BRIGHAM AND WOMEN'S HOSPITAL

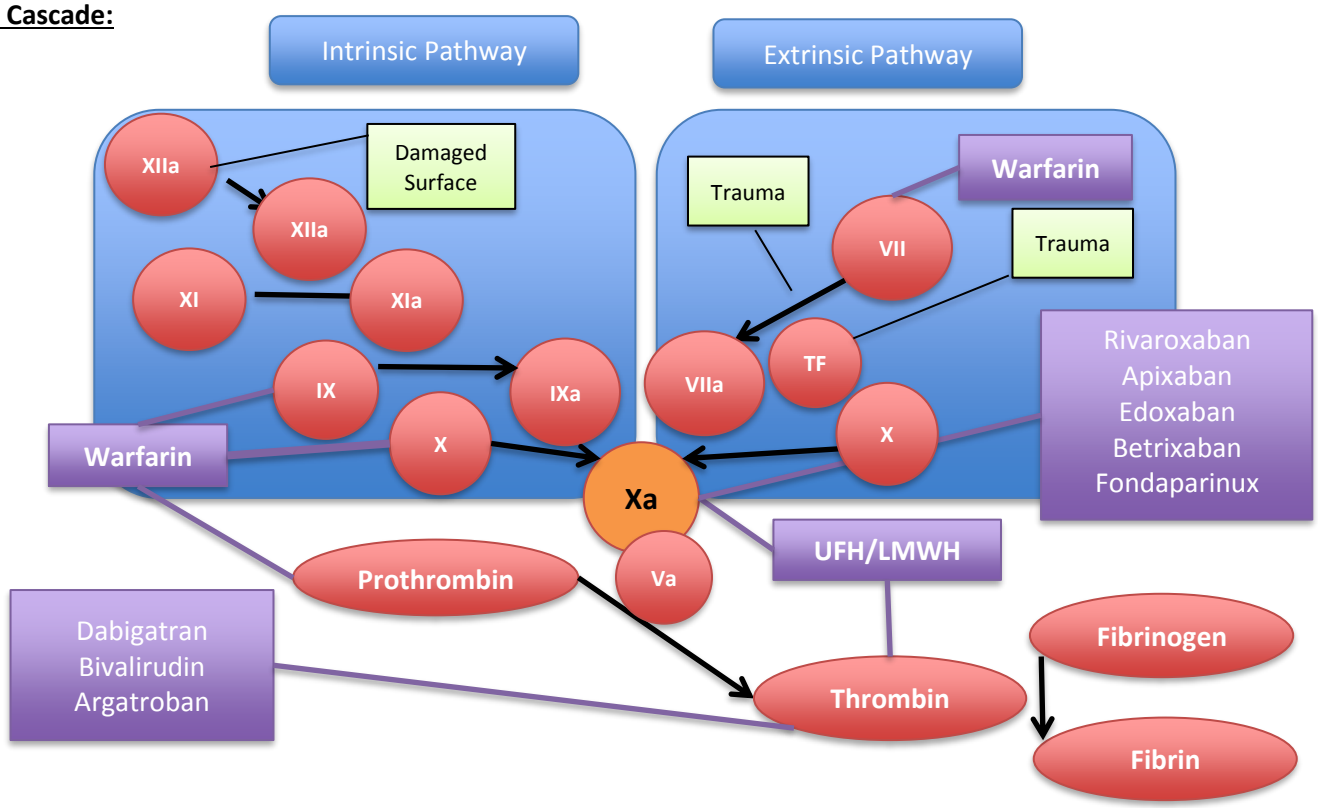
Anticoagulation Management Service

Peri-Procedural Direct Oral Anticoagulant (DOAC) Management

Background:

Direct oral anticoagulants (DOAC) dose-dependently inhibit thrombin (i.e. dabigatran) or activated factor X (i.e. rivaroxaban, apixaban, and edoxaban).[1] This provides potential advantages over warfarin, such as rapid onset and offset of action, absence of an effect of dietary vitamin K intake on their activity, and fewer drug interactions. Individually, DOAC are at least as safe and effective as warfarin for prevention of stroke and systemic embolism in patients with atrial fibrillation and in venous thromboembolism management. Depending on the type of surgery or invasive procedure and the associated bleeding risk, anticoagulation interruption might be warranted. Due to variability in renal clearance amongst agents, procedural bleeding risk and renal function should be assessed.

Clotting Cascade:



DOAC Pharmacokinetics:[2-9]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Drug Class	Direct factor IIa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Brand Name	Pradaxa®	Xarelto®	Eliquis®	Savaysa®	Bevyxxa®
Indication	VTE Prophylaxis, VTE management, SSE prevention in Non-valvular Afib				VTE Prophylaxis in Acute Medical Illness
Time to C_{max}	1 - 2 h	2 - 4 h	3 - 4 h	1 - 2 h	3 – 4 h
Metabolism	P-gp	CYP3A4/5, CYP2J2, P-gp	CYP3A4/5, P-gp	CYP3A4, P-gp	CYP-independent hydrolysis, P-gp
Renal Clearance (%)	>80	66	27	35	11
Fecal Excretion (%)	82 - 88	26.6	46.7 - 56	62.2	82 - 89
Half-Life	12 - 17 h	5 - 9 h	≈12 h	10 - 14 h	19 – 27 h
Dosing Frequency	Twice daily	Daily	Twice daily	Daily	Daily

Afib: atrial fibrillation; C_{max}: time to maximum concentration; P-gp: P-gylcoprotein; SSE: Stroke and systemic embolism; VTE: venous thromboembolism

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DOAC Peri-Operative Management:[10,11]

Pre-Procedure:

- Assess renal function (Calculate creatinine clearance; CrCl mL/min)
- Assess risk of bleeding
- Assess risk of thromboembolism

Calculated CrCl, mL/min	Half-life, hours	Timing of Last Dose Before Surgery‡	
		Low Risk of Bleeding (See Table 1 Below)	High Risk of Bleeding (See Table 1 Below)
Dabigatran		PI: Discontinue 1-2 days before if CrCl ≥50 mL/min, 3-5 days before if CrCl <50 mL/min	PI: Consider longer times if major surgery, spinal puncture, spinal or epidural catheter
>50	14-17	24 hours	2 days
30-50	16-18	2 days	4-5 days
<30	28	4 days	≥5 days
Rivaroxaban		PI: Discontinue ≥24 hours before	PI: Discontinue ≥24 hours before
> 50	8-9	24 hours	2 days
30 - 50	9	24-48 hours	3–4 days
<30	9-10	2 days	4 days
Apixaban		PI: Discontinue ≥24 h before	PI: Discontinue ≥48 h before
> 50	7-8	24 hours	2 days
30 - 50	17-18	24-48 hours	3–4 days
<30	≥ 17.5	2 days	4 days
Edoxaban		PI: Discontinue ≥24 hours before	
>50	6–11	24 hours	48 hours
30 - 50	11-17	24-48 hours	3–4 days
<30	17	2 days	4 days
Betrixaban		PI: Anticoagulant effect can persist for at least 72 hours after the last dose	
≥30	19-27	4 days	4 days
<30	Not Reported	Do not use	Do not use

‡ For minimal bleeding risk procedures: DOAC may be continued and interruption might not be necessary (anticipated effect would be similar to operating while on warfarin or LMWH)

Post-Procedure:

- Consider DOAC's rapid onset of action (1 – 4 hours; depending on the agent)
- After hemostasis is established DOAC can generally be resumed:
  - 24 – 72 hours after a minor procedure
  - 48 – 72 hours after a major surgery

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Table 1: Bleeding Risk Assessment:[12,13]

Assessment of bleeding risk should be discussed with proceduralist/interventionist

HIGH BLEEDING RISK PROCEDURES (2-day risk of major bleed ≥ 2%)	LOW BLEEDING RISK PROCEDURES (2-day risk of major bleed <2%)	MINIMAL BLEEDING RISK PROCEDURES‡
Major surgery with extensive tissue injury • Cancer surgery/ablation • Major orthopedic surgery • Reconstructive plastic surgery **Urologic or Gastrointestinal 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) **Other** • Cardiac, intracranial, or spinal surgery • Surgery in highly vascular organs (kidneys, liver, spleen) • Multiple tooth extractions • Any major operation (procedure duration >45 minutes) • Pacemaker or cardioverter-defibrillator device implantation • Large hernia surgery	• Minor dental procedures (simple dental extractions, restorations, prosthetics, endodontics) • Cutaneous/lymph node biopsies • Shoulder/foot/hand surgery • Coronary angiography • Gastrointestinal endoscopy +/- biopsy • Colonoscopy +/- biopsy (without removal of large polyps) • Abdominal hysterectomy • Laparoscopic cholecystectomy • Uncomplicated laparoscopic procedures • Abdominal hernia repair • Hemorrhoidal surgery • Bronchoscopy +/- biopsy • Epidural injections with INR <1.2 • Pacemaker battery change • Arthroscopy • Cardiac catheterization • Ablation therapy	• Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi) • Cataract procedures • Dental cleanings, fillings ‡ For minimal bleeding risk procedures: DOAC may be continued and interruption might not be necessary (anticipated effect would be similar to operating while on warfarin or LMWH)

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