

An Update on Anticoagulation and Interventional Pain Procedures

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Two Recent Case Reports

Case Report #1¹

- 49 yo male with severe diabetic peripheral neuropathy refractory to conservative medical management
- History of recurrent and diffuse CAD requiring 8 drug-eluting stents and bilateral carotid atherosclerosis (with history of unilateral CEA)
- On dual antiplatelet therapy with clopidogrel and aspirin
- Decided patient was candidate for spinal cord stimulation therapy

Case Report #1¹

- Management
 - Coordinated antiplatelet cessation with primary cardiologist
 - Exhaustively informed patient of risks of procedures and cessation of antiplatelets
 - Continued aspirin 325mg daily throughout
 - Held clopidogrel 7 days prior to trial and restarted 24 hours after lead removal → Trial successful
 - Held clopidogrel 7 days prior to implant and restarted after all surgical site drainage had stopped (another 7 days)
 - Educated on signs and symptoms of epidural hematoma and instructed to present to nearest emergency room

Case Report #2

- 34 yo male with failed back surgery syndrome following partial discectomy at L5-S1 secondary to mortar blast injury
- Pain recurrence 4 years after initial surgery leading to L5-S1 discectomy and fusion with aggravation of bilateral radicular pain symptoms
- Patient had history of arachnoiditis on MRI
- Medications included prazosin, sertraline, sumatriptan, valproic acid
- Medical history of PTSD, TBI

Case Report #2

- Management and outcome
 - Bilateral atraumatic introducer needle placement at T12-L1 without elicitation of paresthesia
 - Advancement of lead to T8 without incident on the left
 - During advancement of right lead at the T11-12 junction, patient reported paresthesia in entire right lower extremity. No CSF or blood return noted upon lead removal.
 - Right sided introducer removed and placed at L1-2
 - No paresthesia with right sided lead advancement to T8
 - Persistent but improving pain in RLE following trial

1: Myelo Single (Series 66)



1: Myelo Single (Series 73)



Case Report #2

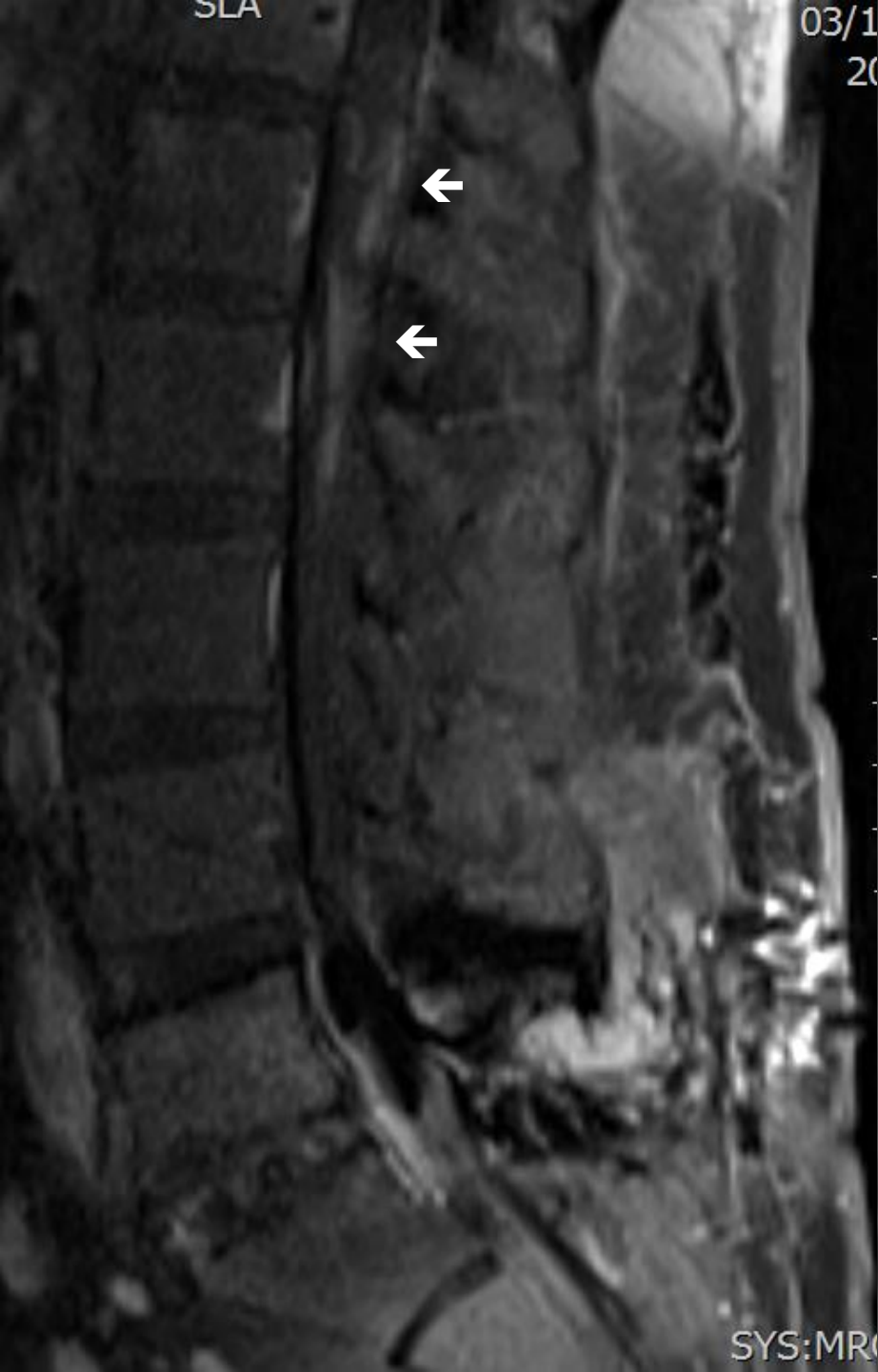
- Management and outcome
 - Presented to ED with RLE edema to ankle and dysesthesia on POD#1 – RLE ultrasound negative, minor improvement with oral narcotics
 - POD#4 – Leads removed, edema had progressed up to right calf, sent to ED for evaluation
 - Thoracic and lumbar MRI showed linear T1 hyperintense, T2 hypointense signal in lumbar portion of thecal sac, consistent with intrathecal blood
 - No dural tear noted
 - Conservative management with narcotics and anticonvulsants
 - Improvement of pain by 30% at one month followup

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Anticoagulation Issues

- Existing American Society of Regional Anesthesia and Pain Medicine guidelines for patients on antiplatelet and anticoagulant medications were deemed insufficient to address all interventional pain procedures
- An ASRA committee attempted to synthesize guidelines with an admitted dearth of evidence from randomized studies or large pooled patient databases²

Anticoagulation Issues

- From a forum at the 2012 ASRA meeting, 124 respondents participated in a poll of anticoagulant / antiplatelet management with interventions
- 98% followed ASRA guidelines for anticoagulants
- 67% had separate protocols for ASA and NSAIDs
- 55% stopped ASA before SCS trials and implants
- 32% stopped ASA before epidurals
- 17% had different protocols for cervical epidural steroid injections

Amplified Bleeding Risk

- Old Age (>65)
- History of Bleeding Tendency or Disorder
- Concurrent use of anticoagulants / antiplatelets
- Liver Cirrhosis / Advanced Liver Disease
- Advanced Renal Disease

Classification Regarding Risk For Serious Bleed

High Risk Procedures

- SCS trial and implant
- Intrathecal catheter and pump placement
- Vertebral augmentation (vertebroplasty / kyphoplasty)
- Epiduroscopy and epidural decompression

Intermediate Risk Procedures

- Interlaminar ESIs
- Transforaminal ESIs
- Facet MBB / RFA
- Paravertebral block
- Intradiscal procedures
- Sympathetic blocks
- Peripheral Nerve Stimulation trial and implant
- Pocket revision / IPG replacement

Classification Regarding Risk For Serious Bleed

Low Risk Procedures

- Peripheral Nerve Blocks
- Peripheral joint and MSK injections
- Trigger Point Injections
- SI joint injections and lateral branch blocks

Anatomic Considerations

- Epidural Space Contents^{3,4}
 - Epidural fat
 - Decreases with age
 - Absent in cervical spine and highest in lumbosacral area
 - Dural Sac
 - Spinal Nerves
 - Extensive Venous Plexuses
 - Fragility increases with age
 - Lymphatics
 - Connective Tissue (Scar tissue after surgery)

Anatomic Considerations

- Epidural Space Measurements⁵
 - 0.4mm at C7-T1
 - 7.5mm in upper thoracic
 - 4.1mm at T11-T12
 - 4-7mm in lumbar regions

Nonsteroidal Anti-inflammatory Drugs

- Inhibit prostaglandin production by inhibiting cyclooxygenase (COX)⁶
 - COX-1 -
 - Constitutive mechanisms
 - Platelet function altered by NSAID inhibition of COX-1 induced acetylation of the serine 529 of COX-1 preventing the formation of PG H₂
 - PG H₂ required for synthesis of thromboxane A₂
 - TXA₂ produced by platelets - prothrombotic effects
 - COX-2 -
 - Inducible, part of inflammatory process

Aspirin

- Irreversible cyclooxygenase inhibitor
- Peak levels 30 minutes after ingestion
- Significant platelet inhibition at 1 hour
- Average lifespan of a platelet is 7 to 10 days
- ASA's antiplatelet effects show significant interindividual variability influenced by age, body mass, and medical conditions (diabetes)⁷

NSAIDs

- Consider discontinuation for high risk procedures
- Consider discontinuation for certain intermediate risk procedures with specific anatomical configurations that may increase risk
 - Cervical ESIs, Stellate ganglion blocks
- Discontinue for 5 half lives to render effects on platelets inactive
 - Exceptions: hypoalbuminemia, hepatic dysfunction, renal dysfunction
- No need for selective COX-3 inhibitor cessation

TABLE 2. Half-Lives of Commonly Administered Non-Aspirin NSAIDs

Agent	Half-life, h	Discontinuation Time, 5 Half-lives, h	Recommended Discontinuation Time, d
Diclofenac ¹⁵⁶	1–2	5–10	1
Etodolac ¹⁵⁷	6–8	30–40	2
Ibuprofen ¹⁵⁸	2–4	10–20	1
Indomethacin ¹⁵⁹	5–10	25–50	2
Ketorolac ¹⁶⁰	5–6	25–30	1
Meloxicam ¹⁶¹	15–20	75–100	4
Nabumetone ¹⁶²	22–30	110–150	6
Naproxen ¹⁶³	12–17	60–85	4
Oxaprozin ¹⁶⁴	40–60	200–240	10
Piroxicam ¹⁶⁵	45–50	225–250	10

Aspirin Recommendations

- Patient and Procedure-specific strategy in tandem with patient's care team
- Review medical record to identify additional medications that may heighten aspirin's anticoagulant effect (SNRIs, dypridamole)
- Primary prophylaxis
 - Recommend discontinuation for high-risk and certain intermediate-risk procedures (CESI, Stellate)
 - Discontinuation for 6 days to ensure complete platelet recovery
- Secondary prophylaxis
 - Shared assessment, risk stratification involving pain physician and physician prescribing aspirin with documentation of decision and risk discussion with patient
 - Length of discontinuation determined on individual basis
 - 4-6 days

Aspirin Recommendations

- Spinal cord stimulator trials
 - No consensus on length of trial – allow sufficient time for patient to determine intent to proceed
 - Platelet rebound phenomenon may occur with discontinuation of aspirin
 - Occurrence of CV event is in the range of 8 to 14 days
- Resumption of therapy
 - NSAIDs – 24 hours postprocedure
 - Aspirin
 - Secondary prevention – 24 hours postprocedure
 - Primary prevention – 24 hours postprocedure after high and intermediate risk procedures
 - Clot stabilization occurs at 8 hours

P2Y12 Inhibitors

Ticlopidine, Clopidogrel, Prasugrel, Ticagrelor

- Thienopyridines (Ticlopidine, Clopidogrel)
 - Block ADP receptor P2Y12 subtype
 - Widely used in treatment of coronary syndromes, cerebrovascular ischemic events, peripheral vascular disease
 - In combination with aspirin for dual antiplatelet therapy to reduce thrombotic events
- Clopidogrel (Plavix)^{8,9,10,11,12,13}
 - Several limitations but widely used
 - Lack of response in 4 to 30% of patients
 - Susceptible to drug-drug interactions and genetic polymorphisms
 - Prodrug – requires 2 metabolic steps to form active drug
 - Time to peak effect takes 24 hours (shortened by loading dose of 300-600mg to 4-6 hours)
 - Maximum platelet inhibition is 50-60% which normalizes 7 days after discontinuation

Clopidogrel

- ASRA Guidelines
 - 7 days for regional anesthetic techniques
- ACC Guidelines
 - 7-10 days for most patients, 5 days in angina high risk
 - In study on decay of antiplatelet effect by Benzon, no difference in % platelet inhibition between 5 and 7 days¹⁴
- For elective pain procedures, stop clopidogrel for 7 days
- For SCS trial
 - Consult with treating physician
 - Stop for 5 days and minimize duration of trial
 - Suggest platelet function test prior to trial
 - VerifyNow P2Y12 assay
 - Platelet mapping portion of TEG
- Restart 12 to 24 hours after spine procedure (24h if loading dose is used)

Clopidogrel

- Low-Risk Procedures
 - Many can be done without cessation
- In patients with higher bleeding risk profiles
 - Shared assessment, risk stratification, and management decision in conjunction with treating physician
 - When taking concomitant antiplatelet medications (aspirin?)
 - With Advanced patient age
 - In Presence of Renal or Liver Disease
 - With Prior history of abnormal bleeding
- Intermediate-High Risk Procedures
 - 7 days
 - If high risk for thromboembolic events, 5 days and assessment with platelet function tests if available

Prasugrel (Effient)

- Irreversible inhibition of P2Y₁₂ receptor
- Unlike Clopidogrel:
 - Requires only 1 active step
 - No drug-drug interactions or genetic polymorphisms
 - Median time to peak effect is 1 hour
 - 90% platelet inhibition¹³
- Patients >75 years old, h/o TIA/CVA, small body mass are at increased risk of bleeding
- Platelet activity does not normalize until 7 days after cessation
- Recommend cessation for 7 to 10 days for intermediate and high risk procedures
- Restart 24 hours after procedure

Ticagrelor (Brilinta)

- Unlike clopidogrel and prasugrel, a direct-acting P2Y₁₂ receptor inhibitor¹⁵
- Major metabolism is liver with minor clearance by the kidney
- With liver disease, concentrations of parent and metabolites are higher but percent platelet inhibition and pharmacodynamics not different from healthy controls¹⁶
- Peak platelet inhibition at 2 to 4 hours after intake
- Mean platelet inhibition of 90%
- Platelet recovery is 5 days after cessation¹⁷
- Recommend cessation of 5 days for intermediate and high risk procedures
- Resume 24 hours after procedure

Warfarin (Coumadin)

- Inhibits the γ -carboxylation of the vitamin K-dependent coagulation factors (II, VII, IX, X) and proteins C and S
- Monitored by INR
- Full anticoagulant effect of warfarin does not occur until 4 days when levels of factor II are significantly decreased
- Narrow therapeutic index and wide interpatient dosing variability with genetic factors accounting for a large proportion of the variations in dose requirements¹⁸
- Normalization of coagulation usually within 5 days

Warfarin (Coumadin)

- Benzon et al. showed levels of clotting factor VII are greater than 40% (levels considered safe for hemostasis) during first 12 to 16 hours after initial warfarin intake¹⁹
- If warfarin given more than 24 h before neuraxial intervention, ASRA recommends INR check
- Epidural catheters can be removed within 24 h of warfarin initiation
 - Removal of the epidural within 48 h is probably safe since levels of X and II are likely adequate for hemostasis
- Beyond 2 days, VII, IX and X are affected and status of II is not assured

Warfarin (Coumadin)

- Low Risk Procedures
 - Consider cessation in conjunction with treating physician
 - Most procedures safe with INR < 3.0
- Intermediate and High Risk Procedures
 - Shared assessment, risk stratification, management decision with treating physician in those at higher bleeding risk
 - Cessation for 5 days with normalization of INR
 - Restart warfarin 24 h following procedure
 - Alternatively, “bridge therapy” with LMWH can be considered in patients at high risk of thrombosis

TABLE 3. Recommended Intervals Between Discontinuation of the Anticoagulants and Interventional Pain Procedure and the Procedure and Resumption of the Anticoagulant

Anticoagulant	Recommended Interval Between Discontinuation of Drug and Pain Procedure	Recommended Interval Between Pain Procedures and Resumption of Drug
Coumadin	5 d, normalization of INR	24 h
IV heparin	4 h	2 h†
Subcutaneous heparin, BID and TID	8–10 h	2 h†
LMWH	24 h	24 h
Fibrinolytic agents	At least 48 h*	At least 48 h*
Fondaparinux	4 d	24 h

*Note that blood clots are not completely stable until approximately 10 days after fibrinolytic therapy and that increased bleeding may occur if pain procedure is done within 10 days of thrombolytic therapy.

†If a moderate- or high-risk procedure was bloody, then a 24-hour interval should be observed.

New Anticoagulants: Dabigatran, Rivaroxaban, Apixaban

- Do not require regular monitoring and there are no dietary restrictions
- No published studies concerning discontinuation, neuraxial procedures, and resumption of drug
- European and Scandinavian guidelines adopted a 2 half-life interval between discontinuation and neuraxial injection (ASRA did not make recommendations)^{20,21}
- No consensus for “exact” time for management
- Pharmacokinetics were studied in young healthy individuals and not elderly patients (with multiple medical comorbidities)
- No specific antidote is available

Dabigatran, Rivaroxaban, Apixaban

- 25% of the drug remains in the plasma after 2 half-lives
- 3% remains after 5 half-lives
- Recommend a 5 half-life interval between discontinuation and neuraxial pain procedures
- If risk of VTE is high, consider bridge with LMWH

Dabigatran, Rivaroxaban, Apixaban

- Resumption following neuraxial injection or epidural catheter removal
- Although thrombolytics are still effective when given within 6 hours of a cerebral embolic clot, thrombolytics are more effective when given 3 hours after onset of stroke
- Studies of thrombolytics imply that anticoagulants may have a hard time lysing a clot if given after 6 hours and most probably will not lyse a clot if given 24-48 h after a neuraxial injection^{22,23}
- Risks posed by elderly with spine abnormalities lead to recommendation of 24 h interval after neuraxial intervention before resumption
- If risk of VTE is high, a 12 h interval may be considered

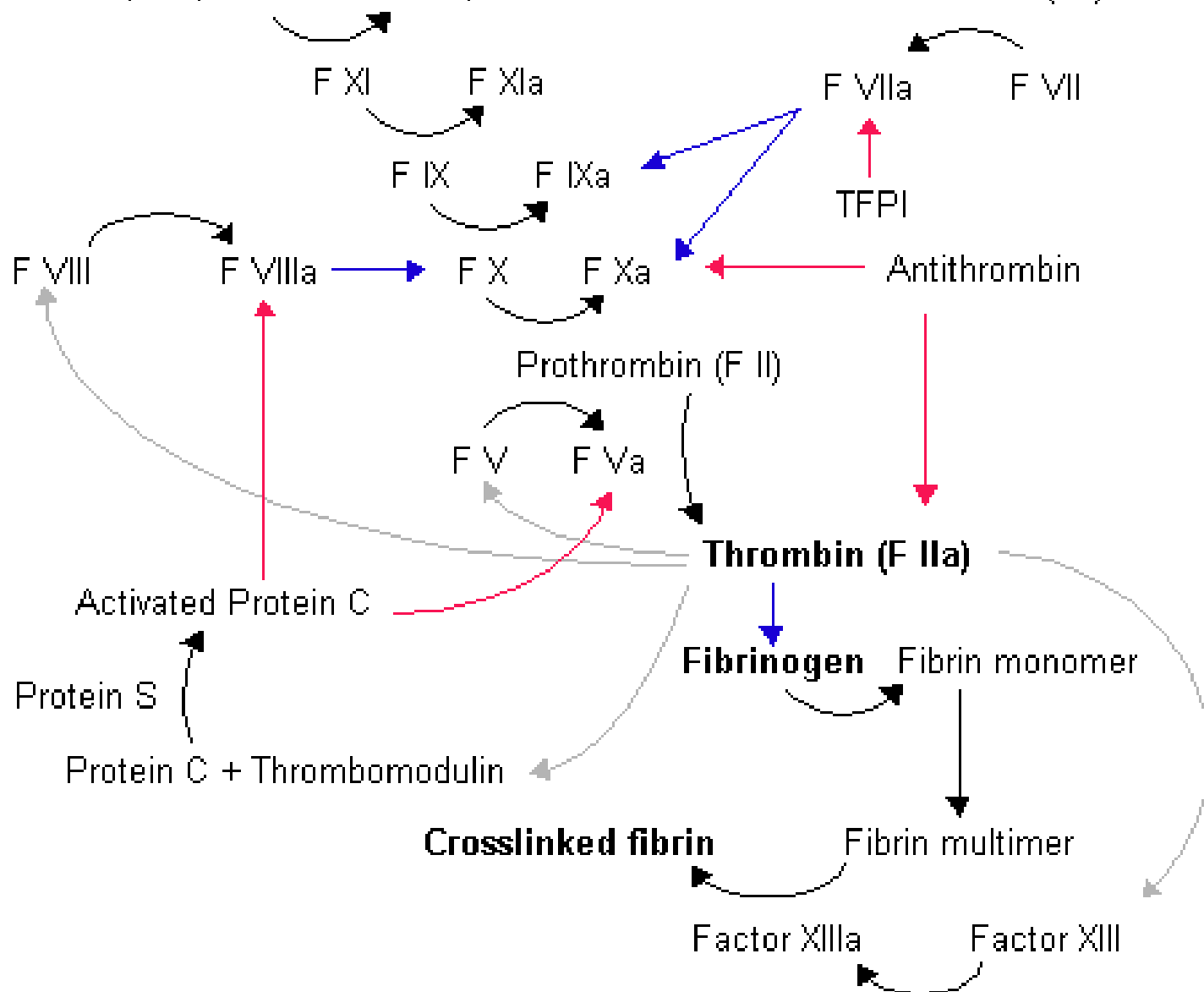
Contact system:

HMWK, PK, F XII

F XIIa, Kallikrein

Cellular injury:

Tissue Factor (TF)



Dabigatran (Pradaxa)

- Direct thrombin inhibitor that blocks interaction of thrombin with substrates – acting independently of antithrombin
- Peak plasma concentration at 1.5 to 3 hours after oral intake with half life of 14-17 hours²⁴
- Pharmacokinetics not affected by sex, body weight, hepatic impairment²⁴
- Renal clearance is 80% with doubling of elimination half time from 14 to 28 hours with ESRD²⁵
- Effective in prevention of stroke in patients with nonvalvular atrial fibrillation in the US (approved in Europe / Canada for prevention of VTE after total hip / knee)²⁶

Dabigatran (Pradaxa)

- 24 hour interval before resumption after interventional pain procedure
- Low risk procedures
 - Shared assessment, risk stratification with treating physician
- Intermediate to High Risk Procedures
 - Cessation of 5 half-life interval (4 to 5 days)
- Special Considerations
 - Patients with ESRD – 6 day interval
 - High risk for VTE – may resume 12 hours after procedure

Rivaroxaban (Xarelto)

- Direct factor Xa inhibitor with peak plasma concentrations within 2.5 to 4 hours and max inhibition of Xa at 3 hours^{27,28}
- Xa inhibition occurs for 12 hours or 24-48 h at high doses in the elderly²⁸
- Half-life is 5.7 to 9.2 hours
- Half-life can be up to 13 hours in elderly secondary to renal function decline with age^{29,30}
- A third of the drug eliminated each by kidneys, fecal / biliary, and breakdown to inactive metabolites²⁷

Rivaroxaban (Xarelto)

- Avoid or use with caution in patients with renal disease or hepatic impairment
- Concomitant use of aspirin and rivaroxaban is an independent risk factor for bleeding
- Aspirin + Clopidogrel + Rivaroxaban = enhanced inhibition of ADP-induced platelet aggregation³¹
- As effective as enoxaparin in treatment of symptomatic VTE, noninferior to warfarin for prevention of embolic stroke during atrial fibrillation, and approved for prevention of VTE after orthopedic surgery^{32,33,34}

Rivaroxaban (Xarelto)

- There is a black box warning about spinal / epidural hematoma and rivaroxaban
 - Factors that increase risk are indwelling epidural catheters, concomitant use of drugs that inhibit platelet function, traumatic epidural / spinal punctures, h/o spinal deformity / surgery³⁵
- In the RECORD studies, epidural catheters were not removed for 2 half lives after last dose and next dose was given 4-6 hours after catheter removal³⁶
 - There were no spinal hematomas in 1411 patients

Rivaroxaban (Xarelto)

- Low Risk Procedures
 - Shared assessment, risk stratification, management decision with treating physician
 - Consider 2 half-life interval
- Intermediate to High Risk Procedures
 - 5 half-live interval cessation (3 days)
- 24 hour interval following interventional pain procedures and resumption of rivaroxaban
 - If high risk of VTE, may resume in 12 hours

Lawsuits with Pradaxa, Xarelto

12:20 pm ET
Aug 29, 2014

UNCATEGORIZED

The Clot Thickens: Lawyers Boost Spending to Solicit Xarelto Lawsuits

The spending increased shortly after Boehringer Ingelheim, which sells a rival blood thinner called Pradaxa, last May agreed to pay \$650 million to settle about 4,000 lawsuits over claims the drug caused serious bleeding episodes. The settlement likely emboldened attorneys to turn their sights toward Xarelto which, like Pradaxa, is one of a relatively new batch of blood thinners.

Also last May, the Institute for Safe Medicines Practices, a watchdog group, issued a **report** indicating the number of serious adverse events for Xarelto had overtaken those for Pradaxa in early 2013. Although the trend likely mirrored increased prescribing for Xarelto, given negative publicity over Pradaxa side effects, the group noted that blood thinners are a "high-risk treatment."

<http://blogs.wsj.com/pharmalot/2014/08/29/the-clot-thickens-lawyers-boost-spending-to-solicit-xarelto-lawsuits/>

Apixaban (Eliquis)

- Specific factor Xa inhibitor
- Attains peak concentrations in 1 to 2 hours.
- Fifteen hours is the approximate high end of the half life
- Eliminated via multiple pathways and direct renal and intestinal excretion³⁷
- Approved in US for stroke prevention in patients with atrial fibrillation
- Noted to be an effective thromboprophylactic agent in total knee / hip arthroplasties, comparable or superior to enoxaparin or warfarin³⁸

Apixaban (Eliquis)

- Low Risk Procedures
 - Shared assessment, risk stratification, management decision with treating physician
 - Consider 2 half-life interval
- Intermediate to High Risk Procedures
 - 5 half-live interval is 3 days
 - However, wide variability in pharmacokinetics leads to 3 to 5 day cessation recommendation
- 24 hour interval following interventional pain procedures and resumption
 - If high risk of VTE, may resume in 12 hours

TABLE 4. Recommended Intervals Between Discontinuation of the New Anticoagulants and Interventional Pain Procedure and Between the Procedure and Resumption of the New Anticoagulants

Drug	Half-life	Recommended Interval Between Discontinuation of Drug and Interventional Pain Procedure* (5 Half-lives)†‡	Recommended Interval Between Procedure and Resumption of Drug
Dabigatran	12–17 h	4–5 d	24 h
	28 h (renal disease)	6 d (renal disease)	
Rivaroxaban	9–13 h	3 d	24 h
Apixaban	15.2 ± 8.5 h	3–5 d‡	24 h

*The procedures include medium- and high-risk interventional pain procedures. For low-risk procedures, a shared decision making should be followed, a 2 half-life interval may be considered.

†Because of the lack of published studies and in view of the added risks involved in patients with spine abnormalities, we took the upper limit of the half-life of each drug in calculating the 5 half-lives.

‡The potency and the wide variability in the pharmacokinetics of these drugs make us recommend a longer interval.

Glycoprotein IIb/IIIa Inhibitors

- Abciximab (ReoPro), Eptifibatide (Integrilin), Tirofiban (Aggrastat)
- Frequently used during percutaneous coronary interventions
- Prevent platelet aggregation and thrombus formation
- Usually administered IV

Glycoprotein IIb/IIIa Inhibitors

- Extreme caution recommended in timing of procedures in patients receiving these medications
- Management is based on labeling precautions
- Crucial to determine platelet count before interventional pain procedures to determine absence of drug-induced thrombocytopenia
- Should medication be administered in the immediate postoperative period, recommend careful neurologic assessment for 24 hours

Glycoprotein IIb/IIIa Inhibitors

- Abciximab
 - Recovery of platelet function in 48 hours
 - However, platelet bound drug is noted up to 10 days and has irreversible binding
 - Minimum of 48 hours for low risk procedures
 - Intermediate to High Risk – at least 5 days based on daily formation of new platelets
- Eptifibatide / Tirofiban
 - Low risk procedure – 8 hours
 - Intermediate to high risk – 24 hours
- Rapid onset of action
 - If medication administered after a procedure, an 8 to 12 hour interval is probably adequate

TABLE 5. GPIIb/IIIa Inhibitors and Interventional Pain Procedures

Drug	Half-life	Recovery of Platelet Function, h	Interval Between Drug Discontinuation and Intervention*	Resumption of Drug After Intervention, h†
Abciximab	10–30 min	48	48–120 h (2–5 d)	8–12
Eptifibatide	2.5 h	4	8–24 h	8–12
Tirofiban	2 h	4–8	8–24 h	8–12

Data from De Luca³²⁹ and Schenider and Aggarwal.³³⁰

*The shorter interval is for low risk whereas the longer interval is for intermediate- and high-risk procedures. These are minimum intervals as there are no studies on regional anesthesia or pain interventional procedures in patients on GPIIb/IIIa inhibitors. Note that although abciximab has a quick onset of action, it causes an irreversible binding with the GPIIb/IIIa. The platelet count should be checked before a procedure.

†The time to resumption of the drug is based on the minimum 8 hour time it takes for the clot to be stable. Note that all the GPIIb/IIIa inhibitors have rapid onsets of action.

Antidepressants and Increased Bleeding Risk

- Serotonin reuptake inhibitors (SRIs) result in depletion of platelet serotonin content (as they do not synthesize serotonin), resulting in inhibition of aggregation and increased bleeding^{39,40}
- Bleeding risk is dependent on potency of serotonin reuptake inhibition rather than selectivity
- Fluoxetine, Paroxetine, fluvoxamine have potent cytochrome P450 enzyme inhibitory effects → increases blood levels of NSAIDs and other antiplatelets⁴¹

Antidepressants and Increased Bleeding Risk

- Evidence
 - Absolute bleeding risk about equivalent to low-dose ibuprofen
 - Risk increases in elderly, liver cirrhosis, anticoagulants and antiplatelets
 - Risk of reoperation due to surgical bleeding after breast cancer surgery was increased 7% among current SSRI users with a 2.6% risk in non-users⁴²
 - In a retrospective followup of 520 patients undergoing orthopedic surgery, risk of intraop transfusion nearly quadrupled in SRI group compared with non-users⁴³

Antidepressants and Increased Bleeding Risk

- SRIs and Antiplatelets
 - Large epidemiologic study
 - SSRI + NSAID = increased relative risk of GI bleed to 12.2
 - SSRI + low-dose ASA = 2.3⁴⁴
- SRIs and Anticoagulants
 - Population based study of 2 million patients on warfarin, SSRI users at significantly increased risk of hospitalization due to non-GI tract bleeding⁴⁵

Antidepressants and Increased Bleeding Risk

- Recommendations
 - Routine discontinuation not recommended
 - Stable depression + high risk of bleeding (old age, advanced liver dz, concomitant ASA, NSAID, antiplatelet, anticoagulant use) = gradual tapering with discontinued usage 1 to 2 weeks before procedure
 - Fluoxetine should be discontinued for 5 weeks prior to procedure due to long half life
 - Unstable depression / suicide risk + high risk of bleeding = switch to nonserotonergics (bupropion, TCAs)
 - Coordinate with treating physician

TABLE 6. The Serotonergic Effects of Commonly Used Antidepressants in a Ranking Order

Antidepressants†	Class	Receptor Occupancy, % ³⁷¹			t1/2, h	5-t1/2 (Approx), d	Active Metabolite ³⁷¹	t1/2, h	5-t1/2 (Approx)
		5-HT Transporter	Norepinephrine Transporter	5-HT2c- Receptor					
Clomipramine ³⁷²	TCA	96.44	11.05	11.62	24	5	N-desmethyldesipramine	69	2 wk
Paroxetine ³⁷³	SSRI	95.7	4.7	0.06	21	5			
Escitalopram ³⁷⁴	SSRI	93.66	0.37	1.04	27–32	5–6			
Citalopram ³⁷⁵	SSRI	93.45	1.08	11.1	35	7			
Fluvoxamine ³⁷⁶	SSRI	92.74	3.33	1.35	16–26	5			
Fluoxetine ³⁷⁷	SSRI	88.96	7.37	19.74	24–72*	5–15	Norfluoxetine	7–15 d	5–10 wk
Sertraline ³⁷⁸	SSRI	88.25	1.14	0.062	24	5	N-desmethylertraline	64–104	2–3 wk
Imipramine ³⁷⁹	TCA	86.17	38.59	35.69	24	5	Desipramine	21	4–5 d
Venlafaxine ³⁸⁰	SNRI	84.52	12.47	14.83	5	1	O-desmethylenlafaxine	11	2 d
Doxepin ³⁸¹	TCA	67.08	82.44	94.03	15	3			
Amitriptyline ³⁸²	TCA	66.49	49.24	91.29	1–36	3–7	Nortriptyline	22–88	1–3 wk
Duloxetine ³⁸³	SNRI	56.25	15.35	0.17	12	2–3			
Nortriptyline ³⁸⁴	TCA	18.83	80.25	42.27	30	7			
Nefazodone ³⁸⁵	SSRI/ Antag	4.22	3.05	40.6	4	1			
Maprotiline ³⁸⁶	Tetra	1.3	87.34	38.57	51	10			
Bupropion ³⁸⁷	Misc	0.74	0.71	0.71	15–22	5	Hydroxybupropion	20	4–5 d
Mirtazapine ³⁸⁸	α-2	0.34	0.73	46.51	20–40	5–7			

Data from several references.^{371–388}

*t1/2 in chronic use is 96 to 144 hours.

†The bottom ones have fewer tendencies to cause increased risk of abnormal bleeding.

Herbals

TABLE 7. Herbal Medications and Their Effects on Coagulation

Herb	Effect on Coagulation	Time to Normal Hemostasis After Stoppage, Comments
Garlic	Inhibits platelet aggregation by reduction and inhibition of formation of thromboxane and lipoxygenase products, inhibition of phospholipase activity, and inhibition of incorporation of arachidonate into platelet phospholipids	7 d; test of platelet function recommended when excessive doses are taken or in the presence of other antiplatelet drugs (aspirin, NSAIDs, SSRIs)
Dong quai	Contains natural coumarin derivatives; potentiates effect of warfarin	Check INR in patients on warfarin
Danshen	Decreases elimination of warfarin; inhibition of platelet aggregation	Check INR in patients on warfarin
Ginkgo biloba	Inhibition of PAF	36 h, check platelet function in the presence of other antiplatelets
Panax ginseng	Reduces effect of warfarin	

Modified from Horlocker et al¹²⁷ with permission. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Procedural Anticoagulation Management Checklist

Evaluate baseline patient specific risk factors for perioperative bleeding:

- History and physical examination signs suggestive of a bleeding disorder:
 - History of unexplained nosebleeds (epistaxis) or menorrhagia
 - Examination signs including petechiae, mucosal bleeding, purpura, or ecchymoses
- Family history of bleeding disorders.
- Screen for antiplatelet, antithrombotic, or thrombolytic therapy.
- Screen for SNRIs, SSRIs, and herbal therapies that may influence coagulation status.
- Order coagulation tests when needed based on history and physical examination and/or medication use.
- Identify aspirin and non-aspirin NSAIDs utilization.

For individuals on aspirin categorize reason for utilization:

- Primary prophylaxis → absence of established cardiovascular disease or risk factor.
- Secondary prophylaxis → presence of cardiovascular disease.

Process the anatomical location of procedural intervention into decision-making.

- Intracanal vs extracanal spinal procedures
- Cervicothoracic neuraxial area or lumbosacral neuraxial area.
- Surrounding vascular structures at risk for penetration.

Review appropriate radiographic imaging to identify and understand anatomic challenges

- Cervical, thoracic, and lumbar spinal stenosis that alter spinal canal anatomy
- Epidural fibrosis and significant scar tissue from previous surgical intervention

Identify and manage pharmacologic coagulopathies

- Understand drug elimination and appropriate discontinuation time.
- Determine appropriate timing for reinitiation of anticoagulation and antiplatelet therapy.
- Practice Informed decision-making involving procedural physician, prescribing medical physician, and patient.

Employ post-procedure surveillance for the detection of bleeding complications

Drug	When to stop			When to restart
	High risk procedures	Intermediate risk procedures	Low risk procedures	
ASA and ASA combinations	-Primary prophylaxis: 6 days -secondary prophylaxis: shared assessment and risk stratification	Shared assessment and risk stratification**	No	24 hours
NSAIDs	5 half-lives	No ²	No	24 hours
Diclofenac	1 day			
Ketorolac	1 day			
Ibuprofen	1 day			
Etoricoxib	2 days			
Indomethacin	2 days			
Naproxen	4 days			
Meloxicam	4 days			
Nabumetone	6 days			
Oxaprozin	10 days			
Piroxicam	10 days			
Phosphodiesterase Inhibitors				
Cilostazol	2 days	No	No	24 hours
Dipyridamol	2 days	No	No	
ASA combinations	Follow ASA recommendations	Shared assessment and risk stratification*		
Anticoagulants				
Coumadin	5 days, normal INR	5 days, normal INR	-No - shared assessment and risk stratification*	24 hours
Acenocoumarol	3 days, normal INR	3 days, normal INR	-No - shared assessment and risk stratification*	24 hours
IV heparin	4 hours	4 hours	4 hours	2 hours**
Subcutaneous heparin, BID & TID	8-10 hours	8-10 hours	8-10 hours	2 hours
LMWH: prophylactic	12 hours	12 hours	12 hours	-4 hours after low risk -12-24 hours after medium/high risk pain procedures
LMWH: therapeutic	24 hours	24 hours	24 hours	-4 hours after low risk procedures -12-24 hours after medium/high risk pain procedures

Drug	When to stop			When to restart
	High risk procedures	Intermediate risk procedures	Low risk procedures	
Fibrinolytic agents	48 hours	48 hours	48 hours	48 hours
Fondaparinux	4 days	4 days	shared assessment and risk stratification	24 hours
P2Y12 inhibitors				
Clopidogrel	7 days	7 days	No	12-24 hours
Prasugrel	7-10 days	7-10 days	No	12-24 hours
Ticagrelor	5 days	5 days	No	12-24 hours
New anticoagulants				
Dabigatran	4-5 days 6 days (impaired renal function)	4-5 days 6 days (impaired renal function)	shared assessment and risk stratification*	24 hours
Rivaroxaban	3 days	3 days	shared assessment and risk stratification*	24 hours
Apixaban	3-5 days	3-5 days	shared assessment and risk stratification*	24 hours
Glycoprotein IIb/IIIa inhibitors				
Abciximab	2-5 days	2-5 days	2-5 days	8-12 hours
Eptifibatide	8-24 hours	8-24 hours	8-24 hours	8-12 hours
Tirofiban	8-24 hours	8-24 hours	8-24 hours	8-12 hours
Antidepressants and Serotonin Reuptake Inhibitors (SRIs)	See text and table 6	No	No	See text and table 6

Major areas of differences from the ASRA guidelines for regional anesthesia are in yellow boxes.

New medications since the latest ASRA guidelines for regional anesthesia are in blue boxes.

* See detailed text in the corresponding section.

**If a moderate or high risk procedure was bloody, then a 24 hour interval should be observed.

¹ Consideration should be given to the discontinuation of aspirin for certain intermediate risk procedures including interlaminar cervical epidural steroid injections and stellate ganglion blocks where specific anatomical configurations may increase the risk and consequences of procedural bleeding.

² Consideration should be given to the discontinuation of NSAIDs for certain intermediate risk procedures including interlaminar cervical epidural steroid injections and stellate ganglion blocks where specific anatomical configurations may increase the risk and consequences of procedural bleeding (Refer to the section entitled Anatomical Considerations for the Development of a Hematoma in Spinal and Nonspinal Areas).

Summary

- Evidence where available was used
- Many recommendations based on pharmacologic principles or consensus
- Intended that outcomes associated with these guidelines be studied for future incremental improvements and updates
- Authors implore reader to strive to understand the reasoning behind guideline recommendations and impact of possible patient and situational confounders on outcomes

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