Procoagulant Therapy for Bleeding Associated with Acquired Bleeding Disorders - Adult - Inpatient Clinical Practice Guideline

Note: Active Table of Contents – Click to follow link

Table of Contents

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Executive Summary

Guideline Overview

This document is intended to guide the use of procoagulant agents for the treatment of adult inpatients and ED patients with acquired bleeding disorders with sustained bleeding or undesired anticoagulation after administration of anticoagulants. Procoagulant therapy for severe bleeding in patients not taking anticoagulants and associated with intracerebral hemorrhage, cardiac surgery, trauma, and uremia is also addressed.

Key Practice Recommendations

1. Aminocaproic Acid

1.1. Aminocaproic acid reduces the number of blood transfusions compared to placebo in surgical patients. (Class I, Level A)

1.2. Dosing

1.2.1. Typical parenteral doses for acute bleeding are an initial loading dose of 4 to 5 grams (50–150 mg/kg), followed by infusion of 1 gram per hour (or 10-15 mg/kg/h) for 8 hours or until bleeding is controlled. (Class IIa, Level B)

1.2.2. Typical doses for cardiac surgery patients are 60-80 mg/kg loading dose (usually 5-10 grams) over 20 minutes followed by a maintenance infusion of 10-30 mg/kg/h (usually 1-2 grams/hour). (Class IIa, Level B)

1.3. If aminocaproic acid is unavailable, tranexamic acid is an appropriate alternative. (Class I, Level C)

2. Tranexamic acid

2.1. Parenteral tranexamic acid is effective in treating bleeding from multiple causes such as GI, surgical, and trauma. (Class I, Level A)

2.2. Multiple dosing regimens are employed based on indication.

2.2.1. Non-cerebral trauma doses utilized:

- Tranexamic acid 1 g over 10 minutes followed by 1 g over 8 hours (Class I, Level A)
- Tranexamic acid 10-15 mg/kg followed by an infusion of 1-5 mg/kg/h (Class I, Level B)

2.2.2. In cardiac surgery doses of tranexamic acid are 2.5 mg/kg to 100 mg/kg followed by maintenance doses of 0.25-4 mg/kg/h over 1-12 hours can be considered. (Class IIb, Level B)

2.3. Tranexamic acid can reduce transfusion requirements during hepatic resection. (Class I, Level A)

2.4. The effects of alteplase can be attenuated with tranexamic acid. (Class IIa, Level B)

2.5. If tranexamic acid is unavailable, aminocaproic acid is an appropriate alternate. (Class I, Level C)

3. Phytonadione (vitamin K) administered by the oral or intravenous route is recommended to reverse the anticoagulant effects of warfarin through promoting the productions of clotting factors II, VII, IX and X. (Class I, Level A)

3.1. Empiric use of phytonadione in patients on warfarin with an INR of 4.5-9.9 and no bleeding is not recommended. (Class III, Level B)

3.2. Low oral doses (1-5 mg) of phytonadione are preferred over the intravenous route for minor bleeding or treatment of INR > 9.9. (Class I, Level C)

3.3. In patients with an elevated INR due to warfarin anticoagulation with major or life-threatening bleeding it is reasonable to give phytonadione 5-10 mg along with PCC to sustain reversal of anticoagulation. (Class IIa, Level A)The intravenous route is reserved for circumstances when fast onset is required for urgent reversal (e.g., life threatening bleeding) or the patient is unable to absorb the enteral formulation. (Class I, Level C)

3.3.1. Slow intravenous administration (over 20-30 minutes) is recommended to avoid severe hypotension and rare anaphylactic reactions. (Class I, Level C)

3.3.2. Rapid reversal of warfarin with intravenous phytonadione is not recommended prior to elective procedures or surgeries. (Class III, Level C)

3.4. Subcutaneous and intramuscular administration is not recommended due to a delayed and unpredictable response. (Class III, Level C)

3.5. Administration of high doses (10 mg or greater) may limit the ability to anticoagulate patients after bleeding is controlled; therefore, it is useful to administer the lowest dose of phytonadione to achieve therapeutic results. (Class I, Level C)

4. Prothrombin Complex Concentrate (PCC)

4.1. PCC is recommended for the reversal of warfarin due to acute major or life-threatening bleeding or prior to emergency surgery or major invasive procedure. (Class I, Level A)

4.2. Dosing of PCC is based on the factor IX component, pre-treatment INR, weight and patient risk factors (Class IIa, Level A)

4.2.1. Administer the PCC dose within 4 hours of reconstitution. (Class I, Level A)

4.3. Contraindications include disseminated intravascular coagulation, heparin induced thrombocytopenia, and known hypersensitivity reactions to the components of PCC. (Class I, Level C)

4.4. If a patient is diagnosed with heparin-induced thrombocytopenia (HIT), but more than 3 months ago, PCC can be administered regardless of heparin content. If HIT was diagnosed less than three months ago, weigh the benefit of procoagulant therapy with the risk of thrombosis and recurrent HIT. (Class I, Level C)

5. Plasma

5.1. Indications include: replacement of single factor deficiencies when a specific coagulation factor concentrate is not available; immediate reversal of warfarin for active bleeding, surgery or procedures; active hemorrhage and multifactor coagulopathy (INR ≥ 1.8); invasive procedure planned within six hours and multifactorial coagulopathy (INR >1.8); massive transfusion; thrombotic thrombocytopenic purpura (TTP) using plasma exchange; plasmapheresis; or complement mediated hemolytic uremic syndrome. (Class I, Level C)

5.2. Usual dose for major or life-threatening bleeding is 10-15 mL/kg with repeat doses administered as required. (Class I, Level C)

5.3. Infuse plasma as quickly as tolerated by the patient.(Class I, Level C)

6. Factor 7A

6.1. Actual body weight should be used for dosing calculations. (Class I, Level C)

6.2. It is useful to round doses down to the nearest 1000 mcg (1 mg) vial size. (Class I, Level C)

6.3. Usefulness of factor 7A in severely acidotic patients in unknown. The blood pH should be above 7.2 prior to administration. (Class I, Level C)

6.4. The short half-life of factor 7A limits activity to 2-3 hours and concomitant use of blood is recommended. (Class I, Level C)

6.5. Contraindications include hypersensitivity to mouse, bovine or hamster proteins or hypersensitivity to recombinant factor 7A or the product components. (Class I, Level C)

7. Desmopressin

7.1. Usual dose for treating uremic bleeding and platelet dysfunction is 0.3 mcg/kg administered over 15 - 30 minutes. (Class I, Level C)

7.2. Do not administered desmopressin for more than three days in a row. (Class III, Level C)

8. Protamine

8.1. The dose of protamine should be sufficient to revere the amount of heparin administered within the last 2 hours (maximum 50 mg). Protamine 1 mg reverses approximately 100 units of heparin. (Class I, Level C)

8.2. If LMWH was administered within the previous 8 hours, give protamine 1 mg per 100 anti-Xa units (maximum dose 50 mg) of LMWH. A longer time frame may be considered in patients with renal insufficiency. (Class I, Level C)

8.3. If LMWH was administered more than 8 hours, but less than 12 hours ago, give protamine 0.5 mg per 100 anti-Xa units (maximum 50 mg) of LMWH. A longer time frame may be considered in patients with renal insufficiency. (Class I, Level C)

8.4. A second dose of protamine (0.5 mg/kg, maximum 25 mg) can be administered if bleeding continues. (Class I, Level C) For patients at risk for a serious allergic reaction to protamine

consider pretreat with H-1 antihistamine and corticosteroid therapy if protamine is medically necessary. (Class I, Level C)

9. Idarucizumab

9.1. If dabigatran was taken within the previous 12 hours OR the thrombin time (TT) is prolonged in patients taking dabigatran, one dose of idarucizumab 5 grams IV is indicted for reversal prior to acute major or life-threatening bleeding, emergent surgery, or major invasive procedure. (Class I, Level B)

9.2. If the last dose of dabigatran was taken more than 12 hours ago, the time of the last dose is uncertain, or the patient has renal insufficiency, it is useful to monitor TT. (Class I, Level C)

9.2.1. If TT is ≥ 21 seconds, then it might be useful to administer dabigatran. (Class IIa, Level C)

9.2.2. If TT is ≤ 20 seconds do not administer dabigatran.(Class III, Level C)

9.3. Repeat doses of idarucizumab for the same bleeding event are not recommended. (Class III, Level A)

General Treatment Management for Sustained Bleeding

10. It is beneficial to identify the source and cause of bleed. (Class I, Level C)

11. Management of hemorrhage includes maintenance of hemodynamic and respiratory stability. When necessary, provide mechanical ventilation, fluid resuscitation, hemodynamic support and therapeutic procedures to stabilize the patient and promote coagulation. (Class I, Level C)

12. Maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. (Class I, Level C)

13. If applicable, recommend use of packing or dressing, use local hemostatic measures or surgical intervention to control bleeding. (Class I, Level C)

14. If an overdose of oral anticoagulant is suspected, administer activated charcoal in patients with low risk for aspiration if the patient does not have a gastric bleed. (Class I, Level C)

15. Consider the risk versus benefit of continuation of anticoagulation therapy. Discontinue anticoagulant and/or concomitant antiplatelet therapy in patients with life threatening or massive trauma hemorrhage. If possible discontinue interacting medications that potentiate or prolong the pharmacodynamics of an anticoagulant (e.g., ciprofloxacin and warfarin). (Class I, Level C)

16. After control of major bleeding stabilizes, reassess for risk of thromboembolism and initiate a short acting agent if anticoagulation is required. (Class I, Level C)

Major Bleeding with Oral Anticoagulants Recommendations (Appendices A, B)

17. **Warfarin** - Recommend monitoring the INR associated with a bleeding event in warfarin treated patients. (Class I, Level C).

18. **Warfarin** - Patients at a high risk for thromboembolism with non-major bleeding may be managed with incomplete warfarin reversal. (Class I, Level C)

18.1. Elevated INR (Class I, Level B)

18.1.1. INR 4.5 – 9.9 - omit 1 - 2 doses of warfarin

18.1.2. INR > 9.9 - omit 1 - 2 doses of warfarin and administer phytonadione 1 - 2.5 mg orally (preferred) or IV.

19. **Warfarin** – Non-major bleeding in warfarin treated patients requiring reversal:

19.1. Omit 1 to 2 warfarin doses or until bleeding subsides. (Class I, Level B)

19.2. Phytonadione 1 – 5 mg orally or IV (dose dependent upon INR, risk of VTE, and extent of bleeding). (Class I, Level B)

19.3. It may be useful to administer plasma 1-2 units (or up to 10-15 mL/kg (supplied in 250 mL units) and repeat as necessary. (Class I, Level B)

20. Warfarin - Major and life-threatening bleeding in patients on warfarin.

20.1. It is useful to discontinue warfarin until bleeding is controlled. (Class I, Level C)

20.2. Administer phytonadione 5-10 mg along with PCC. There is no specific order of administration; administer each agent as soon as it is available. (Class IIa, Level A)

20.2.1. Weight-based dosing of PCC based INR is beneficial. (Table 2, Table 3.)

Table 2. Dose of Prothrombin Complex Concentrate* for **Major** Bleeding (Class I, Level A)

Pre-treatment INR	Dose of PCC	Maximum Dose
1.2 – 1.9	Not recommended	
2.0 – 3.9	25 units/kg	2500 units
4.0- 6.0	35 units/kg	3500 units
≥ 6.1	50 units/kg	5000 units
Repeat dosing is not recommended.		
*Round doses to the nearest vial size. Vial sizes vary from 420 to 600 units.		

Table 3. Dosing of Prothrombin Complex Concentrate for **Life-Threatening** Bleeding

Pre-treatment INR	Dose of PCC	Maximum Dose	le of Recommendation
1.2 - 3.9	25 units/kg	2500 units	Class I, Level C
4.0 - 6.0	35 units/kg	3500 units	Class I, Level A
≥ 6.1	50 units/kg	5000 units	Class I, Level A
Repeat dosing is not recommended.			
*Round doses to the nearest vial size. Vial sizes vary from 420 to 600 units.			

21.2.2 If a patient is reported as HIT positive, but greater 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 versus risk of repeat HIT. (Class I, Level C)

21. Warfarin - Routine use of Factor 7A for reversal of warfarin-related hemorrhage is not recommended.[76-78] (Class III, Level B)

22. Warfarin - It is reasonable to administer PCC (at dosing listed in Table 2) with or without phytonadione and plasma for patients requiring warfarin reversal prior to emergency surgery or major invasive procedures. (Class IIa, Level B)

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23. Dabigatran - Idarucizumab 5 grams IV is recommended for reversal of dabigatran in patients with major or life-threatening bleeding or requiring emergency surgery or invasive procedure if dabigatran was taken within the previous 12 hours in patient with normal renal function (Appendix B). (Level I, Class B)

24. Dabigatran - If the time of the last dose is greater than 12 hours ago, unknown, or the patient has renal insufficiency, then monitoring TT can be useful. (Class I, Level C)

24.1. If TT is ≥ 21 seconds, then administer idarucizumab 5 grams IV once. (Class I, Level C)

24.2. If TT is ≤ 20 seconds then do not administer idarucizumab (Class III, Level C)

25. Apixaban, edoxaban, and rivaroxaban - PCC might be considered for the treatment of major or life-threatening bleeding associated with apixaban, edoxaban, and rivaroxaban unresponsive to other management strategies. The benefit of coagulation must be weighed with the risk of thrombosis based on time of last dose, comorbidities, and patient characteristics. Optimum dosing of PCC is unknown;

however, doses of 25 – 50 Units/kg (maximum 5000 units) might be considered (Appendix B). (Class IIb, Level C)

27. **Argatroban** - Use supportive measures to control bleeding. (Class IIb, Level C)

28. **Bivalirudin** - Use supportive measures to control bleeding. (Class IIb, Level C)

29. **Fondaparinux -** Use supportive measures to control bleeding. (Class IIb, Level C)

30. **Heparin Intravenous** - Protamine rapidly reverses anticoagulant activity of heparin. Calculate the appropriate dose based on the estimated amount of heparin IV administered within the last 2 hours (maximum dose 50 mg). Protamine 1 mg neutralizes approximately 100 Units of heparin administered (Appendix C). (Class I, Level B)

31. **Heparin Intravenous** - Monitor aPTT or ACT to evaluate the extent of heparin reversal.[61] (Class I, Level B)

32. If **LMWH** was administered within the last 8 hours, protamine may partially reverse the anticoagulant effect. This dose may also be considered beyond 8 hours in patients with renal insufficiency. (Class I, Level B)
    32.1. Administer protamine 1 mg per 100 anti-Xa units of LMWH (maximum 50 mg). Enoxaparin 1 mg is approximately 100 anti Xa units. (Class I, Level B)
    32.2. If bleeding persists repeat protamine at a dose of 0.5 mg per 100 anti-Xa units of LMWH (maximum 25 mg dose). Enoxaparin 1 mg is approximately 100 anti Xa units. (Class IIa, Level C)

33. If **LMWH** was administered more than 8 hours, but less than12 hours, then give protamine 0.5 mg per 1 mg (100 Units) of anti-Xa units (maximum protamine dose of 50 mg dose). This dose may also be considered beyond 12 hours in patients with renal insufficiency. (Class IIb, Level C)

No Anticoagulant Use but Life Threatening Bleeding in Specific Conditions (Appendix E)

Spontaneous Intracerebral Hemorrhage in Patients NOT Managed with Anticoagulants

34. Factor 7A is not recommended to reduce mortality in patients with spontaneous intracranial hemorrhage. (Class III, Level A)

Traumatic Hemorrhage in Patients NOT Managed on Anticoagulants

35. Local hemostatic dressings can facilitate local hemostasis and are more effective than standard gauze dressings. (Class I, Level C)

36. If patient is at risk for major hemorrhage administer tranexamic acid 1 gram over 10 minutes followed by 1 gram over 8 hours to trauma patients (without traumatic brain injury) preferably within 3 hours of injury, but within at least 8 hours of injury. Alternative dosing is 10–15 mg/kg followed by an infusion of 1-5 mg/kg/h. (Class I, Level A)

37. If tranexamic acid is unavailable, aminocaproic acid is a suitable alternative for treatment of trauma patients at risk for a major hemorrhage. (Class I, Level C)

38. In coagulopathic trauma patients PCC 25 units/kg might be considered for the treatment of life threatening hemorrhage with a maximum dose of 2500 units. If bleeding persists beyond 30 minutes after completion of PCC, then second dose of PCC 25 units/kg might be considered. (Class IIb, Level B)

39. It is reasonable to administer PCC 25 units/kg in conjunction with plasma 15 mL/kg to patients not on anticoagulants with a traumatic brain injury and INR ≥ 1.5 when a craniotomy is anticipated.[13] (Class IIa, Level B)

40. Factor 7A is not recommended in blunt or penetrating trauma patients.[131-134] (Class III, Level B)

Cardiac Surgery

41. Administer aminocaproic acid or tranexamic acid to reduce blood loss in cardiac surgery patients at high risk for bleeding. (Class I, Level A)

42. In patients with life threatening bleeding unresponsive to standard therapy, factor 7A 40 mcg/kg may reduce transfusion requirements and potentially re-exploration in cardiac surgery patients. If bleeding is uncontrolled a repeat dose of factor 7A 40 mcg/kg is reasonable. (Class IIa, Level B)

43. PCC is only recommended in cardiac surgery patients for factor supplement in patients with prolonged INR due to warfarin anticoagulation. (Class I, Level C)

44. Concomitant use of PCC and factor 7A is not recommended in cardiac surgery patients due to the risk of thrombosis. (Class III, Level C)

45. Desmopressin is not indicated to prevent perioperative blood loss in non-uremic cardiac surgery patients. (Class III, Level A)

Hepatic Surgery

46. Prophylactic use of factor 7A is not recommended in patients undergoing hepatic surgery. (Class III, Level A)

Uremic Patients

47. Patients with active bleeding can receive benefit from dialysis in combination with other treatments. (Class IIa, Level C)

47.1. Administer one dose of desmopressin 0.3 mcg/kg over 30 minutes to improve bleeding in uremic patients. (Class I, Level A)

47.2. Administer conjugated estrogens if all other measures fail to improve bleeding time and clinical bleeding in uremic patients.[150-153] The usual dose of conjugated estrogen is 0.6 mg/kg IV over 30-40 minutes once daily for 5 consecutive days.(Class IIa, Level A)

Companion Documents

1. UW Health Warfarin Management - Adult - Ambulatory - Clinical Practice Guideline
2. UW Health Warfarin Management - Adult - Inpatient Clinical Practice Guideline
3. UW Health Heparin- Induced Thrombocytopenia – Adult – Inpatient Clinical Practice Guideline
4. UW Health Unfractionated Heparin (Therapeutic Dosing) - Adult - Inpatient Clinical Practice Guideline
5. UW Health Antithrombotics in Non-Valvular Atrial Fibrillation - Adult - Inpatient/Ambulatory Clinical Practice Guideline
6. UW Health Indications for Blood Product Transfusion – Adult – Inpatient/Ambulatory Clinical Practice Guideline
8. UW Health IV Administration Guideline – Adult – Inpatient/Ambulatory Clinical Practice Guideline

Pertinent UW Health Policies & Procedures

Pharmacy Operating Procedure for the Emergent Use of Factor 7A (NovoSeven®)
Pharmacy Operating Procedure for the Emergent Use Prothrombin Complex Concentrate (PCC)

Patient Resources

Not applicable

Scope

Disease/Condition(s):

- Treatment of adult non-hemophiliac patients bleeding or with high potential for bleeding (e.g., intra-operatively) due to anticoagulant therapy at UW Health Clinical Sciences Center and The American Center.
- Procoagulant agent use in patients not taking anticoagulants but with intracerebral hemorrhage, cardiac surgery, trauma and uremia at UW Health Clinical Sciences Center and at The American Center.

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 anticoagulant therapy and standardize care within UW Health.

Target Population: Adult inpatient and emergency department patients

Interventions and Practices Considered: Procoagulant agent use includes aminocaproic acid, conjugated estrogen, desmopressin, plasma (commonly referred to as FFP), factor 7A, idarucizumab, PCC, phytonadione, protamine, and tranexamic acid.

Major Outcomes Considered: Control of bleeding, improved neurological, cardiac, renal outcomes.

Guideline Metrics: The use of this guideline will be monitored through reviewing individual patient orders for PCC, factor 7A, and idarucizumab. Monitoring of thrombosis and bleeding events associated with these medications will occur through the Patient Safety Network (PSN).

Methodology

Methods Used to Collect/Select the Evidence:

A literature search was performed using the PUBMED database and International Pharmaceutical Abstracts MEDLINE and International Pharmaceutical Abstracts were searched using the terms procoagulant, aminocaproic acid, idarucizumab, prothrombin complex concentrate, prothrombin complex concentrate, factor VII, tranexamic acid, dabigatran reversal, bivalirudin reversal, rivaroxaban reversal, apixaban reversal, edoxaban reversal, desmopressin and renal dysfunction, uremia and bleeding. References from identified articles were further evaluated.

Rating Scheme for the Strength of the Evidence and Recommendations:

A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology and has been used to assess the Quality and Strength of the Evidence in this Clinical Practice Guideline.[1] (Figure 1)

Figure 1. American Heart Association and American College of Cardiology GRADE

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

Methods Used to Formulate the Recommendations:
Methods for developing recommendation include literature review, cost analysis and consensus of clinical experts via a workgroup.

Cost Analysis:
Cost of procoagulant therapy was considered by the workgroup in determining first line and/or standard therapy.

Definitions

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).[2]
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).[2]
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.[3-6] The risk of hemorrhage is associated with the intensity of anticoagulation.[7] 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 anticoagulant agent and its half-life, the duration of anticoagulation can vary from a few hours to several days. When bleeding is life-threatening or urgent reversal is required prior to surgery anticoagulation may require 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

Parenteral agents for the Treatment of Bleeding

1. Aminocaproic Acid prevents the conversion of plasminogen to plasmin and inhibits the degradation of fibrin clots.[8] Aminocaproic acid can be administered orally, intravenously, and topically.

1.1. Aminocaproic acid reduces the number of blood transfusions compared to placebo in surgical patients.[9-11] (Class I, Level A)

1.2. Dosing of aminocaproic acid varies based on the site and source of bleeding. Due to the short 2 hour half-life, the intravenous formulation is often administered as a continuous infusion.

1.2.1. Typical parenteral doses for acute bleeding are an initial loading dose of 4- 5 grams (50-150 mg/kg), followed by infusion of 1 gram per hour (or 10-15 mg/kg/h) for 8 hours or until bleeding is controlled.[8,12] (Class IIa, Level B)

1.2.2. Typical doses for cardiac surgery patients are 60-80 mg/kg loading dose (usually 5-10 grams) over 20 minutes followed by a maintenance infusion of 10-30 mg/kg/h (usually 1-2 grams/hour).[9] (Class IIa, Level B)

1.3. The risk of thrombosis due to aminocaproic acid treatment is minimal.[9]

1.4. If aminocaproic acid is unavailable, tranexamic acid is an appropriate alternative. (Class I, Level C)

2. **Tranexamic acid** inhibits fibrinolysis by competitively inhibiting plasmin activity and plasminogen activation.[13]

2.1. Parenteral tranexamic acid is effective in treating bleeding from multiple causes such as GI, surgical, and trauma.[13,14] (Class I, Level A)

2.2. The half-life is approximately 2 hours.

2.3. Multiple dosing regimens are employed based on indication.

2.3.1. Non-cerebral trauma doses utilized:

- Tranexamic acid 1 g over 10 minutes followed by 1 g over 8 hours[15,16] (Class I, Level A)
- Tranexamic acid 10-15 mg/kg followed by an infusion of 1 -5 mg/kg/h[17] (Class I, Level B)

2.3.2. In cardiac surgery doses of tranexamic acid are 2.5 mg/kg to 100 mg/kg followed by maintenance doses of 0.25-4 mg/kg/h over 1-12 hours can be considered.[18] (Class IIb, Level B)

2.4. Tranexamic acid can reduce transfusion requirements during hepatic resection.[19] (Class I, Level A)

2.5. The effects of alteplase can be attenuated with tranexamic acid.[20-22] (Class IIa, Level B)

2.6. Tranexamic acid is associated with cerebral infarction in studies of patients with subarachnoid hemorrhage; however, thromboembolism with the use of tranexamic acid is rare.[16] Seizures have been reported in patients on cardiopulmonary bypass.[23]

2.7. If tranexamic acid is unavailable, aminocaproic acid is an appropriate alternate. (Class I, Level C)

3. **Phytonadione (vitamin K)** administered by the oral or intravenous route is effective in reversing the anticoagulant effects of warfarin through promoting the production of clotting factors II, VII, IX and X.[31-33] (Class I, Level A)

3.1. Empiric use of phytonadione in patients on warfarin with an INR of 4.5 – 9.9 without bleeding is not recommended.[34,35] (Class III, Level B) Holding warfarin is usually sufficient to lower the INR without subsequent refractoriness to warfarin.

3.2. Low oral doses (1-5 mg) of phytonadione are preferred over the intravenous route for minor bleeding or treatment of INR > 9.9.[3,36,37] (Class I, Level C)

3.3. In patients with an elevated INR due to warfarin anticoagulation with major or life-threatening bleeding it is reasonable to give phytonadione 5-10 mg along with PCC to sustain reversal of anticoagulation.[34,38] (Class IIa, Level A)

3.3.1. The intravenous route for phytonadione is reserved for circumstances when fast onset is required for urgent reversal (e.g., life threatening bleeding) or the patient is unable to absorb the enteral formulation. (Class I, Level C)

3.3.2. The onset of intravenous phytonadione is faster, however, within 24 hours results of INR reversal are similar to oral phytonadione.[39,40]

3.3.3. Slow intravenous administration (over 20-30 minutes) is recommended to avoid severe hypotension and rare anaphylactic reactions.[41,42] (Class I, Level C)

3.3.4. Rapid reversal of warfarin with intravenous phytonadione is not recommended prior to elective procedures or surgeries.[32] (Class III, Level C)

3.4. Subcutaneous and intramuscular administration is not recommended due to a delayed and unpredictable response.[3,43,44] (Class III, Level C)

3.5. Administration of high doses (10 mg or greater) may limit the ability to anticoagulate patients after bleeding is controlled; therefore, it is useful to administer the lowest dose of phytonadione to achieve therapeutic results.[45] (Class I, Level C)

3.6. The intravenous product is administered for enteral dosing as a cost containment measure.

4. **Prothrombin Complex Concentrate (PCC)** is a biological product of pooled human plasma with therapeutic concentrations of factors II, VII, IX and X.
   - 4.1. KCentra®, the only FDA approved four factor–PCC, contains antithrombotic proteins C and S and heparin 8-40 units in 500 unit vials in addition to factors II, VII, IX, and X. It is FDA approved for the treatment of adult patients treated with vitamin K antagonists (e.g., warfarin) experiencing acute major bleeding.[46]
   - 4.2. PCC is recommended for the reversal of the anticoagulation effects of warfarin with acute major or life-threatening bleeding or prior to emergency surgery or major invasive procedure. (Class I, Level A)
   - 4.3. Dosing is based on the factor IX component, pre-treatment INR, weight and patient risk factors [38,46,47] (Class IIa, Level A)
     - 4.3.1. PCC is available as a single use vial with Factor IX units 420 to 600 units/vial. (The actual potency is stated on the vial.)
     - 4.3.2. Administer dose within 4 hours of reconstitution.[46] (Class I, Level A)
   - 4.4. Contraindications include disseminated intravascular coagulation, heparin induced thrombocytopenia, and known hypersensitivity reactions to the components of PCC.[46] (Class I, Level C)
   - 4.5. Patients with a prior history of PE or DVT may be at an increased risk of thrombosis 30 days after administration of PCC.[48] (Class IIb, Level B)
   - 4.6. Kcentra® contains 8-40 units of heparin per 500 unit vial. If a patient is diagnosed with heparin-induced thrombocytopenia (HIT), but greater than 3 months ago, PCC can be administered regardless of heparin content.[46] If HIT was diagnosed less than three months ago, weigh the benefit of procoagulant therapy with the risk of thrombosis and recurrent HIT. (Class I, Level C)
   - 4.7. PCC has not been studied in patients with a thromboembolic event 3 months prior to administration.

5. **Plasma** is a biological product from pooled human plasma containing clotting factors available in whole blood. Administration of plasma does not reverse anticoagulants, but provides additional clotting factors.
   - 5.1. Indications include: replacement of single factor deficiencies when a specific coagulation factor concentrate is not available; immediate reversal of warfarin for active bleeding, surgery or procedures; active hemorrhage and multifactor coagulopathy (INR ≥ 1.8); invasive procedure planned within six hours and multifactorial coagulopathy (INR >1.8), massive transfusion, thrombotic thrombocytopenic purpura (TTP) using plasma exchange; plasmapheresis, or complement mediated hemolytic uremic syndrome. See UW Health Indications for Blood Transfusion – Adult – Inpatient/Ambulatory Clinical Practice Guideline (Class I, Level C)
   - 5.2. Plasma is stored as frozen product; however, thawed plasma is available at UW Health at all times. (Thawing occurs within 15 - 30 minutes.)
   - 5.3. The recommended dose for major or life-threatening bleeding is 10 - 15 mL/kg with repeat dosing as required for bleeding[49,50] (Class I. Level C)
     - 5.3.1. Plasma as ordered from the blood bank in units. The characteristic volume of one unit of plasma is approximately 250 mL.
     - 5.3.2. Infuse plasma as quickly as tolerated by the patient. (Class I, Level C)
     - 5.3.3. Adverse events associated with plasma include volume overload, transfusion-related acute lung injury (TRALI) and allergic reactions. The FDA reports the number of fatalities related to TRALI and plasma administration is 0-4 per year from 2010 to 2014 [51]

6. **Factor 7A** is a recombinant DNA preparation nearly identical to plasma-derived factor 7A in pharmacokinetics, structure and function. It is FDA approved for the treatment of severe bleeding in patients with Hemophilia A or B, acquired Factor VIII inhibitors, congenital Factor VII deficiency, but has been evaluated in hemorrhagic patients previously treated with anticoagulants, after cardiac surgery, and in trauma patients requiring extensive blood replacement.[52] Little data is available to provide strong dosing recommendations for the treatment of bleeding in patients on enteral or parenteral anticoagulants.

6.1. A 2012 Cochrane review and meta-analysis examined 29 randomized controlled trials evaluating prophylactic and therapeutic factor 7A use in non-hemophilia-related bleeding.[53] Pooled analysis showed no impact on mortality for prophylactic or therapeutic factor 7A, though combined analysis of all 29 trials showed a significant increase in the risk of arterial thromboembolic events.
6.2. Factor 7A has been studied in a wide range of doses for a number of off-label uses, with no clear consensus on optimal dosing and timing or decrease in mortality.[53-55]
6.2.1. Actual body weight should be used in dosing. (Class I, Level C)
6.2.2. Round the dose down to the nearest 1000 mcg (1mg) vial size. (Class I, Level C)
6.3. Usefulness of factor 7A in severely acidotic patients is unknown. The blood pH should be above 7.2 prior to administration. (Class I, Level A)
6.4. Efficacy of factor 7A is lower in patients with hypothermia, hypocalcemia, hypofibrinogenemia or major coagulopathy.[56]
6.5. The short half-life of factor 7A limits activity to 2-3 hours and concomitant use of blood products is recommended. (Class I, Level C)
6.6. INR is rapidly decreased after administration of factor 7A; however, this reduction is not a reliable measure of warfarin reversal or anticoagulation.
6.7. Factor 7A increases the risk of thrombosis when used for treatment of non-hemophilic patients. Product labeling includes a box warning for thrombotic and thromboembolic events.[52]
6.7.1. The risk of arterial thrombosis with factor 7A increases in patients 65 years of age or older.[52]
6.7.2. An increased risk of thrombosis can occur in patients with advanced atherosclerotic disease, crush injuries, disseminated intravascular coagulation (DIC), septicemia or signs or symptoms of an activated coagulation system or thrombosis.[52]
6.8. Contraindications include hypersensitivity to mouse, bovine or hamster proteins or hypersensitivity to recombinant factor 7A or the product components.[52] (Class I, Level C)

7. **Desmopressin** decreases bleeding times in uremic patients with a proposed mechanism of increasing the amount of von Willebrand factor released from endothelial cells. The improved hemostasis sites and is attributed to a large increases in plasma von Willebrand factor.[29]
7.1. Usual dose for treating uremic bleeding and platelet dysfunction is 0.3 mcg/kg.[9] (Class I, Level C)
7.2. Onset is within 1 hour of infusion and bleeding times can return to normal within 24 hours.[9]
7.3. Tachyphylaxis may develop due to depletion of von Willebrand factor in endothelial cells and may result in hyponatremia.[29,57] Hyponatremia can further complicate neurological symptoms or disorders.
7.4. Do not administered desmopressin for more than three days in a row. (Class III, Level C)
7.5. The most common side effects are facial flushing and mild hyponatremia.[8] Hypotension is associated with rapid administration.

8. **Protamine** rapidly reverses heparin by binding to form an inactive complex and neutralize anti-factor IIa.
8.1 The dose of protamine should be sufficient to reverse the amount of heparin administered within the last 2 hours (maximum protamine dose is 50 mg). Protamine 1 mg reverses approximately 100 units of heparin with a maximum dose of 50 mg.[58,59] (Class I, Level C)

Example: for heparin infusing at 1000 Units/h, protamine 20 mg is indicated to neutralize 2000 units of heparin

8.2. Protamine inactivates a variable portion of the anti-Xa activity of LMWH, but does not bind to all fragments of LMWH and therefore does not reverse all of the anticoagulant effect of LMWH.[59,60]
8.2.1. If LMWH administered within the previous 8 hours, give protamine 1 mg per 100 anti-Xa units of LMWH (maximum protamine dose 50 mg). (Enoxaparin 1 mg is approximately 100 anti Xa units.) A longer time frame may be considered in patients with renal insufficiency. (Class I, Level C)
8.2.2. If LMWH was administered more than 8 hours, but less than 12 hours ago, give protamine 0.5 mg per 100 anti-Xa units (maximum protamine dose 25 mg) of LMWH.[61] (Enoxaparin 1 mg is approximately 100 anti Xa units.) A longer time frame may be considered in patients with renal insufficiency. (Class I, Level C)

Example: If patient received 40 mg of enoxaparin within the last 8 hours, administer protamine 40 mg

8.3. A second dose of protamine (0.5 mg/kg, maximum 50 mg) can be administered if bleeding continues.[61] (Class I, Level C)

8.4. Serious adverse events associated with protamine include hypotension, cardiovascular collapse, noncardiogenic pulmonary edema and pulmonary vasoconstriction. High doses and rapid administration are associated with increased risk of adverse events.[8]

8.4.1. Patients with a known sensitivity to fish or who have previously received protamine sulfate containing insulin may experience allergic reactions to protamine.[59-61]

8.4.2. For patients at risk for a serious allergic reaction to protamine pretreat with H-1 antihistamine and corticosteroid therapy.[61] (Class I, Level C)

9. **Idarucizumab** is a humanized monoclonal antibody fragment that binds both free and thrombin bound dabigatran without interfering with the coagulation cascade.[62,63]

9.2. If dabigatran was taken within the previous 12 hours or the thrombin time (TT) is prolonged in patients taking dabigatran, idarucizumab 5 grams is indicted for reversal prior to acute major or life-threatening bleeding, emergent surgery, or major invasive procedure.[64] (Class I, Level B)

9.3. If the last dose of dabigatran was taken more than 12 hours ago the time of the last dose is uncertain, or the patient has renal insufficiency, monitor TT. (Class I, Level C)

9.3.1. If TT ≥ 21 seconds, then administer dabigatran. (Class I, Level C)

9.3.2. If TT is ≤ 20 seconds, then do not administer dabigatran.(Class III, Level C)

9.4. The half-life is 10.3 h, similar to the half-life of dabigatran.[63]

9.5. Repeat doses of idarucizumab for the same bleeding event are not recommended. [63] (Class III, Level A)

9.6. Adverse effects reported in patients include hypokalemia, delirium, constipation, pyrexia, and pneumonia.[49]

General Treatment Management for Sustained Bleeding

10. Identify the source and cause of bleed.[3,61,65] (Class I, Level C)

11. Management of hemorrhage includes maintenance of hemodynamic and respiratory stability.[65,66] When necessary, provide mechanical ventilation, fluid resuscitation, hemodynamic support and therapeutic procedures to stabilize the patient and promote coagulation. (Class I, Level C)

12. Maintain normal body temperature, blood pH, and electrolyte balance to facilitate coagulation.[65-67] (Class I, Level C)

Maintaining adequate serum ionized calcium concentrations is vital since calcium is essential for vitamin K dependent coagulation factor bridging, fibrinogen stabilization and platelet function.[6] Hypocalcemia is not uncommon with the transfusion of rapid administration of large amounts of blood products with major hemorrhages. Saline fluid resuscitation, hypovolemic shock and ischemia contribute to the development of acidosis and the extent of acidosis correlates with mortality.[67] In the severely injured patient hypothermia, acidosis, and hypotension are associated with coagulopathy.

13. If applicable, apply packing or dressing, use local hemostatic measures or surgical intervention to control bleeding.[40] (Class I, Level C)

14. If an overdose of oral anticoagulant is suspected, administer activated charcoal in patients with low risk for aspiration if the patient does not have a gastric bleed.[3,68] (Class I, Level C)

15. Consider the risk versus benefit of continuation of anticoagulation therapy. Discontinue anticoagulant and/or concomitant antiplatelet therapy in patients with life threatening or massive trauma hemorrhage. If possible discontinue interacting medications that potentiate or prolong the pharmacodynamics of an anticoagulant (e.g., ciprofloxacin and warfarin).[50] (Class I, Level C)

16. After control of major bleeding stabilizes, reassess for risk of thromboembolism and initiate a short acting agent if anticoagulation is required.[3,61] (Class I, Level C)

Major Bleeding with Oral Anticoagulants Recommendations (Appendix B, Appendix C)

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.[7,69,70] 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.[7,71-73] The rate of hemorrhage increases markedly in patients with an INR greater than 4.5.[74] Bleeding or potential bleeding of patients on warfarin can be managed by holding warfarin doses, administering phytonadione, plasma and PCC. The approach to treatment is predicated on the indication for warfarin, location of the bleed, extent of bleeding and INR (Appendix 2).[3] 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.

17. Monitor the INR associated with bleeding events in warfarin treated patients.[3] (Class I, Level C).

18. Treat minor bleeding or supra-therapeutic INR in patients on warfarin:
- 18.1. Patients at a high risk for thromboembolism with non-major bleeding may be managed with incomplete warfarin reversal.[50] (Class I, Level C)
- 18.2. Elevated INR (Class I, Level B)
  - 18.2.1. INR 4.5-9.9 - omit 1- 2 doses of warfarin[3]
  - 18.2.2. INR > 9.9 - omit 1 - 2 doses of warfarin and administer phytonadione 1-2.5 mg orally (preferred) or IV. In patients with a high INR no difference in incidence of bleeding was identified in between patients treated with phytonadione versus placebo.[69]

19. Non-major bleeding in warfarin treated patients requiring reversal:
- 19.1. Omit 1 to 2 warfarin doses or until bleeding subsides.[3] (Class I, Level B)
- 19.2. Phytonadione 1-5 mg orally or IV (dose dependent upon INR, risk of VTE, and extent of bleeding)[3] (Class I, Level B)
- 19.3. If needed administer plasma 1-2 units (or up to 10-15 mL/kg (supplied as 250 mL/ units) and repeat as necessary.[3,75] (Class I, Level B)

20. Major and life-threatening bleeding in patients on warfarin.
- 20.1. Discontinue warfarin until bleeding is controlled.[50] (Class I, Level C)
- 20.2. Administer phytonadione 5-10 mg along with PCC. There is no specific order of administration; administer each agent as soon as it is available.[38] (Class IIa, Level A)
  - 20.2.1. Weight-based dosing of PCC based INR is beneficial.(Table 2, Table 3.)[38,46]

Table 2. Dose of Prothrombin Complex Concentrate* for Major Bleeding (Class I, Level A)

Pre-treatment INR	Dose of PCC	Maximum Dose
1.2 – 1.9	Not recommended	
2.0 – 3.9	25 units/kg	2500 units
4.0- 6.0	35 units/kg	3500 units
≥ 6.1	50 units/kg	5000 units
Repeat dosing is not recommended.		
*Round doses to the nearest vial size. Vial sizes vary from 420 to 600 units.		

Table 3. Dosing of Prothrombin Complex Concentrate for Life-Threatening Bleeding

Pre-treatment INR	Dose of PCC	Maximum Dose	Grade of Recommendation
1.2 - 3.9	25 units/kg	2500 units	Class I, Level C
4.0 - 6.0	35 units/kg	3500 units	Class I, Level A
≥ 6.1	50 units/kg	5000 units	Class I, Level A
Repeat dosing is not recommended.			
*Round doses to the nearest vial size. Vial sizes vary from 420 to 600 units.			

20.2.2 If a patient is reported as HIT positive, but greater 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 versus risk of repeat HIT. (Class I, Level C)

21. Routine use of Factor 7A for reversal of warfarin-related hemorrhage is not recommended.[76-78] (Class III, Level B)

22. It is reasonable to administer PCC (at dosing listed in Table 2) with or without phytonadione and plasma for patients requiring warfarin reversal prior to emergency surgery or major invasive procedures.[47,79] (Class IIa, Level B)

Dabigatran is a reversible, oral direct thrombin inhibitor and an association between dose and incidence of bleeding is established in patients with atrial fibrillation.[80] Unlike warfarin, anticoagulation occurs through inhibition of factor II (thrombin), not depletion of the clotting factors. A prolonged aPTT can indicate a patient has taken dabigatran, but does not correlate with the extent of anticoagulation.[81] 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.[3,81]

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23. Idarucizumab 5 grams IV is recommended for reversal of dabigatran in patients with major or life-threatening bleeding or requiring emergent surgery or invasive procedure if dabigatran was taken within the previous 12 hours in patient with normal renal function.[62,64,82] (Level I, Class B)

24. If the time of the last dose is greater than 12 hours ago or unknown or the patient has renal insufficiency, then monitor TT. (Class I, Level C)
24.1. If TT is ≥ 21 seconds (elevated), then administer idarucizumab 5 grams IV. (Class I, Level C)
24.2. If TT is ≤ 20 seconds (not elevated), then do not administer idarucizumab (Class III, Level C)

See UW Health Periprocedural and Regional Anesthesia Management with Antithrombotic Therapy – Adult – Inpatient/Ambulatory Clinical Practice Guideline for information on holding dabigatran prior to surgery.

Apixaban, edoxaban, and rivaroxaban are oral factor Xa inhibitors and, unlike warfarin, anticoagulation occurs through inhibition of factor Xa, not inhibition of production of clotting factors. No reversal agents are available and there are no clinical trials demonstrating improved clinical outcomes with factor 7A or PCC. 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.[89-91]

25. PCC might be considered for the treatment of major or life-threatening bleeding associated with apixaban, edoxaban, and rivaroxaban unresponsive to other management strategies.[86,88,92-94] The benefit of coagulation must be weighed with the risk of thrombosis based on time of last dose, comorbidities, and patient characteristics. Optimum dosing of PCC is unknown; however, doses of 25 – 50 Units/kg (maximum 5000 units) might be considered (Appendix A). (Class IIb, Level C)

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 .[88] 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.

See UW Health Periprocedural and Regional Anesthesia Management with Antithrombotic Therapy – Adult – Inpatient/Ambulatory Clinical Practice Guideline for information on holding dabigatran prior to surgery

Major Bleeding Associated with Parenteral Anticoagulants (Appendix C)

Argatroban is a parenteral direct thrombin inhibitor that prevents fibrin formation, activation of factors V, VIII, XIII, protein C, and platelets.[75] Argatroban has no established reversal agent; however, the plasma half-life is only 45 minutes resulting in a short duration of anticoagulation precluding the need for additional procoagulant therapy.[61](UWHC Guideline for the Diagnosis and Treatment of Heparin Induced Thrombocytopenia)

26. Use supportive measures to control bleeding. Insufficient evidence exists to recommend factor 7A use in argatroban-related hemorrhage. (Class IIb, Level C)

Factor 7A has theoretical applications in reversing argatroban-associated hemorrhage, though clinical experience for off-label use is limited and has not demonstrated benefit.[105,106] 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.[107,108] One case report of an infant receiving argatroban failed to demonstrate hemostasis with factor 7A.[105] Insufficient evidence exists to make recommendations for or against the use of factor 7A for the treatment of life-threatening bleeding with argatroban.

Bivalirudin intravenous is a direct thrombin inhibitor and is an alternative to heparin in patients with heparin-induced thrombocytopenia (UW Health Guideline for the Diagnosis and Treatment of Heparin Induced Thrombocytopenia)and in patients undergoing percutaneous angioplasty for acute coronary syndrome.[109] The half-life is short (25 minutes); but prolonged in dialysis dependent patients. There is no reversal agent for bivalirudin.

27. Use supportive measures to control bleeding. There is insufficient evidence to support the use of factor 7A for the treatment of bleeding in patients managed on bivalirudin. (Class IIb, Level C)

Fondaparinux is a factor Xa inhibitor with an elimination half-life of 17–21 hours.[110] There is no established reversal agent for fondaparinux.[61] Protamine is not effective for the treatment of bleeding associated with fondaparinux. (Class III, Level C)

There is insufficient evidence to recommend for or against treatment of major or life-threatening bleeding due to fondaparinux with factor 7A.[61,108,111] 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.[112] 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.[107] 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.[111] The authors indicated hemostasis was achieved; however, the patient did not survive.

Heparin Intravenous
Heparin 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.[61]

Heparin is a complex chemical compound of variable molecular weight and anticoagulant activity. Given that the half-life is only 60 to 90 minutes, the therapeutic effect is eliminated within three to four hours.

28. Protamine rapidly reverses anticoagulant activity of heparin. Calculate the appropriate dose based on the estimated amount of heparin IV administered within the last 2 hours.[61] Protamine 1 mg neutralizes approximately 100 Units of heparin administered. (Class I, Level B)

29. Monitor aPTT or ACT to evaluate the extent of heparin reversal.[61] (Class I, Level B)

Low Molecular Weight Heparin

Similar to heparin, the primary anticoagulant activity of LMWH (e.g., 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.[61] 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.[60,113,114]

30. If LMWH was administered within the last 8 hours, protamine may partially reverse the anticoagulant effect.[61,115] This dose may also be considered beyond 8 hours in patients with renal insufficiency. (Class I, Level B)

30.1. Administer protamine 1 mg per 100 anti-Xa units of LMWH (maximum 50 mg). Enoxaparin 1 mg is approximately 100 anti Xa units. [39, 111] (Class I, Level B)

30.2. If bleeding persists repeat protamine at a dose of 0.5 mg per 100 anti-Xa units of LMWH (maximum 25 mg dose). Enoxaparin 1 mg is approximately 100 anti Xa units. (Class IIa, Level C)

31. If LMWH was administered more than 8 hours, but 12 hours or less, then give protamine 0.5 mg per 1 mg (100 Units) of anti-Xa (maximum of 50 mg dose).[61] This dose may also be considered beyond 12 hours in patients with renal insufficiency. (Class IIb, Level C)

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.[117] Case reports of life-threatening bleeding in patients treated with LMWH utilized factor 7A 20-120 mcg/kg to reverse bleeding.[118-120]

No Anticoagulant Use but Life Threatening Bleeding in Specific Conditions (Appendix E)

Spontaneous Intracerebral Hemorrhage in Patients NOT Managed with Anticoagulants

32. Factor 7A is not recommended to reduce mortality in patients with spontaneous intracranial hemorrhage.[54,77,121] (Class III, Level A)

Factor 7A administration in intracerebral hemorrhage may decrease the total volume of hemorrhage but has not consistently demonstrated decreased mortality in randomized, controlled trials and meta-analyses and has demonstrated risk for arterial and venous thromboses.

Factor 7A has been evaluated in randomized, controlled trials for use in acute intracerebral hemorrhage.[122,123] Results of a 2005 publication including 399 patients treated with single doses of 40, 80, or 160 mcg/kg of factor 7A demonstrated a significant decrease in the total volume of intracerebral hemorrhage versus placebo in the 80 and 160 mcg/kg groups ($p<0.05$) but not the 40 mcg/kg group ($p=0.07$). In total, the volume of intracerebral hemorrhage, intraventricular hemorrhage, and edema differed significantly from placebo in the 80 mcg/kg and 160 mcg/kg groups, but not the 40 mcg/kg group (-12.2, -14.4, and -6.5 mL, respectively; $p=0.008$, 0.001, and 0.14, respectively, versus placebo).Versus placebo, 90-day mortality was significantly reduced in the 40 mcg/kg treatment group ($p=0.05$) but not the 80 or 160 mcg/kg groups ($p=0.1$ and 0.11, respectively).[122]

In a larger (n=841) follow-up, placebo-controlled study, patients with acute intracerebral hemorrhage were given placebo or 20 or 80 mcg/kg factor 7A (known as the FAST trial).[123] Again demonstrated

was a significant reduction versus placebo in the volume of intracerebral hemorrhage for patients treated with 80 mcg/kg of factor 7A (increase from baseline of 26% versus 11%; p<0.001), though the 20 mcg/kg group failed to reach statistical significance (18% increase from baseline, p = 0.09). In total, the volume of intracerebral hemorrhage, intraventricular hemorrhage, and edema did not differ significantly from placebo (increased from baseline 26%, 22%, and 29% in the 20 mcg/kg, 80 mcg/kg, and placebo groups, respectively; p>0.05). This larger follow-up trial also failed to demonstrate any significant reduction in 90-day mortality (18%, 21%, and 19% for 20 mcg/kg, 80 mcg/kg, and placebo groups, respectively; p>0.05). However, arterial thrombotic events (including renal-artery thrombosis and occlusion and intracardiac thrombus) were significantly increased in the 80 mcg/kg treatment group (p=0.05).[123]

A factor 7A dose-escalation trial in traumatic intracerebral hemorrhage examined 40, 80, 120, 160, and 200 mcg/kg doses of factor 7A. No significant decreases in intracerebral hemorrhage volume or 15-day mortality were noted.[124]

A 2009 Cochrane review examined five trials, including the FAST trial, in patients receiving placebo (n=423), factor 7A (n=973), or epsilon-aminocaproic acid (n=2). Combined analysis showed no significant difference in 90-day mortality, though an association of increased arterial thromboembolic events with factor 7A doses of 120-160 mcg/kg was noted.[121]

A 2010 meta-analysis examined factor 7A use in non-hemophilia patients with acute intracerebral hemorrhage.[125] Despite demonstrating significant reductions in intracranial hemorrhage volumes, no significant difference was found in mortality. Significantly increased risks of arterial and venous thrombosis were noted.[125]

Traumatic Hemorrhage in Patients NOT Managed on Anticoagulants

Common causes of coagulation alteration in patient with massive bleeding include consumption of coagulation factors, dilution with resuscitative fluids, hyperfibrinolysis, acidosis, hypothermia, electrolyte disturbances and anemia.[40,67] The primary objective of hemostatic intervention is to minimize blood loss and avoid unnecessary transfusion of blood products. Coagulation tests (aPTT, INR, fibrinogen) are often monitored to evaluate the extent of coagulation but no correlation with hemorrhagic events has been demonstrated.

33. Local hemostatic dressings can facilitate local hemostasis and are more effective than standard gauze dressings.[17,127] (Class I, Level C)

34. If patient is at risk for major hemorrhage administer tranexamic acid 1 gram over 10 minutes followed by 1 gram over 8 hours to trauma patients (without traumatic brain injury) preferably within 3 hours of injury, but within at least 8 hours of injury.[15,16,128] Alternative dosing is 10-15 mg/kg followed by an infusion of 1-5 mg/kg/h.[17] (Class I, Level A)

A large, multicenter, double-blind, placebo-controlled trial of trauma patients with a significant bleed risk were given tranexamic acid or placebo within the first eight hours of injury.[16] Intent-to-treat analysis demonstrated a relative risk reduction (RR) in all cause, 30 day mortality (the primary outcome) of 9% (14.5% versus 16.9%; RR, 0.91; confidence interval [CI] 0.85-9.97; p=0.0035). Secondary outcomes of vascular occlusive events, transfusion and surgical interventions were not statistically significant (p=0.084, p=0.21, p=0.79, respectively). A potential explanation for lack of difference in transfusion could be that tranexamic acid treated patients survived longer and therefore received more infusions.

35. If tranexamic acid is unavailable, aminocaproic acid is a suitable alternative for treatment of trauma patients at risk for a major hemorrhage. (Class I, Level C)

36. In coagulopathic trauma patients PCC 25 units/kg might be considered for the treatment of life threatening hemorrhage with a maximum dose of 2500 units. If bleeding persists beyond 30 minutes after completion

of PCC, then second dose of PCC 25 units/kg (maximum 2500 units) might be considered.[46,129] (Class IIb, Level B)

37. It is reasonable to administer PCC 25 units/kg (maximum 2500 units) in conjunction with plasma 15 mL/kg to patients not on anticoagulants with a traumatic brain injury and INR ≥ 1.5 when a craniotomy is anticipated.[130] (Class IIa, Level B)

38. Factor 7A is not recommended in blunt or penetrating trauma patients. [131-134] (Class III, Level B)

Factor 7A was evaluated for use in traumatic hemorrhage in two parallel prospective, randomized, double-blind, placebo-controlled trials, one for blunt trauma and one for penetrating trauma.[131] Patients were treated with 200 mcg/kg of Factor 7A, 100 mcg/kg one hour later and another 100 mcg/kg three hours following the first dose. There were 143 patients in the blunt trauma trial and 134 patients in the penetrating trauma trial. Patients were primarily male, coagulopathic, acidotic and hypothermic. In the blunt trauma patients PRBC transfusion was significantly reduced by 2.6 units (p=0.02) within 48 hours of administration. For penetrating trauma patients there was no significant difference in PRBC transfusion (p=0.08). No difference in 48 hour or 30 day mortality was demonstrated between the factor 7A and placebo groups for both the blunt and penetrating trauma patients.

Cardiac Surgery

39. Administer aminocaproic acid or tranexamic acid to reduce blood loss in cardiac surgery patients at high risk for bleeding.[18,135-140] (Class I, Level A)

Tranexamic acid bolus doses in clinical trials range from 2.5 mg/kg to 40 mg/kg followed by maintenance doses of 0.25-4 mg/kg/h over 1-12 hours.[137,138] Preoperative renal dysfunction, age over 75 years, open heart procedure peripheral vascular disease, and total tranexamic acid dose over 100 mg/kg is associated with a risk of early seizure in patients on cardiopulmonary bypass.[23] Typical doses of aminocaproic acid for cardiac surgery patients are 60 – 100 mg/kg loading dose (usually 5 – 10 grams) over 20 minutes followed by a maintenance infusion of 10-30 mg/kg/h (usually 1 – 2 grams/hour).[18,136,139,141]

40. In patients with life threatening bleeding unresponsive to standard therapy, factor 7A 40 mcg/kg may reduce transfusion requirements and potentially re-exploration in cardiac surgery patients.[54,140,142-145] If bleeding is uncontrolled a repeat dose of factor 7A 40 mcg/kg is reasonable. (Class IIa, Level B)

Current evidence does not demonstrate any mortality benefit but does demonstrate potential reductions in blood product transfusion requirements. A 2009 meta-analysis found no significant difference in mortality or surgical re-exploration from pooled results of five small clinical trials totaling 298 patients undergoing cardiac surgery treated with factor 7A (dosed 17-70 mcg/kg with repeat or 90 mcg/kg x 1).[142] The authors did note a non-significant trend toward increased stroke incidence in factor 7A-treated patients (OR 3.17, 95% CI 0.83-12.1; p=0.09).

In a phase II dose-escalation study, 179 cardiac surgery patients were randomized to receive placebo, factor 7A 40 mcg/kg, or factor 7A 80 mcg/kg to assess the safety of these doses. No significant increase in the number of adverse events (death, cerebral or myocardial infarct, or thromboembolism) was noted in patients treated with either dose of factor 7A. Secondary efficacy outcomes showed significant reductions in transfusion requirements and re-operations with both factor 7A doses.[144]

41. PCC is only recommended in cardiac surgery patients for factor supplement in patients with prolonged INR due to warfarin anticoagulation. (Class I, Level C)

42. Concomitant use of PCC and factor 7A is not recommended in cardiac surgery patients due to the risk of thrombosis. (Class III, Level C)

43. Desmopressin is not indicated to prevent perioperative blood loss in non-uremic cardiac surgery patients.[55,146] (Class III, Level A) Trials demonstrate desmopressin minimally reduces perioperative blood loss; however, it does not reduce transfusion requirements or the need for re-operation.[55,84]

Hepatic Surgery

44. Prophylactic use of factor 7A is not recommended in patients undergoing hepatic surgery.[19,147] (Class III, Level A)

Factor 7A has been evaluated for the prevention of hemorrhage in patients with liver surgery in a meta-analysis.[147] Four industry-sponsored trials investigated prophylactic doses ranged from 20-120 mcg/kg and were compared to placebo. No significant differences in mortality, red blood cell transfusion requirements, serious adverse events, or thromboembolic events were noted in the included studies (n=671). A Cochrane review including two trials assessed by Chavez et al also found no significant difference in mortality, primary graft non-function, serious adverse events or thromboembolism.[19]

Uremic Patients

45. Patients with active bleeding can receive benefit from dialysis in combination with other treatments.[148,149] (Class IIa, Level C) Although there is limited data of the clinical effectiveness of dialysis in bleeding uremic patients, dialysis facilitates the removal of accumulated uremic toxins which can inhibit coagulation.

45.1. Administer one dose of desmopressin 0.3 mcg/kg over 30 minutes to improve bleeding in uremic patients[148] (Class I, Level A)

45.2. Administer conjugated estrogens if all other measures fail to improve bleeding time and clinical bleeding in uremic patients.[150-153] The usual dose of conjugated estrogen is 0.6 mg/kg IV over 30-40 minutes once daily for 5 consecutive days.(Class IIa, Level A)

UW Health Implementation

Potential Benefits and Harms:

The benefit of the guideline is consistent and evidence-based used of procoagulant agents in select bleeding circumstances. A potential risk of thromboembolism exists with the administration of procoagulant agents and is related to underlying clinical conditions, comorbidities, agent adminstered and dose. [154]

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.

Implementation Plan/Tools

1. Guideline will be housed on U-Connect in a dedicated folder for CPGs.
2. Release of the guideline will be advertised in the Clinical Knowledge Management Corner within the Best Practice newsletter.
3. Links to this guideline will be updated and/or added in appropriate Health Link or equivalent tools, including medication order records.

Disclaimer

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice 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.

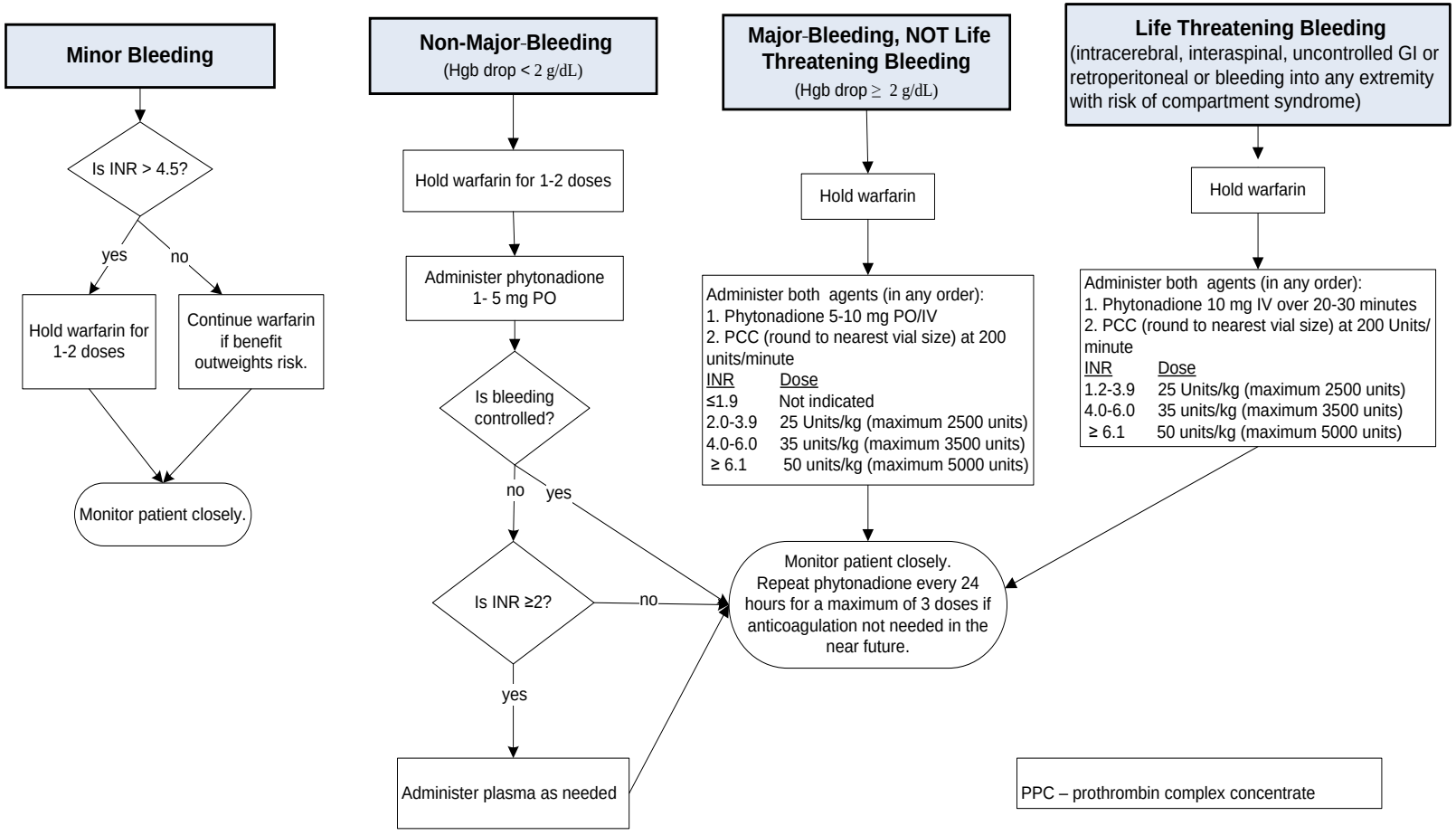
Appendix A. Treatment of Bleeding Associated with Oral Anticoagulants

<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
Edoxaban
Rivaroxaban</td><td>12 h
10-14 h
5-9 h</td><td>• 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>-No clinical trials using PCC are available
-Administer PCC at a maximum rate of 200 units/min</td><td>NA</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 ≥ 21 seconds</td><td>Hemodialysis removes approximately 60% within 2 h</td><td></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.[35] Consider phytonadione 1-2.5 mg in patients with a high risk for bleeding
• INR >9.9 – omit 1-2 doses, phytonadione 1-2.5 mg PO[37]</td></tr>
<tr><td>Major, non-life threatening bleed , emergency surgery or major procedure</td><td>• If ingestion within 3 hours, consider activated charcoal 50 g PO
• Plasma - at least 2 units (≥15 mL/kg may be required)
• phytonadione (5-10 mg) PO or 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>≤1.9</td><td>Not indicated</td></tr>
<tr><td>2-3.9</td><td>25 units/kg (maximum 2500 units)</td></tr>
<tr><td>4.0-6.0</td><td>35 units/kg (maximum 3500 units)</td></tr>
<tr><td>≥ 6.1</td><td>50 units/kg (maximum 5000 units)</td></tr>
</table></td></tr>
<tr><td>Life threatening bleed , emergent surgery or major procedure excluding intracerebral or intraspinal</td><td>If ingestion within 3 hours, administer activated charcoal 50 g PO or per feeding tube
Give each agent as soon as it is available:
1. phytonadione 10 mg IV
2. PCC based on INR and weight
<table>
<tr><th>Pre-treatment INR</th><th>Dose of PCC</th></tr>
<tr><td>1.2- 3.9</td><td>25 units/kg (maximum 2500 units)</td></tr>
<tr><td>4.0- 6.0</td><td>35 units/kg (maximum 3500 units)</td></tr>
<tr><td>≥ 6.1</td><td>50 units/kg (maximum 5000 units)</td></tr>
</table></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 Warfarin

Procoagulant Algorithm for the Treatment of Bleeding Patients on Warfarin

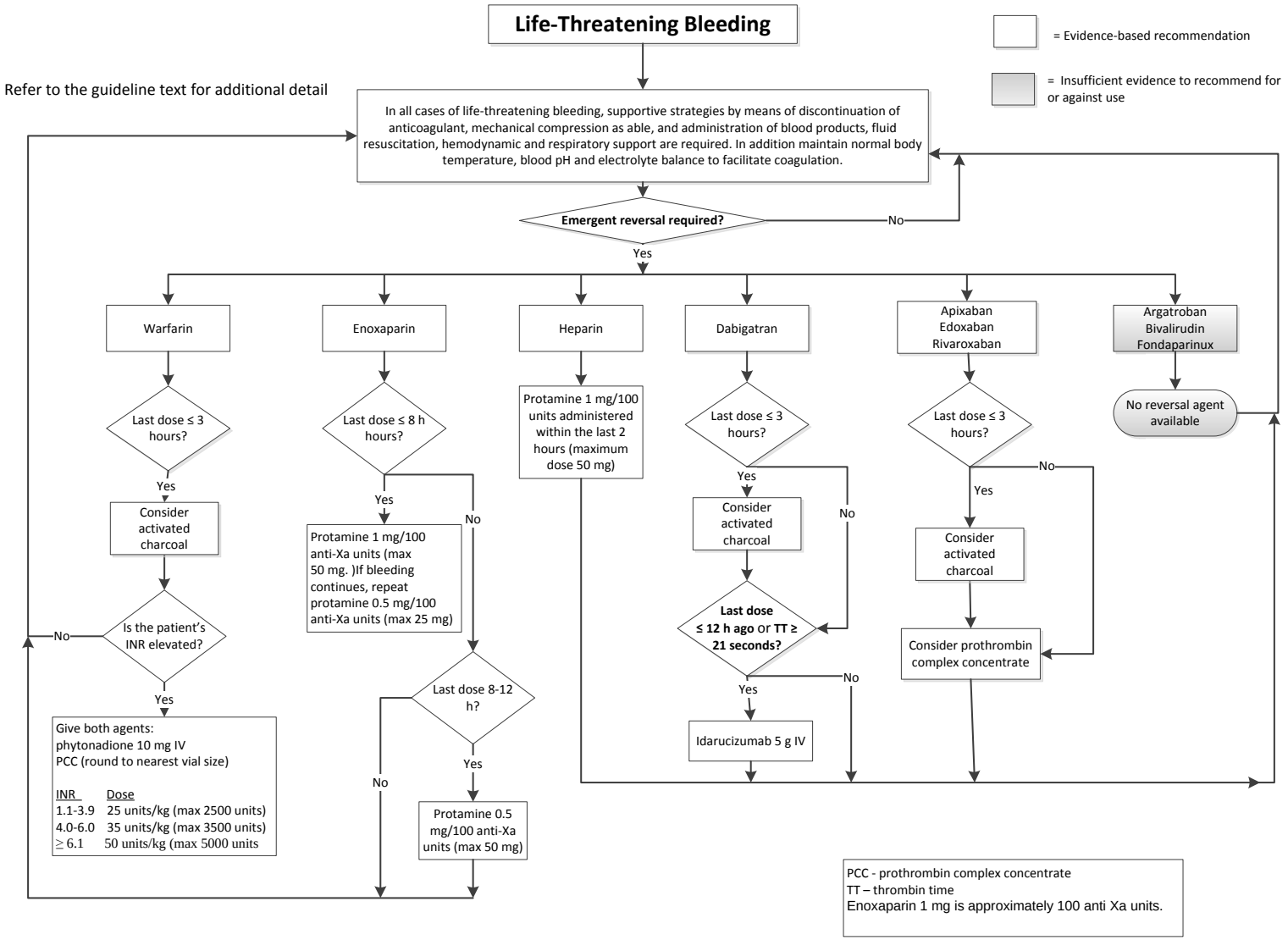
Maintain body temperature, blood pH and electrolyte balance to facilitate coagulation in all patients. If applicable apply packing, dressing and/or pressure.



Appendix C. 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 Thrombin time
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 aPTT 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	aPTT anti-Xa ACT
LMWH **Subcutaneous** (e.g., enoxaparin, dalteparin)	3 -5 h	Time of Last Dose / Treatment Measures: 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) 8 – 12 h ago: Protamine 0.5 mg/ 100 units anti-Xa units (maximum 50mg) Dose > 12 h ago: Protamine may not be necessary	- If patient has renal insufficiency consider wider timeline for administering protamine	anti-Xa

Appendix D. Treatment of Life-Threatening Bleeding Associated with Anticoagulants



Appendix E. Procoagulant Treatment for Specific Conditions NOT Associated with Anticoagulant Therapy

Condition		Bleeding Treatment
In all cases of substantial bleeding supportive strategies by means of 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 UWHC Adult Guidelines for Blood Product Transfusion)		
Trauma patients not on anticoagulant therapy	At risk for severe hemorrhage	Tranexamic acid 1 g, followed by 1 g over 8 hours within 3 hours of injury (or 10 – 15 mg/kg followed by an infusion of 1 -5 mg/kg)
	Life threatening bleeding	Life threatening bleeding PCC 25 units/kg (maximum 2500 units). If bleeding persists beyond 30 min repeat dose for a maximum total dose of PCC 50 units/kg (total maximum dose 5000 units)
Traumatic brain injury not on anticoagulants	INR ≥ 1.5 with anticipated craniotomy	PCC 25 units/kg (maximum 2500 units) and plasma 15 mL/kg
Cardiac Surgery	At risk for severe hemorrhage	Aminocaproic acid 60 – 80 mg/kg (5 – 10 g) loading dose, followed by 10- 30 mg/kg/h (1 – 2 g/h)
		Tranexamic acid 2.5 – 100 mg/kg loading dose followed by 0.25 – 4 mg/kg/h
	Life threatening bleeding	Factor 7A 40 mcg/kg, a repeat dose may be required
Uremia	Bleeding (outside of minor bleeding)	Dialysis
		Desmopressin 0.3 mcg/kg IV once
	Persistent bleeding unresponsive to other therapies	Conjugated estrogen 0.6 mg/kg IV once daily for 5 consecutive days
PCC – prothrombin complex concentrate		

Appendix F – Administration Rate of Intravenous Procoagulant Agents

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

Medication	**Rate of Administration**
Aminocaproic Acid	Loading dose over 15-60 minutes, maintenance dose as a continuous infusion or every 4 hours
Desmopressin	Over 20 – 30 minutes
Factor 7A	Over 2 minutes
Idarucizumab	Over 10 - 20 minutes
Phytonadione	Over 20 – 30 minutes
Plasma	As fast as patient tolerates based on comorbidities and patient characteristics
Protamine	10 mg over 1 – 3minutes, 50 mg over 10 minutes minimum
Prothrombin Complex Concentrate (PCC)	100 units/minute, maximum 200 units/minute
Tranexamic Acid	Loading dose over 13-50 minutes, then continuous infusion based on indication

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