UPMC LIFE CHANGING MEDICINE

Direct Oral Anticoagulants (DOACs): Everything You Ever Wanted To Know

Objectives

- To know the indications for and dosing of DOACs in VTE
- To understand the PK and PD properties of DOACs
- To recognize the effects of drug interactions on DOACs
- To identify the role of laboratory monitoring with DOACs
- To know how to perform anticoagulation conversion and manage periprocedural anticoagulation with DOACs
- To understand the role of DOAC use in special populations (unusual sites of VTE, thrombophilias, cancer, women, and obesity)

Outline

- Mechanism of action
- Indications and dosing (VTE-related)
- Dosage adjustments (VTE-related)
- PD and PK
- Drug interactions
- Laboratory monitoring
- Anticoagulation reversal
- Anticoagulation conversion
- Periprocedural anticoagulation

Outline

- Special populations
  - unusual sites of VTE
  - thrombophilias
  - cancer
  - women
  - obesity

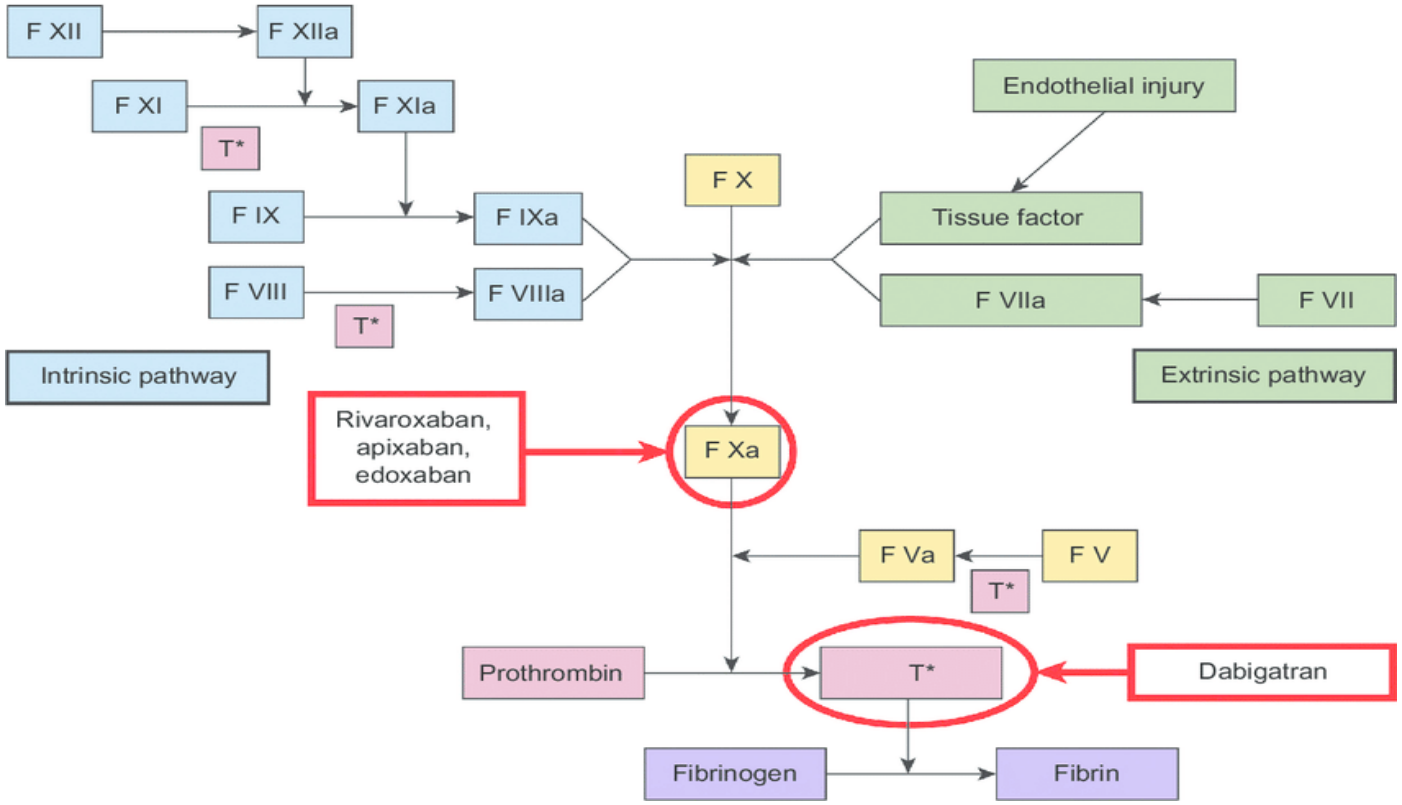
DOACs

- Apixaban
- Dabigatran
- Edoxaban
- Rivaroxaban

Mechanism of action

- Apixaban, rivaroxaban, and edoxaban
  - direct factor Xa inhibitor
- Dabigatran
  - direct thrombin inhibitor

Coagulation Cascade



Akinboboye O. Use of oral anticoagulants in African-American and Caucasian patients with atrial fibrillation: is there a treatment disparity? *Journal of Multidisciplinary Healthcare.* 2015;8:217-228.

UPMC LIFE CHANGING MEDICINE

Apixaban Indications and Dosing

- Treatment of DVT and PE *(AMPLIFY)*
  - 10 mg bid x 7 days then 5 mg bid
- Reduction in the risk of recurrence of DVT and PE *(AMPLIFY-EXT)*
  - 2.5 mg bid following initial 6 months of therapy
- Prophylaxis against DVT and PE following hip and knee replacement *(ADVANCE)*
  - 2.5 mg bid x 12 days (knee) or 35 days (hip)

Rivaroxaban Indications and Dosing

- Treatment of DVT and PE *(EINSTEIN DVT and PE)*
  - 15 mg bid x 21 days then 20 mg daily with food
- Reduction in the risk of recurrence of DVT and PE *(EINSTEIN CHOICE)*
  - 10 mg daily following initial 6 months of therapy with or without food

Rivaroxaban Indications and Dosing

- Prophylaxis against DVT and PE in acutely ill hospitalized patients not at high risk for bleeding *(MAGELLAN AND MARINER)*
  - 10 mg daily x 31-39 days with or without food
- Prophylaxis against DVT and PE following hip and knee replacement *(RECORD)*
  - 10 mg daily x 12 days (knee) or 35 days (hip) with or without food

Edoxaban Indications and Dosing

- Treatment of DVT and PE *(Hokusai-VTE)*
  - 60 mg daily after 5-10 days of parenteral anticoagulation

Dabigatran Indications and Dosing

- Treatment of DVT and PE *(RE-COVER)*
  - 150 mg bid after 5-10 days of parenteral anticoagulation
- Reduction in the risk of recurrence of DVT and PE *(RE-MEDY and RE-SONATE)*
  - 150 mg bid following initial 3 months of therapy
- Prophylaxis against DVT and PE following hip replacement *(RE-NOVATE)*
  - 110 mg POD 1 then 220 mg daily x 28-55 days

Apixaban Dosage Adjustments

- Renal impairment
  - no dosage adjustment for treatment of DVT and PE
    - reduce dose to 2.5 mg bid for the reduction of risk of stroke and systemic embolism in nonvalvular AF if 2 of the following are present: age >=80, weight <=60 kg, or Cr >=1.5 mg/dl
  - paucity of data in patients with severe renal failure or on HD
    - clinical trials excluded patients with Cr >2.5 mg/dl or CrCl <25 ml/min
    - FDA indication in this population was based on single dose PK/PD study measuring systemic drug exposure pre/post HD

Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. *Journal of Clinical Pharmacology.* 2016;56: 628-636.

Apixaban Dosage Adjustments

- Hepatic impairment
  - avoid use in severe hepatic impairment (Child-Pugh class C)

Rivaroxaban Dosage Adjustments

- Renal impairment
  - avoid use if CrCl <30 ml/min
- Hepatic impairment
  - avoid use in moderate and severe hepatic impairment (Child-Pugh class B and C)

Edoxaban Dosage Adjustments

- Renal impairment
  - reduce dose to 30 mg daily if CrCl 15-50 ml/min
  - avoid use if CrCl<15 ml/min
- Hepatic impairment
  - avoid use in moderate and severe hepatic impairment (Child-Pugh class B and C)
- Weight
  - reduce dose to 30 mg daily if weight <=60 kg

Dabigatran Dosage Adjustments

- Renal impairment
  - avoid use if CrCl <30 ml/min
- Hepatic impairment
  - no dosage adjustment

PD and PK

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Bioavailability	~50%	20 mg dose: ~66% (fasting; increased with food) 10 mg dose: 80-100%	62%	3-7%
Tmax	3-4 hrs	2-4 hrs	1-2 hrs	1-3 hrs
Half-life	8-13 hrs	7-13 hrs	10-14 hrs	12-14 hrs
Protein-binding	~87%	~92-95%	55%	35%
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic
Renal Elimination	25%	67%	50%	80%

Dubois V, Dincq AS, Douxfils J, et al. Perioperative management of patients on direct oral anticoagulants. *Thrombosis Journal.* 2017;15:14.

Drug Interactions

	Drug class	Package insert recommendations
Apixaban	Combined P-gp inhibitor and strong CYP3A4 inhibitor Combined P-gp inducer and strong CYP3A4 inducer	Reduce dose to 2.5 mg bid Avoid use
Rivaroxaban	Combined P-gp inhibitor and strong CYP3A4 inhibitor Combined P-gp inducer and strong CYP3A4 inducer	Avoid use Avoid use
Edoxaban	P-gp inhibitor P-gp inducer	No dose adjustment Avoid use with rifampin
Dabigatran	P-gp inhibitor P-gp inducer	If CrCl 30-50 ml/min, consider reducing dose to 75 mg bid with dronedarone or ketoconazole Avoid use with rifampin

Eliquis [package inset]. New York, NY. Bristol-Myers Squibb; 2012.

Drug Interactions

P-gp	CYP3A4
Inhibitors	**Strong inhibitors**
Antihypertensive/heart rate control	Anti-infectives
Verapamil	Clarithromycin
Dronedarone	Telithromycin
Anti-infectives	Itraconazole
Itraconazole	Ketoconazole
Ketoconazole	Antidepressants
Voriconazole	Nefazodone
Posaconazole	Protease inhibitors
Clarithromycin	Atazanavir
	Darunavir
	Indinavir
	Lopinavir
	Nelfinavir
	Ritonavir
	Saquinavir
	Tipranavir
Inducers	**Strong inducers**
Anti-infectives	Anti-infectives
Rifampin	Rifampin
Anticonvulsants	Anticonvulsants
Carbamazepine	Carbamazepine
Phenytoin	Phenytoin
Barbiturates	Barbiturates
Natural products	Natural products
St. John's wort	St. John's wort

Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Advances.* 2018;2:3257-3291.

Drug Interactions

- ASH recommendations
  - suggest use of an alternative anticoagulant when using a P-gp and/or strong CYP3A4 inhibitor/inducer *(my clinical practice)*
    - when use of an alternative anticoagulant is not an option then consider laboratory monitoring *(my clinical practice)*

Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Advances.* 2018;2:3257-3291.

Laboratory Monitoring

- Routine laboratory monitoring not necessary (except when it is)
  - major bleeding
  - emergent surgery
  - renal impairment
  - drug interactions
  - impaired absorption
  - extremes in weight

Laboratory Monitoring

	Laboratory tests
Dabigatran	**aPTT -** Normal aPTT does not exclude the presence of dabigatran. **Thrombin time (TT) -** Normal TT excludes the presence of dabigatran. **Dilute TT and ecarin based assays -** Based on plasma concentration estimation.
Apixaban **Rivaroxaban** **Edoxaban**	**PT -** Normal PT does not exclude the presence of drug (PT most sensitive to rivaroxaban and least sensitive to apixaban) **Chromogenic anti-Xa assay -** Based on plasma concentration estimation. Each assay is calibrated to the specific drug.

Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants; a practical guide for clinicians. *JTH.* 2017;16:209-219.

Laboratory Monitoring

Table 1. Steady-state plasma DOAC concentrations

Drug	Dose, mg	Trough concentration, ng/mL		Peak concentration, ng/mL	
		Median	5th to 95th percentile	Median	5th to 95th percentile
Dabigatran[2]	150 BID	90	31-225	184	64-443
Rivaroxaban[3]	20 daily	26	6-87	270	189-419
Apixaban[4]	5 BID	103	41-230	171	91-321
Edoxaban[5]	60 daily	22	10-40*	170	120-250*

* Interquartile range.

- important to note that there is no established “therapeutic range” for DOACs

Cuker A and Siegal D. Monitoring and reversal of direct oral anticoagulants. *ASH Education Program.* 2015:117-124.

Laboratory Monitoring

Table 2 Impact of direct oral anticoagulants (DOACS) on select special coagulation assays

Assay	Anti-FIIa DOAC	Anti-FXa DOAC
Clauss fibrinogen	May be falsely decreased	No effect
PT mixing study	May demonstrate incomplete correction	May demonstrate incomplete correction
APTT mixing study	May demonstrate incomplete correction	May demonstrate incomplete correction
One stage APTT-based factor assays (FVIII, FIX, FXI, FXII)	May demonstrate false decrease in factor activity	May demonstrate false decrease in factor activity
One stage PT-based factor assays (FII, FV, FVII, FX)	May demonstrate false decrease in factor activity	May demonstrate false decrease in factor activity
Chromogenic FVIII activity	No effect	May demonstrate false decrease in activity
Bethesda assay	False inhibitor present	False inhibitor present
AT activity: thrombin substrate	May demonstrate false increase in AT activity; may mask AT deficiency	No effect
AT activity: FXa substrate	No effect	May demonstrate false increase in AT activity; may mask AT deficiency
PC activity: clot-based	May demonstrate false increase in PC activity; may mask PC deficiency	May demonstrate false increase in PC activity; may mask PC deficiency
PS activity: chromogenic	No effect	No effect
PS activity: clot-based	May demonstrate false increase in PS activity; may mask PS deficiency	May demonstrate false increase in PS activity; may mask PS deficiency
PS activity: ELISA-based or LIA-based	No effect	No effect
LA testing	**Possible to misclassify as LA present**	**Possible to misclassify as LA present**
Activated PC resistance assay	Falsely increased ratio; possible to misclassify as FV Leiden mutation absent	Falsely increased ratio; possible to misclassify as FV Leiden mutation absent

Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants; a practical guide for clinicians. *JTH.* 2017;16:209-219.

UPMC Oral Anticoagulant Reversal Algorithm

Immediate anticoagulant reversal indicated for:

Intracranial hemorrhage (ICH)

patient taking

Apixaban OR Rivaroxaban

Andexxa (Coagulation factor Xa) — OR — **Kcentra (4F-PCC) 5000 units** Repeat dose not permitted

Andexxa dosing dependent on:
1. Specific drug & dose being reversed
2. Time elapsed from last dose

See Andexxa PowerPlan for full dosing details
Repeat dosing not recommended

Lower dose may be considered in low body weight patients (3000 units suggested)

OR

Edoxaban

Kcentra (4F-PCC) 5000 units Repeat dose not permitted — OR — **Profilnine 50 units/kg** (max. 5000 units) + NovoSeven (rFVIIa) 1 mg

(alternate reserved for patients with HIT)

Urgent/emergent invasive procedure OR non-ICH bleeding

patient taking

Apixaban, Edoxaban, OR Rivaroxaban

Kcentra (4F-PCC) 2000 units Repeat dose available, if hemostasis not achieved

Repeat Kcentra Dose
(with attending physician approval in setting of ongoing, life-threatening bleeding)
< 60 kg: 500 units | 60-69 kg: 1000 units | 70-79 kg: 1500 units
80-89 kg: 2000 units| 90-99 kg: 2500 units | ≥ 100 kg: 3000 units

OR **Profilnine 50 units/kg** (max. 5000 units) + NovoSeven (rFVIIa) 1 mg

Combination reversal with Andexxa, Kcentra and/or Profilnine not recommended

Dabigatran

Praxbind (Idarucizumab) **2.5 g dose x 2 (5 g total)** no more than 15 minutes apart

OR

(alternate) **Hemodialysis +/- NovoSeven (rFVIIa) 40 mcg/kg**

Dabigatran

Warfarin

Vitamin K 10 mg IV — PLUS — **Kcentra, dosed by INR**

- INR 1.5 - < 4 → 25 units/kg (max. 2500)
- INR 4 - 6 → 35 units/kg (max. 3500)
- INR > 6 → 50 units/kg (max. 5000)
- INR unknown → 3000 units

OR **Profilnine +** NovoSeven (rFVIIa) 1 mg

(alternate reserved for patients with HIT)

- INR < 5 → 25 units/kg (max. 2500)
- INR ≥ 5 or unknown → 50 units/kg (max. 5000)

OR **Kcentra (4F-PCC) 1500 units** Repeat dose available, if hemostasis not achieved

Repeat Kcentra Dose
(with attending physician approval in setting of ongoing, life-threatening bleeding **and** repeat INR > 2)
500 – 1000 units

Warfarin

*If dose ingested within previous two hours, may also administer activated charcoal 25 g - 100 g

Reviewed and approved by Anticoagulation Subcommittee of System P&T 1/2022

Anticoagulation Reversal

- Idarucizumab
  - mechanism of action
    - monoclonal antibody fragment that binds dabigatran
  - PD/PK
    - onset of action <5 min and half-life 45 min
  - dosing
    - 5 g IV (administered as two separate 2.5 g doses more than 15 min apart)
      - may require 2nd dose should bleeding reoccur with evidence of persistent drug effect (due to drug redistribution)

Pollack CV, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal: full cohort analysis. *NEJM.* 2017;377:431-441.

Anticoagulation Reversal

- Andexanet
  - mechanism of action
    - inactivated recombinant FXa protein that binds to and sequesters FXa inhibitors
    - inhibits tissue factor pathway inhibitor (TFPI)
      - promotes tissue factor mediated thrombin generation
  - PD/PK
    - onset of action 2-5 min and half-life 30-60 min

Connolly SJ, Milling TJ, Eikelboom JW, eta. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *NEJM.* 2016;375:1131-1141.

Anticoagulation Reversal

– dosing

TABLE 2 Dosing and administration of andexanet alfa according to the United States Food and Drug Administration package insert

Drug	Last Dose	Time from last dose: <8 h or unknown	Time from last dose: ≥8 h
Rivaroxaban	≤10 mg	Low dose[a]	Low dose[a]
	>10 mg or unknown	High dose[b]	
Apixaban	≤5 mg	Low dose[a]	
	>5 mg or unknown	High dose[b]	

[a]Initial 400 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 4 mg/min for up to 120 min.
[b]Initial 800 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 8 mg/min for up to 120 min.

Very expensive - high dose $48,400!

  - no data regarding safety of repeat dosing
– TFPI inhibition may increase risk of thrombosis
  - 10% of patients at 30 days in *ANNEXA-4* experienced thrombosis
    – 4.2% of patients at 30 days in *RE-VERSE AD* (idarucizumab) experienced thrombosis

Cuker A, Burnett A. Triller D, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. AJH. 2019;94:697-709.

Anticoagulant Conversion

- Warfarin
  - warfarin to DOAC
    - begin DOAC when INR <2
  - DOAC to warfarin
    - stop DOAC 3 days after beginning warfarin
- Heparin
  - heparin to DOAC
    - begin DOAC immediately
  - DOAC to heparin
    - begin heparin at time of next scheduled dose of DOAC

Chen A, Stecker E, Warden BA. Direct oral anticoagulant use: a practical guide to common clinical challenges. *JAHA.* 2020;9:e017559. DOI: 10.1161/JAHA.120.01755.

Anticoagulant Conversion

- Enoxaparin
  - enoxaparin to DOAC
    - begin DOAC at time of next scheduled dose of enoxaparin
  - DOAC to enoxaparin
    - begin enoxaparin at time of next scheduled dose of DOAC

Chen A, Stecker E, Warden BA. Direct oral anticoagulant use: a practical guide to common clinical challenges. *JAHA.* 2020;9:e017559. DOI: 10.1161/JAHA.120.01755.

Periprocedural Anticoagulation

Table 6 Suggested periprocedural direct oral anticoagulant therapy interruptions (adapted from [4])

Drug	Renal function	Low bleeding risk surgery	High bleeding risk surgery*	Resumption of therapy	
				Low bleeding risk surgery	High bleeding risk surgery
Dabigatran	CrCl > 50 mL min^{-1} CrCl 30–50 mL min^{-1}	Last dose: 2 days before procedure Last dose: 3 days before procedure	Last dose: 3 days before procedure Last dose: 4–5 days before procedure	Resume ~ 24 h after procedure	Resume 2–3 days after procedure (48–72 h postoperatively)†
Rivaroxaban	CrCl > 50 mL min^{-1} CrCl 30–50 mL min^{-1} CrCl 15–29.9 mL min^{-1}‡	Last dose: 2 days before procedure Last dose: 2 days before procedure Last dose: indivualized on the basis of patient and procedural factors for bleeding and thrombosis	Last dose: 3 days before procedure Last dose: 3 days before procedure Last dose: indivualized on the basis of patient and procedural factors for bleeding and thrombosis	Resume ~ 24 h after procedure	Resume 2–3 days after procedure (48–72 h postoperatively)†
Apixaban	CrCl > 50 mL min^{-1} CrCl 30–50 mL min^{-1} CrCl 15–29.9 mL min^{-1}	Last dose: 2 days before procedure Last dose: 2 days before procedure Last dose: indivualized on the basis of patient and procedural factors for bleeding and thrombosis	Last dose: 3 days before procedure Last dose: 3 days before procedure Last dose: indivualized on the basis of patient and procedural factors for bleeding and thrombosis	Resume ~ 24 h after procedure	Resume 2–3 days after procedure (48–72 h postoperatively)†
Edoxaban	CrCl > 50 mL min^{-1}	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Resume ~ 24 h after procedure	Resume 2–3 days after procedure (48–72 h postoperatively)†

– no bridging necessary with DOACs (warfarin only)!

Cuker A, Burnett A. Triller D, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. AJH. 2019;94:697-709.

Periprocedural Anticoagulation

TABLE 1 Risk stratification for procedural bleed risk as suggested by the ISTH Guidance Statement and BRIDGE Trial[3,22]

High bleeding risk procedures[a] (30-d risk of major bleed >2%)	Major surgery with extensive tissue injury Cancer surgery, especially solid tumor resection Major orthopaedic surgery, including shoulder replacement surgery Reconstructive plastic surgery Urologic or gastrointestinal surgery, especially anastomosis surgery Transurethral prostate resection, bladder resection, or tumor ablation Nephrectomy, kidney biopsy Colonic polyp resection Bowel resection Percutaneous endoscopic gastrotomy (PEG) placement, endoscopic retrograde cholangiopancreatography (ERCP) Surgery in highly vascular organs (kidneys, liver, spleen) Cardiac, intracranial, or spinal surgery Any major operation (procedure duration >45 min) Neuraxial anaesthesia[b]
Low/moderate bleeding risk procedures[c] (30-d risk of major bleed 0%-2%)	Arthroscopy Cutaneous/lymph node biopsies Foot/hand surgery Coronary angiography[d] Gastrointestinal endoscopy +/− biopsy Colonoscopy +/− biopsy Abdominal hysterectomy Laparoscopic cholecystectomy Abdominal hernia repair Hemorrhoidal surgery Bronchoscopy +/− biopsy Epidural injections
Minimal bleeding risk procedures[e] (30-d risk of major bleed ~0%)	Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi) Opthalmological (cataract) procedures Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings Pacemaker or cardioverter-defibrillator device implantation

Spyropoulps AC, Brohl K, Caprini J, et al. SSC Communication; Guidance document on the periprocedural management of patients on chronic oral anticoagulant therapy. *JTH.* 2019;17:1966-1972.

UPMC LIFE CHANGING MEDICINE

Unusual sites of VTE

- Unusual sites of VTE
  - locations other than lower extremity and pulmonary vasculature
  - account for approximately 10% of cases of VTE
  - patients with unusual sites of VTE were not included in phase 3 clinical trials conducted on DOACs

Abbattista M, Capecchi M, Martinelli I. Treatment of unusual thrombotic manifestations. *Blood.* 2020;135:326-334.

Unusual sites of VTE

- Cerebral venous thrombosis
  - several case reports/series describe favorable efficacy and safety profiles with DOACs
  - *RE-SPECT CVT*
    - 60 patients each randomized to dabigatran and warfarin
      - no recurrent VTEs in either group
      - 1 major bleed in dabigatran group and 2 major bleeds in warfarin group

Ferro JM, Coutinho JM, Dentali F, et al. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: a randomized clinical trial. *JAMA Neurology.* 2019;76:1457-1465.

Unusual sites of VTE

- Splanchnic vein thrombosis
  - several case reports/series describe favorable efficacy and safety profiles with DOACs
  - RCT of 40 patients each with HCV-related compensated cirrhosis randomized to rivaroxaban 10 mg bid and warfarin
    - 0 vs 4 (22.2%) patient experienced recurrent VTE in the rivaroxaban and warfarin groups, respectively
    - 0 vs 17 (43.3%), p=0.001, patients experienced GIB in the rivaroxaban and warfarin groups, respectively

Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis. *Vascular Pharmacology.* 2019;113:86-91.

Unusual sites of VTE

- Renal, ovarian, and retinal vein thrombosis
  - limited data with few case reports describing favorable results with DOAC use

Montiel FS, Ghazvinian R, Gottsater A, et al. Treatment with direct oral anticoagulants in patients with upper extremity deep vein thrombosis. *Thrombosis Journal.* 2017;15:26.

Unusual sites of VTE

- Prospective study comparing 352 patients with VTE at typical locations vs 36 patients with VTE at atypical locations (CVT, SVT, RVT, and OVT)
  - no difference in recurrent VTE or major bleeding

Janczak DT, Mimier MK, McBane RD, et al. Rivaroxaban and apixaban for initial treatment of acute venous thromboembolism of atypical location. *Mayo Clinic Proceedings.* 2018;93:40-47.

Thrombophilias

Table 2
Current evidence on the use of DOACs in low risk thrombophilia.

Type of thrombophilia	Treatment arms	Study population (n)	VTE recurrence (n)	RR; 95% CI	MB/CRNMB (n)	RR; 95% CI
Randomized controlled trials [10]						
Prothrombin gene mutation	DOAC	38	0		3	
	Warfarin/heparin	37	2		4	
Factor V Leiden	DOAC	217	5		17	
	Warfarin/heparin	239	3		19	
Total	DOAC	255	5	RR = 1.10; [0.31–3.86]	20/254	RR = 0.93; [0.52–1.67]
	Warfarin/heparin	276	5		23/275	
Retrospective database analysis [23]						
Congenital thrombophilia	Rivaroxaban	403		HR = 0.70, (0.33–1.49)		HR = 0.55, (0.16–1.86)
	Warfarin	403				

95% CI: 95% confidence interval; RR: risk ratio; MB/CRNMB: major bleeding/clinically relevant non-major bleeding events, HR: hazard ratio.

Alameddine R, Nassabein R, Le Gal G, et al. Diagnosis and management of congenital thrombophilia in the era of direct oral anticoagulants. *Thrombosis Research.* 2020;185:72-77.

Thrombophilias

Table 3
Current evidence on the use of DOACs in high risk thrombophilia.

Pooled data from large randomized controlled trials [10]

Type of thrombophilia	Treatment arm	Study population (n)	VTE recurrence (n)	RR; 95% CI	MB/CRNMB (n)	RR; 95% CI
Antithrombin deficiency	DOAC	15	0		2	
	Warfarin/heparin	11	0		1	
Protein C deficiency	DOAC	40	0		3	
	Warfarin/heparin	28	0		3	
Protein S deficiency	DOAC	37	1		4	
	Warfarin/heparin	40	0		4	
Total	DOAC	92	1	RR = 2.58 [0.11–62.47]	9/92	RR = 0.97 [0.39–2.38]
	Warfarin/heparin	79	0		8/79	

Case reports

	Thrombophilia	Medications	Key findings
Van Bruwaene et al. [24]	AT deficiency: 5 PC deficiency: 3 PS deficiency: 4 FVL homozygous: 1 FII homozygous: 3 Mixed defects: 17	Rivaroxaban, Apixaban, Dabigatran	During a median 21 (range 8–34) months follow-up, only one on treatment VTE recurrence (9%) was observed
Hermans et al. [25]	PC and PS deficiency: 2 PS deficiency: 1 PC deficiency: 1 FVL and PC deficiency: 1	Rivaroxaban Apixaban	Rivaroxaban and Apixaban safe and effective in 5 patients with CT
Menon et al. [26]	AT deficiency	Apixaban	Apixaban safe and effective for more than 6 months after an extensive VTE.
Cook et al. [27]	AT deficiency	Rivaroxaban	Rivaroxaban effective in preventing recurrent VTE after hip fracture surgery
Menon et al. [28]	Protein C deficiency	Rivaroxaban	Rivaroxaban safe and effective in a child with warfarin induced skin necrosis.
Yagi et al. [29]	Protein S deficiency	Edoxaban	Recurrence of VTE attributed to non-adherence.
Sakai et al. [30]	AT deficiency	Edoxaban	Successful treatment and prevention of VTE after extensive femoral-inferior vena cava thrombosis with PE treated by pregnancy interruption and Edoxaban. Patient successfully continued edoxaban for 55 weeks until subsequent pregnancy.

95% CI: 95% confidence interval; RR: risk ratio; MB/CRNMB: major bleeding/clinically relevant non-major bleeding events.

Alameddine R, Nassabein R, Le Gal G, et al. Diagnosis and management of congenital thrombophilia in the era of direct oral anticoagulants. *Thrombosis Research.* 2020;185:72-77.

Unusual sites of VTE and Thrombophilias

- While better evidence is necessary, based on the current state of the data, DOAC use in unusual sites of thrombosis and thrombophilias is accepted (except APLS)

APLS

- *TRAPS*
  - phase 3, open-label, non-inferiority RCT
    - patients with a clinical diagnosis of APLS
      - history of thrombosis and LAC, ACL IgM/IgG antibodies, and B2GP IgM/IgG antibodies (triple positive)
        - » Sapporo criteria for diagnosis: 1) arterial/venous thrombosis and 2) LAC, ACL IgM/IgG, or B2GP IgM/IgG antibodies present on 2 occasions at least 12 weeks apart
    - rivaroxaban 20 mg daily (15 mg daily if CrCl 30-50 mL/min) or warfarin daily with goal INR 2-3

Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood.* 2018;132:1354-1371.

APLS

Table 4. Adjudicated efficacy and safety outcomes

Outcome, n	"As treated" analysis			
	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	*P*
Thromboembolic events, major bleeding, and vascular death	11 (19)	2 (3)	6.7 (1.5-30.5)	.01
Arterial thrombosis Ischemic stroke Myocardial infarction	7 (12) 4 (7) 3 (5)	0 0 0	—	—
Venous thromboembolism	0	0		
Major bleeding	4 (7)	2 (3)	2.5 (0.5-13.6)	.3
Death	0	0	—	—

– study terminated prematurely due excess thrombotic events in the rivaroxaban arm

Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood.* 2018;132:1354-1371.

APLS

- RCT of rivaroxaban vs warfarin in APLS
  - phase 3, open-label, non-inferiority RCT
    - patients with a clinical diagnosis of APLS
      - history of thrombosis and LAC, ACL IgM/IgG antibodies, OR B2GP IgM/ IgG antibodies
        - » 60% of patients “triple positive”
    - rivaroxaban 20 mg daily (15 mg daily if CrCl 30-50 mL/min) or warfarin daily with goal INR 2-3

Ordi-Ros J, Saez-Comet L, Perez-Conesa M, et al. Rivaroxaban versus vitamin K antagonist in antiphospholipid syndrome: a randomized non-inferiority trial. *Annals of Internal Medicine.* 2019;10:685-694.

APLS

Table 2. Efficacy End Points of Recurrent Thrombotic Events*

Study Population	Events, *n* (%)		Risk Ratio (95% CI)	*P* Value
	Rivaroxaban Group (*n* = 95)	VKA Group (*n* = 95)†		
Per protocol, as treated				
All events	11 (11.6)	6 (6.3)	1.83 (0.71-4.76)	0.21
Arterial events§	10 (10.5)	3 (3.2)	3.33 (0.95-11.73)	0.060
Venous events§	2 (2.1)	3 (3.2)	0.67 (0.11-3.90)	0.65
Stroke	9 (9.5)	0 (0)	19.00 (1.12-321.9)	<0.001

P for non-inferiority = 0.29

Table 3. Safety End Points of Bleeding Events*

Variable	Events, *n* (%)		Risk Ratio (95% CI)	*P* Value
	Rivaroxaban Group (*n* = 95)	VKA Group (*n* = 95)		
Major bleeding				
Any	6 (6.3)	7 (7.4)	0.86 (0.30-2.46)	0.77
Decrease in hemoglobin level >2 g/dL	6 (6.3)	5 (5.3)	1.20 (0.38-3.80)	0.76
Transfusion	5 (5.3)	5 (5.3)	1.00 (0.30-3.34)	1.00
Critical bleeding‡	0	4 (4.2)	0.00 (0.00-1.51)	0.060
Fatal bleeding	0	0	–	–
Intracranial hemorrhage	0	2 (2.1)	0.00 (0.00-5.32)	0.25
Any bleeding	31 (32.6)	26 (27.4)	1.19 (0.77-1.85)	0.43
Nonmajor clinically relevant bleeding	9 (9.5)	5 (5.3)	1.80 (0.63-5.17)	0.28
Minor bleeding	16 (16.8)	14 (14.7)	1.14 (0.59-2.21)	0.69

Ordi-Ros J, Saez-Comet L, Perez-Conesa M, et al. Rivaroxaban versus vitamin K antagonist in antiphospholipid syndrome: a randomized non-inferiority trial. *Annals of Internal Medicine.* 2019;10:685-694.

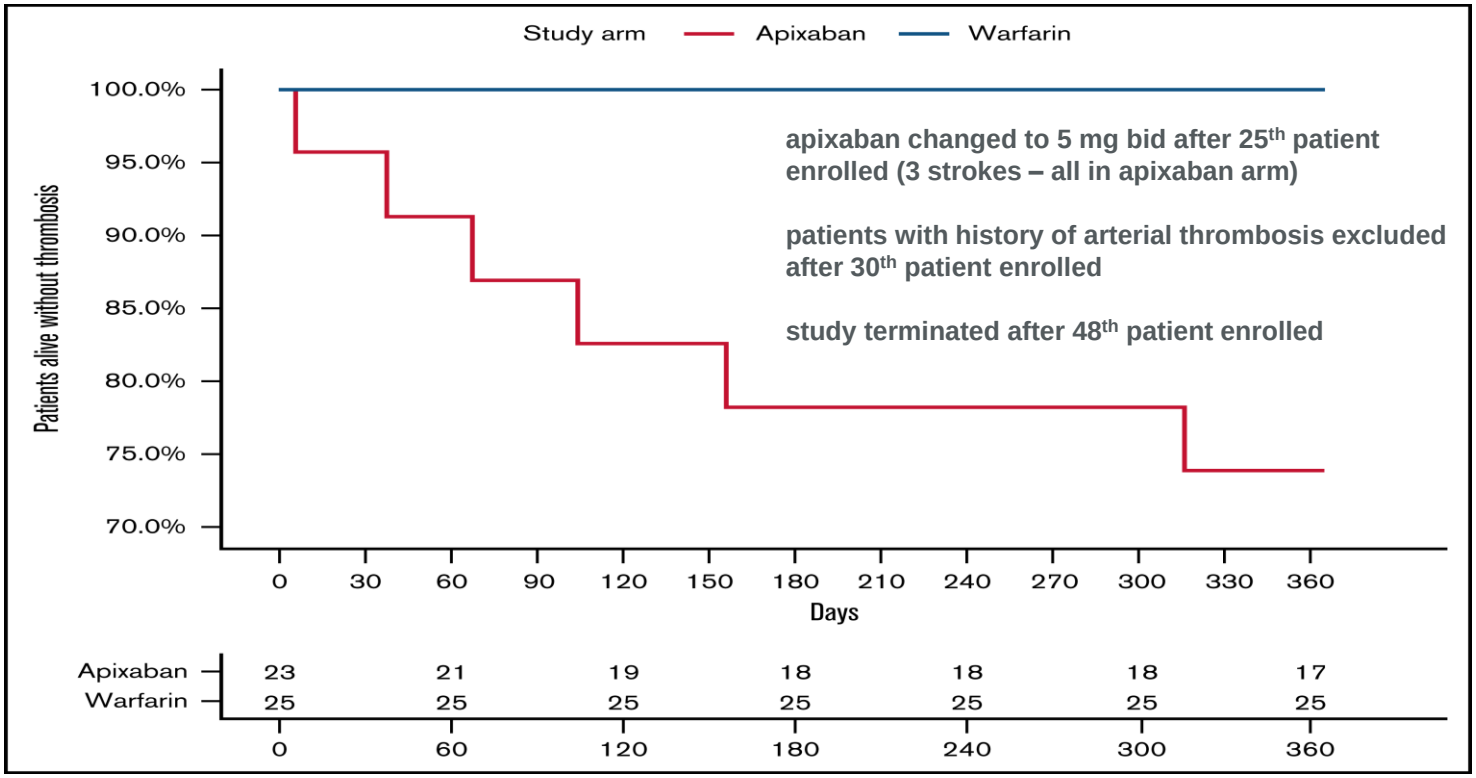
UPMC LIFE CHANGING MEDICINE

APLS

- RCT of apixaban vs warfarin in APLS
  - pilot, open-label, non-inferiority RCT
    - patients with a clinical diagnosis of APLS
      - history of thrombosis and LAC, ACL IgM/IgG antibodies, OR B2GP IgM/ IgG antibodies
        - » 29% of patients “triple positive”
    - apixaban 2.5 mg bid or warfarin daily with goal INR 2-3

Woller SC, Stevens SM, Kaplan D, et al. Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial. *Blood Advances.* 2022; 6:1661-1670.

APLS



Woller SC, Stevens SM, Kaplan D, et al. Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial. *Blood Advances.* 2022; 6:1661-1670.

APLS

- Based on available evidence, DOACs not recommended in APLS
  - prefer warfarin or enoxaparin to DOACs in patients with APLS

DOACs in CAT

Clinical trial	Efficacy	Bleeding
Hokusai-VTE Cancer	Edoxaban was non-inferior to dalteparin for prevention of recurrent VTE or major bleeding, 12.8 vs 13.5% (HR 0.96; 95% CI: 0.70-1.36; p<0.01)	Edoxaban was associated with a greater risk of major bleeding, 6.9 vs 4.0% (HR 1.77; 95% CI: 1.03-3.04, p=0.04) Most major bleeding events were GI and GI cancer was associated with a greater risk of bleeding in subgroup analyses
SELECT-D	Rivaroxaban was superior to dalteparin for prevention of recurrent VTE, 4 vs 11% (HR 0.43; 95% CI, 0.19 to 0.99)	Rivaroxaban was not associated with a greater risk of major bleeding, 6 vs 4% (HR 1.83; 95% CI: 0.68 to 4.96) Most major bleeding events were GI with a trend towards association of esophageal and GE cancer with GIB
ADAM-VTE	Apixaban was superior to dalteparin for prevention of recurrent VTE and arterial thrombosis, 0.7 vs 6.3% (HR, 0.099; 95% CI, 0.013 to 0.78; p=0.03)	Apixaban was not associated with a greater risk of major bleeding, 0 vs 1.4% (HR not estimable; p=0.14)
Caravaggio	Apixaban was non-inferior to dalteparin for prevention of recurrent VTE, 5.6 vs 7.9% (HR, 0.63; 95% CI, 0.37 to 1.07; p<0.001)	Apixaban was not associated with a greater risk of major bleeding, 3.8 vs 4.0% (HR 0.82; 95% CI: 0.40-1.69; p=0.60) OR major GIB, 1.9 vs 1.7% (HR 1.05; 95% CI: 0.44-2.50)

Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *NEJM.* 2018; 378: 615-624.

Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism; results of a randomized trial (SELECT-D). *JCO.* 2018;36:2017-2023.

McBane RD, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. *JTH.* 2019;00:1-11.

Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. *NEJM.* 2020;382:1599-1607.

DOACs in CAT

- ISTH recommendations
  - DOACs are an acceptable alternative to LMWH except GI and GU malignancies
    - guidelines prior to *ADAM-VTE* and *Caravaggio* results
    - apixaban use favored

Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. *JTH.* 2018;16:1891-1894.

DOACs and Women

- DOACs contraindicated in pregnancy and breastfeeding
- Real-world observations of HMB with FXa inhibitors prompted post-hoc analyses of phase 3 trial data
  - FXa inhibitors carry a higher risk of HMB compared with warfarin
    - dabigatran associated with a lower risk of HMB compared with warfarin

Beyer-Westendorf, J. DOACS in women: pros and cons. *Thrombosis Research.* 2019;S19-S22.

DOACs and Obesity

- ISTH recommendations
  - initial recommendations in 2016 suggested not using DOACs when BMI >40 kg/m^2 or weight >120 kg due to limited clinical data and altered PK/PD
    - since these recommendations, literature has not shown inferior efficacy or increased bleeding
      - updated recommendations in 2021 suggest apixaban and rivaroxaban (more data available on rivaroxaban) are appropriate for use regardless of BMI or weight

Martin K, Beyer-Westendorf J, Davidson BL, et al. Use of the direct oral anticoagulants in obese patients; guidance from the SSC of the ISTH. *JTH.* 2016;14:1308-1313.

Martin K, Beyer-Westendorf J, Davidson BL, et al. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. *JTH.* 2021;19:1874-1882.

DOACs and Obesity

DOAC	Site of Absorption in Gastrointestinal Tract	Surgical Intervention and Anticipated Effect on Absorption		
		Gastric Banding	Partial/Sleeve Gastrectomy	RYGB
Apixaban	Primarily upper GI tract, with possible limited absorption in the colon; absorption decreased by when delivered to the distal small bowel compared with oral administration[39]	Unlikely affected	Unlikely affected	Possibly reduced
Dabigatran	Lower stomach and proximal small intestine[41,42,49]	Possibly reduced	Possibly reduced	Possibly reduced
Edoxaban	Proximal small intestine, dependent on acidic environment [43,44]	Possibly reduced	Possibly reduced	Possibly reduced
Rivaroxaban	Largely stomach, some small intestine, but absorption reduced when released distal to stomach[43-45]	Possibly reduced	Possibly reduced	Possibly reduced

- ISTH recommendations
  - use parenteral anticoagulant in the 1st 4 weeks after bariatric surgery then may consider DOAC (if DOAC used then check trough level)

Martin K, Beyer-Westendorf J, Davidson BL, et al. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. *JTH.* 2021;19:1874-1882.

QUESTIONS?