CDI QUALITY INSTITUTE

CLINICAL GUIDELINES

Guidelines for the Management of Patients on Oral Anticoagulation and Antiplatelet Therapy Undergoing Percutaneous Image-Guided Needle Procedures: 2020 revision

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Introduction

In this revision, the CDI Quality Institute Anticoagulation Guideline is updated to reflect changes in the 2019 Society of Interventional Radiology Consensus Guidelines for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided interventions. The guideline was published in two parts: The first review discusses the specific anticoagulation agents and clinical considerations (Davidson). The second updates specific SIR recommendations (Patel). The guideline relies on the 2018 ASRA guideline recommendations. When recommendations diverge, the CDI guideline defaults to the SIR recommendations for body procedures and to the ASRA recommendations for spine and joint procedures.

This is a guideline, not a policy. It is a summary and distillation of relevant specialty society guidelines. The purpose of the CDI Quality Institute guidelines is to facilitate and accelerate the integration of medical evidence and best practices into daily clinical practices. Guidelines provide relevant medical evidence to support the development of policies in each individual practice. While individual practice policies may be based on recommendations in the CDI Quality Institute guidelines, they may also reflect local standards of care, associated hospital or network policies, the performance of procedures in hospital versus outpatient settings, different patient populations, differing levels of experience and different risk-tolerance profiles. Local practice policies should also be modified to account for new information or publications that become available between guideline revisions.

Patient management

The risk of bleeding in patients undergoing image-guided needle procedures is increased in patients with bleeding disorders and in patients taking anticoagulant or antiplatelet medications. Depending on the procedure being performed, anticoagulation and antiplatelet drugs may need to be withheld prior to the procedure. Withholding medications may decrease the risk of bleeding; however, it may also increase the risk of recurrent thromboembolism. These risks need to be balanced on a patient-by-patient basis.

Patient assessment: Patients undergoing image-guided needle procedures need to be screened for bleeding disorders and for anticoagulation or antiplatelet medication use. In general, outpatient needle procedures should be avoided in any patient with known bleeding disorders. If a needle procedure is absolutely needed, it should only be performed with hematology-directed management of their coagulation status (generally with assessment of the relevant clotting parameters and the administration of fresh frozen plasma or platelets, depending on their particular condition). The management of these disorders is not addressed in this review.

The management of patients taking anticoagulation and antiplatelet medication is summarized in Table 1. The risk of bleeding associated with the anticipated needle procedure needs to be determined prior to the procedure. If the patient's anticoagulant or antiplatelet medication needs to be withheld, the patient needs to contact their treating physician to get permission to withhold their medications or to obtain bridge therapy for the procedure. Laboratory data, if needed, should be obtained and checked prior to the procedure and compliance with instructions needs to be confirmed with the patient prior to injection.

Risk stratification of injection procedures (Table 2): The bleeding risk associated with different procedures is ranked relative to vascularity of the anatomic site, compressibility of the procedure site, needle size, procedural difficulty and risk of neurologic injury. If a tumor is being biopsied, the risk of tumor dissemination needs to be considered.

Anticoagulant and antiplatelet drug management (Table 3 and addendum): If the patient's anticoagulation or antiplatelet medications are to be withheld, drug-specific instructions need to be given to the patient. The management of individual anticoagulation and antiplatelet drugs depends on the class of drug, any confounding medications, the procedure being ordered, and, in some cases, the liver and renal function.

Bridge therapy (Table 4): If the risk of thromboembolism is high, the patient may be prescribed a bridge anticoagulation regimen for the procedure. In general, warfarin is stopped and the patient is started on a subcutaneous regimen of Lovenox. Lovenox has a short half-life and can be discontinued 12-24 hours prior to the procedure, minimizing the risk of thromboembolism to the patient. The protocol in Table 4 is an example of a bridge therapy regimen. The patient's regimen may differ from this and in general the patient should follow the instructions provided by their provider.

Table 1: Procedural anticoagulant management checklist:

1. Evaluate baseline patient risk factors:
    a. Screen for antiplatelet, antithrombotic or thrombolytic drug use;
    b. Ask if patients taking Warfarin (Coumadin, etc.) or Acenocoumarol are getting regular INR checks, and ask what the results have been;
    c. Screen for SSRI or herbal medication use;
    d. History of severe renal or liver disease;
    e. History or clinical evidence (excessive epistaxis or menorrhagia) of a bleeding disorder*;
    f. Family history of a bleeding disorder*;
    g. Order coagulation tests if a bleeding disorder is suspected based on this history.
2. Assess the risk of bleeding for the ordered injection procedure. The risk of bleeding for various image-guided needle procedures is categorized in Table 2 with respect to the following factors:
    a. Needle size;
    b. Compressibility;
    c. Procedural difficulty;
    d. Risk of neurologic injury; and
    e. Risk of tumor dissemination.
3. If indicated, manage anticoagulation drug use as follows:
    a. Ask the patient to contact their treating physician to make sure it is safe to discontinue anticoagulation therapy or to secure bridge therapy if appropriate;
    b. If the treating provider has given permission to withhold the anticoagulation or antiplatelet medications, the patient should be given drug-specific instructions as listed in Table 3;
    c. If the patient is unable to stop their medications, ask whether a bridge anticoagulation protocol has been prescribed;
    d. If the patient is unable to stop their medications and bridge anticoagulation medications has not been prescribed, consult with the proceduralist to see of the procedure can still be performed. Do not cancel a procedure without first checking with the doctor.
    e. Immediately prior to the procedure, confirm with the patient that the anticoagulation medication was withheld as instructed; and
    f. Check the INR, PTT and/or platelet levels if indicated prior to the procedure.

* In general, spinal procedures should be avoided in any patient with a known bleeding disorder. If a needle procedure is absolutely needed, it should only be performed with directed management of their coagulation status (generally with the administration of fresh frozen plasma or platelets depending on their particular condition).

Table 2: Risk stratification of injection procedures†:

Low risk of bleeding (ASRA 2018, SIR 2019): Procedures with a low risk of bleeding, and/or bleeding easy to detect and control. No need to withhold anticoagulant or antiplatelet therapy. Check INR if patient taking Coumadin or Acenocoumarol (INR < 3.0).

MSK injections

- Peripheral joint injections and aspirations
- Sacroiliac joint injections and aspiration
- Tendon injections
- Bursal injections
- Trigger point injections including piriformis injections

Neural/spine injections*

- Peripheral nerve blocks
- Facet joint injections (intraarticular T and L)
- Thoracic facet MBNB, lumbar facet MBNB and lateral sacral branch blocks
- Facet nerve radiofrequency ablations (T, L)**

Body procedures

- Superficial aspiration and biopsy (LN, mass or breast)
- Thyroid FNA (Hold anticoagulants per radiologist)
- Superficial abscess drainage
- Thoracentesis and paracentesis
- Drainage catheter exchange

Breast procedures

- Breast and axillary biopsies
- Cyst aspirations (Hold anticoagulation per radiologist as some may convert to biopsies)

Vascular procedures

- Diagnostic arteriography and arterial interventions: peripheral, sheath < 6 F
- Venography
- IVC filter placement and removal
- PICC line placement and removal

Moderate risk of bleeding: Bleeding more difficult to control or detect, or has risk of catastrophic neurologic compromise. Hold warfarin for 5 days. Check INR prior to the procedure; should be < 1.5. Do not need to withhold ASA, NSAIDs or phosphodiesterase inhibitors.

Neural/spine injections and procedures*

- Interlaminar ESIs (C, T, L) (Consider holding ASA for cervical and thoracic procedures)
- Transforaminal ESIs (C, T, L, S) (Consider holding ASA for cervical and thoracic procedures)
- Caudal ESIs
- Lumbar punctures
- Cervical facet joint injections (intra-articular) (Consider holding ASA for C1-2 procedures)
- Cervical MBNB and RFA
- Facet cyst aspiration/rupture (C, T, L)
- Intradiscal injections (C, T, L)
- Sympathetic blocks (stellate, thoracic splanchnic, celiac, lumbar and hypogastric) (Consider holding ASA)

High risk of bleeding: This group includes procedures that have a high risk of uncontrolled or excessive bleeding. This group also includes biopsies of suspected sarcomas, as hemorrhage can result in tumor dissemination and can have an adverse effect on patient prognosis. Hold anticoagulation drugs, antiplatelet drugs, ASA, NSAIDs and phosphodiesterase inhibitors per guidelines. Check INR (< 1.5), aPTT (< 1.5 control), platelet count (> 50,000) and hematocrit prior to the procedure.

MSK procedures

- Primary bone and soft tissue biopsies with possible diagnosis of sarcoma

Neural/spine injections and procedures*

- Spinal Cord Stimulator trial and implant
- Dorsal root ganglion stimulation, trial and implant
- Vertebral augmentation (vertebroplasty and kyphoplasty)
- Intrathecal catheter and pump placement

Body procedures

- Solid organ biopsies
- Deep non-organ biopsies
- Urinary tract interventions
- Biliary interventions
- Gastrostomy placement
- Radiofrequency ablation procedures: solid organs, bone, soft tissue, lung
- Deep abscess drainage

Vascular procedures

- Arterial interventions: > 7-F sheath, aortic, pelvic, mesenteric
- Intrathoracic venous interventions

- Portal vein interventions
- TIPS

† Adapted from ASRA 2018, SIR 2019, Jaffe 2015, Ahmed 2012, Salvati 2003, and Clearfield 2012.

* Low or intermediate risk procedures should be treated as intermediate or high risk, respectively, in patients with additional risk factors for bleeding. Factors placing patients at increased risk of bleeding include old age, history of bleeding tendency, concurrent use of other anticoagulants/antiplatelets, liver cirrhosis, advanced liver disease and advanced renal disease.

**The classification of thoracic and lumbar RFAs as low or moderate risk of bleeding should be made on a case-by-case basis, as this procedure typically utilizes larger bore needles and multiple sticks.

Table 3: Peri-procedural management recommendations for anticoagulant and antiplatelet medications:

DRUG	When to stop			When to restart
	Low-risk procedures	Moderate-risk procedures	High-risk procedures	
ASA†				
Aspirin/ASA	No	No†	6 days	24 hours
NSAIDs†				
Diclofenac (Cambia®, Cataflam®, Voltaren®, Voltaren-XR®, Zipsor®, Zorvolex®)	No	No*	1 day	24 hours
Ketorolac (Toradol ®)	No	No*	1 day	24 hours
Mefenamic acid (Ponstel®)	No	No*	1 day	24 hours
Ketoprofen	No	No*	1 day	24 hours
Ibuprofen (Motrin ®, Advil ®, Vicoprofen®, Combunox®)	No	No*	1 day	24 hours
Etodolac (Lodine®, Lodine XL®)	No	No*	2 days	24 hours
Indomethacin (Indocin®)	No	No*	2 days	24 hours
Naproxen (Aleve ®, Naprosyn ®, Anaprox®, Naprelan®, Naprapac®)	No	No*	4 days	24 hours
Meloxicam (Mobic®, Vivlodex®)	No	No*	4 days	24 hours
Nabumetone (Relafen®)	No	No*	6 days	24 hours
Oxaprozin (Daypro®)	No	No*	10 days	24 hours
Piroxicam (Brexidol ®, Candyl ®, Feldene ®)	No	No*	10 days	24 hours
Phosphodiesterase inhibitors				
Dipyridamole (Persantine)	No	No	2 days	24 hours
Dipyridamole/ASA (Aggrenox ®)	No	No†	6 days	24 hours
Cilostazol (Pletal ®)	No	No	2 days	24 hours
Pentoxifylline (Trental ®, Pentoxil ®)	No	No	2 days	24 hours
Cox-2 inhibitors				
Celecoxib (Celebrex)	No	No	No	
Anticoagulants				
Warfarin (Jantoven®, Coumadin®, Marevan®, Uniwarfin®)	No, INR (<3)	5 days, INR (<1.5)	5 days, INR (<1.5)	Evening of the procedure or next day
Acenocoumarol	No, INR (<3)	3 days, INR (<1.5)	3 days, INR (<1.5)	24 hours
†In patients taking ASA or NSAIDs for primary prophylaxis, consider holding ASA for certain intermediate-risk procedures such as cervical and thoracic interlaminar epidural steroid injections, C1-2 injections and stellate ganglion blocks.				

P2Y12 inhibitors				
Clopidogrel (Plavix®)	No	5-7 days	5-7 days	12 hrs usual daily dose; 24 hrs if loading dose
Prasugrel (Effient®)	No	7 days	7-10 days	24 hours
Ticagrelor (Brilinta®)	No	5 days	5 days	24 hours
Factor Xa Inhibitors				
Rivaroxaban (Xarelto®)	No	3 days	3 days	24 hrs, 1/2 dose at 12 hrs if high risk of VTE
Apixaban (Eliquis®)	No	3 days	3 days	24 hrs, 1/2 dose at 12 hrs if high risk of VTE
Edoxaban (Savaysa®)	No	3 days	3 days	24 hrs, ½ dose at 12 hrs if high risk of VTE
Betrixaban (Bevyxxa®)	No	5 days	5 days	24 hours
Fondaparinux (Arixtra®)	No	4 days	4 days	6 hrs low risk, 24 hrs int/high risk
Direct Thrombin Inhibitors				
Dabigatran (Pradaxa®)	No	5 days	5 days	24 hours, ½ dose at 12 hrs if high risk of VTE
SSRI and SNRI				
Paroxetine, Escitalopram, Citalopram, Fluvoxamine, Fluoxetine, Setraline, Velafaxine, Duloxetine	Routine discontinuation is not recommended. If the patient is at high risk of bleeding, these drugs may be slowly tapered in patients with stable depression under the supervision of the patient's treating psychiatrist.			
Subcutaneous Low-Dose Heparin				
Enoxaparin (Lovenox) low dose for prophylaxis		1 dose or 12 hours	1 dose or 12 hours	4 hours, 12-24 if int. or high risk procedure
Enoxaparin (Lovenox) therapeutic dose (≥1 mg/kg every 12 hours)		24 hours	24 hours	4 hours, 12-24 if int. or high risk procedure
Dalteparin (Fragmin®, Eisai®)		24 hours	24 hours	4 hours, 12-24 if int. or high risk procedure
Herbal medications				
Garlic and ginkgo biloba	Hold for 1 week for high-risk procedures. Test platelet function if garlic >1000mg/day or if taken with ASA, NSAIDs or SRIs. Hold if bleeding time elevated.			

Dong quai and danshen	Hold for 1 week for high-risk procedures. Check INR in patients on warfarin or acenocoumarol.
Dietary supplements	
Vitamin E	Consider stopping Vitamin E for 6 days prior to high-risk procedures. Consider stopping Vitamin E consumption prior to low or intermediate-risk procedures in patients on concomitant antiplatelet medications.
Fish oil	Consider stopping fish oil for 6 days prior to high-risk procedures.
Other Medications	
Pentosan Polysulfate Sodium (Elmiron)	Pentosan polysulfate sodium should be withheld for 5 days prior to intermediate and high-risk procedures. Restart 24 hours after the procedure.
Nattokinase	Hold for 1-2 weeks before intermediate or high-risk procedures.

Table 4: Example bridge therapy regimen:

The following is an example of the low-dose bridging regimen used in the CDI Vascular Center at St. Louis Park.

1. Hold warfarin starting 5 days prior to procedure.

2. Pre-procedure (three days of bridging):
    a. Initiate Lovenox injections 3 days prior to procedure with one AM dose of 40mg Lovenox SQ each day.
    b. Hold Lovenox on the morning of the procedure.

3. Post-procedure (5 days of bridging post-procedure):
    a. Begin Lovenox 40mg SQ 4 hours after a low-risk procedure and 12 hours after an intermediate- or high-risk procedure.
    b. Warfarin (double patient's lowest dose) PM for 2 days beginning the day of the procedure.
    c. Continue Lovenox 40mg PM SQ WITH warfarin (return to normal scheduled dose) for 3 days.
    d. Check INR (6 days post-procedure) and call with result to 952-738-4498.
    e. Based on the INR, may prescribe additional doses of Lovenox.

Addendum A: Anticoagulation and antiplatelet drug management

Oral antiplatelet agents-aspirin and NSAIDs: Nonsteroidal anti-inflammatory drugs inhibit platelet cyclooxygenase and prevent the synthesis of thromboxane A2. Platelets from patients being treated with NSAIDS have normal subendothelial plug formation and normal primary plug formation. Aspirin has a mild antiplatelet effect.

With aspirin, platelet function is compromised for the life of the platelet. Restoration of clotting depends on the restoration of functioning platelets. 10% of the platelet pool is replaced daily and at 5-6 days, approximately 50% of platelets will function normally (ASRA). Within 3 days of discontinuing aspirin, there will be at least 50-60 x 10^9/L fully functional platelets which should be adequate to normalize bleeding risk, even for high-risk interventions (SIR).

NSAIDs reversibly inhibit COX-1 and/or COX-2 and have weak antiplatelet effects. They produce a short-term effect and restoration of platelet function parallels the plasma half-life of the individual NSAID drug. For high-risk procedures, an NSAID should be held for five times the plasma half-life of the drug.

Recommendations:

- **Low-dose aspirin (ASA)**
  - Not been shown to increase the risk of bleeding with low-risk procedures.
  - Consider holding ASA for certain intermediate-risk procedures, including interlaminar cervical ESIs and stellate ganglion blocks, where anatomical configurations may increase the risk and consequences of procedural bleeding (ASRA 2018).
  - For patients taking ASA for primary prophylaxis, hold 3-6 days for patients undergoing high-risk procedures (SIR 2019, 3-5 days; ASRA 2018, 6 days; JVIR, NEJM, 7-10 days; ACCP, 7-10 days).
  - For patients taking ASA for secondary prophylaxis, after shared decision making and risk stratification, consider holding for 3-5 days for patients undergoing high-risk procedures or consider bridging therapy (SIR 2019, 3-5 days; ASRA 2018 4, days).
  - Consider withholding ASA in patients taking ASA in combination with anticoagulation drugs, other antiplatelet drugs, dipyridamole, Vitamin E, feverfew, ginkgo, garlic, fish oil or SSRI drugs (Celexa, Lexapro, Prozac, Paxil, Pexeva, Zoloft, Viibryd) (ASRA 2018).
  - May restart 24 hours after a high-risk procedure (ASRA 2018, ACCP, and NEJM). The anticoagulant effect of ASA can be seen as soon as 1 hour after an oral dose.

- **NSAIDs**

- Do not need to be withheld for low-risk and most intermediate-risk injection procedures.
- Consider holding NSAIDs for certain intermediate-risk procedures (such as interlaminar cervical ESIs and stellate ganglion blocks) where certain anatomical configurations may increase the risk and consequences of procedural bleeding (ASRA 2018).
- Hold for 5 half-lives prior to high-risk procedures:
  - **Diclofenac (Cambia®, Cataflam®, Voltaren®, Voltaren-XR®, Zipsor®, Zorvolex®)** T½ = 1-2 hours - Hold 1 day;
  - **Ketorolac (Toradol ®)** T½ = 5-6 hours - Hold 1 day;
  - **Mefenamic acid (Ponstel®)** T½ = 2 hours - Hold 1 day;
  - **Ketoprofen** T½ = 2-5 hours **-** Hold 1 day
  - **Ibuprofen (Motrin®, Advil®, Vicoprofen®, Combunox®)** T½ = 2-4 hours – Hold 1 day;
  - **Etodolac (Lodine®, Lodine XL®)** T½ = 6-8 hours - Hold 2 days.
  - **Indomethacin (Indocin®)** T½ = 5-10 hours - Hold 2 days.
  - **Naproxen (Aleve ®, Naprosyn ®, Anaprox®, Naprelan®, Naprapac®)** 12-17 hours - Hold 4 days.
  - **Meloxicam (Mobic®, Vivlodex®)** T½ = 15-20 hours - Hold 4 days.
  - **Nabumetone (Relafen®)** T½ = 22-30 hours - Hold 6 days.
  - **Oxaprozin (Daypro®)** T½ = 41 hours - Hold 10 days.
  - **Piroxicam (Brexidol®, Candyl®, Feldene®)** T½ = 45-50 hours - Hold 10 days.
  - **Sulindac (Clinoril®)** T½ = 16 hours (active metabolite) – Hold for 3 days (80 hours)
  - **Diflunisal (Dolobid)** T½ = 8-12 hours – Hold for 3 days (40-60 hours)
- Consider holding longer in patients with severe renal or hepatic dysfunction, hypoalbuminemia, alcohol abuse or a history of serious post-procedural bleeding.
- May restart 24 hours after a high-risk procedure (ASRA 2018, NEJM).

Oral antiplatelet agents – Phosphodiesterase inhibitors: These drugs selectively inhibit phosphodiesterase, thereby increasing the intracellular level of CAMP. Phosphodiesterase inhibitors have vasodilatory and weak reversible platelet aggregation inhibitory actions. When used in combination with aspirin, an increased bleeding risk has been reported.

Recommendations:

- **Dipyridamole (Persantine®)**
  - Oral, T½ = 10-12 hours
  - Not been shown to increase the risk of clinically significant post-procedural bleeding.

- Does not need to be withheld for low or moderate-risk procedures (ASIPP 2013, ACCP, AAPM&R: 7 days).
- Hold for 2 days prior to high-risk procedures (ASRA 2018).
- May restart as soon as possible after the procedure.

- **Dipyridamole/ASA (Aggrenox®)**
  - Oral
  - Does not need to be withheld for low or moderate-risk neuro/MSK procedures (ASRA 2018, ASIPP 2013, ISIS - 3 days; UWMC - 7 days, ACCP).
  - Does not need to be withheld for low-risk body/breast procedures (SIR 2019).
  - Hold for 3-6 days in patients for high-risk procedures (SIR 2019 3-5 days; ASRA 2018 6 days; NEJM 7-10 days).
  - May restart 24 hours after the procedure (ASRA 2018).

- **Cilostazol (Pletal®)**
  - Oral, T½ = 10 hours
  - Does not need to be withheld prior to low or moderate-risk injection procedures (ASIPP 2013).
  - Hold for 2 days prior to high-risk procedures (ASRA 2018 2 days; NEJM 2 days; SIR no recommendation).
  - May restart after hemostasis is achieved.

- **Pentoxifylline (Trental®, Pentoxil®)**
  - Oral
  - Biologic T½ = 1-1.6 hours.
  - Does not need to be withheld prior to low- or moderate-risk injection procedures.
  - Hold for 2 days prior to high-risk procedures (AAPM).
  - Restart as soon as possible after the procedure.

COX-2 inhibitors: Celecoxib selectively inhibits COX-2, an enzyme that is not expressed in platelets. Platelet dysfunction has not been reported in patients undergoing therapy with COX-2 inhibitors.

Recommendations:

- **Celecoxib (Celebrex®),**
  - COX-2 inhibitors do not need to be withheld in anticipation of a neural axis procedure (ASRA 2018).
  - These drugs can be used for pain management in patients who might require injection therapy.

Low Molecular Weight Heparins (LMWH): Heparin is an injectable anticoagulant that activates antithrombin III, preventing fibrin formation and platelet activation. Low-dose heparin inhibits clot formation, while higher doses prevent clot extension. LMWH is often used as a bridge for patients on warfarin therapy. A black-box warning has been issued concerning the risk of epidural or spinal hematoma in patients undergoing neuraxial procedures.

Recommendations:

- **Enoxaparin (Lovenox®, Xaparin®, Clexane®);**
  - SQ
  - Elimination is impaired in patients with severe renal disease (Stage IV and V).
  - Withhold one dose or 12 hours prior to the procedure in patients receiving low doses of enoxaprin (30 mg bid or 40 mg qd) (ASRA 2018, SIR 2019).
  - Withhold 24 hours with higher doses (0.75 - 1.0 mg/kg bid or 1.5 mg/kg qd)
  - May restart 4 hours after low-risk procedures and 12 hours after intermediate- and high-risk procedures.

- **Dalteparin (Fragmin®, Eisai®)**
  - SQ
  - Elimination is impaired in patients with severe renal disease (Stage IV and V).
  - Withhold 12 hours with lower doses e.g. 2,500 IU/kg qd
  - Withhold 24 hours with higher doses 200 IU/kg qd or 120 IU/kg bid (NEJM: 24 hours, ASRA 2018).
  - May restart 4 hours after low-risk procedures and 12 hours after intermediate- and high-risk procedures.

Warfarin: Warfarin and acenocoumarol are oral anticoagulants that inhibit Vitamin K oxide reductase, an enzyme that recycles oxidized Vitamin K, thereby affecting the production of coagulating factors II, VII, IX and X.

The biologic response to warfarin therapy can vary significantly with age, sex, and preexisting medical conditions. It can also be affected by certain foods, dietary supplements and commonly used medicines. As a result, regular blood monitoring (international normalized ratio-INR) is done to check for effectiveness and safety, and is recommended prior to injection therapy and invasive procedures. Please note that concomitant administration of antiplatelet medications and heparin can potentiate the anticoagulant effect of warfarin.

Management of warfarin and acenocoumarol is based on the time for Vitamin K components to regenerate. When long-term warfarin therapy is discontinued, the activity of factors II, VII, IX and X recover at different rates. Factor VII activity rapidly increases. An INR of 1.5 is associated with a factor VII activity of 40% and should be associated with normal hemostasis. However, factors II, IX and X activities recover much more slowly. Theoretically, there may be

a time when the INR is normal and factors II and X have not recovered to the 40% level impairing hemostasis. As a result, infusion of Vitamin K or fresh frozen plasma may be needed in urgent or emergent cases. An FDA boxed warning has been issued concerning the risk of epidural or spinal hematoma with spinal procedures.

Recommendations:

- **Warfarin (Jantoven®, Coumadin®, Marevan®, Uniwarfin®)**
  - Does not need to be held for low-risk procedures providing the INR is within therapeutic ranges (< 3.0), the patient is not a high risk for bleeding, and the patient does not have a history of serious post-procedural bleeding (ASRA 2018, SIR 2019).
  - Hold 5 days with INR normalized (< 1.5) for moderate-risk (including spine) and high-risk procedures (NEJM, ASRA 2018 (INR< 1.2), ACCP, SIR 2019 (INR<1.8)).
  - In patients receiving concomitant therapy with ASA, NSAIDs, ticlopidine, clopidogrel, UFH and LMWH, further delay may be considered depending on the specific medication used. These medications might increase the risk of bleeding complications without influencing the INR.
  - Restart the evening of or the next day after the procedure (ASRA 2018, NEJM).

- **Acenocoumarol**
  - Does not need to be held for low-risk procedures providing the INR is within therapeutic ranges (< 3.0), the patient is not a high risk for bleeding, and the patient the patient does not have a history of serious post-procedural bleeding (ASRA 2018).
  - Hold 3 days with INR normalized (< 1.5) for moderate-risk (including spine) and high-risk procedures (NEJM, ASRA 2018, ACCP).
  - In patients receiving concomitant therapy with ASA, NSAIDs, ticlopidine, clopidogrel, UFH and LMWH, further delay may be considered depending on the specific medication used. These medications might increase the risk of bleeding complications without influencing the INR.
  - Restart the next day after the procedure (ASRA 2018, NEJM).

Antiplatelet agents – P2Y12/platelet aggregation inhibitors: These drugs are thienopyridine derivatives whose pharmacologic effect derives from the inhibition of adenosine diphosphate-induced platelet aggregation. These drugs affect both primary and secondary platelet aggregation and interfere with platelet-fibrinogen binding and subsequent platelet-platelet interactions.

The effects of clopidogrel and prasugrel are irreversible and management is based on the time for new platelets to regenerate. 10% of platelets are replaced each day, and at 5-6 days,

approximately 50% of platelets will function normally. A black-box warning has been issued for epidural and spinal hematoma with neuraxial procedures.

Recommendations:

- **Clopidogrel (Plavix®)**
  - Do not need to hold for procedures (ASRA 2018, SIR 2019).
  - Stop 5-7 days prior to intermediate and high-risk procedures (NEJM 5 days; ISIS 2013 7 days; ACCP 7 days; ASRA 2018 7 days; AAPM&R 10 days; ACCP 7-10 days; SIR 2019 5 days).
  - May restart the usual daily dose (75mg) 6-12 hours after the procedure, or 24 hours after the procedure if a loading dose is used (ASRA 2018, SIR 2019).

- **Prasugrel (Effient®)**
  - Do not need to hold for low-risk MSK/neuro procedures (ASRA 2018, SIR 2019).
  - Stop 7-10 days prior to intermediate (spine) and high-risk procedures (NEJM: 7 days, ISIS, ASRA 2018: 7-10 days).
  - May restart 24 hours after the procedure (ASRA 2018).

- **Ticagrelor (Brilinta®)**
  - Oral, T½ = 7-9 hours
  - Do not need to hold for low-risk procedures. (ASRA 2018, SIR 2019).
  - Discontinue 5 days before intermediate (spine) and high-risk procedures (NEJM, ASRA 2018, SIR 2019).
  - May restart 24 hours after the procedure (ASRA 2018).

Direct factor Xa inhibitors: Factor Xa inhibitors are synthetic compounds composed of the essential pentasaccharide sequence that selectively inhibits factor Xa. Factor Xa is generated by both the extrinsic and intrinsic coagulation pathways. It activates prothrombin to thrombin, which activates the final components of the coagulation pathway to form clots.

Anticoagulant management is based on 5 half-lives for moderate or high-risk procedures and 2 half-lives for low-risk procedures. These agents are excreted by the kidneys, and clearance may be prolonged in patients with renal impairment.

A black-box warning has been issued concerning the risk of epidural or spinal hematomas with neuraxial procedures. An additional black box warning has also been issued for the direct factor Xa inhibitors (rivaroxaban, apixaban and edoxaban): Avoid the abrupt discontinuation of apixaban, rivaroxaban and edoxaban in the absence of adequate alternative anticoagulation. Discontinuing these drugs puts patients at an increased risk of thrombotic events. If apixaban, rivaroxaban or edoxaban must be discontinued for reasons other than pathological bleeding or completion of a course of therapy, consider administering another anticoagulant.

Recommendations:

- **Rivaroxaban (Xarelto®)**
  - Oral, T½ = 9-13 hours
  - After shared assessment, risk stratification, and management decision making in conjunction with the treating physician, may consider holding 1 day for low-risk procedure (ASRA 2018 1 day; SIR 2019 No).
  - Hold 3 days for moderate or high-risk procedures (ASIPP 2013, ASRA 2018 - 3 days; SIR 2019 – 2 doses CrCl ≥ 50 mL/min, 2 doses CrCl < 30-50 mL/min, 3 doses CrCl < 15-30 mL/min; FDA – 24 hours).
  - May restart 24 hours after the procedure. If the risk of VTE is high, ½ the usual dose can be given at 12 hours (ASRA 2018, SIR 2019 – 24 hours).

- **Apixaban (Eliquis)**
  - Oral, T½ = 15.0 hours
  - After shared assessment, risk stratification and management decision in conjunction with the treating physician, may consider holding 1 day for low-risk procedure (ASRA 2018).
  - Do not hold for low-risk body/breast procedures (SIR 2019).
  - Hold 3 days for moderate or high-risk procedure (ASRA 2018 3 days; SIR 2019 – 4 doses CrCl ≥ 50 mL/min, 6 doses Cr/Cl < 50 mL/min; FDA – 48 hours).
  - May restart 24 hours after the procedure. If the risk of VTE is high, ½ the usual dose can be given at 12 hours (EMA, ASRA 2018, and SIR 2019 – 24 hours).

- **Edoxaban (Savaysa®)**
  - Oral, T ½ = 9-14 hours
  - After shared assessment, risk stratification and management decision in conjunction with the treating physician, may consider holding two half-lives (1 day) for low-risk procedure (ASRA 2018: 2 days, SIR: 1 day).
  - Do not hold for low-risk body/breast procedures (SIR 2019).
  - Hold 3 days before the moderate or high-risk procedure (ASRA 2018, NEJM - 36-48 hours; SIR 2019 - 2 doses/2 days; FDA – 24 hours).
  - May restart 24 hours after the procedure. If the risk of VTE is high, ½ the usual dose can be given at 12 hours (ASRA 2018, SIR 2019 – 24 hours).

- **Betrixaban (Bevyxxa)**
  - Oral, T ½ = 19-27 hours (PDR), 37 hours (SIR 2019).
  - Do not withhold for low risk procedures (SIR 2019).
  - Withhold 5 days (5 half-lives) prior to moderate or high risk procedures (SIR 2019 – 3 doses).

- May restart 24 hours after the procedure (SIR 2019).

- **Fondaparinux (Arixtra®)**
  - SQ, T ½ = 17-21 hours
  - After shared assessment, risk stratification and management decision in conjunction with the treating physician, may consider holding two half-lives (2 days) for low-risk procedure (ASRA 2018 2 days, SIR 1 day).
  - Do not for low-risk body/breast procedures (SIR 2019).
  - Hold 4 days before the moderate or high-risk procedure (ASRA 2018, NEJM - 36-48 hours; SIR 2/3 doses CrCl ≥ 50 mL/min, 3-5 doses CrCl < 50 mL/min).
  - May restart 24 hours after the procedure (ASRA 2018, SIR 2019).

Direct thrombin inhibitors: Thrombin inhibitors are anticoagulants that bind to and inhibit the activity of both free and fibrin-bound thrombin. It is excreted by the kidneys and the risk of bleeding is increased in patients with renal impairment. Activity can be assessed with a thrombin time measurement.

Anticoagulant management is based on 5 half-lives for moderate- or high-risk procedures and 2 half-lives for low-risk procedures. Risk increases with concomitant treatment with NSAIDs, platelet inhibitors, and other anticoagulants.

There is an FDA black-box warning concerning the risk of epidural or spinal hematoma and paralysis with neuraxial anesthesia. An additional black box warning has also been issued for dabigatran: Avoid the abrupt discontinuation of dabigatran in the absence of adequate alternative anticoagulation. Discontinuing dabigatran puts patients at an increased risk of thrombotic events. If dabigatran must be discontinued for reasons other than pathological bleeding or completion of a course of therapy, consider administering another anticoagulant.

Recommendations:

- **Dabigatran (Pradaxa®)**
  - Oral, T ½ = 12-17 hours
  - After shared assessment, risk stratification and management decision in conjunction with the treating physician, consider holding 2 days for low-risk procedures (ASRA 2018 2 days; SIR 2019 No).
  - Withhold 4 days for moderate- or high-risk procedures, 5-6 days if renal disease (ASIPP 2013 2-4 days; ASRA 2018 4 days; SIR 2019 4 doses/6-8 doses).
  - May restart 24 hours after the procedure, 12 hours if the risk of VTE is high (ASRA 2018, SIR 2019).

SRIs: SSRIs have an inhibitory effect on platelet aggregation, and the risk of bleeding approximates that associated with low dose ibuprofen. Both SSRIs and SRNIs have been

associated with increased risk of bleeding with concomitant use of antiplatelet drugs or anticoagulation drugs, and in patient with chronic liver disease.

- **Paroxetine, Escitalopram, Citalopram, Fluvoxamine, Fluoxetine, Setraline, Velafaxine, Duloxetine**
    - Routine discontinuation of SRIs before pain procedures is not recommended.
    - Consider stopping in patients with stable depression who are at high risk for bleeding (old age, advanced liver disease, concomitant ASA, NSAIDs, antiplatelet or anticoagulant use).
    - If SRI therapy is to be discontinued, the dose should be gradually tapered and discontinued for 5 half-lives prior to the procedure, and should be coordinated with the treating psychiatrist.

Herbal medications:

- **Garlic**
    - Stop one week prior to high-risk procedures.
    - Not necessary to stop prior to low- or medium-risk procedures as long as other anticoagulant and antiplatelet drugs have been stopped according to the recommendations above.
    - Consider stopping one week prior to low- or medium-risk procedures in patients at high risk for bleeding (patients with advanced age, renal and/or hepatic disease), or in patients with a history of major bleeding following previous injection procedures.
    - Check the bleeding time prior to low- or medium-risk procedures when patients take doses greater than 1000mg/d, or when there is concomitant intake with ASA, NSAIDs or SSRIs. If the bleeding time is high, then hold garlic for one week prior to the procedure.
- **Dong quai**
    - Stop for one week prior to high-risk procedures.
    - Check INR in patients on dong quai and warfarin who are undergoing medium- or high-risk procedures. Stop dong quai for one week if the INR is markedly elevated.
- **Danshen**
    - Stop for one week prior to high-risk procedures.
    - Check INR in patients who are taking danshen and warfarin prior to medium- and high-risk procedures. Stop danshen for one week if the bleeding time is markedly elevated.
    - Consider stopping danshen for one week in patients who are also taking other antiplatelet drugs (ASA, NSAIDs and SSRIs) prior to undergoing medium- and high-risk procedures.

- **Ginkgo biloba**
    - Stop for one week prior to high-risk procedures.
    - Check platelet function in patients who are taking other antiplatelet drugs (ASA, NSAIDs and SSRIs) prior to high-risk procedures. If elevated, stop Ginkgo biloba one week prior to undergoing the procedure.

Dietary supplements:

- **Vitamin E**
    - Vitamin E has been shown to markedly decrease platelet function at doses between 400 and 1200 IU daily.
    - Consider stopping Vitamin E consumption prior to low- or intermediate-risk procedures in patients on concomitant antiplatelet medications.
    - Consider stopping Vitamin E for 6 days prior to high-risk procedures.
- **Fish Oil**
    - While fish oil is unlikely to significantly increase the risk of bleeding, caution suggests that it be treated like other antiplatelet drugs.
    - There is no need to stop fish oil consumption prior to low- or intermediate-risk procedures.
    - Consider stopping fish oil for 6 days prior to high-risk procedures.

Miscellaneous medications:

- **Nattokinase**
    - An enzyme isolated from fermented soybeans.
    - Fibrinolytic absorbed by the duodenum/intestines.
    - Little data on the pharmacology of nattokinase and on the length of the fibrinolytic effect.
    - Consider holding for 1-2 weeks for intermediate- or high-risk procedures.
- **Pentosan Polysulfate Sodium (Elmiron)**
    - Pentosan polysulfate sodium is a plant-derived semisynthetic mucopolysaccharide which possesses anticoagulant activity similar to LMWH.
    - T ½ = 20-27 hours
    - Pentosan polysulfate sodium should be withheld for 5 days prior to intermediate- and high-risk procedures.
    - It may be restarted 24 hours after the conclusion of the procedure.

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