Introduction:

Hemorrhage is a significant risk with injection procedures. Anticoagulation therapy can be discontinued prior to the procedure in patients at low or moderate risk for thromboembolism. Requests to hold the patient’s anticoagulant therapy should be made to the treating physician according to the specific recommendations noted below. If the patient is at high risk for thromboembolism, procedures can be performed with bridge anticoagulation therapy as indicated by the treating physician. Dr. Michael Cumming manages bridging anticoagulation for his patients in the CDI Vascular Center at St. Louis Park, MN and has provided his protocol for review.

In general, spinal procedures should be avoided in any patient with a known coagulopathy from any cause. If a procedure is indicated in a patient with a coagulopathy, it should only be performed following the directed management of their coagulation status (generally with the administration of fresh frozen plasma or platelets depending on their particular condition).

Anticoagulants:

Oral and subcutaneous anticoagulants are indicated for the primary and secondary treatment of DVT and PE, and in conditions known to predispose to thromboembolism. Oral anticoagulation is indicated for stroke prevention in patients with a history of stroke or TIA, in patients with large vessel disease or dissection, and with other disorders known to predispose to stroke. Cardiac events associated with an increased risk of stroke include non-valvular atrial fibrillation, coronary artery stents and mechanical heart valves. Prophylactic anticoagulation is indicated in patients undergoing total hip replacement and total knee replacement, and for any surgery with moderate or high risk for thromboembolism.

For drugs with reversible effects, the recommended hold times are based on the half-life of the drug. In general, the drug is withheld for 1-2x the half-life for low risk procedures and 3-5x the half-life for moderate and high-risk procedures. For drugs whose functional half-life is based
primarily on direct renal excretion of active drug, the hold times need to be extended in patients
with compromised renal function. The recommendations made in this guideline are made with
the assumption that the patient may have decreased renal function. If more urgent intervention is
required, the creatinine clearance (CrCl) or glomerular filtration rate (GFR) needs to be assessed
in advance of the procedure.

For drugs with irreversible effects, the hold times are based on the recovery of functions
components of the clotting cascade. For warfarin, the hold times are based on the recovery times
of vitamin K dependent clotting factors. For aspirin (ASA) and clopidogrel, the hold times are
based on the recovery times for platelets.

**Warfarin:** Warfarin is an oral anticoagulant that inhibits Vitamin K oxide reductase, an enzyme
that recycles oxidized vitamin K, thereby affecting the production of coagulating factors II, VII,
IX and X. 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.
Factors II, IX and X activities recover much more slowly, however, and theoretically, there may
be a time when the INR is normal and factors II and X has 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.

The biologic response to warfarin therapy varies significantly between patients. It can vary with
age, sex, and preexisting medical conditions. It can be affected by certain foods, dietary
supplements and many 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 or to any invasive procedure.

Please note that concomitant administration of antiplatelet medications and heparin can
potentiate the anticoagulant effect of warfarin. An FDA boxed warning has been issued
concerning the risk of epidural or spinal hematoma with spinal procedures.

Recommendations:

- **Warfarin (Jantoven®, Coumadin®, Marevan®, Uniwarfin®)**
  - Hold 3 days with INR <2.0 for low risk procedures.
  - Hold 5 days with INR normalized (<1.5) for moderate risk (including spine) and
    high-risk procedures (NEJM, ARSA 2010, ACCP).
  - In patients receiving concomitant therapy with ASA, NSAIDs, ticlopidine,
    clopidogrel, UFH and LMWH spinal injection therapy might be delayed further
depending on the specific medication used. These medications might increase the
risk of bleeding complications without influencing the INR.
  - Restart the evening of the procedure (NEJM).
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. A black-boxed warning has been issued concerning the risk of epidural or spinal hematoma in patients undergoing neuraxial procedures.

Recommendations:

- **Enoxaparin (Lovenox®, Xaparin®, Clexane®); Dalteparin (Fragmin®, Eisai®); Tinzaparin (Innohep®)**
  - SQ
  - Elimination is impaired in patients with severe renal disease (Stage IV and V).
  - Withhold one dose or 12 hours prior to the procedure (ARSA 2010).
  - Withhold 24 hours with higher doses such as enoxaparin 1.5 mg/kg daily, dalteparin 200 IU/kg daily, tinzaparin 175 U/kg daily. (NEJM 24 hours, ARSA 2010).
  - May restart 6-8 hours after the procedure.

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. A black-boxed warning has been issued concerning the risk of epidural or spinal hematomas with neuraxial procedures.

Recommendations:

- **Rivaroxaban (Xarelto®)**
  - Oral, T½ = 9-13 hours
  - Hold 1-2 days if low risk procedure (EMA).
  - Hold 3 days if history of renal failure and/or for moderate or high-risk procedures (ASIPP 2013, ASRA 4th edition 3 days).
  - Need CrCl if urgent procedure needed: Hold 1 day with normal renal function; 2 days with CrCl 60-90 ml/min; 3 days with CrCl 30-59 ml/min; 4 days with CrCl < 30 ml/min (NEJM).
  - May restart 6 hours after the procedure (EMA, ASRA 4th edition); 48 hours after high risk or traumatic procedure (NEJM).

- **Apixaban (Eliquis)**
  - Oral, T½ = 7-8 hours
  - Hold 24 hours for low risk procedure (EMA).
Hold 3 days for moderate or high-risk procedure (ASRA 4th edition, EMA 48 hours).
Need CrCl if history of renal problems or if more urgent injection needed: Hold 1-2 days with CrCl > 60 ml/min; 3 days with CrCl 30-59 ml/min; 5 days with CrCl <30 ml/min) (NEJM).
May restart 6 hours after the procedure (EMA, ASRA 4th edition); 48 hours after a high risk procedure (NEJM).

Fondaparinux (Arixtra®)
- SQ, T½ = 17-21 hours
- Elimination is impaired in patients with impaired renal function (Stage IV or V).
- Hold 24 hours for procedure with low risk of bleeding.
- Hold 3 days before the moderate or high-risk procedure (NEJM 36-48 hours).
- May restart 24 hours after the procedure; 48 hours after a high risk procedure.

Direct thrombin inhibitors: Thrombin inhibitors are anticoagulants that bind to and inhibit the activity of both free and fibrin bound thrombin. There is an FDA boxed warning concerning the risk of epidural or spinal hematoma and paralysis with neuraxial anesthesia. Risk increases with concomitant treatment with NSAIDs, platelet inhibitors, and other anticoagulants.

Recommendations:

Dabigatran (Pradaxa®)
- Oral, T½ = 12-17 hours
- Withhold 2 days for low risk procedures.
- Withhold 5 days for moderate or high-risk procedures (ASIPP 2013 2-4 days, ASRA 4th edition 5 days).
- Need CrCl for more urgent injections: hold 1-2 days for CrCl > 50mL/min; and 3-5 days for CrCl < 50 mL/min. (EMA, NEJM, ARSA).
- May restart 6 hours after the procedure (ASRA 4th edition); 48 hours after a high risk procedure (NEJM).

Desirudin (Iprivask)
- SQ, T½ = 2 hours
- Hold for 2 hours before the injection procedures (NEJM).
- Hold 10 hours before high risk procedures (NEJM).
- May restart 6 hours after the procedure.

Antiplatelet agents – 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. A black-box warning has been issued for epidural and spinal hematoma with neuraxial procedures.
Recommendations:

- **Clopidogrel (Plavix®)**
  - Oral, T½ = 4 hours
  - The effect on platelets is irreversible.
  - Withholding clopidogrel for 5-7 days will allow for recovery of 30-50% of platelets allowing for normal hemostasis.
  - Stop 5-7 days prior to the procedure (NEJM 5 days, ISIS 2013 7 days, ACCP 7 days, ARSA 2010 7 days, AAPM&R 10 days, ACCP 7-10 days).
  - May restart within 24 hours after the procedure (ACCP, NEJM).

- **Prasugrel (Effient ®)**
  - Oral, T½ = 7 hours
  - Stop 7-10 days prior to an injection procedure (NEJM 7 days, ISIS, ASRA 4th edition 7-10 days).
  - May restart 6 hours after the procedure (ASRA 4th edition); 24 hours after a moderate or high risk procedure (NEJM).

- **Ticlopidine (Ticlid ®)**
  - Oral, T½ = 8-13 hours
  - Stop 10-14 days prior to an injection procedure (NEJM 10-14 days, ISIS 10 days, ARSA 2010 14 days, AAPM&R 14 days).
  - May restart 6 hours after the procedure.

- **Ticagrelor (Brilinta ®)**
  - Oral, T½ = 7-9 hours
  - Injection of dexamethasone (and other steroids) will induce CYP3A expression and substantially reduce ticagrelor blood levels.
  - Discontinue 5-7 days before an injection procedure (NEJM 5 days, ASRA 4th edition 5-7 days).
  - May restart 6 hours after the procedure (ASRA 4th edition); 24 hours after a moderate or high risk procedure (NEJM).

**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. With aspirin platelet function is compromised for the life of the platelet and function normalizes after 7 days. Low dose aspirin (60-325mg/d) poses a greater risk of bleeding than does therapy with larger doses. NSAIDs produce a short term reversible effect that normalizes after 3 days.

Recommendations:

- **Low dose Aspirin (ASA)**
Not been shown to increase the risk of bleeding with injection procedures.
- Withholding ASA for 5-7 days will allow for recovery of 30-50% of platelets allowing for normal hemostasis.
- Does not need to be withheld for low or moderate risk injections.
- Caution should be used in patients taking ASA in combination with other anticoagulation drugs, Vitamin E, feverfew, Ginkgo, garlic, fish oil or SSRIs (ASIPP, ISIS, NEJM, AAPM&R 7 days).
- Hold 7-10 days for patients undergoing high-risk procedures (JVIR, NEJM 7-10 days, ACCP 7-10 days).
- May restart within 24 hours after the procedure (ACCP, NEJM).

**NSAIDs** (Ibuprofen (Motrin®, Advil®, Vicoprofen®, Combunox®); Indomethacin (Indocin®); Ketorolac (Toradol®); Mefenamic acid (Ponstel®); Nabumetone (Relafen®); Naproxen (Aleve®, Naprosyn®, Anaprox®, Naprelan®, Naprapac®); Oxaprozin (Daypro®); Piroxicam (Brexidol®, Candyl®, Feldene®))
- Not been shown to increase the risk of bleeding with injection procedures.
- Does not need to be withheld for low or moderate risk injection procedures.
- Caution should be used in patients taking NSAIDS in combination with other anticoagulation drugs, Vitamin E, fish oil, feverfew, Ginkgo, garlic or SSRIs (ARSA 2010, ASIPP, ISIS, AAPM&R 3 days).
- Hold for 3 days prior to high-risk procedures.
- May restart within 24 hours after the procedure (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.

**Recommendations:**

- **Dipyridamole (Persantine®)**
  - Oral, \( T_{\frac{1}{2}} = 12 \) 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.
  - May restart as soon as possible after the procedure.

- **Dipyridamole/ASA (Aggrenox®)**
  - Oral
  - Does not need to be withheld for low or moderate risk procedures (ASIPP 2013, ISIS 3 days, UWMC 7 days, ACCP).
o Hold for 7 days in patients for high-risk procedures (NEJM 7-10)
o May restart within 24 hours after the procedure.

**Cilostazol (Pletal ®)**

o Oral, $T_{1/2} = 10$ hours
o Does not need to be withheld prior to low or moderate risk injection procedures (ASIPP 2013).
  o Hold for 2 days prior to high-risk procedures (NEJM).
  o May restart after hemostasis is achieved.

**Pentoxifylline (Trental ®, Pentoxil ®)**

o Oral
o Does not need to be withheld prior to low or moderate risk injection procedures.
o Hold for 2 days prior to high-risk procedures (AAPM).
o Restart as soon as possible after the procedure.

**COX-2 inhibitors:** Celecoxib 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 ®)**
  o COX-2 inhibitors do not need to be withheld in anticipation of a neural axis procedure (ARSA 2010).
  o These drugs might be considered for pain management in patients who might require injection therapy.
Recommendations for bridge therapy:

In general, patients receiving dual antiplatelet therapy with ASA and a thienopyridine post stent placement should not have either medication held for any reason during the first month following placement of a bare metal stent, or the first 12 months after drug eluting stent insertion. If a procedure needs to be performed in these patients, bridging therapy will be required. Bridging therapy is often required for patients with mechanical heart valves, TIA or stroke within 6 months, venous thromboembolism (VTE) within the last 3 months, VTE with antiphospholipid antibodies, severe thrombophilia or CHADS score of 5 or 6. Bridging therapy may be required in patients with atrial fibrillation, venous thromboembolism within the past 3-12 months, a cardiac thrombus, CHADS score of 3-4 or active cancer. Bridging therapy is typically managed by the treating physician. The following is a low dose bridging regimen currently utilized by Dr. Michael Cumming in the Vascular Center at St. Louis Park, MN.

1. Hold your Coumadin starting 5 days prior to your 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. Do not take Lovenox on the morning of your procedure.

3. Post-Procedure (5 days of bridging post-procedure)
   a. Lovenox 40mg SQ AND Coumadin (double patient's lowest dose) PM for two days beginning the day of the procedure.
   b. Continue Lovenox 40mg PM SQ WITH Coumadin (return to normal scheduled dose) for 3 more days.
   c. Check INR (6 days post procedure) and call us with your result at 952-738-4498.
   d. Based on your INR, we may prescribe additional doses of Lovenox.
References:


Parenteral antithrombotic/antiplatelet drugs not included

Parenteral Direct Thrombin Inhibitors:

- **Bivalirudin (Angiomax)**
  - IV for acute coronary interventions
  - Only minimal renal excretion

- **Argatroban (Acova)**
  - IV for treatment of Heparin-induced thrombocytopenia

- **Lepirudin**
  - Removed from the European market in 2012. No longer manufactured.

Parenteral anti-Platelet agents - GP IIb/IIIa receptor antagonists: Blocks the P2Y12/Integrin receptor, the final common pathway for many metabolic activators of platelet aggregation. Generally only used in the treatment of acute coronary artery syndrome. Not likely to see in an outpatient practice.

- **Abciximab (Reopro)**
  - Hold for 24-48 hours prior to the procedure

- **Eptifibatide (Itegrilin)**
  - Return to normal clotting usually within one hour of discontinuing the infusion
  - Hold for 4-8 hours prior to the procedure

- **Tirofiban (Aggrastat)**
  - Renal clearance issues (< 30 mL/min)
  - Hold for 4-8 hours prior to the procedure