Antithrombotic Reversal – Adult – Inpatient
Clinical Practice Guideline

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Pharmacy & Therapeutics Committee (Last Periodic Review: 11/2017)

Release Date: October 2017 **|** **Next Review Date:** Choose a date. (2-3 yr. cycle)
Original Release 2013

Executive Summary

Guideline Overview

The intent of this guideline is to provide evidence-based recommendations for the treatment of bleeding in patients on antithrombotic therapy and standardize care within UW Health. The guideline provides reversal recommendations for the following: warfarin, oral and intravenous direct thrombin inhibitors, oral anti-Xa inhibitors, heparin-based medications, fondaparinux, NSAIDs, P2Y12 ASP receptor inhibitors, phosphodiesterase inhibitors and glycoprotein IIb/IIIa inhibitors. Procoagulant agent use includes desmopressin, plasma (commonly referred to as FFP), factor 7A, idarucizumab, prothrombin complex concentrate (PCC), phytonadione, and protamine.

Key Revisions (2017 Periodic Review)

List any MAJOR revisions which were made between full periodic reviews or during last review.

1. Addition of low, fixed dose prothrombin complex concentrate for warfarin reversal
2. Addition of reversal recommendations for antiplatelet agents

Key Practice Recommendations

To quickly view reversal recommendations for specific antithrombotic medications select hyperlink below.

1. Warfarin and Prothrombin Complex Concentrate (PCC)
2. Dabigatran
3. Anti-Xa: Apixaban, Rivaroxaban, Edoxaban
4. Heparin and Low Molecular Weight Heparin
5. Direct Thrombin Inhibitors: Argatroban and Bivalirudin
6. Fondaparinux
7. Aspirin
8. Non-steroidal Anti-inflammatory Drugs (NSAIDs)
9. P2Y12 ADP Receptor Inhibitors (clopidogrel, prasugrel, ticagrelor)
10. Phosphodiesterase Inhibitor (cilostazol)
11. Glycoprotein IIb/IIIa inhibitor (eptifibatide, abciximab)

Companion Documents

1. Appendix A Treatment of Bleeding Associated with Oral Anticoagulants
2. Appendix B Treatment of Bleeding Associated with Parenteral Anticoagulants
3. Appendix C Treatment of Life Threatening Bleeding Associated with Anticoagulants
4. Appendix D Administration Rate of Intravenous Procoagulant Agents
5. UW Health Warfarin Management - Adult - Ambulatory - Clinical Practice Guideline
6. UW Health Warfarin Management - Adult - Inpatient Clinical Practice Guideline
7. UW Health Heparin- Induced Thrombocytopenia – Adult – Inpatient Clinical Practice Guideline
8. UW Health Unfractionated Heparin (Therapeutic Dosing) - Adult - Inpatient Clinical Practice Guideline
9. UW Health Antithrombotics in Non-Valvular Atrial Fibrillation - Adult - Inpatient/Ambulatory Clinical Practice Guideline
10. UW Health Indications for Blood Product Transfusion – Adult – Inpatient/Ambulatory Clinical Practice Guideline
11. UW Health IV Administration Guideline – Adult – Inpatient/Ambulatory Clinical Practice Guideline

Scope

Disease/Condition(s): Treatment of adult non-hemophiliac bleeding or with high potential for bleeding (i.e. intra-operatively) due to antithrombotic therapy at UW Health.

Clinical Specialty: Neurology, Trauma, Critical Care, Cardiology, Surgery, Emergency, Nursing, Pharmacy

Intended Users: Physicians, mid-level providers, pharmacists, nurses, students

Objective(s): Provide evidence-based recommendations for the treatment of bleeding in patients on antithrombotic therapy and standardize care within UW Health.

Target Population: Adult inpatient and emergency department patients

Interventions and Practices Considered: Procoagulant agent use includes desmopressin, plasma (commonly referred to as FFP), factor 7A, idarucizumab, prothrombin complex concentrate (PCC), phytonadione, and protamine.

Major Outcomes Considered: Control of bleeding, improved neurological, cardiac, and renal outcomes. Thromboembolic events post reversal.

Methodology

Methods Used to Collect/Select the Evidence:
Electronic database searches (e.g., PUBMED) were conducted by the guideline author(s) and workgroup members to collect evidence for review. Expert opinion and clinical experience were also considered during discussions of the evidence.

Methods Used to Formulate the Recommendations:
The workgroup members agreed to adopt recommendations developed by external organizations and/or arrived at a consensus through discussion of the literature and expert experience. All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees (as appropriate).

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1** in Appendix A).

Rating Scheme for the Strength of the Evidence/Recommendations:
See Appendix A for the rating scheme(s) used within this document.

Cost Analysis: Table 1. Procoagulant Cost Estimate for an 80 Kg Patient

Procoagulant	UW Health Estimated Cost per Dose ($)
Desmopressin 0.4 mcg/kg	
Phytonadione 5 – 10 mg, parenteral (given as IV and enteral)	
Plasma 4 units (approximately 1000 mL)	188.00
Protamine 50 mg	7.02
Factor 7A 40 -90 mcg	4846.50 – 10,904.63.
Idarucizumab 5 g	3500.00
Prothrombin Complex Concentrate (PCC) 1000 units	1,320.00

Recognition of Potential Health Care Disparities: N/A

Definitions[1]

1. Minor bleed – epistaxis lasting less than 1 hour, small amount of blood in stool, urine or oral cavity.
2. Non- major bleeding – bleeding with decline in Hgb of <2 g/dL or requiring ≤ 1 unit of blood or packed cells.
3. Major bleed - Acute major bleeding that includes one of the following: potentially life-threatening, acute Hgb decline of ≥ 2 g/dL or acute bleeding requiring at least two units of blood or packed cells (International Society on Thrombosis and Haemostasis).
4. Life-threatening bleed – fatal bleeding, symptomatic intracranial bleeding, reduction in hemoglobin of at least 5 g/dL, transfusion of at least 4 units of blood or packed cells, bleeding associated with hypotension requiring use of intravenous inotropic agents, bleeding necessitating surgical intervention (International Society on Thrombosis and Haemostasis).
5. Massive trauma bleeding – loss of complete blood volume (approximately 0.7 L/kg lean body weight) within 24 hours or half of blood volume within three hours.

Introduction

Bleeding is a major complication for any type of anticoagulant therapy and can result in a chronic debilitating condition or death.[2-5] The risk of hemorrhage is often associated with the intensity of anticoagulation.[6] Another consideration is the increased risk of bleeding with concomitant treatment such as antiplatelet medication, non-steroidal anti-inflammatory agents and cyclooxygenase type-2 inhibitors. Depending on the antithrombotic agent and its half-life, the duration of action can vary from a few hours to several days. When bleeding is life-threatening or when urgent reversal is required prior to surgery, there may be the need for reversal. . The risk of bleeding versus thromboembolism must be evaluated for each specific patient. The optimal approach must take into account patient comorbidities, extent of anticoagulation and target level of anticoagulation after reversal. Treatment goals include cessation of bleeding while minimizing the risk of untoward thrombosis with improvement in clinical outcome.

Inherent limitations in non-randomized, non-comparator trials must be considered while examining the evidence. Over time, natural hemostasis is expected in hemorrhagic injury. Thus non-randomized, non-comparator case studies reporting reduction or cessation of bleeding after administration of procoagulants must be interpreted with caution, as the influence of time cannot be assessed without a comparator, and the true influence of the administered reversal agent cannot be accurately assessed.

Recommendations

Oral Anticoagulants: *Listed by drug class*

Vitamin K Antagonist (i.e. Warfarin)

Warfarin inhibits the activation of vitamin K dependent clotting factors II, VII, IX and X by inhibiting two specific enzymes, vitamin K epoxide reductase (VKOR) and vitamin K_1 reductase, and blocking the production of pharmacologically active vitamin K clotting factors. The incidence of hemorrhagic events associated with warfarin therapy is based on target INR, duration of therapy, use on concomitant antiplatelet therapy, patient factors, and quality of monitoring.[6-8] Patient factors such as prior history of bleeding, advanced age, cancer, renal or hepatic insufficiency, arterial hypertension, prior stroke and alcohol abuse are associated with a higher risk of hemorrhage.[6,9-11] The rate of hemorrhage increases markedly in patients with an INR greater than 4.5.[12] Bleeding or potential bleeding of patients on warfarin can be managed by holding warfarin doses, administering phytonadione, plasma and/or PCC. The approach to treatment is predicated on the indication for warfarin, location of the bleed, extent of bleeding and INR (Appendix 2).[2] For further information on warfarin treatment, see UW Health Warfarin Management - Adult - Ambulatory - Clinical Practice Guideline or UW Health Warfarin Management - Adult - Inpatient Clinical Practice Guideline.

1. The INR and either the extent of bleeding or timing of surgical intervention should be used to determine the level of warfarin reversal.[2] Table 2 provides common clinical scenarios and reversal options. *(UW Health high quality of evidence, strong recommendation)*

Table 2. Considerations for Warfarin Reversal Based on Clinical Scenario

Clinical Scenario	Reversal Strategy	Recheck INR	Other Considerations
INR 4.5 – 9.9 with NO significant bleeding	Omit 1-2 doses of warfarin	24–48 hours	For high INR no difference in incidence of bleeding was seen between patients treated with phytonadione versus placebo[7]
INR > 9.9 with NO significant bleeding	Omit warfarin until INR is near or within target range Phytonadione 1 – 2.5 mg orally (preferred) or IV	24 hours	
Any INR with non-major bleeding	Omit 1-2 doses of warfarin *May consider:* *Phytonadione 1 - 5 mg orally (preferred) or IV*	24–48 hours	Dose phytonadione based on INR, risk of thrombosis, and extent of bleeding

Any INR with major or life threatening bleeding	Stop warfarin until bleeding controlled Phytonadione 5-10 mg IV **AND** PCC dose based on INR	30 mins after PCC dose	Administer each agent as soon as it is available. There is no specific order of administration[13]
Any INR with need for reversal for planned procedure (> 24 hours)	Omit warfarin *May consider based on timing: Phytonadione 5 mg IV*	12 hours	If INR remains elevated then may consider repeating phytonadione dose or checking INR prior to surgery
Any INR with need for reversal for emergent surgery (< 24 hours)	Stop warfarin until safe to resume post-operatively PCC dose based on INR *May consider: Phytonadione 5-10 mg IV if not planning to resume warfarin immediately post-operatively*	30 mins after PCC dose	If expected length of surgery > 6 hours, phytonadione should be administered with PCC

2. It is reasonable to administer PCC (at dosing listed in Table 3) with or without phytonadione for patients requiring warfarin reversal prior to emergency surgery or major invasive procedures.[14,15] *(UW Health moderate level of evidence, weak/conditional recommendation)*
   2.1. There is data to support the use of low fixed dosed PCC for warfarin reversal. See Appendix E for literature summary. In the literature the majority of patients achieved the targeted INR goal after low dose PCC was administered without the need for supplemental PCC dosing. Failure to hit target INR goals were more commonly seen when the INR was > 6.0.[16-23] *(UW Health moderate level of evidence, weak/conditional recommendation)*
   2.2. If a patient is HIT positive, but more than 3 months ago, PCC can be administered (despite heparin content in PCC). If HIT was diagnosed less than 3 months ago evaluate benefit of procoagulant use versus risk of repeat HIT.[24] *(UW Health very low level of evidence, weak/conditional recommendation)*

Table 3. Prothrombin Complex Concentrate Dosing for Warfarin Reversal[16-23] *(UW Health moderate level of evidence, weak/conditional recommendation)*

Pre-Treatment INR	Dose of PCC	Recheck INR
< 6.0	1000 units	15 – 30 mins after dose
≥ 6.1	2000 units	15 – 30 mins after dose
Any INR with CNS bleed	2000 units	15 – 30 mins after dose
May repeat with 500 units if INR goal or clinical outcome is not achieved		

3. Routine use of FFP for reversal of INR or warfarin-related hemorrhage should be limited. *(UW Health low level of evidence, weak/conditional recommendation)*
   3.1. Studies have shown FFP fails to consistently reach the target INR goal when compared to PCC for INR reversal.[25-29]
   3.2. FFP is associated with higher fluid volumes per dose and transfusion related acute lung injury (TRALI)[30]

3.3. FFP may be used for emergent partial INR reversal (i.e. INR goal ≤ 2) or when large volumes of blood are being replaced.[31] *(UW Health low level of evidence, weak/conditional recommendation)*

4. Routine use of Factor 7A for reversal of warfarin-related hemorrhage is not recommended.[32-34] *(UW Health high level of evidence, strong recommendation)*

Direct Thrombin Inhibitor (i.e. Dabigatran)

Dabigatran is a reversible, oral direct thrombin inhibitor and an association between dose and incidence of bleeding is established in patients with atrial fibrillation.[35] Unlike warfarin, anticoagulation occurs through inhibition of factor II (thrombin), not depletion of the clotting factors. The half-life is 12 to 17 hours (in patients with normal renal function) and within 24 hours of stopping dabigatran, concentrations are reduced by approximately 75% of the original concentration in patients with normal renal function. Due to the short duration of effect, discontinuation of dabigatran could be sufficient to mitigate anticoagulant effects.[2,36]

5. The time of last dose, renal function, and either the extent of bleeding or time to surgical intervention should be used to determine the level of reversal needed. Table 4 provides common clinical scenarios and reversal options. *(UW Health moderate level of evidence, weak/conditional recommendation)*

Table 4. Considerations for Dabigatran Reversal Based on Clinical Scenario[37-39] *(UW Health moderate level of evidence, weak/conditional recommendation)*

Clinical Scenario	Reversal Strategy	Lab Monitoring	Other Considerations
Minor or non-clinically relevant bleeding	Hold dabigatran	N/A	Within 24 hours of stopping, dabigatran concentrations are reduced by 75% in normal renal function
Major or Life Threatening Bleeding	Hold dabigatran If dose taken ≤ 12 hrs (normal renal function): Idarucizumab If dose taken > 12 hrs, if last dose unknown or renal insufficiency then check TT: • If TT ≥ 25 secs: Idarucizumab • If TT < 25 secs: no reversal needed	Creatinine Thrombin Time (TT)	
Planned Surgery	Hold dabigatran UW Health Periprocedural and Regional Anesthesia Management with Antithrombotic Therapy – Adult – Inpatient/Ambulatory Clinical Practice Guideline	Creatinine (at least 7 days prior)	
Emergent Surgery	Hold dabigatran If dose taken ≤ 12 hrs (normal renal function): Idarucizumab	Creatinine Thrombin Time (TT)	

	If dose taken > 12 hrs, if last dose unknown or renal insufficiency then check TT: • If TT ≥ 25 secs: Idarucizumab • If TT < 25 secs: no reversal needed

Anti-Xa Inhibitors (i.e. apixaban, edoxaban, rivaroxaban)

With oral factor Xa inhibitors, unlike warfarin, anticoagulation occurs through inhibition of factor Xa, not inhibition of production of clotting factors. No direct reversal agent is available. Apixaban, edoxaban, and rivaroxaban have relatively short half-lives in patients with normal renal function (apixaban 12 hours, rivaroxaban 5- 9 hours, edoxaban 10-14 hours). The anticoagulant effect of these agents is minimal in patients 48 hours after ingestion[40-42] The benefit of coagulation must be weighed with the risk of thrombosis based on time of last dose, comorbidities, and patient characteristics.

There is data from cross over studies, utilizing healthy volunteers that suggest PCC is effective in correcting anticoagulation laboratory values. Dosing of PCC in these studies used 25 – 50 units/kg/dose.[43-46] While promising the major limitation to these studies is application to clinical bleeding outcomes. Limited data exists for use of PCC in bleeding caused by Xa inhibitors. Case reports and retrospective reviews show PCC to be effective in managing bleeding in 33-69% of patients treated. Failure to achieve hemostasis was more commonly seen in ICH.[47-52]

Factor 7A was also evaluated in the *ex vivo* study of healthy volunteers receiving one dose of rivaroxaban 20 mg and decreased time to reach the maximum concentration of thrombin, but did not increase thrombin generation potential to the same extent as PCC .[44] There are no data to recommend for or against use of factor 7A for the treatment of life-threatening bleeding associated with factor Xa inhibitors.

6. For minor or non-clinically significant bleeding hold Xa inhibitor until bleeding subsides and it is deemed safe to resume anticoagulation. For planned surgical procedures hold Xa inhibitor per UW Health Periprocedural and Regional Anesthesia Management with Antithrombotic Therapy – Adult – Inpatient/Ambulatory Clinical Practice Guideline recommendations. *(UW Health moderate level of evidence, strong recommendation)*

7. For major or life-threatening bleeding or the need for emergent surgery PCC may be considered.[43-52] *(UW Health low level of evidence, weak/conditional recommendation)*
    7.1 Optimum dosing of PCC is unknown; however, doses of 25 – 50 Units/kg (maximum 5000 units) might be considered[43-52] *(UW Health low level of evidence, weak/conditional recommendation)*

Parenteral Anticoagulants: *Listed by drug class*

Heparinoids (i.e. unfractionated heparin, low molecular weight heparin)
Unfractionated heparin (UFH) binds to anti-thrombin III to enhance the rate of neutralization of factors II (thrombin) and Xa. Therapeutic doses neutralize thrombin and thereby prevent the

conversion of fibrinogen to fibrin.[53] The half-life is only 60 to 90 minutes therefore; therapeutic effect is eliminated within three to four hours.

Similar to UFH, the primary anticoagulant activity of low molecular weight heparin (LMWH) (i.e., enoxaparin, dalteparin) is through antithrombin inhibition of coagulation factors. However, LMWH binds to factor Xa to a greater extent than thrombin and exhibits a more predictable dose response than unfractionated heparin.[53] The risk of bleeding from LMWH correlates with the extent of anticoagulation, but no established method for total reversal of anticoagulation from LMWH exists. Protamine will only neutralize thrombin activity and has limited, if any activity, on anti-factor Xa activity.[54-56]

8. The dose, time of last dose and renal function should be used to determine the dose of protamine needed for reversal. Table 5 provides reversal strategies for UFH and LMWH. *(UW Health high level of evidence, strong recommendation)*

Table 5. Considerations for Protamine in UFH or LMWH Reversal[53, 57-59] *(UW Health high level of evidence, strong recommendation)*

Drug	Reversal Strategy	Monitoring	Other Considerations
UFH	Protamine 1 mg per 100 units of heparin administered within last 2 hours (Max dose 50 mg) [61]	Anti-Xa aPTT ACT	
LMWH	If given in last 8 hrs: Protamine 1 mg per 100 anti-Xa units (1 mg) of LMWH (Max 50 mg) [39,111]	Anti-Xa	In renal insufficiency may consider protamine use beyond 12 hours
	If given > 8 hr but < 12 hr: Protamine 0.5 mg per 100 anti-Xa units (1 mg) of LMWH [61]		May consider redosing if bleeding persists 0.5 mg per 1 mg (max 25 mg)

Insufficient evidence exists to make recommendations for or against the use of Factor 7A in patients with life-threatening bleeding unresponsive to other therapies. Factor 7A 40mcg/kg may facilitate bleeding control in patients treated with LMWH.[60] Case reports of life-threatening bleeding in patients treated with LMWH utilized factor 7A 20-120 mcg/kg to reverse bleeding.[11861-63]

Direct Thrombin Inhibitors (i.e argatroban, bivalirudin)

Argatroban and bivalirudin are parenteral direct thrombin inhibitors.[64,65] There are no established reversal agents; however the short half-lives (argatroban 45 minutes; bivalirudin 25 minutes) result in a short duration of anticoagulation action often precluding the need for additional procoagulant therapy.[53]

Factor 7A has theoretical applications in reversing argatroban-associated hemorrhage, though clinical experience for off-label use is limited and has not demonstrated benefit.[66,67] Although a report demonstrates factor 7A could overcome argatroban anticoagulation based on normal thromboelastography, this does not represent recovery of thrombin generation and normalized coagulation.[68,69] One case report of an infant receiving argatroban failed to demonstrate hemostasis with factor 7A.[66] Insufficient evidence exists to make recommendations for or against the use of factor 7A for the treatment of life-threatening bleeding with argatroban.

9. Use supportive measures to control bleeding. Insufficient evidence exists to recommend factor 7A use in argatroban or bivalirudin related hemorrhage.[66-69] *(UW Health very low level of evidence, weak/conditional recommendation)*

Anti-Xa Inhibitor (i.e. fondaparinux)

Fondaparinux is a factor Xa inhibitor with an elimination half-life of 17–21 hours.[70] There is no established reversal agent for fondaparinux.[53]

There is insufficient evidence to recommend for or against treatment of major or life-threatening bleeding due to fondaparinux with factor 7A.[53,59,69] No clinical trial is available to demonstrate improved clinical outcomes in patients treated with factor 7A; only case reports are available. In 16 healthy male subjects weighing less than 100 kg treated with 10 mg of fondaparinux, a single dose of factor 7A 90 mcg/kg reduced the thrombin generation time, activated partial thromboplastin time, and prothrombin time, and increased the endogenous thrombin potential within 1.5 hours of administration.[71] Young and colleagues again demonstrated in-vitro reversal of fondaparinux-induced anticoagulation with factor 7A using concentrations the authors anticipate would be achieved with factor 7A dosing of 90-270 mcg/kg.[68] Reversal of clinically-significant bleeding from fondaparinux has not been clearly demonstrated with factor 7A, though a case report notes management of fondaparinux-associated intracerebral hemorrhage with factor 7A administration (90 mcg/kg x 1) and neurosurgical evacuation.[59] The authors indicated hemostasis was achieved; however, the patient did not survive.

10. For major or life-threatening bleeding factor 7A may be considered.[59,68,71] *(UW Health low level of evidence, weak/conditional recommendation)*

11. Protamine is not effective for the treatment of bleeding associated with fondaparinux.[53] *(UW Health low level of evidence, strong recommendation)*

Antiplatelets

There are several classes of antiplatelet agents available: cyclo-oxygenase inhibitors (COX-inhibitors): i.e. aspirin, ibuprofen, naproxen; P2Y12 ADP receptor inhibitors (i.e. clopidogrel, prasugrel, ticagrelor, ticlopidine); phosphodiesterase inhibitor (i.e. cilostazol) and glycoprotein IIb/IIIa inhibitors (i.e. eptifibatide, abciximab). Antiplatelets associated with a higher level of platelet inhibition are suspected to cause higher incidence of ICH, ICH volume growth, need for craniotomy and mortality. There is no specific antidote for antiplatelet agents. In general, platelet function is restored after 3-5 half-lives of a reversible antiplatelet and not until new platelets are regenerated for irreversible antiplatelets. This can influence the approach to antiplatelet reversal.[72-74] For recommendations on reversal for planned procedures see: UW Health Periprocedural and Regional Anesthesia Management with Antithrombotic Therapy – Adult – Inpatient/Ambulatory Clinical Practice Guideline.

When considering reversal options for antiplatelet agents it is important to consider the severity of bleeding and if it demonstrates reversible or irreversible antiplatelet effect. General recommendations for antiplatelets include[72,75]:

12. Reversal of antiplatelets is usually only recommended in life threatening bleeding (i.e. intracranial hemorrhage). *(UW Health moderate level of evidence, strong recommendation)*

13. Supportive measures should be used to help manage bleeding. *(UW Health low level of evidence, weak/conditional recommendation)*

14. Surgical procedures should be delayed, when possible but if emergent surgery is needed then supportive measures intraoperatively can be used for managing bleeding *(UW Health low level of evidence, weak/conditional recommendation)*

Cyclo-oxygenase inhibitor (COX-inhibitors): i.e. aspirin, ibuprofen, naproxen
Non-selective cox-inhibitors prevent the conversion of arachidonic acid to thromboxane A_2, thus inhibiting platelet activation and aggregation. Aspirin causes irreversible inhibition of platelet aggregation. The effect of aspirin can last 5-7 days after discontinuation. Other non-steroidal anti-inflammatory drugs (NSAIDs) inhibit COX with a reversible dose dependent effect. As the drug concentration decreases, COX activity returns. The effect is dependent on the elimination half-life of each drug.[72,76]

Aspirin
There is some data to suggest platelet transfusion can be used in patients with intracranial hemorrhage undergoing craniotomy. In one randomized, controlled trial, patients who received platelet transfusion experienced less intraparenchymal hemorrhage recurrence, lower post-operative hematoma volume, and decreased mortality.[77]

The PATCH trial studied platelet transfusion for intracerebral hemorrhage associated with antiplatelet use. All antiplatelets were included, but COX inhibitor monotherapy represented the largest antiplatelet therapy in both groups (73% in transfusion and 84% standard care). Patients who underwent surgical evacuation within 24 hours of admission were excluded. The results showed platelet transfusions associated with worsening outcomes regarding functional status and death and no change in volume growth.[78]

15. Intracranial hemorrhage undergoing surgical evacuation (i.e. craniotomy) platelet transfusion may be considered[72,77,78] *(UW Health low level of evidence, weak/conditional recommendation)*
    15.1 Allow 3-5 have lives of the implicated antiplatelet agent to elapse before attempting to infuse platelets. This will minimize pharmacologic inhibition of the transfused platelets.[72] *(UW Health low level of evidence, weak/conditional recommendation)*

16 Intracranial hemorrhage without surgical evacuation platelet transfusion is not recommended. [72,77,78] *(UW Health low level of evidence, weak/conditional recommendation)*

While not well studied, desmopressin (DDAVP) may be considered. A single dose of DDAVP was used in patients on aspirin undergoing CABG. The DDAVP group resulted in less chest tube output and total blood loss but no difference in transfusion requirements.[79] Another study used two doses of DDVAP in open cholecystectomy. It demonstrated shortened bleeding time when compared to placebo.[80] Another study in intracranial hemorrhage showed platelet

stabilization through platelet function measurements with a single dose, although effect only lasted 3 hours.[81]

17. Intracranial hemorrhage may consider DDAVP 0.4 mcg/kg[72,79-81] *(UW Health low level of evidence, weak/conditional recommendation)*
    17.1 DDAVP can be used in addition to platelet transfusion[72] *(UW Health low level of evidence, weak/conditional recommendation)*

NSAIDs (i.e. ibuprofen, naproxen)
Due to the reversible platelet inhibition and short half-life of most NSAIDs, there is not an established role for using specific reversal agents.[72]

18. Use supportive measures to control bleeding. Insufficient evidence exists to recommend platelet transfusion or DDVAP to treat related hemorrhage.[72] *(UW Health low level of evidence, weak/conditional recommendation)*

P2Y12 ADP Receptor Antagonists (i.e. clopidogrel, prasugrel, ticagrelor, ticlopidine)
Platelet inhibition occurs by binding to the adenosine diphosphate (ADP) receptor on platelets and preventing activation. This inhibition is irreversible and the effect is present until the drug is eliminated and new platelets are generated.[82,83] The exception is with ticagrelor which reversibly inhibits platelet action.[82]

The use of platelet transfusion for reversal remains controversial. A single-center prospective, observational study with IPH and decreased platelet function due either to aspirin or clopidogrel. Platelet transfusion was associated with smaller hemorrhage size, however, there was no control group and different transfusion doses were given. Other studies have failed to show benefit in mortality, hemorrhage growth, or patient functionality from platelet transfusion.[84-86]

The PATCH trial studied platelet transfusion for intracerebral hemorrhage associated with antiplatelet use. All antiplatelets were included, but use of ADP inhibitor either as monotherapy or combination therapy with a COX inhibitor was not well represented (<4% in both comparator groups). Patients who underwent surgical evacuation within 24 hours of admission were excluded. The results showed platelet transfusions associated with worsening outcomes regarding functional status and death and no change in volume growth.[78]

19. Intracranial hemorrhage undergoing surgical evacuation (i.e. craniotomy) platelet transfusion may be considered[78,84-86] *(UW Health low level of evidence, weak/conditional recommendation)*
    19.1 Allow 3-5 have lives of the implicated antiplatelet agent to elapse before attempting to infuse platelets. This will minimize pharmacologic inhibition of the transfused platelets.[72] *(UW Health low level of evidence, weak/conditional recommendation)*

20. Intracranial hemorrhage without surgical evacuation platelet transfusion is not recommended. [78,84-86] *(UW Health low level of evidence, weak/conditional recommendation)*

DDAVP has not been well studied to control bleeding from P2Y12 ADP inhibitors. A case report showed transient restoration of platelet function after single dose DDAVP[87]**.** In healthy subjects, DDAVP showed improvements in bleeding time and platelet function tests.[88,89]

21. Intracranial hemorrhage may consider DDAVP 0.4 mcg/kg[72,87-89] *(UW Health low level of evidence, weak/conditional recommendation)*

21.1 DDAVP can be used in addition to platelet transfusion[72] *(UW Health low level of evidence, weak/conditional recommendation)*

Phosphodiesterase Inhibitor (i.e. cilostazol)
Phosphodiesterase inhibitors reversibly inhibit platelet aggregation. Due to the reversible platelet inhibition and relatively short half-life, there is not a role for using specific reversal agents.[72]

22. Use supportive measures to control bleeding. Insufficient evidence exists to recommend platelet transfusion or DDVAP to treat related hemorrhage[72] *(UW Health low level of evidence, weak/conditional recommendation)*

Glycoprotein IIb/IIIa Inhibitors (i.e. eptifibatide, abciximab)
Platelet inhibition occurs through the blocking of the platelet glycoprotein IIb/IIIa receptor and reversibly inhibiting platelet aggregation. Due to the short half-life of these medications, platelet function returns within 4-8 hours after discontinuation. There is no specific reversal agent available.[90]

23. Use supportive measures to control bleeding. Insufficient evidence exists to recommend platelet transfusion or DDVAP to treat related hemorrhage.[72] *(UW Health low level of evidence, weak/conditional recommendation)*

UW Health Implementation

Potential Benefits:
- Standardized approach to antithrombotic reversal
- Recommendations for antithrombotics where data is limited

Potential Harms:
- Limited literature for some antithrombotic agents
- Risks for continued bleeding if reversal not complete
- Risks for thrombotic event after reversal

Qualifying Statements: Most studies evaluating procoagulant use in bleeding patients are small and/or case series or conducted in normal volunteers. Recommendations are subject to change with the publication of clinical trials and FDA approval of additional agents.

Pertinent UW Health Policies & Procedures
1. Pharmacy Operating Procedure for the Emergent Use of Factor 7A (NovoSeven®)
2. Pharmacy Operating Procedure for the Emergent Use Prothrombin Complex Concentrate (PCC)

Patient Resources
Not applicable

Guideline Metrics
1. Metric #1: Use of appropriate agent and dosing strategy for each antithrombotic
2. Metric #2: Successful reversal
3. Metric #3: Thrombotic event post reversal

Implementation Plan/Clinical Tools

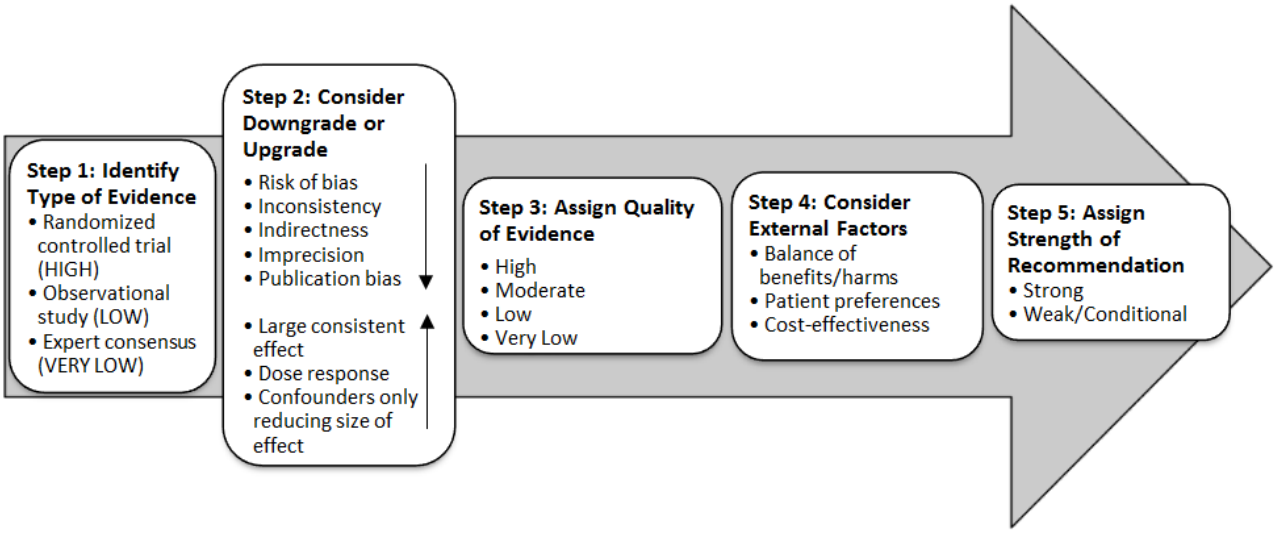
1. Guideline will be posted on uConnect in a dedicated location for Clinical Practice Guidelines.
2. Release of the guideline will be advertised in the Physician/APP Briefing newsletter.
3. Content and hyperlinks within clinical tools, documents, or Health Link related to the guideline recommendations (such as the following) will be reviewed for consistency and modified as appropriate.

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Appendix A. Evidence Grading Scheme(s)

Figure 1. GRADE Methodology adapted by UW Health



GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.

Weak/conditional	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

Appendix A. Treatment of Bleeding Associated with Oral Anticoagulants

<table>
<tr><th>Anticoagulant</th><th>Half-life[8]</th><th>Reversal Agent / Bleeding Treatment</th><th>Comments</th><th>Lab</th></tr>
<tr><td colspan="5">In all cases of substantial bleeding supportive strategies by means of discontinuation of anticoagulant, mechanical compression and administration of blood products, fluid resuscitation, hemodynamic and respiratory support are required. In addition maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. (See UW Health Indications for Blood Product Transfusion – Adult – Inpatient/Ambulatory Clinical Practice Guideline)</td></tr>
<tr><td>Apixaban</td><td>12 h</td><td rowspan="2">• If ingestion within 3 hours, consider activated charcoal 50 g
• Plasma is not indicated unless the patient has received at least 4 units of PRBCs and the INR is prolonged (i.e., hemodilution).
• PCC 25-50 units/kg (maximum 2500 - 5000 units) might be considered for life-threatening conditions or urgent surgery.</td><td rowspan="2">-Administer PCC at a maximum rate of 200 units/min</td><td rowspan="2">NA</td></tr>
<tr><td>Edoxaban
Rivaroxaban</td><td>10-14 h
5-9 h</td></tr>
<tr><td>Dabigatran</td><td>12-17 h</td><td>• If ingestion within 3 hours, consider activated charcoal 50 g Po or per enteral tube
• Idarucizumab 5 grams IV if dabigatran was taken within the previous 12 hours OR TT is ≥ 25 secs</td><td>Hemodialysis removes approximately 60% within 2 h</td></tr>
<tr><td>Warfarin</td><td>36-42 h</td><td>
<table>
<tr><th>Severity of Bleeding</th><th>Treatment Measures</th></tr>
<tr><td>No bleeding or minor bleeding</td><td>• INR 4.5-9.9 omit 1-2 doses
• INR >9.9 – omit 1-2 doses, phytonadione 1-2.5 mg PO/IV</td></tr>
<tr><td>Major, Life threatening bleed , emergency surgery or major procedure</td><td>• Phytonadione 5-10 mg IV with the dose dependent upon risk thromboembolism and severity of bleed
• PCC based on INR and weight
<table>
<tr><th>Pre-treatment INR</th><th>Dose of PCC</th></tr>
<tr><td>≤6.0</td><td>1000 units</td></tr>
<tr><td>≥ 6.1</td><td>2000 units</td></tr>
<tr><td>Any INR with CNS bleed</td><td>2000 units</td></tr>
</table>
May repeat with 500 units if INR goal or clinical outcome not achieved
Give each agent as soon as it is available</td></tr>
</table>
</td><td>-High doses of phytonadione can cause difficulty in anticoagulating patients after resolution of the bleeding episode

-Administer phytonadione IV over 20-30 minutes, faster administration can result in anaphylaxis

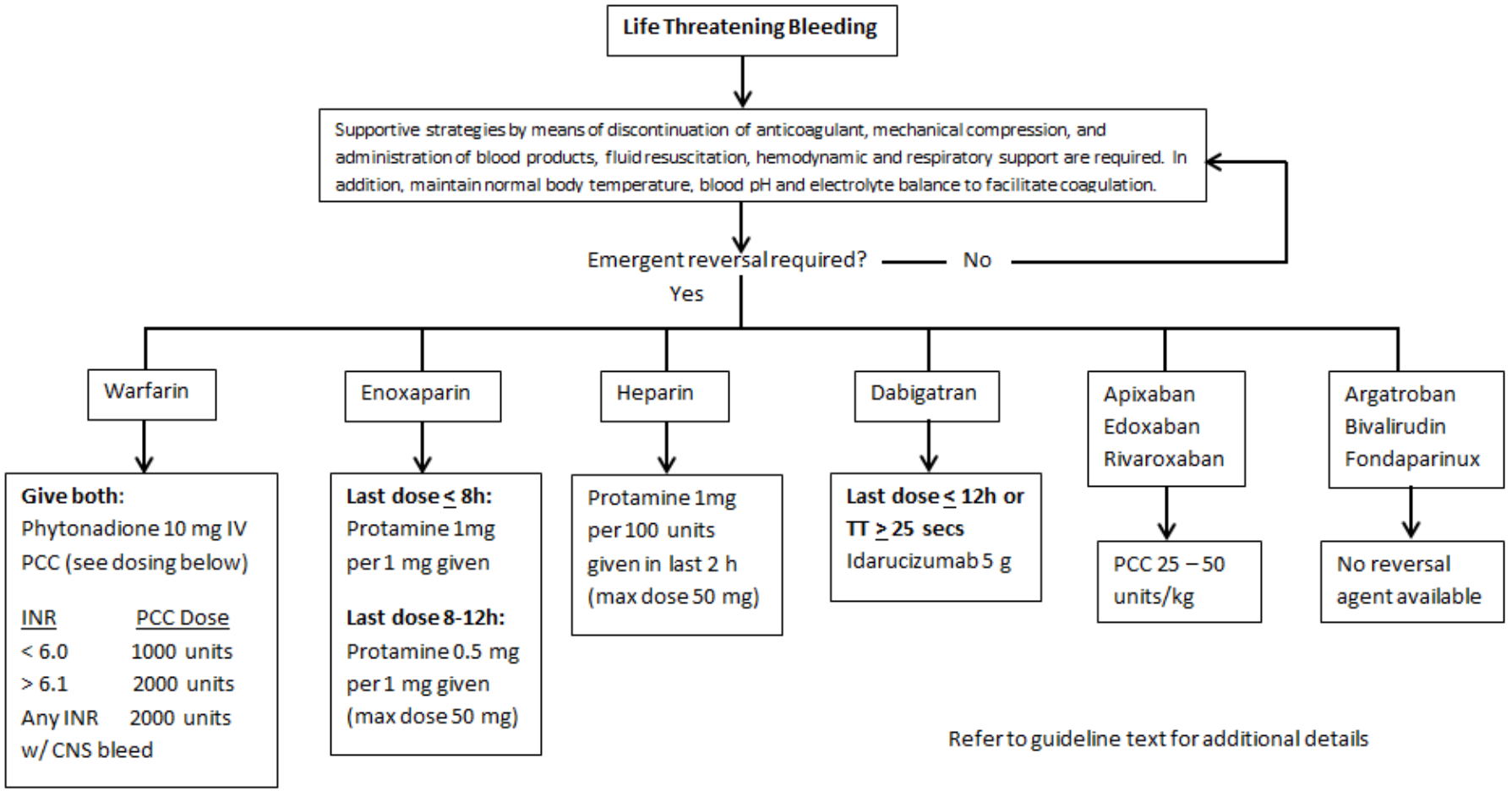
-Administer PCC at a maximum rate of 200 units/min

-PCC can cause hypersensitivity reactions</td><td>INR</td></tr>
<tr><td colspan="5">NA – not applicable; PCC – prothrombin complex concentrate</td></tr>
</table>

Appendix B. Treatment of Bleeding Associated with Parenteral Anticoagulants

Anticoagulant	Usual Half-life	Reversal Agent / Bleeding Treatment	Comments	Lab Monitoring
In all cases of substantial bleeding supportive strategies by means of discontinuation of anticoagulant, mechanical compression and administration of blood products, fluid resuscitation, hemodynamic and respiratory support are required. In addition maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. (See				
Argatroban IV	45 min	General supportive measures		aPTT
Bivalirudin IV	25 min	General supportive measures		aPTT
Fondaparinux Subcutaneous	17-21 h	General supportive measures	.	anti-Xa
Heparin IV	1 - 1.5 h	• Protamine 1 mg per100 units of heparin administered within the last 2 hours. Maximum dose 50 mg. • Consider monitoring trends in anti-Xa or ACT to determine requirement for subsequent protamine dosing	- high doses of protamine can enhance anticoagulation -administer protamine over 10 minutes -protamine can cause anaphylaxis	anti-Xa ACT
LMWH Subcutaneous (e.g., enoxaparin, dalteparin)	3 -5 h	Time of Last Dose: Within last 8 h — Protamine 1 mg/100 anti-Xa units (maximum 50 mg); If bleeding continues, repeat protamine 0.5 mg/100 anti-Xa units (maximum 25 mg) Time of Last Dose: 8 – 12 h ago — Protamine 0.5 mg/ 100 units anti-Xa units (maximum 50mg) Time of Last Dose: Dose > 12 h ago — Protamine may not be necessary	- If patient has renal insufficiency consider wider timeline for administering protamine	anti-Xa

Appendix C – Treatment of Life Threatening Bleeding Associated with Anticoagulants



Appendix D – Administration Rate of Intravenous Procoagulant Agents

(See also Intravenous Administration Guideline – Adult – Inpatient/Ambulatory Clinical Practice Guideline

Medication	Rate of Administration
Desmopressin	Over 20 – 30 minutes
Factor 7A	Over 2 minutes
Idarucizumab	Over 10 - 20 minutes
Phytonadione	Over 20 – 30 minutes
Protamine	10 mg over 1 – 3minutes, 50 mg over 10 minutes minimum
Prothrombin Complex Concentrate (PCC)	100 units/minute, maximum 200 units/minute

Appendix E – Literature Summary for Low Fixed Dose PCC

Reference	Patient Population	PCC Type	N	PCC Dose	INR Goal	INR Outcome Achieved	Comments
Abdoellakhan R, 2017	Warfarin reversal for ICH	4 Factor (Cofact)	N = 28 N = 25	Fixed dose 1000 IU Weight based (WB)	≤1.5	68% FD 96% WB	Mean dose WB: 1750 IU Median INR: 3.1 (WB) and 3.3 (FD) Per study FD may have been too low for ICH bleeding
Kantorovich A, 2015	Heart transplant surgery	3 Factor	N = 16	INR ≤ 3.5: 10 units/kg INR > 3.5: 20 units/kg	< 1.7	75%	Median INR 2.46 (2.2-2.9) Average weight 80.8 kg Higher percentage of patients received the 20 units/kg dose
Klein L, 2015	Warfarin reversal for any reason	4 Factor (Kcentra)	N = 39	Fixed dose 1500 IU	< 2.0 ≤1.5	92.3% 71.8%	Average weight 79.5 kg Median INR: 3.3 (2.5-4.0) *Second dose needed in 1 patient*
Quick JA, 2015	Acute care surgery	3 Factor	N = 41	15 units/kg	< 1.5	78%	Median INR 2.52 Higher percentage of failure seen with INR > 4.3
Hirri HM, 2014	Warfarin reversal for any reason	4 Factor (Octaplex)	N = 67	CNS bleeds 2000 IU Other bleeds 1500 IU Non-bleeding 1000 IU	≤1.5	83.6%	Higher percentage of failure seen with INR > 6 None needed a second dose
Varga C, 2013	Warfarin reversal for any reason	4 Factor (Octaplex)	N = 103	1000 IU	≤1.5 < 2.0	48.5% 92.2%	Median INR: 2.8 (1.4 – 24) Higher INR may require higher PCC dosing (not clear in study the definition of higher INR)
Khorsand N, 2012	Warfarin reversal for any reason (except ICH)	4 Factor	N = 101 N = 139	Fixed dose 1040 IU Weight based (WB)	< 2.0	92% FD 95% WB	Median INR FD 5.1 and WB 5.9 Higher percentage of failure seen with INR > 7.5
Khorsand N, 2011	Warfarin reversal for any reason (except ICH)	4 Factor (Cofact)	N = 35 N = 32	1040 IU for bleeding 520 IU for procedure reversal	<1.5 <2.0 (if epidural use < 1.8)	70% 81%	Median INR: 4.7 (2.0 - > 9.0) Higher percentage of failure seen with INR > 5 Clinical outcomes achieved 91% and 94%

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