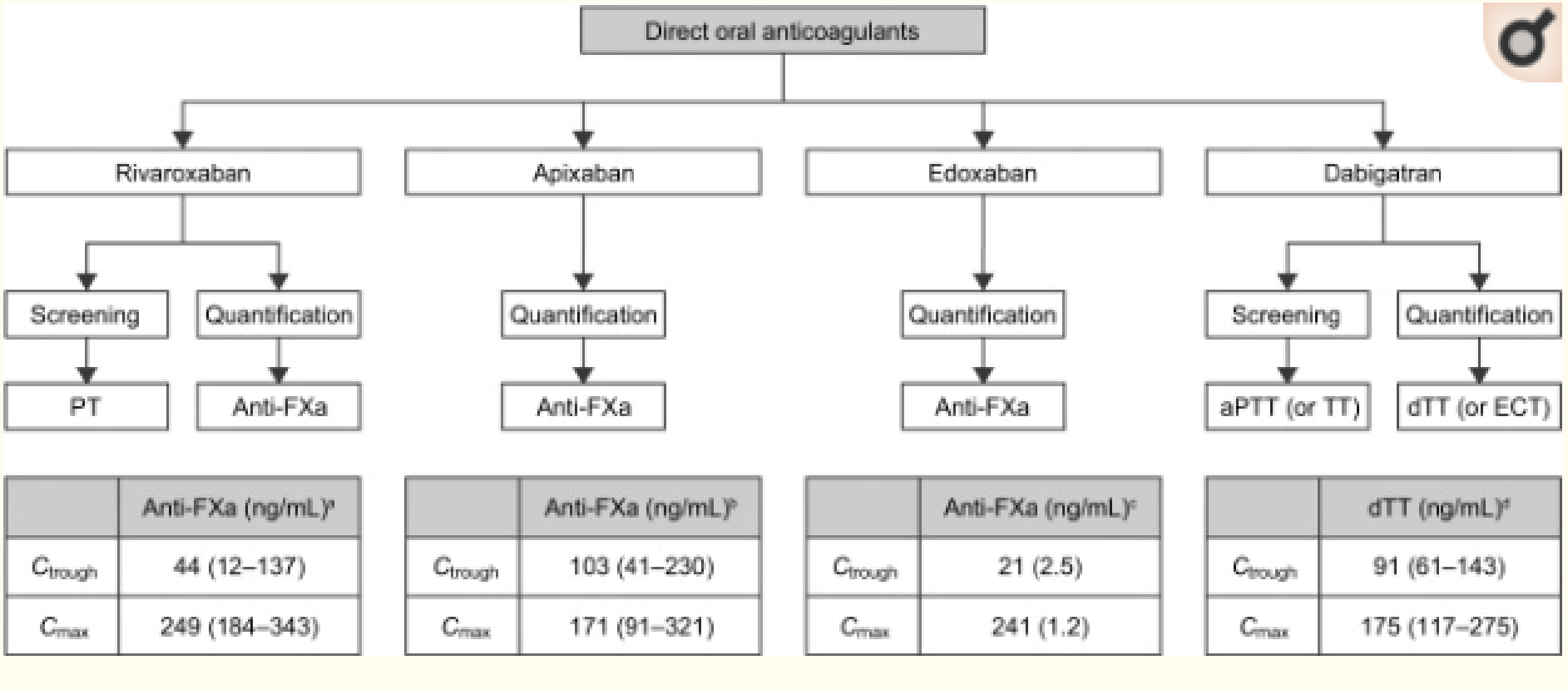
Table 5. Select Reported DOAC Plasma Concentrations			
Drug	**Patient Population**	**Peak (ng/mL)**	**Trough (ng/mL)**
Dabigatran 150 mg BID	AF & VTE (n=35)	45 – 487	18 – 206
Rivaroxaban 20 mg QD	DVT (n=870)	189 – 419	6 – 87
Apixaban 5 mg BID	VTE (n=unknown)	59 – 302	22 – 177
Edoxaban 60 mg QD	AF (n=234)	120 – 150	10 – 40

BID=twice daily; AF=atrial fibrillation; VTE=venous thromboembolism; QD=daily; DVT=deep vein thrombosis

IF YOU CHOOSE TO USE A DOAC

Can I Use Any Other Parameters to Measure Efficacy?

What About Other Measurements



	Anti-FXa (ng/mL)[a]
C_{trough}	44 (12–137)
C_{max}	249 (184–343)

	Anti-FXa (ng/mL)[b]
C_{trough}	103 (41–230)
C_{max}	171 (91–321)

	Anti-FXa (ng/mL)[c]
C_{trough}	21 (2.5)
C_{max}	241 (1.2)

	dTT (ng/mL)[d]
C_{trough}	91 (61–143)
C_{max}	175 (117–275)

What Happens if the Patient Bleeds?

FIGURE 1 Summary Graphic

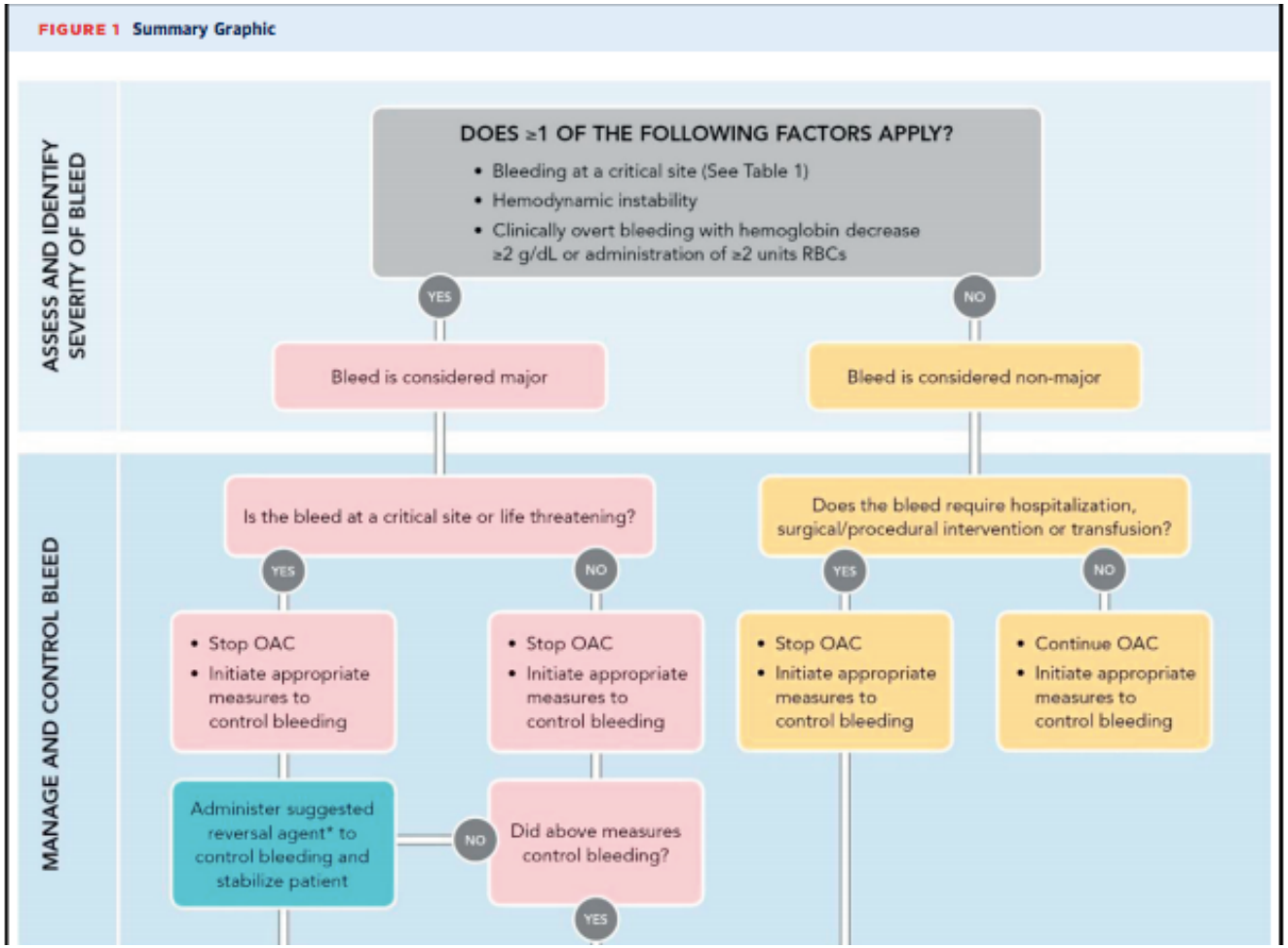
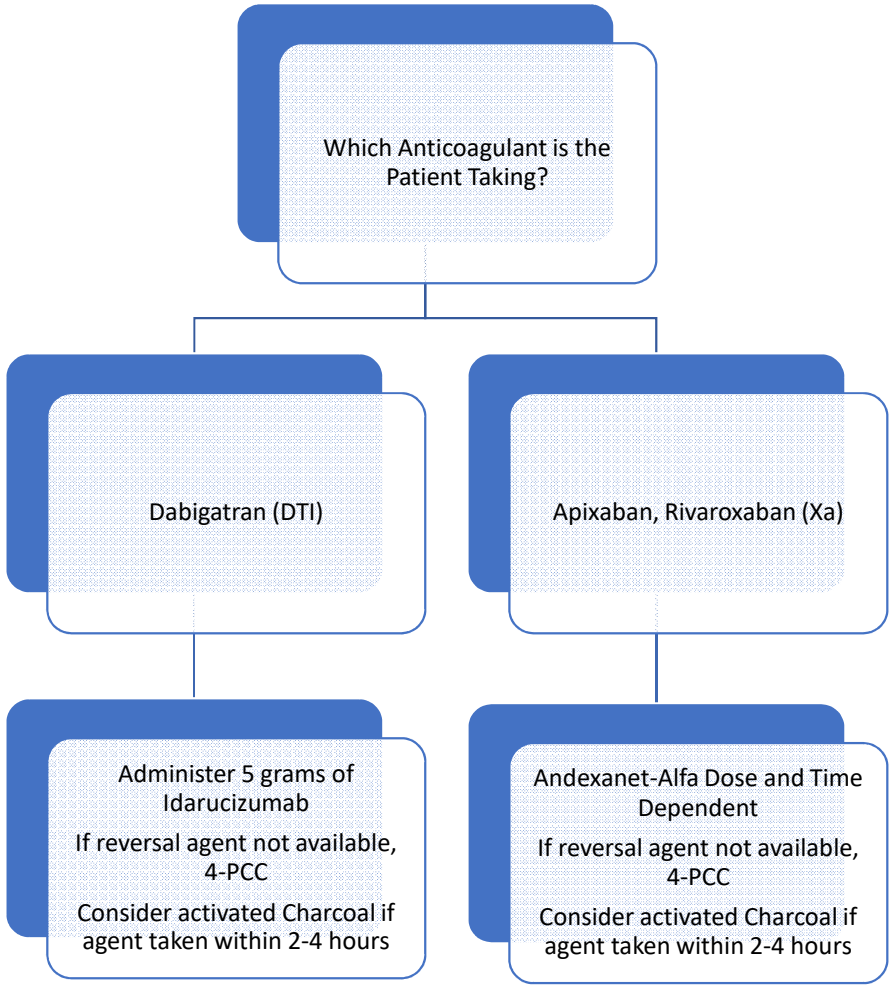


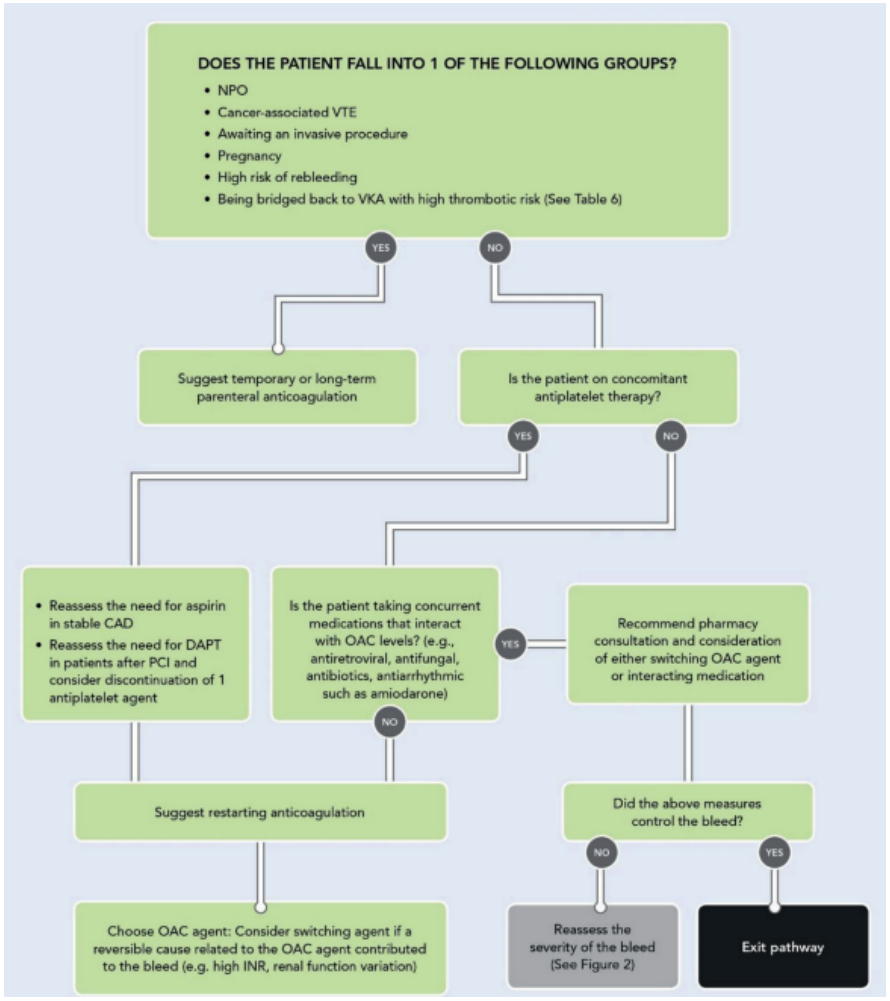
TABLE 1 Critical Site Bleeds

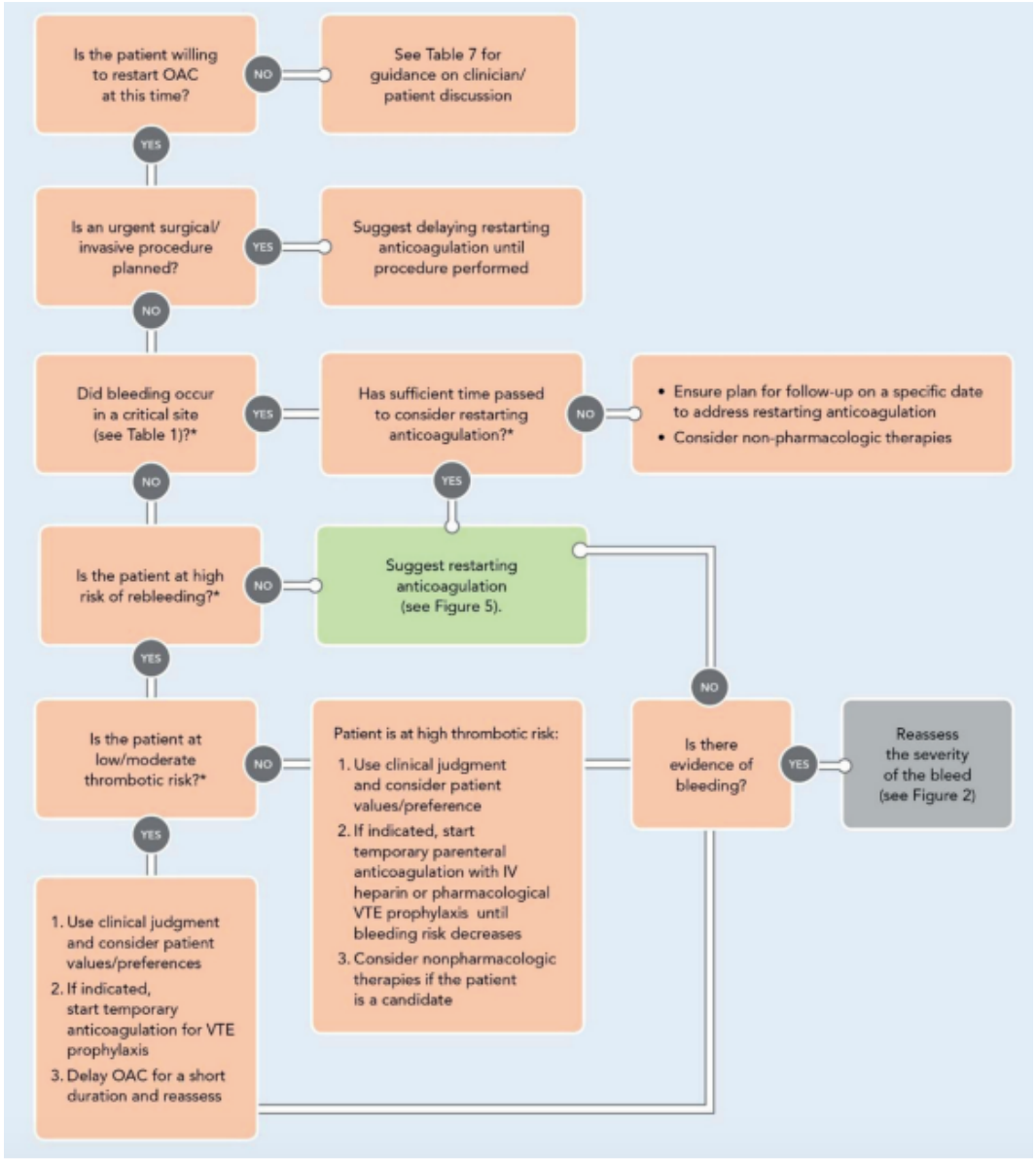
Type of Bleed	Initial Signs and Symptoms	Potential Consequences of Bleed
Intracranial hemorrhage: Includes intraparenchymal, subdural, epidural, and subarachnoid hemorrhages	**Unusually intense headache, emesis** **Neurological signs:** e.g., reduced LOC, vision changes, numbness, weakness, aphasia, ataxia, vertigo, seizures	Stupor or coma Permanent neurological deficit Death
Other central nervous system hemorrhage: Includes Intraocular, intra- or extra-axial spinal hemorrhages	**Intraocular:** monocular eye pain, vision changes, blindness **Spinal:** back pain, bilateral extremity weakness or numbness, bowel or bladder dysfunction, respiratory failure	**Intraocular:** permanent vision loss **Spinal:** permanent disability, paraplegia, quadriplegia, death
Pericardial tamponade	Shortness of breath, tachypnea Hypotension, jugular venous distension Tachycardia, muffled heart sounds, rub	Cardiogenic shock Death
Airway, including posterior epistaxis	**Airway:** hemoptysis, shortness of breath, hypoxia **Posterior epistaxis:** profuse epistaxis, hemoptysis, hypoxia, shortness of breath	Hypoxemic respiratory failure, Death
Hemothorax, intra-abdominal bleeding, and RPH	**Hemothorax:** tachypnea, tachycardia, hypotension **Intra-abdominal (nongastrointestinal):** abdominal pain, distension, hypotension, tachycardia **RPH:** Back/flank/hip pain, tachycardia, hypotension	**Hemothorax:** respiratory failure **RPH:** femoral neuropathy **All:** hypovolemic shock, death
Extremity bleeds: includes intramuscular and intra-articular bleeding	**Intramuscular:** pain, swelling, pallor, paresthesia, weakness, diminished pulse **Intra-articular:** joint pain, swelling, decreased range of motion	**Intramuscular:** compartment syndrome, paralysis, limb loss **Intra-articular:** irreversible joint damage

LOC = loss of consciousness; RPH = retroperitoneal hematoma.

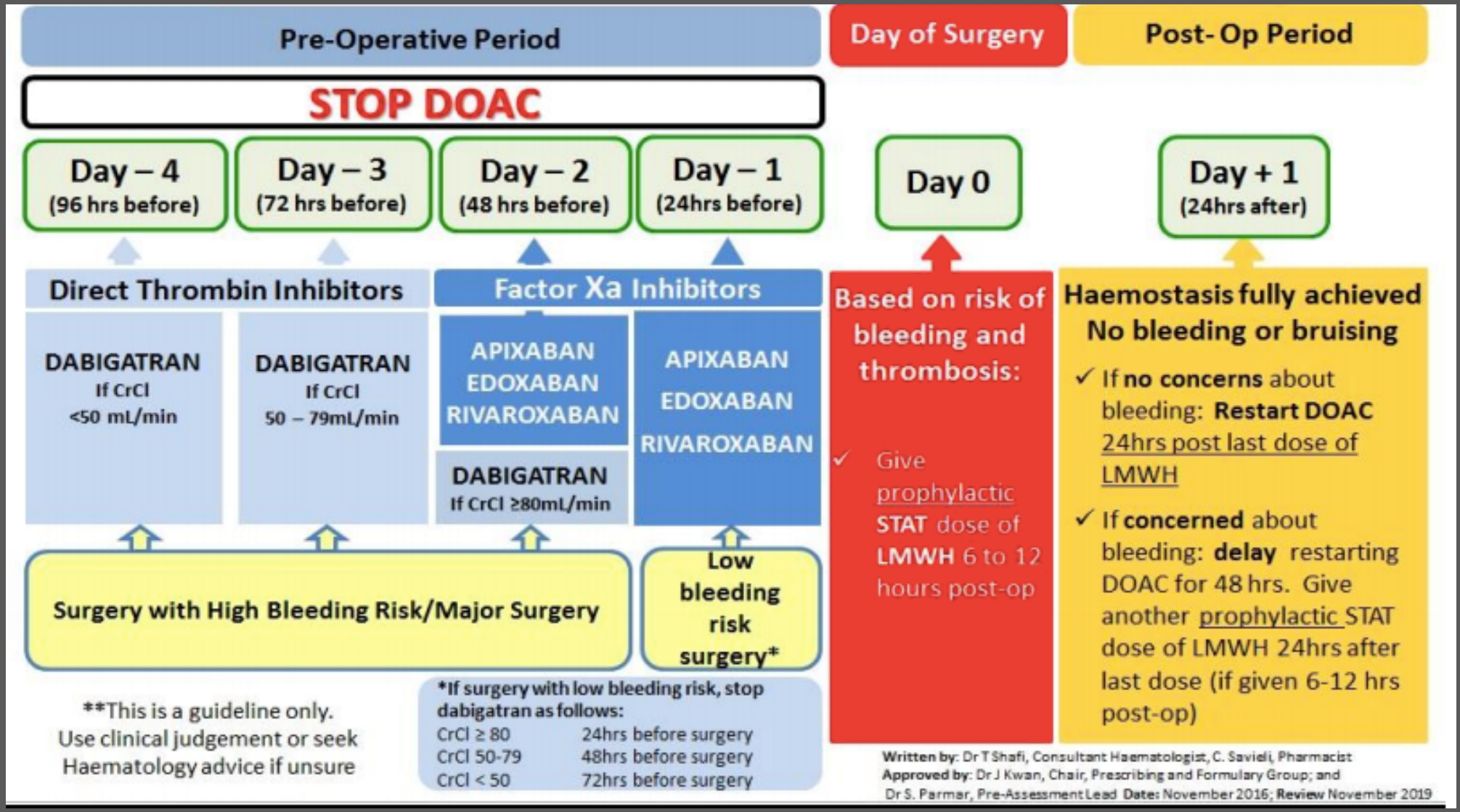

Which Anticoagulant is the Patient Taking?
Dabigatran (DTI)
Apixaban, Rivaroxaban (Xa)
Administer 5 grams of Idarucizumab
If reversal agent not available, 4-PCC
Consider activated Charcoal if agent taken within 2-4 hours
Andexanet-Alfa Dose and Time Dependent
If reversal agent not available, 4-PCC
Consider activated Charcoal if agent taken within 2-4 hours

The Patient Bled, Now What?


DOES THE PATIENT FALL INTO 1 OF THE FOLLOWING GROUPS?
• NPO
• Cancer-associated VTE
• Awaiting an invasive procedure
• Pregnancy
• High risk of rebleeding
• Being bridged back to VKA with high thrombotic risk (See Table 6)
YES
NO
Suggest temporary or long-term parenteral anticoagulation
Is the patient on concomitant antiplatelet therapy?
YES
NO
• Reassess the need for aspirin in stable CAD
• Reassess the need for DAPT in patients after PCI and consider discontinuation of 1 antiplatelet agent
Is the patient taking concurrent medications that interact with OAC levels? (e.g., antiretroviral, antifungal, antibiotics, antiarrhythmic such as amiodarone)
YES
Recommend pharmacy consultation and consideration of either switching OAC agent or interacting medication
NO
Suggest restarting anticoagulation
Did the above measures control the bleed?
NO
YES
Choose OAC agent: Consider switching agent if a reversible cause related to the OAC agent contributed to the bleed (e.g. high INR, renal function variation)
Reassess the severity of the bleed (See Figure 2)
Exit pathway


Is the patient willing to restart OAC at this time?
NO
See Table 7 for guidance on clinician/ patient discussion
YES
Is an urgent surgical/ invasive procedure planned?
YES
Suggest delaying restarting anticoagulation until procedure performed
NO
Did bleeding occur in a critical site (see Table 1)?*
YES
Has sufficient time passed to consider restarting anticoagulation?*
NO
• Ensure plan for follow-up on a specific date to address restarting anticoagulation
• Consider non-pharmacologic therapies
NO
YES
Is the patient at high risk of rebleeding?*
NO
Suggest restarting anticoagulation (see Figure 5).
YES
NO
Is the patient at low/moderate thrombotic risk?*
NO
Patient is at high thrombotic risk:
1. Use clinical judgment and consider patient values/preference
2. If indicated, start temporary parenteral anticoagulation with IV heparin or pharmacological VTE prophylaxis until bleeding risk decreases
3. Consider nonpharmacologic therapies if the patient is a candidate
Is there evidence of bleeding?
YES
Reassess the severity of the bleed (see Figure 2)
YES
1. Use clinical judgment and consider patient values/preferences
2. If indicated, start temporary anticoagulation for VTE prophylaxis
3. Delay OAC for a short duration and reassess

Peri-Operative Management of DOAC's


Pre-Operative Period
Day of Surgery
Post- Op Period
STOP DOAC
Day – 4
(96 hrs before)
Day – 3
(72 hrs before)
Day – 2
(48 hrs before)
Day – 1
(24hrs before)
Day 0
Day + 1
(24hrs after)
Direct Thrombin Inhibitors
Factor Xa Inhibitors
DABIGATRAN
If CrCl
<50 mL/min
DABIGATRAN
If CrCl
50 – 79mL/min
APIXABAN
EDOXABAN
RIVAROXABAN
DABIGATRAN
If CrCl ≥80mL/min
APIXABAN
EDOXABAN
RIVAROXABAN
Surgery with High Bleeding Risk/Major Surgery
Low bleeding risk surgery*
Based on risk of bleeding and thrombosis:
✓ Give prophylactic STAT dose of LMWH 6 to 12 hours post-op
Haemostasis fully achieved
No bleeding or bruising
✓ If no concerns about bleeding: Restart DOAC 24hrs post last dose of LMWH
✓ If concerned about bleeding: delay restarting DOAC for 48 hrs. Give another prophylactic STAT dose of LMWH 24hrs after last dose (if given 6-12 hrs post-op)
**This is a guideline only.
Use clinical judgement or seek Haematology advice if unsure
*If surgery with low bleeding risk, stop dabigatran as follows:
CrCl ≥ 80 24hrs before surgery
CrCl 50-79 48hrs before surgery
CrCl < 50 72hrs before surgery
Written by: Dr T Shafi, Consultant Haematologist, C. Savieli, Pharmacist
Approved by: Dr J Kwan, Chair, Prescribing and Formulary Group; and
Dr S. Parmar, Pre-Assessment Lead Date: November 2016; Review November 2019

Switching Anticoagulants

Vitamin K Antagonists		
Warfarin	heparin, argatroban, or bivalirudin infusion	■ Stop warfarin ■ Initiate infusion when INR < 2
	LMWH/subcutaneous agents (enoxaparin, fondaparinux, dalteparin)	■ Stop warfarin ■ Initiate agent when INR is 2
	dabigatran	■ Stop warfarin ■ Start dabigatran when INR < 2
	rivaroxaban	■ Stop warfarin ■ Start rivaroxaban when INR < 3
	apixaban	■ Stop warfarin ■ Start apixaban when INR < 2
	edoxaban	■ Stop warfarin ■ Start edoxaban when INR ≤ 2.5

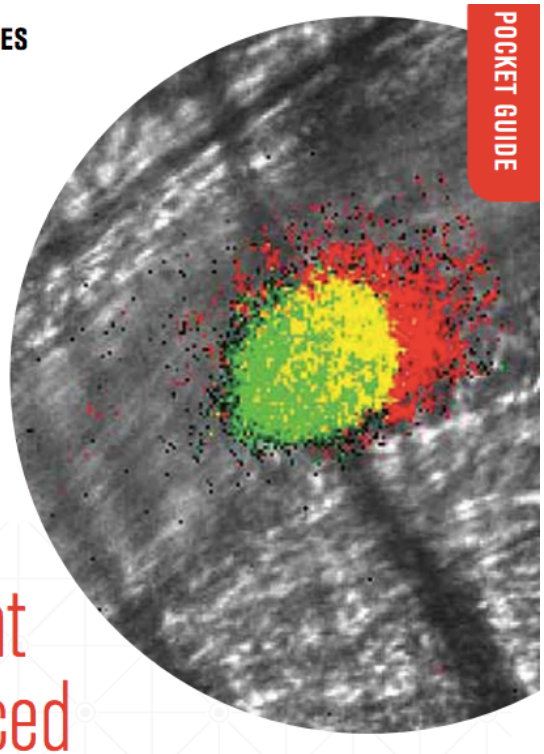
Heparinoids/SC Agents, *continued*		
LMWH/ subcutaneous (Enoxaparin, Dalteparin, Fondaparinux)	heparin infusion	■ Stop LMWH/SC agent ■ Start heparin infusion at time when next dose of LMWH/SC agent is due
	dabigatran	■ Stop LMWH/SC agent ■ Start DOAC ≤2 hours prior to the time of the next scheduled dose of LMWH/SC agent
	rivaroxaban	
	apixaban	■ Stop LMWH/SC agent ■ Start DOAC at time when next dose of LMWH/SC agent is due
	edoxaban	
	warfarin	■ Begin when clinically indicated ■ Can overlap therapy to achieve goal INR
	argatroban/bivalirudin infusion	■ Stop LMWH/SC agent ■ Start bivalirudin infusion at time when next dose of LMWH/SC agent is due

Heparinoids/SC Agents		
Heparin Infusion	LMWH, subcutaneous	■ Stop heparin ■ Start agent at time heparin infusion is stopped ■ If more conservative strategy is preferred, start LMWH/SC agent 2 hours after heparin infusion is stopped
	dabigatran	■ Stop heparin ■ Start DOAC at the time of stopping heparin infusion
	apixaban	
	rivaroxaban	
	edoxaban	■ Stop heparin ■ Start edoxaban 4 hours after stopping heparin infusion
	warfarin	■ Begin when clinically indicated ■ Can overlap therapy to achieve therapeutic INR ■ Heparin dosage should decrease as INR increases
	argatroban/bivalirudin infusion	■ Stop heparin ■ Start infusion immediately after heparin infusion is stopped.

Heparin Induced Thrombocytopenia

ASH CLINICAL PRACTICE GUIDELINES
VENOUS THROMBOEMBOLISM (VTE)

POCKET GUIDE



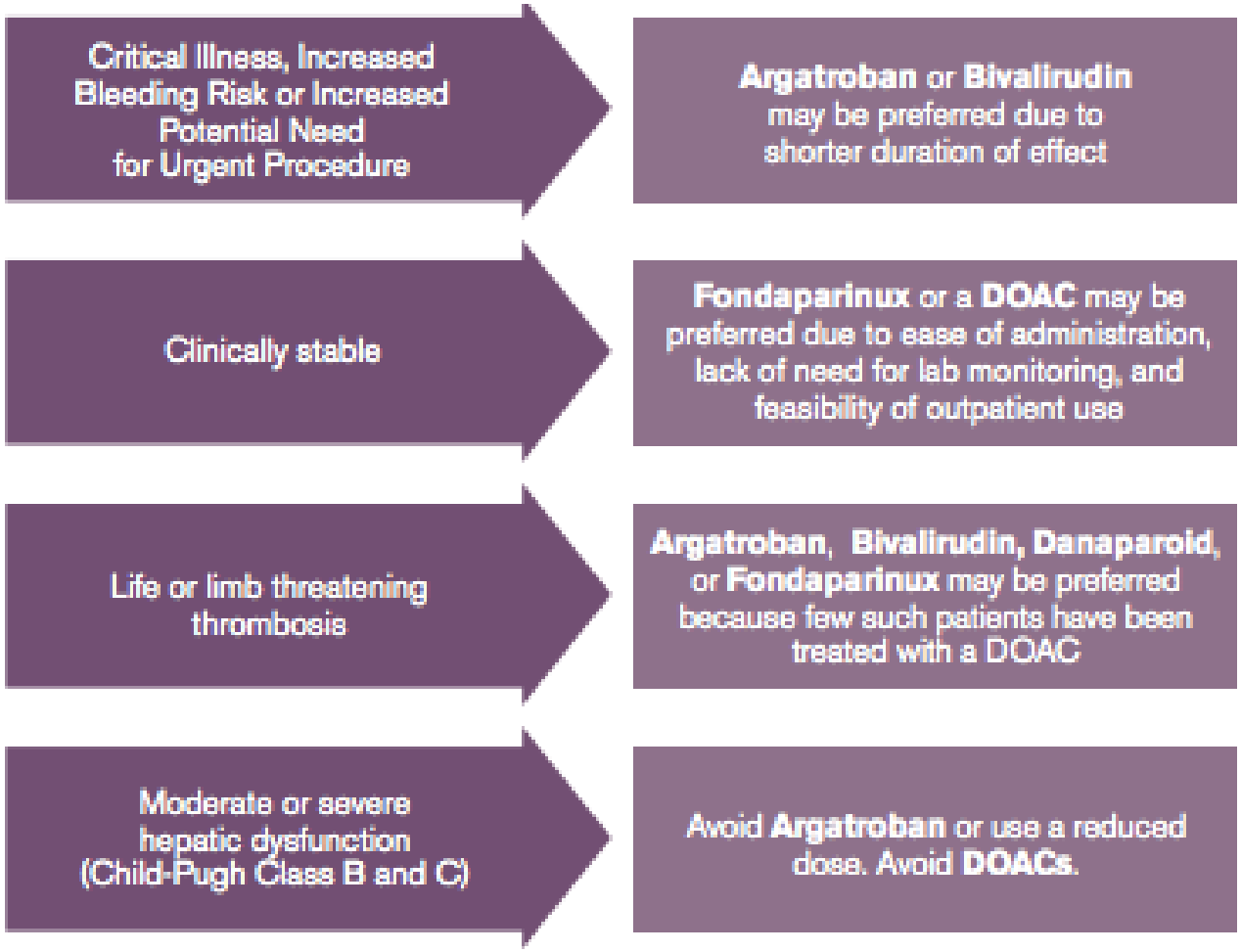
Diagnosis and Management of Heparin-Induced Thrombocytopenia (HIT)

A POCKET GUIDE FOR THE CLINICIAN

DECEMBER 2018

THE 4Ts: A CLINICAL PROBABILITY SCORING SYSTEM[1,2]

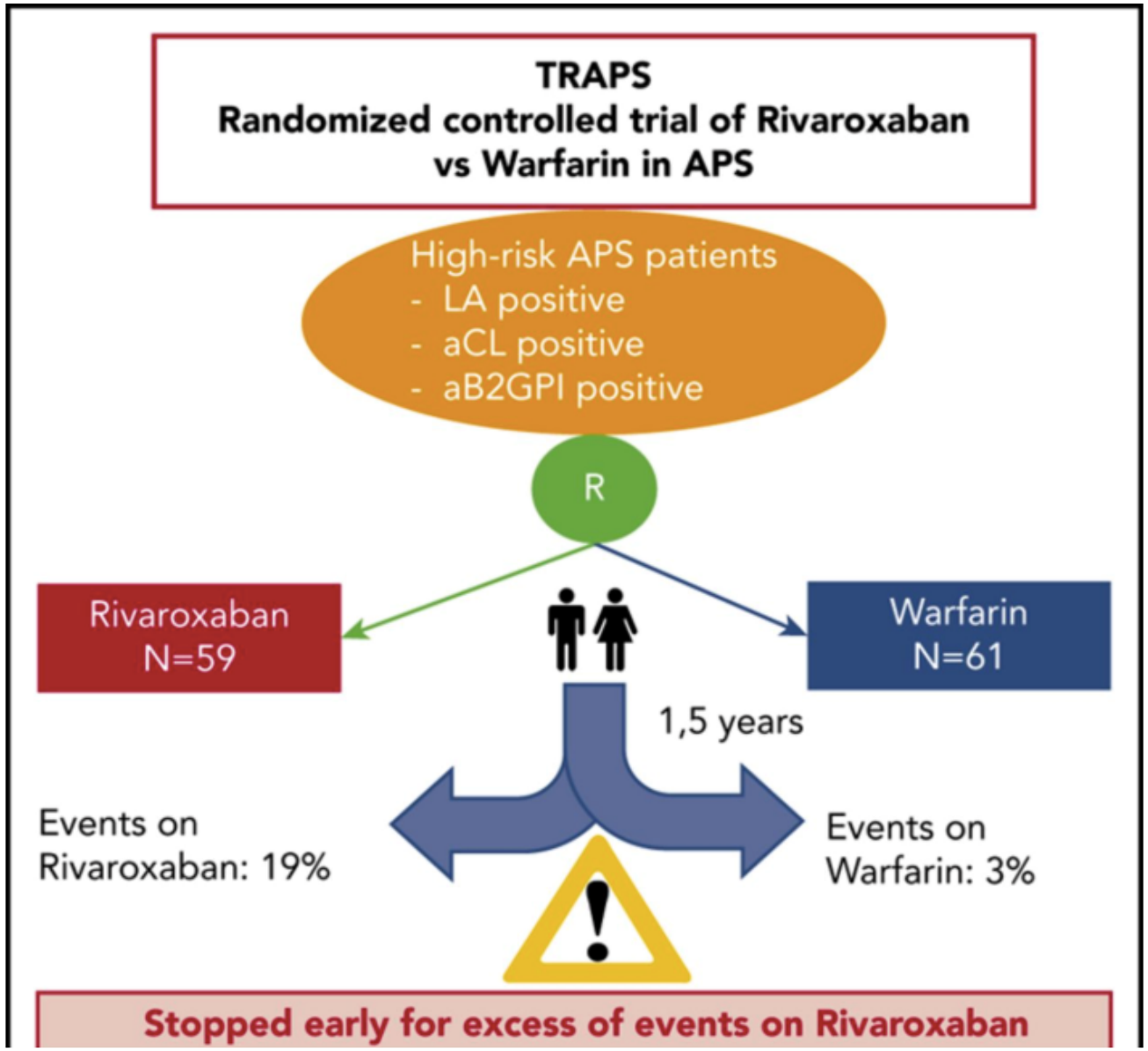
4Ts	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count fall > 50% **and** platelet nadir ≥20 x 10^9/L	Platelet count fall 30-50% **or** platelet nadir 10-19 x 10^9/L	Platelet count fall < 30% **or** platelet nadir < 10 x 10^9/L
Timing of platelet count fall	Clear onset between days 5-14 **or** platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-14 fall, but not clear (e.g., missing platelet counts) **or** onset after day 14 **or** fall ≤ 1 day (prior heparin exposure 30-100 days ago)	Platelet count fall ≤4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus; adrenal hemorrhage	Progressive or recurrent thrombosis; Non-necrotizing (erythematous) skin lesions; Suspected thrombosis (not confirmed)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite


Critical Illness, Increased Bleeding Risk or Increased Potential Need for Urgent Procedure
Argatroban or Bivalirudin may be preferred due to shorter duration of effect
Clinically stable
Fondaparinux or a DOAC may be preferred due to ease of administration, lack of need for lab monitoring, and feasibility of outpatient use
Life or limb threatening thrombosis
Argatroban, Bivalirudin, Danaparoid, or Fondaparinux may be preferred because few such patients have been treated with a DOAC
Moderate or severe hepatic dysfunction (Child-Pugh Class B and C)
Avoid Argatroban or use a reduced dose. Avoid DOACs.

What About Patients with Antiphospholipid Syndrome?

In a Nutshell

- Patients with triple positive serology randomized to two groups
  - INR target 2.5
  - Rivaroxaban 20 mg daily
- Outcome
  - Increased risk of arterial thromboembolism and bleeding in the rivaroxaban arm



What About Patients with Mechanical Heart Valves?

ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D., Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D., Michael J. Mack, M.D., Jon Blatchford, C.Stat., Kevin Devenny, B.Sc., Jeffrey Friedman, M.D., Kelly Guiver, M.Sc., Ruth Harper, Ph.D., Yasser Khder, M.D., et al., for the RE-ALIGN Investigators*

What About Patients with End Stage Renal Disease?

Circulation

ORIGINAL RESEARCH ARTICLE

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

What About Patients with Liver Disease

Table 8 **Calculation of the Child-Turcotte-Pugh score and use of NOACs in hepatic insufficiency**

Parameters	1 point	2 points	3 points
Encephalopathy	No	Grade 1–2 (suppressed with medication)	Grade 3–4 (refractory/chronic)
Ascites	No	Mild (diuretic-responsive)	Moderate–severe (diuretic-refractory)
Bilirubin	<2 mg/dL	2–3 mg/dL	>3 mg/dL
	<34 μmol/L	34–50 μmol/L	>50 μmol/L
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
	>35 g/L	28–35 g/L	<28 g/dL
INR	<1.7	1.71–2.30	>2.30

Child–Pugh category	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
A (5–6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7–9 points)	Use with caution	Use cautiously	Use cautiously	Do not use
C (10–15 points)	Do not use	Do not use	Do not use	Do not use

So How Do I Decide?

	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN	BETRIXABAN
Non-Valvular Atrial Fibrillation	✓	✓	✓	✓	
VTE Prophylaxis THR VTE Prophylaxis TKR	✓	✓ ✓	✓ ✓		
VTE Acute VTE Extended	✓ ✓	✓ ✓	✓ ✓	✓	
MACE in CAD/PAD		✓			
Extended Medical VTE Prophylaxis					✓

FDA Approved Indications for DOAC's

Characteristic	Drug Choice	Rationale
All Oral (no lead in parenteral)	Rivaroxaban or Apixaban	Dabigatran and Edoxaban need parenteral lead in for VTE
Dyspepsia	Rivaroxaban, apixaban or edoxaban	Dyspepsia in 10% of patients taking dabigatran
Recent GI bleeding	Apixaban	More bleeding with others
Recent ACS	Rivaroxaban, apixaban or edoxaban	Small MI signal with dabigatran
Compliance with BID dosing	Rivaroxaban or edoxaban	Apixaban and dabigatran with BID dosing
Impaired renal function	Rivaroxaban, edoxaban, apixaban	Less affected by renal function
ESRD	Apixaban?	Less data to support the others
CrCl > 90	Apixaban, rivaroxaban, dabigatran	Avoid edoxaban
Feeding tube	Apixaban, rivaroxaban	Avoid dabigatran
Issues with taking with a meal	Dabigatran, apixaban, edoxaban	Rivaroxaban must be taken with food
Issues with taking capsules	Rivaroxaban, apixaban, edoxaban	Avoid dabigatran if capsule broken

DOAC administration instructions:

Dabigatran (Pradaxa®)	• Swallow whole with or without food • Do not chew or open capsule • Keep in original packaging • Do not transfer capsule to a dose administration aid	
Apixaban (Eliquis®)	• Swallow whole with or without food • Can be used in dose administration aids	
Rivaroxaban (Xarelto®)	• 10 mg tablet may be taken with or without food • 15 mg and 20 mg tablet should be taken **with food** • Can be used in dose administration aids	

DOAC Initiation Checklist

Task	Comments
Establish appropriate dose based on anticoagulant selected, indication and patient factors such as renal function.	See FDA approved anticoagulants for indication and dosing information.
Evaluate for medication interactions that may necessitate DOAC dose adjustment.	See DOAC drug interaction table
Evaluate renal function (Cockcroft-Gault equation to estimate CrCl) prior to DOAC initiation[1] and establish a baseline for CBC and liver function[2]	Use actual body weight in Cockcroft-Gault equation. Online calculator available at: http://touchcalc.com/calculators/cg
Establish clear expectations for length of treatment based on indication.	
Consider co-administration with a proton-pump inhibitor.[2]	Proton-pump inhibitors do not appear to impact DOAC efficacy based on the clinical trials and may be helpful in reducing dyspepsia (dabigatran) and the risk of gastrointestinal bleeding[3]
If converting from warfarin, see warfarin to DOAC conversion instructions.	
Provide comprehensive patient education.	See DOAC education topic checklist • If rivaroxaban, make sure patient knows to take with the largest meal of the day (typically the evening meal) • If dabigatran, make sure patient knows to take with a full glass of water, to store in the original package, and to not crush.
Establish follow-up plan.	Follow-up plan should include: • Who will the patient follow-up with? • How often will follow-up occur? • When is the next follow-up?