Adult Inpatient/Emergency Department Procoagulant Clinical Practice Guideline (CPG) Cover Sheet

Target Population: Adult inpatients and emergency department patients with sustained bleeding requiring administration of procoagulant agents.

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Committee Approvals/Dates: Anticoagulation Committee - January 2013
Pharmacy Practice Anticoagulation Committee

Release Date: January 2013

Clinical Practice Guideline (CPG)
Executive Summary

Guideline Title:

Adult Procoagulant Therapy for Treatment of Non-Hemophiliac Bleeding - Clinical Practice Guideline

Guideline Overview

This document is intended to guide the use of procoagulant agents for the treatment of adult non-hemophiliac inpatients and emergency department patients 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.

Procoagulant agents in this guideline include:

Aminocaproic acid (Amicar®)
Conjugated estrogen (IV)
Desmopressin (DDAVP®, Stimate®)
Fresh frozen plasma (FFP)
Factor 7A (Novoseven®)
PCC (factor 9 complex), (Profilnine®, Bebulin®)

Factor 9 recombinant (BeneFix®) consists of solely recombinant factor 9. It is not appropriate for treatment in non-hemophiliac patients and is not addressed in this guideline.

Phytonadione (Mephyton®)
Protamine
Tranexamic acid (Cyklokapron®, Lysteda®)

Definitions

1. Minor bleed – epistaxis lasting less than 1 hour, small amount of blood in stool, urine or oral cavity
2. Major, non-life threatening bleed – is considered a significant amount of blood loss accompanied by a drop in Hgb >2 mg/dL or transfusion of PRBC.
3. Life-threatening bleed – intracerebral, uncontrolled GI and retroperitoneal or bleeding into any extremity with risk of compartment syndrome
4. 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
5. Recommendation – a statement based on sufficient evidence from case reports, clinical trials, or expert opinion to warrant strong consideration by the clinician for or against use in patient cases within the scope of this guideline.
6. Therapeutic option – a statement or list of potential therapies which are not sufficiently supported by evidence from case reports, clinical trials, or expert opinion to constitute recommendations for or against the use of listed agents within the scope of this guideline.

Practice Recommendations and Therapeutic Options

General Treatment Management for Bleeding and Major Hemorrhages

1. Identify the source and cause of bleed. (Class I, Level C)
2. 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)
3. Maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. (Class I, Level C)
4. If applicable, apply packing or dressing, use local hemostatic measures or surgical intervention to control bleeding. (Class I, Level C)
5. 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 pharmcodymanics of an anticoagulant (e.g., ciprofloxacin and warfarin). (Class I, Level C)
6. If an overdose of oral anticoagulant is suspected, administer activated charcoal in patients with low risk for aspiration. (Class I, Level C)
7. After major bleeding is controlled and the patient is stabilized, reassess patient for risk of thromboembolism and initiate a short acting agent if anticoagulation is required. (Class I, Level C)

Oral Anticoagulant Bleeding Recommendations (Appendix 2, Appendix 5)

Warfarin (Appendix 3)

8. Monitor an INR associated with bleeding event in patients treated with warfarin. (Class I, Level C).
9. Treatment for minor bleeding or supra-therapeutic INR in patients on warfarin.
   - 9.1. Patients at a high risk for thromboembolism with non-major bleeding may be managed with incomplete warfarin reversal. (Class I, Level C)
   - 9.2. Elevated INR in patients with minor bleeding (Class I, Level B)
     - 9.2.1. INR 4.5 – 9.9 - omit 1 - 2 doses of warfarin
     - 9.2.2. INR > 9.9 - omit 1 - 2 doses of warfarin and administer phytonadione 2.5 mg orally (preferred) or IV.
10. Major, non-life threatening bleeding in patients on warfarin
    - 10.1. Omit 1 to 2 warfarin doses or until bleeding subsides. (Class I, Level B)
    - 10.2. Administer FFP 10 – 15 mL/kg (2 units) and repeat as necessary (Class I, Level B)
    - 10.3. Phytonadione 5 – 10 mg IV (dose dependent upon risk for VTE versus extent of bleeding (Class I, Level B)
11. Life-threatening bleeding in patients on warfarin
    - 11.1. Discontinue warfarin until bleeding is controlled. (Class I, Level C)
    - 11.2. Administer phytonadione, PCC (factor 9 complex), and FFP. Administer each treatment as soon as it is available.(Class IIa, Level B)
      - 11.2.1. Phytonadione 10 mg IV (Class IIa, Level B)
      - 11.2.2. PCC (Factor 9 complex) dosing
        - 11.2.2.1. Non-intracerebral or intraspinal hemorrhages: 25 units/kg rounded to the nearest vial size (approximately 500 units). If bleeding persists (or a target INR is not attained) 30 minutes after completion of administration of the last procoagulant, then a single repeat dose of PCC (factor 9 complex) 25 units/kg can be administered. (Class IIa, Level B)
        - 11.3.2.2 Interacerebral or intraspinal hemorrhage: 50 Units/kg rounded to the nearest 500 unit vial. If the patient rebleeds after 6 hours, another dose of 25 units/kg can be considered. (Class IIb, Level C)
      - 11.2.3. FFP at least 2 units and repeat as required. (Class IIb, Level B)
    - 11.3. The half-life of PCC (factor 9 complex) is 24 ± 8 hours and subsequent dosing is unnecessary unless a patient rebleeds after stabilization. (Class I, Level C)
    - 11.4. There are no clinical trials using both PCC (factor 9 complex) and factor 7A for the treatment of life threatening bleeding. It is unknown if combined use increases efficacy or substantially increases the risk for thrombosis. Combined use of PCC (factor 9 complex) and factor 7A is considered investigational. (Class III, Level C)
    - 11.5. Factor 7A is not preferred for reversal of warfarin-associated hemorrhage. (Class IIb, Level B)

Dabigatran

12. Hemodialysis effectively removes dabigatran and enhances removal if a patient received a dose prior to a major bleeding episode or in the event of a recent overdose. Consider hemodialysis for any bleeding patient with impaired renal function treated with dabigatran. Within two hours of hemodialysis 62% of dabigatran was removed in an open label study of patients receiving dabigatran 50 mg. (Class IIb, Level B)
13. FFP is not indicated for treatment of bleeding associated with dabigatran unless the patient has received at least 4 units of PRBC and the INR is prolonged (i.e., hemodilution).

Therapeutic Option A. For life-threatening bleeding unresponsive to all other management strategies, factor 7A can be considered, weighing the risk for thrombosis. There is no recommended dose of factor 7A for the treatment of bleeding associated with dabigatran, but doses of 40 – 90 mcg/kg have been used to treat life threatening bleeding in patients on warfarin.

NOTE: Some animal data indicates PCC at high doses may be effective, but this has not been validated in humans. Four-factor PCC (factor 9 complex) did not reverse the prolongation of aPTT, ecarin clotting time (ECT), or thrombin time (TT) after administration of dabigatran to twelve healthy volunteers.

Apixaban and Rivaroxaban

14. FFP is not indicated for treatment of bleeding associated with dabigatran unless the patient has received at least 4 units of PRBC and the INR is prolonged (i.e., hemodilution).

Therapeutic Option B. Although no human evidence demonstrates clinical effectiveness, PCC (factor 9 complex should be strongly considered for the treatment of life-threatening bleeds unresponsive to all other management strategies in conjunction with FFP (minimum of two units). There is no standard recommended dose of PCC (factor 9 complex) for the treatment of bleeding associated with rivaroxaban therapy, but doses of 25 – 50 Units/kg are utilized for the treatment of bleeding in patients on warfarin therapy.

NOTE: Only animal studies have utilized factor 7A for the treatment of bleeding associated with rivaroxaban.

Parenteral Anticoagulant Bleeding Recommendations (Appendix 4, Appendix 5)

Argatroban

Therapeutic Option C - Use supportive measures to control bleeding. Insufficient evidence exits to recommend use of factor 7A or PCC (factor 9 complex) for argatroban-related hemorrhage. The short duration of action of argatroban usually precludes the use of further procoagulant agents.

Fondaparinux Bleeding Recommendations

Therapeutic Option D - In patients anticoagulated with fondaparinux suffering a severe, life-threatening hemorrhage resistant to usual management, consider factor 7A 90 mcg/kg x 1 dose.

Heparin Intravenous

15. Protamine rapidly reverses anticoagulant activity of heparin utilizing doses calculated on the estimated amount of heparin IV administered within the last 2 hours. Protamine 1 mg neutralizes approximately 100 Units of heparin administered. (Class I, Level B)
16. Monitor aPTT or ACT to evaluate the extent of heparin reversal. (Class I, Level B)

Lepirudin

Therapeutic Option E - 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 lepirudin.

Low Molecular Weight Heparin (LMWH) Bleeding Recommendations

17. If a LMWH was administered within the last 8 hours protamine may partially reverse the anticoagulant effect. (Class I, Level B) Patients with renal insufficiency may benefit from treatment beyond 8 hours.
  17.1. Administer protamine 1 mg per 100 anti-Xa units of LMWH (maximum 50 mg). Enoxaparin 1 mg is approximately 100 anti Xa units.
  17.2. If bleeding persists repeat protamine at a dose of 0.5 mg per 100 anti-Xa units of LMWH (maximum 50 mg). Enoxaparin 1 mg is approximately 100 anti Xa units.

18. If LMWH was administered more than 8 hours ago, then administer protamine.0.5 mg/kg. (Class IIb, Level C) Patients with renal insufficiency may benefit from treatment beyond 12 hours.

Therapeutic Option F- In patients with life-threatening bleeding unresponsive to other therapies, factor 7A 40mcg/kg may facilitate bleeding control in patients treated with LMWH.

No Anticoagulant Use, but Life threatening Bleeding in Specific Conditions (Appendix 6)

Intracerebral Hemorrhage on patients not managed with anticoagulants

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

20. For coagulopathic patients undergoing emergent surgical treatment for an intracerebral bleed, factor 7A 90 mcg/kg may reduce the amount of blood products required for transfusion. (Class IIb, Level C)

Traumatic Hemorrhage in patients not managed on anticoagulants

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

22. If a 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 trauma. Alternative dosing is 10 – 15 mg/kg followed by an infusion of 1 -5 mg/kg/h. (Class I, Level B)

23. Administer PCC (factor 9 complex) 25 units/kg for life threatening hemorrhage along with FFP. If bleeding persists beyond 30 minutes after completion of infusion of procoagulant agents, then administer a second dose of PCC (factor 9 complex) 25 units/kg.(Class IIb, Level B)

24. Factor 7A is not recommended in blunt or penetrating trauma patients. (Class III, Level C)

Cardiac Surgery

25. Aminocaproic acid and tranexamic acid are effective in reducing blood loss in cardiac surgery patients in high risk patients.
  25.1. Tranexamic acid bolus doses in clinical trials range from 2.5 mg/kg to 100 mg/kg followed by maintenance doses of 0.25 – 4 mg/kg/h over 1 – 12 hours.
  25.2. Typical doses of aminocaproic acid 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 I, Level A)

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

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

Hepatic Surgery

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

Uremic Patients

29. Dialysis in combination with other treatments can limit bleeding in uremic patients. (Class IIa, Level C)

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

31. Administer conjugated estrogens 0.6 mg/kg for five consecutive days if all other measures fail to improve clinical bleeding in uremic patients. (Class IIa, Level A)

Pertinent UWHC Policies & Procedures
Guidelines:
Ambulatory Guideline for Management of Warfarin in Adults
Inpatient Guideline for Management of Warfarin in Adults
UWHC Dabigatran Use Guideline
Heparin Induced Thrombocytopenia Guideline

Operating Procedures:
Operating Procedure for the Emergent Use of Factor 7A (NovoSeven®)
Operating Procedure for the Emergent Use of Factor 9 Complex (Profilnine SD®)

Adult Procoagulant Therapy for Treatment of Non-Hemophiliac Bleeding

Clinical Practice Guideline

A. Scope

This document is intended to guide practitioner use of procoagulant agents for the treatment of adult non-hemophiliac inpatients and emergency department patients with sustained bleeding or undesired anticoagulation after administration of therapeutic anticoagulants. The guideline also includes recommendations for use of procoagulants in patients with intracerebral hemorrhage, cardiac surgery, trauma and uremia not on anticoagulants. Procoagulant agent use includes aminocaproic acid, conjugated estrogen, desmopressin, fresh frozen plasma (FFP), factor 7A, PCC (factor 9 complex), phytonadione, protamine, and tranexamic acid.

B. Methodology

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 (Figure 1).[1]

MEDLINE and International Pharmaceutical Abstracts were searched using the terms prothrombin complex concentrate, factor IX complex, PCC, factor VII, tranexamic acid, dabigatran reversal lepirudin reversal, rivaroxaban reversal, apixaban reversal, desmopressin and renal dysfunction, uremia and bleeding. References from identified articles were further evaluated.

The cost of some procoagulant agents for the treatment of hemorrhage is substantial and considered in determining recommendations (Table 1.)

Table 1. Procoagulant cost

Procoagulant	UWHC Estimated Cost per Dose ($)
Aminocaproic acid, parenteral	2.34 - 2.88
Conjugated estrogen, parenteral	243.84
Desmopressin	3.54
Phytonadione tab	0.15
Phytonadione, parenteral	7.33
Protamine	3.14
Fresh frozen plasma (FFP)	300.00
PCC (factor 9 complex)	1580 – 3160.00
Factor 7A	4187.34 - 9770.46
Tranexamic acid, parenteral	120.00

C. Definitions

1. Minor bleed – epistaxis lasting less than 1 hour, small amount of blood in stool, urine or oral cavity
2. Major, non-life threatening bleed – is considered a significant amount of blood loss accompanied by a drop in Hgb >2 mg/dL or transfusion of PRBC.
3. Life-threatening bleed – intracerebral, uncontrolled GI and retroperitoneal or bleeding into any extremity with risk of compartment syndrome
4. 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

5. Recommendation – a statement based on sufficient evidence from case reports, clinical trials, or expert opinion to warrant strong consideration by the clinician for or against use in patient cases within the scope of this guideline.
6. Therapeutic option – a statement or list of potential therapies which are not sufficiently supported by evidence from case reports, clinical trials, or expert opinion to constitute recommendations for or against the use of listed agents within the scope of this guideline.

D. 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 associated with the intensity of anticoagulation.[6] Another consideration is the increased risk of bleeding in patients with concomitant treatment with antiplatelet medications, non-steroidal anti-inflammatory agents and cyclooxygenase type- 2 inhibitors. Depending on the anticoagulant agent, the half-life and 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.

Agents recommended to promote coagulation include:

1. **Aminocaproic Acid** prevents the conversion of plasminogen to plasmin and inhibits the degradation of fibrin clots.[7] 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.[8]
   - 1.2. Dosing of aminocaproic acid varies based on the site and indication for bleeding. Due to the short half-life of 2 hours, the intravenous formulation is administered as a continuous infusion
     - 1.2.1. Typical parenteral doses for acute bleeding are an initial loading dose of 4 to 5 grams, followed by infusion of 1 gram per hour for 8 hours or until bleeding is controlled.[7]
     - 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).[8, 9]
   - 1.3. The risk of thrombosis due to aminocaproic acid treatment is minimal.[8]

2. **Conjugated estrogen (IV)** is not a procoagulant, but can limit bleeding in both male and female uremic patients unresponsive to other therapies.[10]
   - 2.1. The mechanism of action is unknown, but one theory is a reduction in nitrous oxide concentrations potentially leading to an increase in thromboxane A_2.
   - 2.2. Usual dose of conjugated estrogen 0.6 mg/kg IV over 30-40 minutes once daily for 5 consecutive days.[10]
   - 2.3. Onset is within approximately 6 hours with a maximum effect within 5-7 days and duration of approximately 14 – 21 days.[11-13]

3. **Desmopressin** decreases bleeding times in uremic patients with a proposed mechanism of increasing the amount of vonWillebrand factor released from endothelial cells. [10, 14, 15] The improved hemostasis is attributed to a large increase in plasma vonWillebrand factor.
   - 3.1. Usual dose for treating uremic bleeding patients is 0.3 mcg/kg administered over 30 minutes.[10, 15]
   - 3.2. Onset is within 1 hour of infusion and bleeding times return to normal within 24 hours.[16]

3.3. Tachyphylaxis may develop due to depletion of vonWillenbrand factor in endothelial cells and repeat doses are not warranted.[17]

3.4. The most common side effects are facial flushing and mild hyponatremia.[7] Hypotension is associated with administration.[18]

3.5. Reports of arterial thrombosis are documented in patients with atherosclerosis and bleeding disorders.[18-20]

4. **Phytonadione** administered by the oral or intravenous route is effective in reversing the anticoagulant effects of warfarin.[21, 22] (Class I, Level A)

4.1. Low oral doses of phytonadione are preferred over the intravenous route for minor bleeding or treatment of INR > 9.9.[2, 23]

4.2. The intravenous product may be administered orally for doses less than 2.5 mg.

4.3. The intravenous route is reserved for circumstances when fast onset is required for urgent reversal.

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

4.3.2. Slow intravenous administration (over 30 minutes) is recommended to avoid severe hypotension and rare anaphylactic reactions.[25, 26]

4.3.3. Rapid reversal with intravenous phytonadione is not indicated prior to elective procedures or surgeries.[22]

4.4. Subcutaneous and intramuscular administration are not recommended due to delayed and unpredictable responses.[2, 27, 28]

4.5. Administration of high doses (10 mg or greater) may limit the ability to anticoagulate patients after bleeding is controlled.

5. **Protamine** rapidly reverses heparin by binding to form an inactive complex and neutralize anti-factor IIa.

5.1. Protamine 1 mg reverses approximately 100 units of heparin.[29]

5.1.1. The dose of protamine should be sufficient to reverse the amount of heparin administered within the last 2 hours.

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

5.2. Protamine inactivates a variable portion of the anti-Xa activity of LMWH, but does not bind to all fragments of LMWH.[30]

5.2.1. If administered within the last 8 hours, give protamine 1 mg per 100 anti-Xa units of LMWH. (Enoxaparin 1 mg is approximately 100 anti Xa units.)

5.2.2. If greater than 8 hours, but 12 hours or less since administration of LMWH, give protamine 0.5 mg per 100 anti-Xa units of LMWH. (Enoxaparin 1 mg is approximately 100 anti Xa units.)

5.2.3. Examples:

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

5.2.3.2 If patient received 5000 units of dalteparin within the last 8 hours administer protamine 50 mg

5.2.4 Patients with renal insufficiency may benefit from protamine beyond 8 or 12 hours because of the longer half-life of LMWH in this population

5.3. Maximum dose of protamine is 50 mg per single administration.[31]

5.4. Administer protamine at rate of 50 mg over 10 minutes. Rapid administration is associated with increased risk of adverse events.

5.5. 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.[7]

5.5.1. Patients with a known sensitivity to fish or who have previously received protamine sulfate containing insulin may experience allergic reactions to protamine.[29, 32]

5.5.2. For patients at risk for a serious allergic reaction to protamine pretreat with H-1 antihistamine and corticosteroid therapy.

6. **Fresh frozen plasma** (FFP) is a biological product from pooled human plasma containing factors II, VI, IX, X. Administration of FFP does not reverse anticoagulants, but provides additional clotting factors.
   6.1. Indications include: replacement of single factor deficiencies; immediate reversal of warfarin in patients with active bleeding, surgery or procedures; massive transfusion, DIC with evidence of bleeding, thrombotic thrombocytopenic purura (TTP), liver disease and cardiopulmonary bypass.[2]
   6.2. Since FFP contains isohemagglutinins it is cross matched to blood group.
   6.3. FFP is stored as frozen product; however, thawed FFP is available at UWHC at all times. (Thawing occurs within 15 - 30 minutes.)
   6.4. Usual dose for bleeding is 10 - 15 mL/kg with repeated doses administered as required for bleeding[33]
      6.4.1. FFP as ordered from the blood bank in units. The characteristic volume of a unit of FFP is approximately 200 mL.
      6.4.2. A typical infusion rate is 10-20 mL/kg/h.
   6.5. Adverse events include volume overload, transfusion-related acute lung injury (TRALI), acute hemolytic transfusion reaction, urticaria[2]

7. **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 with inhibitors, but has been evaluated in hemorrhagic patients previously treated with anticoagulants, after cardiac surgery or trauma patients requiring extensive blood replacement.[34] Little data is available to provide strong dosing recommendations for the treatment of bleeding in patients on enteral or parenteral anticoagulants.
   7.1. UW Health Pharmacy and Therapeutics Committee formulary restriction: Treatment of life-threatening bleed and approval by an attending physician on the critical care, cardiac surgery, neurosurgery, trauma surgery, vascular surgery, hematology, anesthesiology or emergency department services.
   7.2. A 2012 Cochrane review and meta-analysis examined 29 randomized controlled trials evaluating prophylactic and therapeutic factor 7A use in non-hemophilia-related bleeding.[35] 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.
   7.3. 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.[36, 37]
      7.3.1. Actual body weight should be used in dosing.
      7.3.2. Round the dose down to the nearest 1000 mcg (1mg) vial size.
   7.4. Factor 7A is ineffective in severely acidotic patients; pH should be above 7.2 prior to administration.[38]
   7.5. The short half-life of factor 7A limits activity to 2 - 3 hours and concomitant use of blood products is often required.
   7.6. INR is rapidly decreased after administration of factor 7A; however, this reduction is not a reliable measure of warfarin reversal.[39]
   7.7. Factor 7A increases the risk of thrombosis when used for treatment of non-hemophilic patients[40]
      7.7.1. The risk of arterial thrombosis with factor 7A increases in patients 65 years of age or older.
      7.7.2. An increased risk of thrombosis can occur in patients with advances atherosclerotic disease, crush injuries, disseminated intravascular coagulation (DIC), septicemia or signs or symptoms of an activated coagulation system or thrombosis.
      7.7.3. Product labeling includes a black box warning for thrombotic and thromboembolic events.[34]
   7.8. Contraindications include hypersensitivity to mouse, bovine or hamster proteins or hypersensitivity to recombinant factor 7A or the product components.[34]
   7.9. Emergent preparation and administration instructions can be located in the Pharmacy Operations Manual: Operating Procedure for the Emergent Use of Factor 7A (NovoSeven®).

8. **PCC (factor 9 complex),** referred to as prothrombin complex concentrate, PCC, and factor 9 complex, is a biological product of pooled human plasma. The only FDA approved PCC (factor 9 complex) products (Profilnine® and Bebulin®) contain therapeutic concentrations of factors II, IX and

X. Products available in Europe (Proplex T®, Beriplex®, Octaplex®, Cofact®) also contain therapeutic amounts of factor VII and may provide improved therapeutic results.

Factor 9 recombinant (BeneFix®) consists of solely recombinant factor 9. It is not appropriate for treatment in non-hemophiliac patients and is not addressed in this guideline.

8.1. UW Health Pharmacy and Therapeutics Committee formulary restriction: Treatment of life-threatening bleeds in patients treated with warfarin. All other indications require approval by an attending physician from critical care, cardiac surgery, neurosurgery, trauma surgery, vascular surgery, hematology, anesthesiology and emergency department.

8.2. Dosing varies widely in the literature for PCC (factor 9 complex).[39, 41-48] Some studies use standard dosing of 1000 to 2000 Units and others use weight based dosing from of 20 to 65 units/kg.

8.2.1. Non-cerebral or spinal hemorrhages: 25 units/kg rounded to the nearest vial size (approximately 500 units).
If bleeding persist 30 minutes after infusion of phytonadione, FFP and PCC (factor 9 complex) or a target INR is not attained, then repeat another dose of 25 units/kg.

8.2.2. Cerebral or spinal hemorrhage: 50 units/kg rounded to the nearest vial size (approximately 500 units). If the patient bleeds again after 6 hours, a second dose may be warranted after consideration of the risk of embolism versus the risk of bleeding

8.3. The half-life of PCC (factor 9 complex) is 24 ± 8 hours and subsequent dosing is usually unnecessary.[49, 50] Because factor II (thrombin) and factor X have longer half-lives than factor IX, repeat doses may cause an accumulation of these factors with resultant increase in coagulation risk.

8.4. There are no clinical trials using both PCC (factor 9 complex) and factor 7A for the treatment of life threatening bleeding. It unknown if combined use increases efficacy or results in a tolerable risk for thrombosis. Combined use of PCC (factor 9 complex) and factor 7A is considered investigational.

8.5. Administer at a rate of 100 – 200 units/min (1 – 2 mL/min)[2, 44]

8.5.1. Rapid infusion may induce thrombosis, fever, chills, headaches, nausea/vomiting.[49]

8.5.2. Risk of thrombosis may be increased in patients with history of thrombosis or liver disease[47]

8.6 Emergent preparation and administration instructions can be located in the Pharmacy Operations Manual: Operating Procedure for the Emergent Use of Factor 9 Complex (Profilnine SD®)

9. **Tranexamic acid** inhibits fibrinolysis by competitively inhibiting plasmin activity and plasminogen activation.[51]

9.1. Parenteral tranexamic acid is effective in treating bleeding from multiple causes such as GI, surgical and trauma.[15, 51]

9.2. The half-life is approximately 2 hours.

9.3. Multiple dosing regimens are employed based on indication.

9.3.1. In non-cerebral trauma doses utilized:

9.3.1.1. Tranexamic acid 1 g over 10 minutes followed by 1 g over 8 hours[52, 53]

9.3.1.2. Tranexamic acid 10 – 15 mg/kg followed by an infusion of 1 -5 mg/kg/h[54]

9.3.2. 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

9.4. Tranexamic acid is associated with cerebral infarction in studies of patients with subarachnoid hemorrhage; however, thromboembolism with the use of tranexamic acid is rare. [53, 55]

E. Recommendations and Therapeutic Options

General Treatment Management for Sustained Bleeding

1. Identify the source and cause of bleed.[2, 29, 56] (Class I, Level C)

2. Management of hemorrhage includes maintenance of hemodynamic and respiratory stability.[56, 57] When necessary provide mechanical ventilation, fluid resuscitation, hemodynamic support and therapeutic procedures stabilize the patient and promote coagulation. (Class I, Level C)

3. Maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation.[56-58] (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.[5] 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.[58] In the severely injured patient hypothermia, acidosis and hypotension are associated with coagulopathy.

4. If applicable, apply packing or dressing, use local hemostatic measures or surgical intervention to control bleeding.[59] (Class I, Level C)

5. 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 pharmcodymanics of an anticoagulant (e.g., ciprofloxacin and warfarin).[60] (Class I, Level C)

6. 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.[2, 61] (Class I, Level C)

7. After major bleeding is controlled and the patient is stabilized, reassess patient for risk of thromboembolism and initiate a short acting agent if anticoagulation is required.[2, 29] (Class I, Level C)

Oral Anticoagulant Bleeding Recommendations and Therapeutic Options (Appendix 2, Appendix 3)

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. Hemorrhagic events in patients managed on warfarin are based upon the, target INR, duration of therapy, use on concomitant antiplatelet therapy and quality of monitoring.[6, 62, 63] 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, 64-66] The rate of hemorrhage increases markedly in patients with an INR greater than 4.5.[67] Bleeding or potential bleeding of patients on warfarin can be managed by holding warfarin doses, administering phytonadione, FFP and PCC (factor 9 complex). The approach to treatment is predicated on the indication for warfarin, location of the bleed, extent of bleeding and INR elevation (Appendix 2).[2] For further information on warfarin treatment see Ambulatory Guideline for Management of Warfarin in Adults or Inpatient Guideline for Management of Warfarin in Adults.

8. Monitor an INR associated with bleeding event in patients treated with warfarin.[2] (Class I, Level C).

9. Treatment for minor bleeding or supra-therapeutic INR in patients on warfarin:
   - 9.1. Patients at a high risk for thromboembolism with non-major bleeding may be managed with incomplete warfarin reversal.[60] (Class I, Level C)
   - 9.2. Elevated INR (Class I, Level B)
     - 9.2.1. INR 4.5 – 9.9 - omit 1 - 2 doses of warfarin[2]
     - 9.2.2. INR > 9.9 - omit 1 - 2 doses of warfarin and administer phytonadione 2.5 mg orally (preferred) or IV.

9.2.3. In patients with a high INR no difference in incidence of bleeding was identified in between patients treated with phytonadione versus placebo.[62]

10. Major, non-life threatening bleeding in patients on warfarin and requiring reversal:
- 10.1. Omit 1 to 2 warfarin doses or until bleeding subsides.[2] (Class I, Level B)
- 10.2. Administer FFP 10 – 15 mL/kg (2 units) and repeat as necessary.[2, 68] (Class I, Level B)
- 10.3. Phytonadione 2.5 – 10 mg orally or IV, (dose dependent upon risk for VTE versus extent of bleeding)[2] (Class I, Level B)

11. Life-threatening bleeding in patients on warfarin.
- 11.1. Discontinue warfarin until bleeding is controlled.[60] (Class I, Level C)
- 11.2. Administer phytonadione, PCC (factor 9 complex) and FFP.[46, 48, 54, 69, 70] There is no specific order of administration; administer each agent as soon as it is available (Class IIa, Level B)
  - 11.2.1. Phytonadione 10 mg IV - due to the long half-life of warfarin, and the short half-life of clotting factors, administer phytonadione along with FFP.[2] (Class IIa, Level B)
  - 11.2.2. PCC (factor 9 complex) dosing
    - 11.2.3.1 Hemorrhages excluding intracerebral or intraspinal: 25 units/kg rounded to the nearest vial (approximately 500 units). If bleeding persists (or a target INR is not attained) 30 minutes after completion of administration of all indicated procoagulants, then a single repeat dose of PCC (factor 9 complex) 25 units/kg can be administered.[39, 42, 47] (Class IIa, Level B)
    - 11.2.3.2 Intracerebral or intraspinal hemorrhage: 50 Units/kg rounded to the nearest 500 unit vial. If the patient rebleeds after 6 hours, another dose of PCC (factor 9 complex) 25 units/kg may be considered.[41, 71] (Class IIb, Level C)
  - 11.2.3. FFP - at least 2 units and repeat as required.[33] (Class IIa, Level B)
- 11.3. The half-life of PCC (factor 9 complex) is 24 ± 8 hours and repeat dosing after a maximum of 50 units/kg is not required for a single bleeding event.[49, 50] (Class I, Level C)
- 11.4. No clinical trials exist using both PCC (factor 9 complex) and factor 7A for the treatment of life threatening bleeds. It is unknown if combined use increases efficacy or substantially increases the risk for thrombosis. Combined use of PCC (factor 9 complex) and factor 7A is considered investigational and is not recommended. (Class III, Level C)
- 11.5. Factor 7A is not preferred for reversal of warfarin-associated hemorrhage. Routine use for the reversal of warfarin-related hemorrhage is not recommended.[72, 73] (Class III, Level B)

  Factor 7A has been assessed in a randomized, double-blind, placebo-controlled trial for the reversal of warfarin-associated bleeding in healthy men aged 18-45 years (African Americans were excluded due to high variability in bleeding duration).[74] Following titration of warfarin to achieve INR of 2.5 (n=85), administration of factor 7A at single doses of 5, 10, 20, 40, or 80 mcg/kg failed to produce a statistically significant decrease in bleeding duration or blood loss despite significant reductions in measured INR values, activated partial thromboplastin times, and prothrombin times. No additional reversal agents (such as phytonadione) were administered. No significant adverse events were noted in this trial.[74]

Dabigatran is a reversible, oral direct thrombin inhibitor and an association between dose and incidence of bleeding is established in patients with atrial fibrillation.[75] Unlike warfarin, anticoagulation occurs through inhibition of factor II (thrombin), not depletion of the clotting factors and no reversal agent is available. A prolonged aPTT can indicate a patient has taken dabigatran, but does not correlate with the extent of anticoagulation.[76] 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. Due to the short duration of effect, discontinuation of dabigatran could be sufficient to mitigate anticoagulant effects.[2, 76] No established reversal agent is available. (For more information see UWHC Dabigatran Use Guideline)

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12. Hemodialysis effectively removes dabigatran and enhances removal if a patient receives a dose prior to a major bleeding episode or in the event of a recent overdose.[77, 78] Consider hemodialysis for any bleeding patient with impaired renal function treated with dabigatran. Within two hours of

hemodialysis 62% of dabigatran was removed in an open label study of patients receiving dabigatran 50 mg. (Class IIb, Level B)

13. FFP is not indicated for treatment of bleeding associated with dabigatran unless the patient has received at least 4 units of PRBCs and the INR is prolonged (i.e., hemodilution). (Class IIb, Level C)

Therapeutic Option

Option A - For life-threatening bleeding unresponsive to all other management strategies, factor 7A can be considered, weighing the risk for thrombosis.[79] There is no recommended dose of factor 7A for the treatment of bleeding associated with dabigatran, but doses of 40 – 90 mcg/kg have been used to treat life threatening bleeding in patients on warfarin.[37]

No clinical trial supports the effectiveness of recombinant factor 7A for limiting dabigatran-associated hemorrhage in humans.[2, 76] Animal and in vitro data demonstrate mixed results for bleeding control in subjects treated on dabigatran treated with factor 7A.[76] The proposed mechanism of action is through activation thrombin on the surface of platelets.[80]

NOTE: Animal data indicates PCC (factor 9 complex) at high doses may be effective, but this has not been validated in humans. Four-factor PCC (factor 9 complex) did not reverse the prolongation of aPTT, ecarin clotting time (ECT), or thrombin time (TT) after administration of dabigatran to twelve healthy volunteers.[79]

Apixaban and rivaroxaban are oral factor Xa inhibitors and unlike warfarin, anticoagulation occurs through inhibition of a clotting factor, not depletion of the clotting factors. No reversal agents are available and there are no clinical trials that demonstrate improved clinical outcomes with factor 7A or PCC (factor 9 complex). Apixaban and rivaroxaban have relatively short half-lives in patients with normal renal function (apixaban 12 hours, rivaroxaban 5- 9 hours). The anticoagulant effect of these agents is minimal in patients 48 hours after ingestion.[81-83] If a bleeding event in patients on oral factor Xa inhibitors requires substantial PRBC transfusion, then additional FFP administration may be required.

14. FFP is not indicated for treatment of bleeding associated with dabigatran unless the patient has received at least 4 units of PRBC and the INR is prolonged (i.e., hemodilution). (Class IIb, Level C)

Therapeutic Option B. Although no human evidence demonstrates clinical effectiveness, PCC (factor 9 complex should strongly be considered for the treatment of life-threatening bleeds unresponsive to all other management strategies in conjunction with FFP (minimum of two units). There is no standard recommended dose of PCC (factor 9 complex) for the treatment of bleeding associated with rivaroxaban therapy, but doses of 25 – 50 Units/kg are utilized for the treatment of bleeding in patients on warfarin therapy. [39, 41, 42, 47, 71]

Four-factor PCC (factor 9 complex) reversed prolongation of PT, thrombin potential after administration of supra-therapeutic doses (20 mg twice daily) of rivaroxaban to twelve healthy volunteers.[79]

NOTE: Factor 7A has not been evaluated in humans for the reversal or rivaroxaban. In a rabbit model of massive doses of rivaroxaban with associated hemorrhage, factor 7A successfully reduced aPTT and ear bleeding time, but did not decrease total blood loss.[84] Given the lack of human data for the use of factor 7A in the reversal of rivaroxaban-associated hemorrhage, no clear consensus exists for optimum factor 7A dosing at this time. In the failure of alternative management strategies outlined above, factor 7A may be considered in life-threatening hemorrhage in patients who are therapeutically anticoagulated with rivaroxaban.[2]

Parenteral Anticoagulant Bleeding Recommendations and Therapeutic Options
(Appendix 4)

Argatroban is a parenteral direct thrombin inhibitor that prevents fibrin formation, activation of factors V, VIII, XIII, protein C, and platelets.[68] 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.[29] (UWHC Guideline for the Diagnosis and Treatment of Heparin Induced Thrombocytopenia)

Therapeutic Option:
Option C - Use supportive measures to control bleeding. Insufficient evidence exists to recommend factor 7A use in argatroban-related hemorrhage.

Factor 7A has theoretical applications in reversing argatroban-associated hemorrhage, though clinical experience for off-label use is limited and has not demonstrated benefit.[85, 86] 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.[87, 88] One case report of an infant receiving argatroban failed to demonstrate hemostasis with factor 7A.[85]

Fondaparinux is a factor Xa inhibitor with an elimination half-life of 17–21 hours.[89] There is no established reversal agent for fondaparinux.[29] Protamine is not effective for the treatment of bleeding associated with fondaparinux.

Therapeutic Option
Option D - In patients anticoagulated with fondaparinux suffering a severe, life-threatening hemorrhage resistant to usual management, consider factor 7A 90 mcg/kg. [29, 87, 90]

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.[90] 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.[87] 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.[91] While hemostasis was achieved per the authors, 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.[29] Heparin is a large 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.

15. 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.[29] Protamine 1 mg neutralizes approximately 100 Units of heparin administered. (Class I, Level B)

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

Lepirudin Intravenous
Lepirudin, a recombinant hiruidin, is a specific direct thrombin inhibitor. (UWHC Guideline for the Diagnosis and Treatment of Heparin Induced Thrombocytopenia). The half-life is short (1.5 hours), but extensively prolonged in patients with renal insufficiency.[7] There is no reversal agent for lepirudin; use supportive measures to limit bleeding.

> *Therapeutic Option E* - 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 lepirudin.

Low Molecular Weight Heparin
Similar to heparin, the primary anticoagulant activity of LMWH (e.g., dalteparin, enoxaparin) 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.[29] The risk of bleeding from a LMWH correlates with the extent of anticoagulation, but no established method for total reversal of anticoagulation from LMWH exists. Protamine will only neutralize anti-factor IIa activity and has limited, if any activity, on anti-factor Xa activity.[30, 92, 93]

17. If a LMWH was administered within the last 8 hours, protamine may partially reverse the anticoagulant effect.[29] (Class I, Level B) This dose may also be considered beyond 8 hours in patients with renal insufficiency.
- 17.1. Administer protamine 1 mg per 100 anti-Xa units of LMWH (maximum 50 mg). Enoxaparin 1 mg is approximately 100 anti Xa units.
- 17.2. If bleeding persists repeat protamine at a dose of 0.5 mg per 100 anti-Xa units of LMWH (maximum 50 mg dose). Enoxaparin 1 mg is approximately 100 anti Xa units.

18. 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).[29] (Class IIb, Level C) This dose may also be considered beyond 12 hours in patients with renal insufficiency.

A double-blind study in 15 healthy adults demonstrated almost complete reversal aPTT by protamine after a dose of dalteparin 1 mg per 100 Units; however there was only minor impact on normalization of anti-Xa.[94] In case series of 3 patients, protamine did not reverse clinical bleeding in two of three patients.[93]

Therapeutic Option
Option F - In patients with life-threatening bleeding unresponsive to other therapies, factor 7A 40mcg/kg may facilitate bleeding control in patients treated with LMWH.[95]

Case reports of life-threatening bleeding in patients treated with LMWH utilized factor 7A 20-120 mcg/kg to reverse bleeding.[96-98] Factor 7A was used in conjunction with supportive measures and deemed at least partially effective by the authors.

No Anticoagulant Use but Life Threatening Bleeding in Specific Conditions (Appendix 6)

Intracerebral Hemorrhage in patients not managed with anticoagulants

19. Factor 7A is not recommended to reduce mortality in patients with intracranial hemorrhage.[36, 73] (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.[99, 100] Results of a 2005 publication including 399 patients treated with single doses of 40, 80, or 160 mcg/kg of factor 7A showed 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).[99]

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).[100] 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 ($p=0.05$).[100]

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.[101]

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.[102]

A 2010 meta-analysis examined factor 7A use in non-hemophilia patients with acute intracerebral hemorrhage.[103] 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.[103]

20. For coagulopathic patients undergoing emergent surgical treatment for an intracerebral bleed, factor 7A 90 mcg/kg may reduce the amount of blood products transfused.[104] (Class IIb, Level C)

One small retrospective case series of patients with coagulopathy due to hepatic dysfunction, dilutional coagulopathy or anticoagulants demonstrated normalization of INR and aPTT along with reduced transfusion requirements.[104]

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.[58, 59] 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 hypocoagulation but have never been demonstrated to correlate with hemorrhagic events.

21. Local hemostatic dressings can facilitate local hemostasis and are more effective than standard gauze dressings.[54, 105] (Class I, Level C)

22. 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 surgery.[52, 53, 55] Alternative dosing is 10 – 15 mg/kg followed by an infusion of 1 -5 mg/kg/h.[54] (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.[53] 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.

23. Administer PCC (factor 9 complex) 25 units/kg for life threatening hemorrhage along with FFP. If bleeding persists beyond 30 minutes after completion of infusion of FFP and PCC (factor 9 complex), then administer a second dose of PCC (factor 9 complex) 25 units/kg.[45] (Class IIb, Level B)

24. Factor 7A is not recommended in blunt or penetrating trauma patients. [106-109] (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.[106] 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

25. Administer aminocaproic acid or tranexamic acid to reduce blood loss in cardiac surgery patients at high risk for bleeding.[8, 110] (Class I, Level A)

Tranexamic acid bolus doses in clinical trials range from 2.5 mg/kg to 100 mg/kg followed by maintenance doses of 0.25 – 4 mg/kg/h over 1 – 12 hours. Typical doses of aminocaproic acid 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).[8, 9]

26. 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. [36, 111-114] If bleeding is uncontrolled a repeat dose of factor 7A 40 mcg/kg may be required. (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).[111] 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.[112]

Guidelines from the European Association for Cardio-Thoracic Surgery suggest, based on a single randomized, controlled trial and several retrospective case studies demonstrating reductions in blood transfusion requirements, that factor 7A may be considered in the case of post-cardiac surgery bleeding that is refractory to conventional measures described above, though no dosing recommendations are provided and a notation about the risk of fatal thrombosis is made.[115]

27. Desmopressin is not indicated to prevent perioperative blood loss in non-uremic cardiac surgery patients.[37, 116] (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.[18, 37]

Hepatic Surgery

28. Prophylactic use of factor 7A is not recommended in patients undergoing hepatic surgery.[117, 118] (Class III, Level A)

Factor 7A has been evaluated for the prevention of hemorrhage in patients with liver surgery in a meta-analysis.[117] 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.[118]

Uremic Patients

29. Patients with active bleeding can receive benefit from dialysis in combination with other treatments.[10, 17] (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.

30. Administer one dose of desmopressin 0.3 mcg/kg over 30 minutes to improve bleeding in uremic patients[10] (Class I, Level A)

31. Administer conjugated estrogens if all other measures fail to improve bleeding time and clinical bleeding in uremic patients.[11-13, 119] 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)

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G. Benefits/Harms of Implementation

The benefit of the guideline is consistent and safe use of procoagulant agents in select bleeding situations. The risk of implementing the guideline and administering procoagulants is increased thromboembolism and is related to underlying clinical conditions, comorbidities and dose.[120]

H. Qualifying Statements

Most studies evaluating procoagulants are small and/or case series and recommendations are subject to change with the publication of clinical trials.

I. Implementation Strategy

UWHC authorized prescribers for factor 7A and prothrombin complex (PCC) include attending physicians on the critical care, cardiac surgery, neurosurgery, trauma surgery, anesthesiology and emergency department services. The guideline will be available electronically on UConnect.

J. Implementation Tools/Plan

The name of the authorizing attending prescriber will be added to factor 7A and prothrombin complex (PCC) medication records in Health Link. Pharmacists will be educated on the guideline through staff meetings and grand rounds.

K. Disclaimer

This Clinical Practice Guideline provides an evidence-based approach for use of procoagulant agents. It is understood that occasionally patients will not match the conditions considered in the guideline.

Appendix 1: Grades for Recommendation

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 *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
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	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

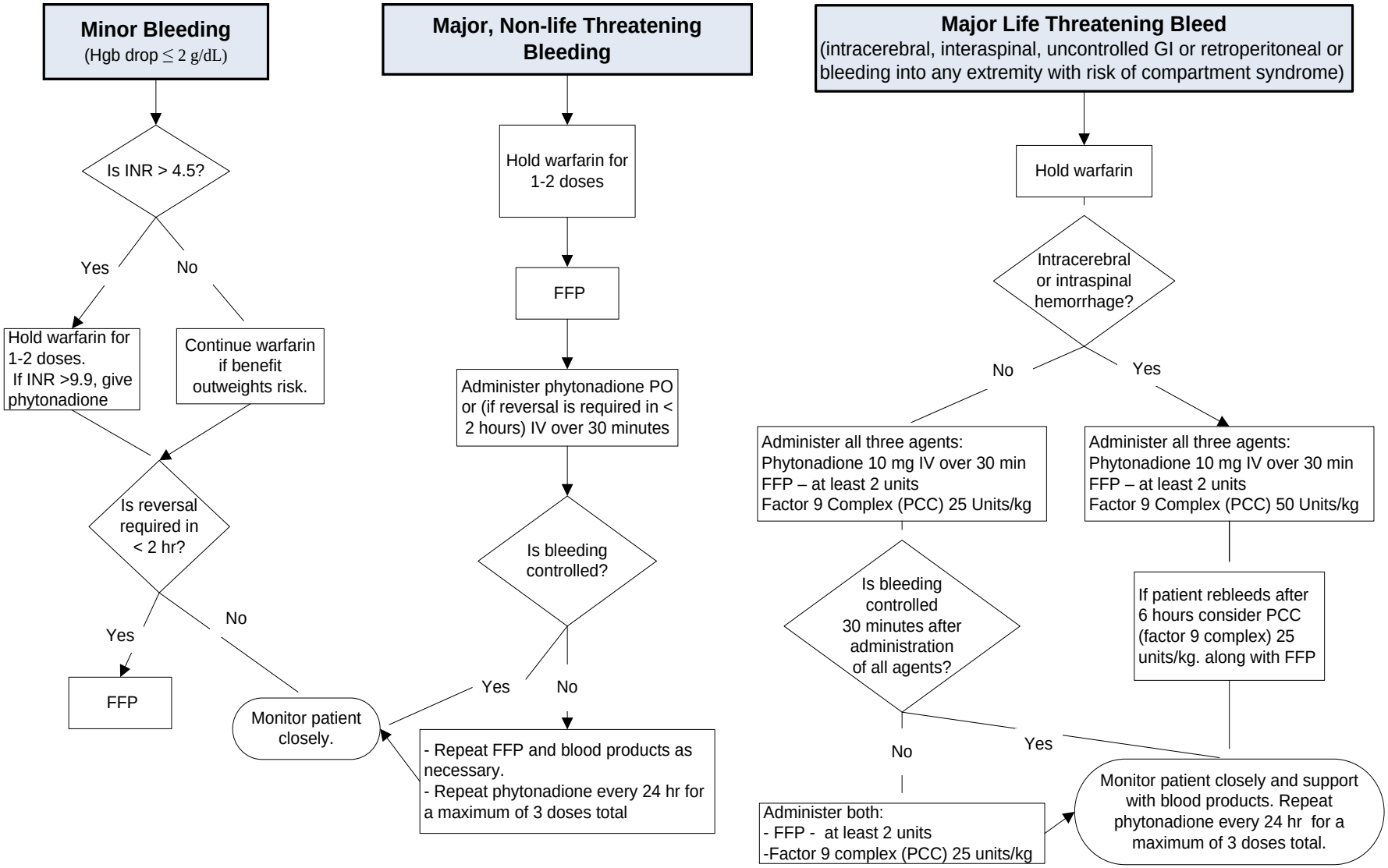
Appendix 2. Treatment of Bleeding Conditions in Patients Taking Oral Anticoagulants

Anticoagulant	Half-life	Reversal Agent / Bleeding Treatment		Comments	Lab
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 UWHC Adult Guidelines for Blood Product Transfusion)					
Apixaban	12 h	If ingestion within 3 hours, administer activated charcoal 50 g		-No clinical trials using PCC (factor 9 complex) are available -Administer PCC (factor 9 complex) at rate of 100-200 units/min	
		FFP is not indicated unless the patient has received at least 4 units of PRBCs and the INR is prolonged (i.e., hemodilution).			
		Strongly consider PCC (factor 9 complex concentrate) with at least 2 units of FFP. (Option B)			
Dabigatran	12-17 h	If ingestion within 3 hours, administer activated charcoal 50 g		Hemodialysis removes approximately 60% within 2 h	
		Consider hemodialysis for all bleeding patients treated with dabigatran, especially those with renal impairment			
		FFP is not indicated unless the patient has received at least 4 units of PRBCs and the INR is prolonged (i.e., hemodilution)		Blood products do not reverse dabigatran anticoagulation	
		For life threatening bleeds, unresponsive to other therapy consider factor 7A (Option A)		No clinical trials with factor 7A	
Rivaroxaban	5-9 h	If ingestion within 3 hours, administer activated charcoal 50 g		-No clinical trials using PCC (factor 9 complex) are available -Administer PCC (factor 9 complex) at rate of 100-200 units/min	
		FFP is not indicated unless the patient has received at least 4 units of PRBCs and the INR is prolonged (i.e., hemodilution)			
		PCC (factor 9 complex concentrate) with at least 2 units of FFP. (Option B)			
Warfarin	36-42 h	Severity of Bleeding	Treatment Measures	-High doses of phytonadione can cause difficulty in anticoagulating patients after resolution of the bleeding episode -Administer phytonadione IV over 30-60 minutes, faster administration can result in anaphylaxis	INR
		No bleeding or minor bleeding	INR 4.5 - 9.9– omit 1-2 doses		
			INR >9.9 – omit 1-2 doses, phytonadione 2.5 mg PO		
		Major, non-life threatening bleed	If ingestion within 3 hours, administer activated charcoal 50 g		
			FFP- at least 2 units		
			phytonadione (2.5 – 10 mg) PO or IV, dose dependent upon risk thromboembolism and severity of bleed		
		Life threatening bleed - excluding intracerebral or intraspinal	If ingestion within 3 hours, administer activated charcoal 50 g		
			Give each agent as soon as it is available: 1. phytonadione 10 mg IV 2. PCC (factor 9 complex) 25 Units/kg; MR x 1 if life-threatening bleeding persists beyond 30 minutes after administration 3. FFP – at least 2 units		
		Life threatening bleeding intracerebral or intraspinal	If ingestion within 3 hours, administer activated charcoal 50 g		
			Give each agent as soon as it is available : 1. phytonadione 10 mg IV 2. PCC (factor 9 complex) 50 Units/kg 3. FFP – at least 2 units		

Appendix 3. Procoagulant Algorithm for the Treatment of Bleeding Patients on Warfarin

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 UWHC Adult Guidelines for Blood Product Transfusion)

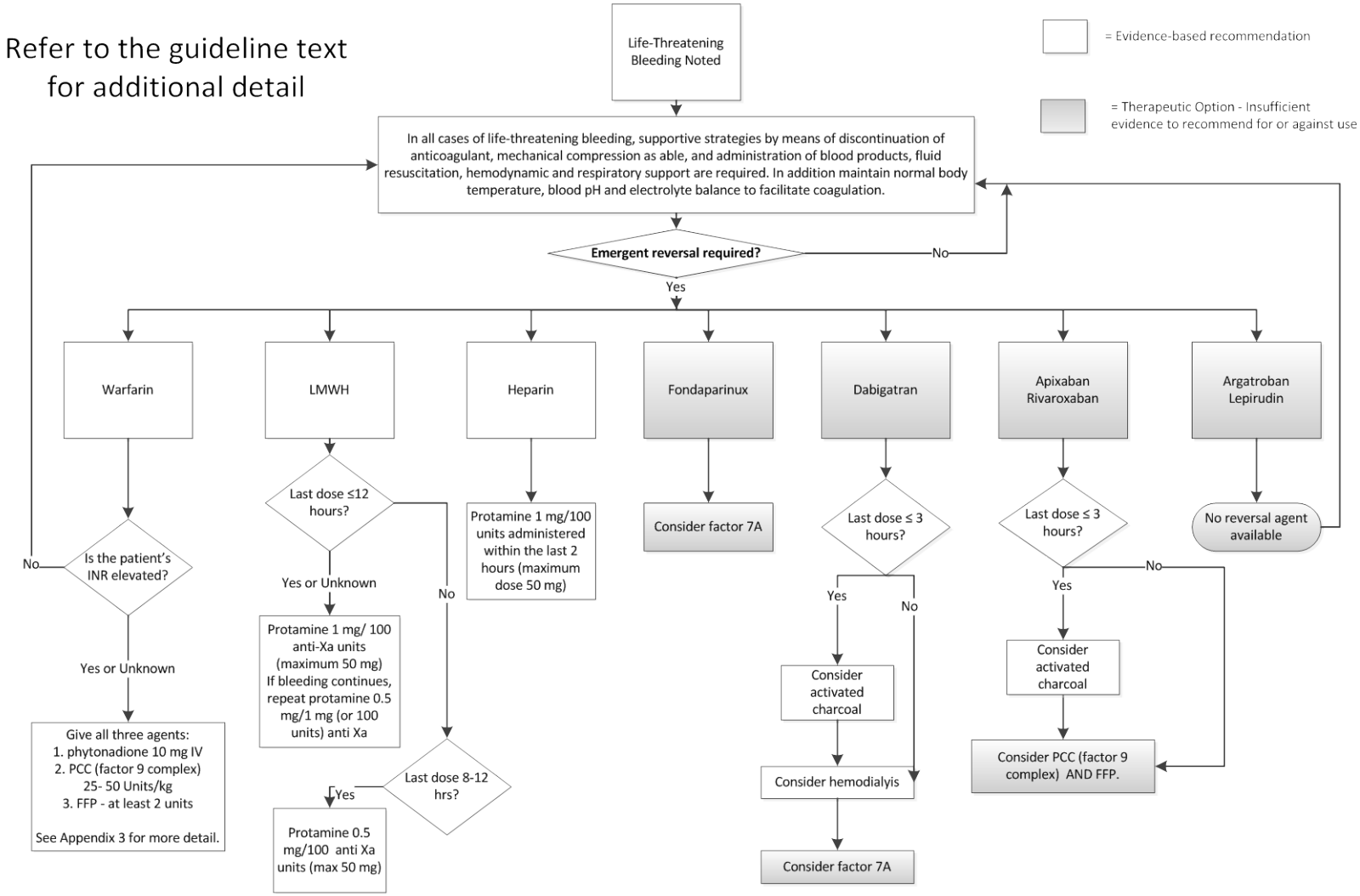
Maintain body temperature, blood pH and electrolyte balance facilitate coagulation for all patients. If applicable apply packing, dressing and/or pressure.



Appendix 4. Parenteral Anticoagulant Agent Bleeding Treatment

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 UWHC Adult Guidelines for Blood Product Transfusion)					
Argatroban IV	45 min	General supportive measures (see Option C).			aPTT Thrombin time
Fondaparinux Subcutaneous	17-21 h	For life threatening bleeds unresponsive to other measures consider factor 7A 90 mcg/kg IV (see Option D)		No clinical trials available.	anti- Xa
Heparin IV	1 - 1.5 h	Protamine 1 mg/100 units administered within the last 2 hours		- high doses of protamine can enhance anticoagulation -administer protamine over 10 minutes -protamine can cause anaphylaxis	aPTT anti Xa
Lepirudin IV	1.5 h	General supportive measures.(see Option E)			aPTT
LMWH Subcutaneous (e.g., enoxaparin, dalteparin)	3 -5 h	Time of Last Dose	Treatment Measures	-incomplete neutralization occurs with protamine -enoxaparin 1 mg is approximately 100 anti-Xa units -protamine can have an anticoagulant effect with high doses -administer protamine over 10 minutes -protamine can cause anaphylaxis	anti -Xa
		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 50 mg)		
		Dose over 8 h ago, but up to 12 h	Protamine 0.5 mg/ 100 units anti-Xa (maximum 50mg)		
		Dose > 12 h ago	Protamine may not be necessary. Consider factor 7A for life-threatening bleeding. (see Option F)		

Appendix 5. Treatment of Life-Threatening Bleeding in Patients on Anticoagulant Agents



Appendix 6. Procoagulant Treatment Associated with Specific Conditions

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)		
Intracranial hemorrhage patients requiring surgery, not on anticoagulants prior to bleed		Factor 7A 90 mcg/kg once
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 (factor 9 complex) 25 units/kg along with FFP. If bleeding persists beyond 30 min repeat dose for a maximum total dose of PCC (factor 9 complex) 50 units/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