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Update on Regional Anesthesia in Patients on Anticoagulation

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I have nothing to disclose.

In accordance with ACCP guidelines, for each of the antithrombotic agents, it is recommended that clinicians follow the FDA-approved dosing guidelines.

Goals and Objectives

1. Assess the bleeding risk factors for patients undergoing neuraxial anesthesia

2. Review the pharmacology and physiology of direct acting oral anticoagulants

3. Highlight the new ASRA 4th practice advisory guidelines for these medications

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Monday Morning: 1st Case

- 78 yo female for THA
- PMH
  - Atrial fibrillation
  - Chronic kidney disease
    - CrCl 40 ml/min
  - Severe COPD
- Medications
  - Aspirin 81 mg QD
  - Dabigatran 150 mg PO BID (last dose Friday)
  - Atenolol 50 mg po BID
  - Inhalers, herbals, vitamins

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Monday Morning: 1st Case

- Standard of care in my hospital
  - Posterior lumbar plexus block (psoas)
  - Spinal vs General
- What will you do??
  - Order lab work?
  - Cancel the case?
  - Proceed with posterior lumbar plexus block?
  - Proceed with spinal?

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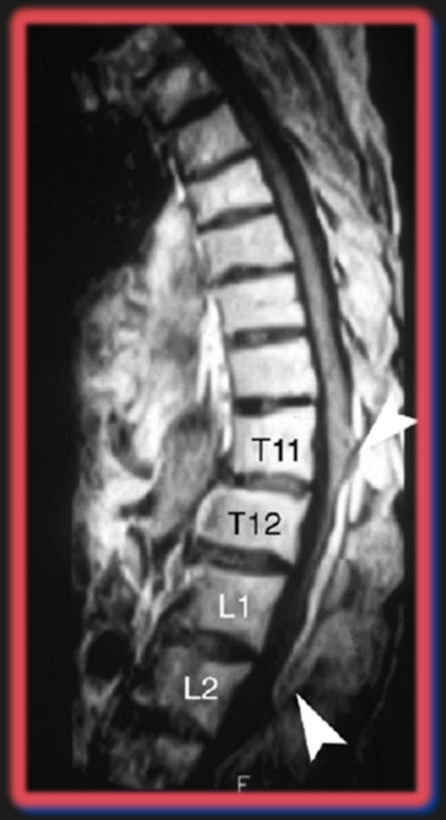
Bleeding Risk Factors

- Increased age
- Female gender
- Spinal canal pathology
- Renal and/or hepatic disfunction
- Regional technique
  - Spinal < epidural; single inj < catheter, lumbar < thoracic < cervical
  - Traumatic puncture
- Intensity of anticoagulant effect
  - Concomitant aspirin therapy
  - Length of therapy



Moen et al. Anesthesiology 2004

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Neurologic Complications after Central Neuraxial Blockade in Sweden

- Retrospective review
  - 1,260,000 spinals
  - 450,000 epidurals (200,000 OB)
    - Permanent nerve damage in 85
    - 14 had preexisting spinal stenosis
      - 1 was diagnosed preop
    - Incidence of cauda equina & spinal hematoma increased with age

Preexisting spinal canal pathology may be a “neglected risk factor”

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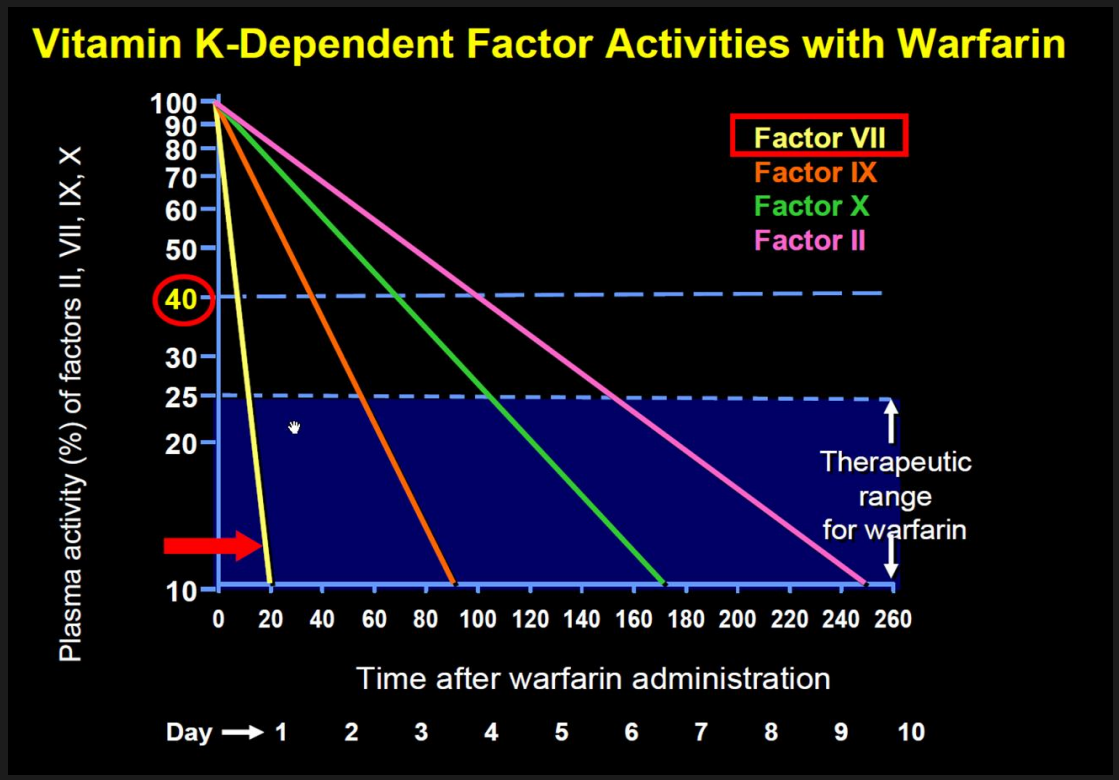
Moen et al. Anesthesiology 2004

Regional Anesthetic Management of the Patient on Warfarin

- Chronic *preoperative* anticoagulation
  - Adequate levels of II, VII, IX, and X may not be present until INR is normal
  - Stop warfarin 4-5 days before procedure
  - INR must be normalized



*Differs from INR ≤ 1.4 by ESA

Horlocker et al. RAPM 2010

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Regional Anesthetic Management of the Patient on Warfarin

- In general, patients receiving 2.5mg- 5mg warfarin will not have significant hemostatic alterations for 48 hrs after initiation of therapy
- In patients receiving an initial dose of warfarin before surgery, we suggest that the INR should be checked 24 hrs after the preoperative dose.
- In patients receiving low-dose warfarin therapy during epidural analgesia, we suggest that the INR be monitored on a daily basis.

*ESA does not recommendation warfarin in combination with neuraxial catheters

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Catheter Management on Warfarin

- Epidural may be maintained with an INR < 1.5 during initiation of therapy
  - Clotting factor activity > 40%
- INR > 1.5 and < 3
  - Catheters may be maintained with caution based on INR and duration of therapy
    - 48 hr levels of VII and IX will be depressed

Factor	Half-Life, hrs
Factor VII	6–8
Factor IX	24
Factor X	25–60
Factor II	50–80

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Plexus & Peripheral Blockade

- 670 continuous lumbar plexus blocks
  - On warfarin, catheter removed on POD 2
    - 36% with INR > 1.5
    - Local bleeding in 1 patient (INR 3.0)
- Case reports of bleeding
  - All neurodeficits resolved within 6-12 months
    - Expandable peripheral site may be protective
    - Blood loss may be the most serious complication
- *Treat deep blocks similarly to neuraxial blocks (1C)*

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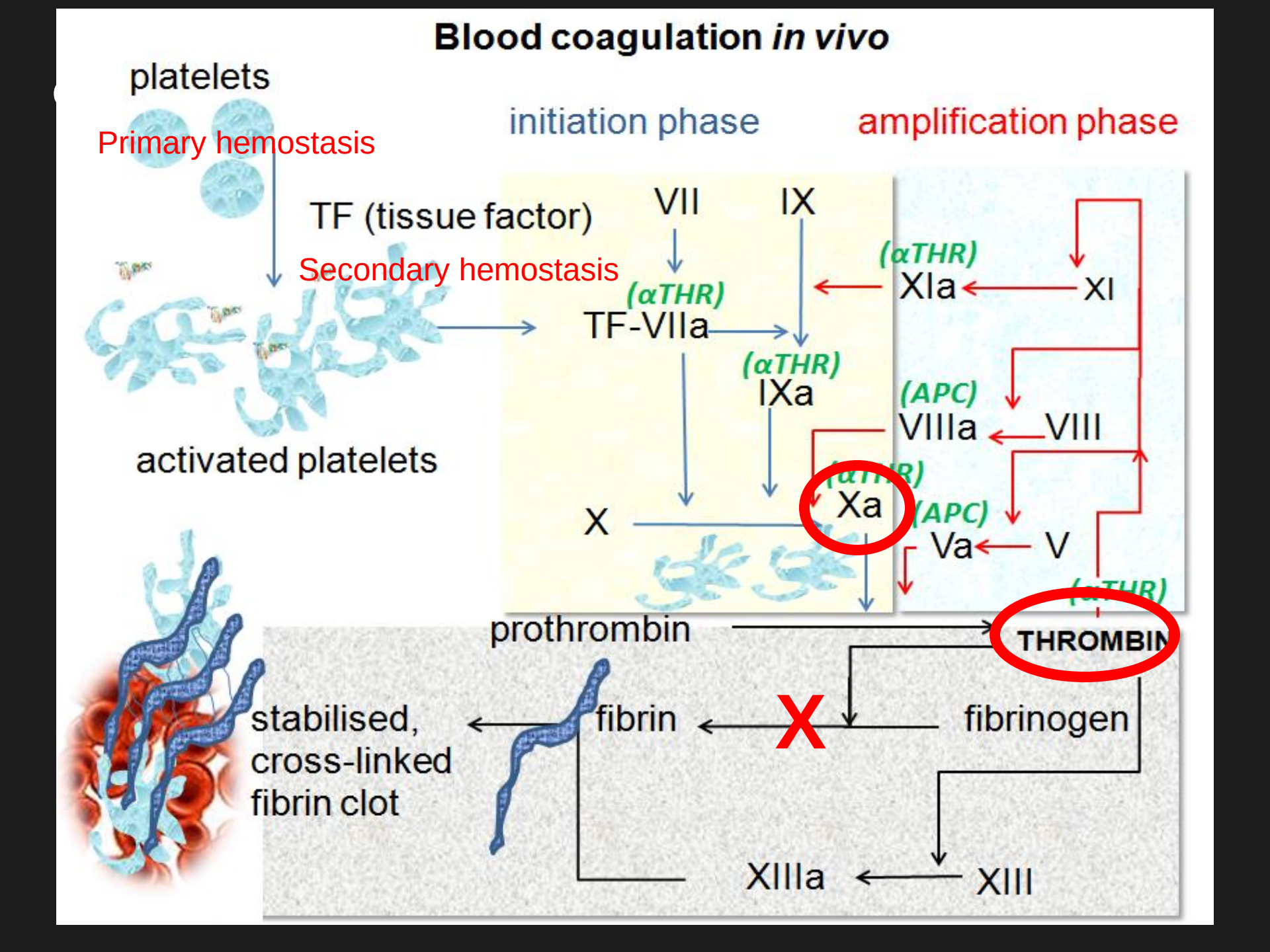
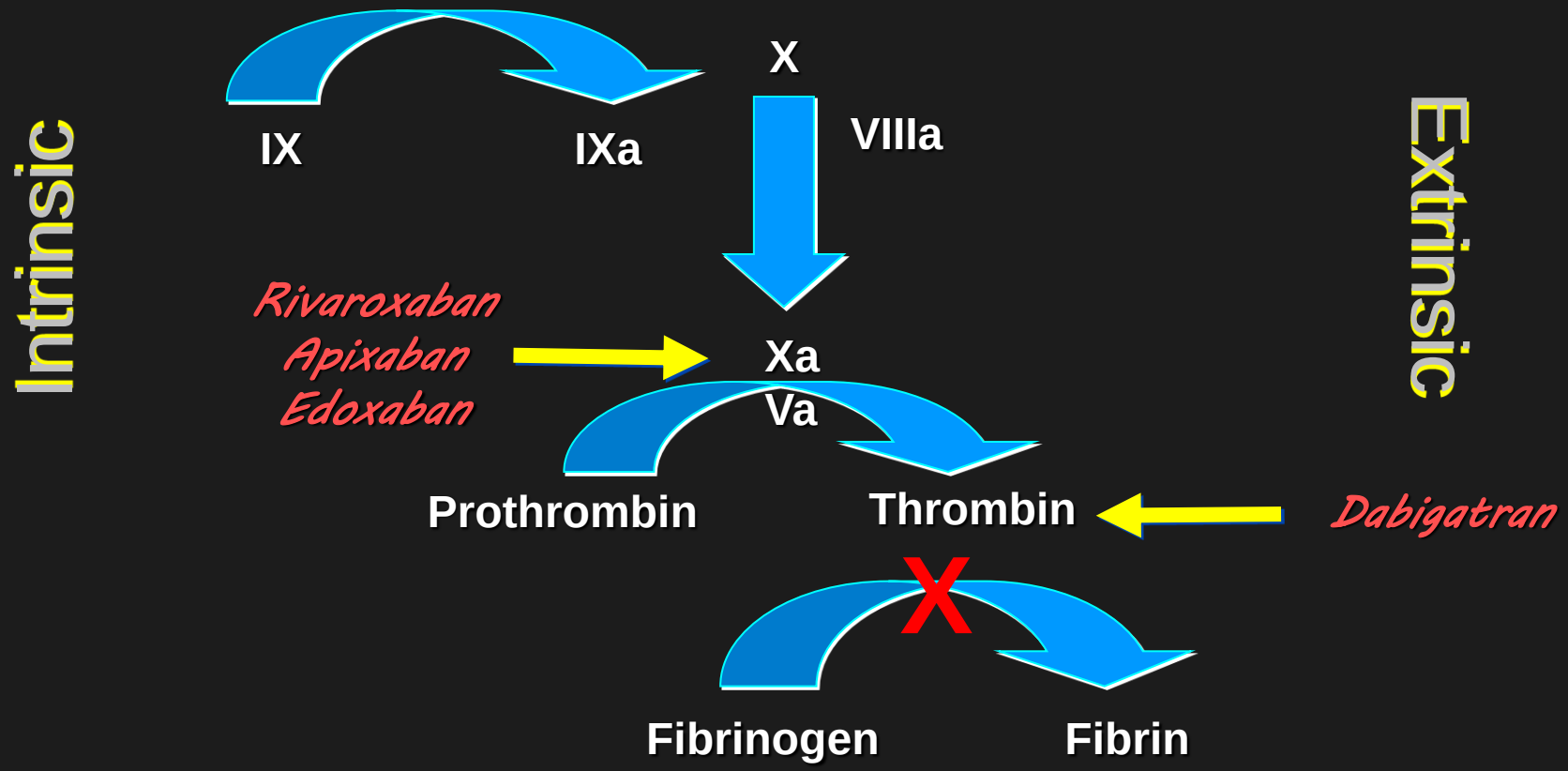
Chelly et al. Br J Anaesth 2008
Horlocker et al. RAPM 2010

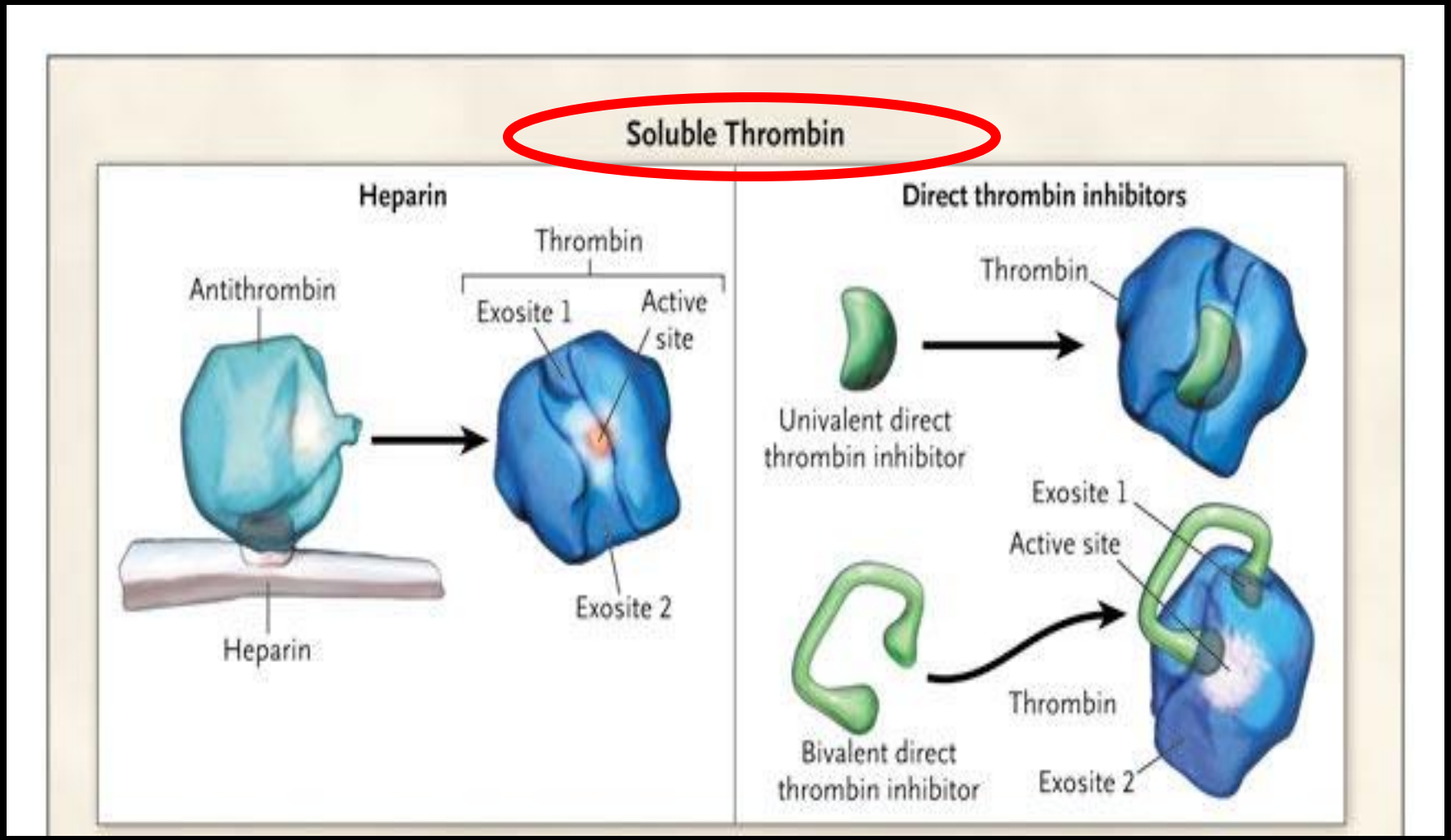
Blood coagulation *in vivo*



Targets of New Inhibitors



Mechanism of Action of Direct Thrombin Inhibitors as Compared with Heparin



Di Nisio M et al. N Engl J Med 2005

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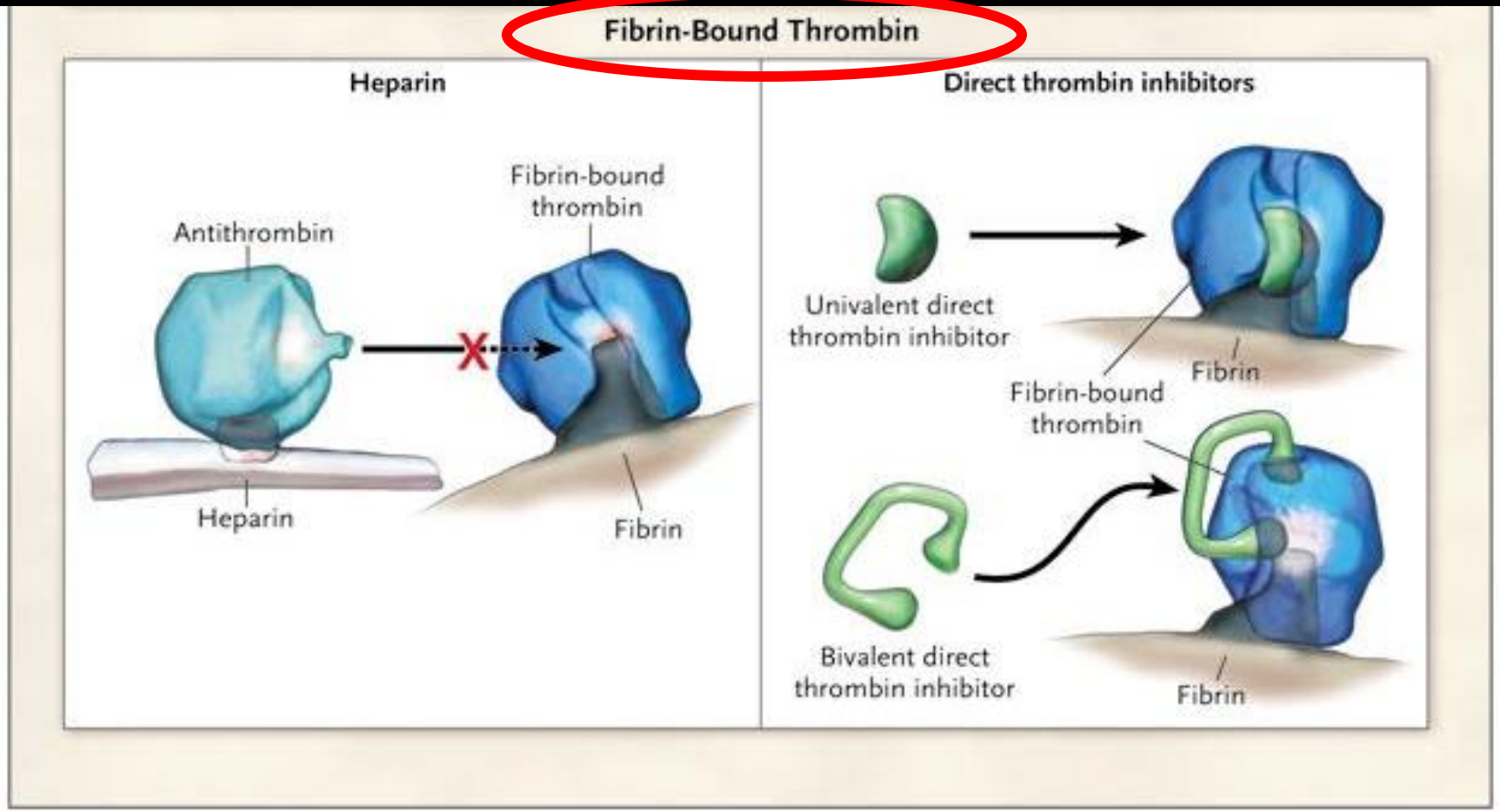

Di Nisio M et al. N Engl J Med 2005

Efficacy of DOAC compared to warfarin in Non-Valvular A-fib

- Meta-analysis 71,683 patients in 4 studies
  - Higher-dose DOACs associated with reductions
    - *All* stroke (19%, p<0.0001)
    - Ischemic stroke (8%, p=0.10)
    - Intracranial hemorrhage (52%, p<0.0001)
    - All-cause mortality (10%, p<0.001)
  - Increase in major GI bleeding (25%, p=0.04)

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Ruff CT. et al. Lancet March 2014

Recommendations from our Cardiology Colleagues

- **Canadian Cardiovascular Society**
  - "…we suggest…that…most patients should receive dabigatran, rivaroxaban, or apixaban in preference to warfarin…"
- **European Society of Cardiology**
  - "One of the new OACs, either a DTI or fXa inhibitor should be considered rather than dose-adjusted VKA…for most patients (IIaA)"
- **AHA**
  - "Warfarin, dabigatran, apixaban, and rivaroxaban are…indicated for the prevention of …stroke in…non-valvular a-fib."

Skanes AC et al. Can J Cardiol 2012
Camm AJ et al. Eur Heart J 2012
Furie KL et al. Stroke 2012

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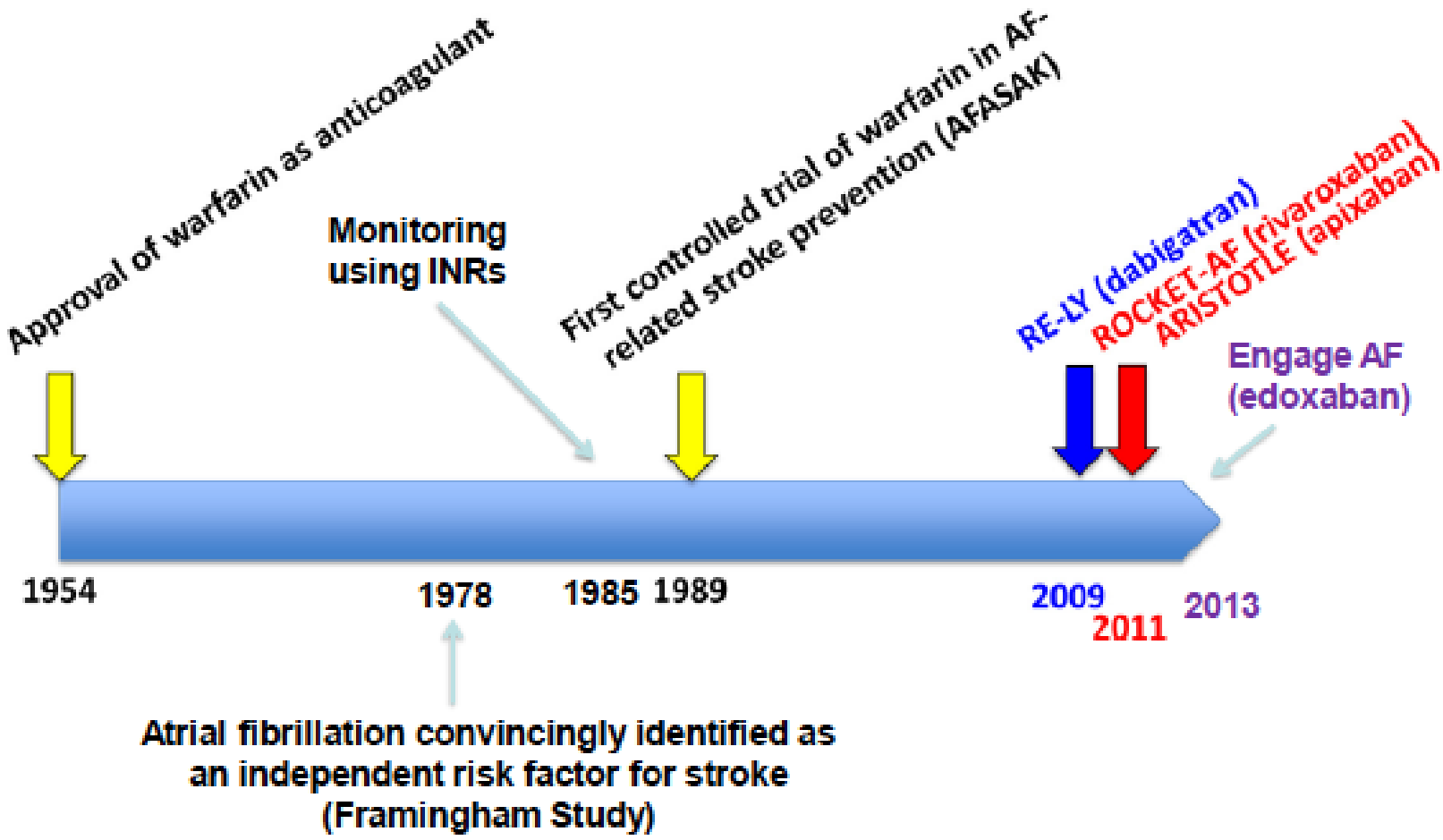
Time line for oral anticoagulants for atrial fibrillation



DOACs vs Warfarin: Caveats

- Advantages disappear with very good INR control
- Trial experience not the same as real world
- Short half-life—avoid missing doses
- Can’t assess patient adherence with test
- No antidote—reversibility may be difficult
- Not studied on certain populations
- Cost: warfarin $50/yr, DOACs $1200/yr

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Ansell J. Circ 2012

PHARMACOKINETIC PROPERTIES OF NEW ORAL ANTICOAGULANTS

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dosing	150 mg BID**	10 mg/day	2.5 mg BID	60 mg QD
Onset of action	1.5-3 hrs	2-4 hrs	3 hrs	1-3 hrs
Half-life	14-17 hrs	5-9 hrs Elderly 11-13 hrs	8-15 hrs	10-14 hrs
Metabolism Excretion	80% renal 20% fecal	66% renal 33% fecal	25% renal 75% biliary/fecal	50% renal 50% biliary
Detection of effect	TT, ECT	Anti-Xa assay	Anti-Xa assay	Anti-Xa assay
Dialyzable	Yes Limited clinical experience	No	No	No

Surgical Procedures at High Risk for Bleeding

- Open Heart Surgery
- Abdominal/Vascular Surgery
- Neurosurgery
- Major Cancer Surgery
- Urologic Procedures

Problem: Many procedures with ***low-moderate*** bleeding risk use ***neuraxial anesthesia***!

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New Oral Anticoagulants

Drug	T1/2	Renal Excretion
DABIGATRAN	**12-17**	**80%**
RIVAROXABAN	**11-13**	**60%**
APIXABAN	**10-15**	**33%**
EDOXABAN	**10-14**	**55%**

- Needle/catheter placement: discontinue 5 half lives prior *(treatment/a-fib dose)*
- Catheter removal: delay for 2 half lives *(prophylactic dose)*
- First dose after catheter removal: 8 hours minus time to maximum anticoagulant effect

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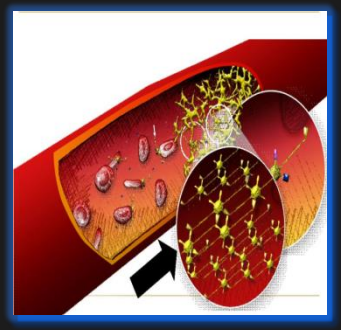
ASRA 4th Practice Advisory

ASRA Spring Meeting, April 2014

Thrombin Inhibitors



- Dabigatran (*Pradaxa*)
  - Discontinue at least **5** days prior
  - Consider checking TT or ECT if < 5 days
    - Result must be “no activity” to assure safe performance
  - Remove deep peripheral/plexus or neuraxial catheters 6 hrs *prior* to first postoperative dose
    - No indwelling catheters
  - Unanticipated administration with indwelling catheter
    - Hold dabigatran for 34-36 hrs (2 drug half-lives in a renal insufficient patient) then remove catheter

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ASRA 4th Practice Advisory

ASRA Spring Meeting, April 2014

Direct Xa Inhibitors

- Rivaroxaban (*Xarelto*)
  - Discontinue at least **3** days prior
  - Consider checking anti-Xa level if < 3 days
    - Result must be “no activity” to assure safe performance
  - Remove deep peripheral/plexus or neuraxial catheters 6 hrs *prior* to first (postoperative) dose
    - No indwelling catheters
  - Unanticipated administration with indwelling catheter-hold rivaroxaban for 22-26 hrs (2 drug half-lives in a renal insufficient patient) then remove

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ASRA 4th Practice Advisory

ASRA Spring Meeting, April 2014

Direct Xa Inhibitors

- Apixaban (Eliquis)
  - Discontinue at least **3** days prior
  - Consider checking anti-Xa level if < 3 days
    - Result must be “no activity” to assure safe performance
  - Remove deep peripheral/plexus or neuraxial catheters 6 hours *prior* to first (postoperative) dose
    - No indwelling catheters
  - Unanticipated administration with indwelling catheter- hold rivaroxaban for 20-28 hrs (2 drug half-lives in a renal insufficient patient) then remove

ASRA 4th Practice Advisory

ASRA Spring Meeting, April 2014

Direct Xa Inhibitors

- Edoxaban (Savaysa)
  - Discontinue at least **3** days prior
  - Consider checking anti-Xa level if < 3 days
    - Result must be “no activity” to assure safe performance
  - Remove deep peripheral/plexus or neuraxial catheters 6 hours *prior* to first (postoperative) dose
    - No indwelling catheters
  - Unanticipated administration with indwelling catheter- hold rivaroxaban for 26-30 hrs (2 drug half-lives in a renal insufficient patient) then remove
  - Not for use if CrCl > 95 ml/min

ASRA 4th Practice Advisory

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Test	Sensitive to deficiency of	Dabigatran	Rivaroxaban Apixaban Edoxaban
Prothrombin time PT/INR	I, II, V, VII, X	Too sensitive	May show some linearity with selective reagents.
Activated partial thromboplastin time APTT	I, II, V, VIII, IX, X,XI, XII,	Somewhat sensitive, increases in non-linear fashion. May underestimate high levels	Prolongs dose dependently but is less sensitive than the PT
Thrombin time TT	I, (IIa)	Standard TT is oversensitive, dilute TT or HEMOCLOT appears suitable option	Insensitive
Chromogenic Anti-Xa assay	Xa	Insensitive	Standard assay is too sensitive. Modified anti-Xa appears suitable
Ecarin Clotting Time ECT	II (activated)	Sensitive. Appears to be a reasonable option	Insensitive
dRVVT assay Russell Viper Venom Time	I, II, V, X	Sensitive but requires more extensive evaluation	Sensitive but requires more extensive evaluation

Specific Antidotes

	Idaracixamab *Praxbind*	**Andexanet alpha**	**PER977**
Structure	Humanized Fab fragment	Human rXa variant	Synthetic small molecule
Target	Dabigatran	fXa inhibitors	Universal
Binding	Non-competitive High Affinity	Competitive	?
Clinical studies	Rapid complete reversal	Rapid, near complete reversal	?

Lauw M et al. Can J Cardiol 2014

Reversing Direct Xa Inhibitors

- Control of bleeding by surgery, compression, radiological procedures
- Oral activated charcoal
  - Must be given within in few hours
  - Not ideal prior to surgery
- Prothrombin complex concentrate
  - May improve thrombin generation, risks
- FFP
  - Unlikely to overcome fXa or thrombin inhibition

Peripheral Nerve Blocks

- Serious hemorrhagic complications have been reported following plexus/peripheral blocks
  - Approx half had altered hemostasis
  - Cases of major bleeding were after psoas compartment or lumbar sympathetic block
  - In the presence of anticoagulants or antiplatelet agents
  - Neurologic compromise was not always reported

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Horlocker et al. RAPM 2010

Femoral Catheters in Patients Taking Rivaroxaban

- 504 patients
  - Preoperative femoral catheter for TKA
    - Continued for 36-48 hours
  - Rivaroxaban 10 mg daily
    - Catheter removed 20 hours after first dose
  - Assessed for hematoma causing neurovascular compromise or ecchymosis formation
    - No neurovascular compromise

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Idestrup C, et al. RAPM 2014

Femoral Catheters in Patients Taking Rivaroxaban

Variable	POD 1	POD 2	POD 3
Primary outcome			
Hematoma with neurovascular compromise, n	0	0	0
% (95% CI)	0 (0.0–0.8)	0 (0.0–0.8)	0 (0.0–0.8)
Secondary outcomes			
Ecchymosis, n (size, cm)	7 (1 × 2 to 15 × 6)	56 (1 × 1 to 38 × 9)	61 (1 × 1 to 38 × 9)
% (95% CI)	1.4 (0.4–2.4)	11.1 (8.4–13.9)	12.1 (9.3–15.0)
Tenderness, n	0	3	2
% (95% CI)	0 (0.0–0.8)	0.6 (0–1.3)	0.4 (0v1.0)
Oozing at site, n	15	26	3
% (95% CI)	3.0 (1.5–4.5)	5.2 (3.2–7.1)	0.6 (0–1.3)
Decreased motor function, n	108	9	1
% (95% CI)	21.4 (17.9–25.0)	1.8 (0.6–3.0)	0.2 (0–0.6)
Decreased sensory function, n	290	11	2
% (95% CI)	57.5 (53.2–61.9)	2.2 (0.9–3.5)	0.4 (0–1.0)

Data presented as incidence number (n), percentage (%), and 95% CI (lower confidence limit to upper confidence limit).

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Idestrup C, et al. RAPM 2014

Plexus/Peripheral Block Recommendations

- Paucity of information in form of case reports
- Difficult to make definitive recommendations
- Bleeding complications are *typically* less serious than neuraxial bleeding
  - Nerve palsy or hematoma
- Dependent on compressibility of the site and structures in the vicinity

Antiplatelet Medications

- Time interval between discontinuation and neuraxial blockade is:
  - ASA/NSAIDs no contraindication
  - Ticlopidine 10 days
  - Clopidogrel 5-7 days
  - Prasugrel 7 days (ideally 10 days)
  - Ticagrelor 5 days

Unfractionated Heparin

- Subcutaneous heparin
  - 5000 U twice or three times daily, there is no contraindication to leaving a catheter
  - Place needle/catheter a minimum of 4 hrs (ideally 6 hrs) after SQ dose
  - Post procedure dose may be administered immediately after needle/cath insertion or removal
  - Consider a platelet count in patients treated for more than 4 days

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Horlocker et al. *RAPM* 2010

Recommended Time Intervals Before and After Neuraxial Block or Catheter Removal*

DRAFT

Drug	Time before puncture/catheter manipulation or removal	Time after puncture/catheter manipulation or removal
Dabigatran	5 days	6 hours
Apixaban	3 days	6 hours
Rivaroxaban	3 days	6 hours
Prasugrel	7-10 days	6 hours
Ticagrelor	5-7 days	6 hours

*Developed at 4th ASRA Practice Advisory for Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy

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QUESTIONS?