Salem Health®
Hospitals & Clinics

Adult Reversal of Anticoagulation and Anti-platelet Agents for Life-Threatening Bleeding or Emergency Surgery Protocol

Latest P&T Review: May 2016	**Next P&T Review:** May 2018
Changes Made: Review, minor revisions, changed to Kcentra for all warfarin reversal	

Adult Reversal of Anti-platelet Agents for Life-Threatening Bleeding

Oral antiplatelet agents (aspirin, dipyridamole, prasugrel, clopidogrel, ticagrelor):

1. Discontinue anti-platelet agent
2. Desmopressin 0.3 mcg/kg (based on actual body weight) IV over 30 minutes every 12 hours for up to 48 hours total.
3. If an intervention is going to be performed, consider platelet transfusion[1]
    a. Lower risk procedure: start with 1 unit of platelets
    b. Higher risk procedure or life threatening bleeding: start with 2 units of platelets
    c. Consider risk of inducing stent occlusion if less than 3 months after bare metal stent was placed. Duration of risk longer with drug eluting stents (perhaps up to a year).

	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Onset:	1 hour	No loading dose: 3-5 days 300 mg LD: <6 hours 600 mg LD: 2-4 hours	No loading dose: 3 days 60 mg LD: 60 minutes	180 mg LD: 30-60 minutes
Metabolism	Hydrolysis	Hepatic	Hepatic	Hepatic
Elimination	100% urine	50% urine 46% feces	68% urine 27% feces	26% urine 58% feces
T ½	20-30 minutes	6 hours	7 hours	7 hours
Reversible platelet inhibition?[1]	Yes	Yes	Yes	No
Platelet recovery	7 - 10 days	7 – 10 days	7 - 10 days	3 - 5 days

1. Irreversible platelet inhibitors will interfere with platelet function for the life of the platelet (7-10 days). Circulating quantities of platelet inhibitors can continue to interfere with platelet function. Reversible platelet inhibitors can be overcome by platelet transfusions after a few half-lives.

IV antiplatelet agents: eptifibatide & abciximab & tirofiban

1. Discontinue anti-platelet agent
2. Glycoprotein IIb-IIIa inhibitors can be substantially reversed with platelet transfusion and / or
3. Desmopressin 0.3 mcg/kg IV x1 over 30 minutes

1. Infused platelets require up to 6 hours for activation**.**

Latest P&T Review: May 2016	**Next P&T Review:** May 2018
Changes Made: Review, minor revisions, changed to Kcentra for all warfarin reversal	

Adult Reversal of Anticoagulation for Life-Threatening Bleeding

Unfractionated Heparin Infusion:

1. Discontinue heparin infusion (if not already done).
2. Determine heparin infused over the last 2.5 hours (units/hour * hours infused)
3. Determine time elapsed since infusion stopped
4. See table below:

Time Elapsed Since Infusion Stopped	**Dose of Protamine (based on amount of heparin infused over the last 2.5 hours)**
Less than 30 minutes	1 mg per 100 units of heparin infused
30 to 60 minutes	0.75 mg per 100 units of heparin infused
60 to 120 minutes	0.5 mg per 100 units of heparin infused
Greater than 120 minutes	0.375 mg per 100 units of heparin infused

5. Maximum dose: 50 mg
6. Administer as a slow IV push (NTE 5 mg per minute)
7. Example: Heparin at 1,500 units per hour, stopped within the last 10 minutes.
    a. 1,500 units/hour * 2.5 hours = 3,750 units
    b. 3,750 units * 1 mg/100 units infused = 37.5 mg protamine dose
    c. Infuse over at least 8 minutes

Unfractionated Subcutaneous Heparin Injection:

1. Total dose: 1 mg of protamine per 100 units of heparin injected
2. Administer half of the dose IV at a rate not to exceed 5 mg/min. Infuse the remainder as a slow infusion over the next 8 hours.

Low Molecular Weight Heparin Subcutaneous Injection:

Protamine will at the most reverse 60-75% of the anti-Xa activity of LMWH.

1. Discontinue LMWH (if not already done)
2. Determine time from the last administered dose.
    a. If the last dose was greater than 24 hours ago, reversal is not indicated
    - Enoxaparin, less than 8 hours since the last dose
        - 1 mg of protamine per mg of enoxaparin, up to 50 mg maximum.
    - Enoxaparin, more than 8 hours, but less than 24 hours since the last dose:
        - 0.5 mg of protamine per mg of enoxaparin, up to 25 mg maximum.
    - Tinzaparin or dalteparin: give 1 mg of protamine for each 100 units of tinzaparin or dalteparin administered. Maximum dose: 50 mg.
3. Check a PTT in 2-4 hours
4. If PTT remains greater than 40 or if bleeding is not controlled, give additional 0.5 mg of protamine per mg of enoxaparin (or 100 units of tinzaparin / dalteparin), up to 25 additional mg.

Direct Thrombin Inhibitors: dabigatran:

1. Discontinue dabigatran.
2. Assess timing of the last dose taken – if within the last 2 hours, activated charcoal, 50 grams PO once.
3. Check a STAT PTT (lab draw)
4. If the PTT is less than 40, it is unlikely that dabigatran (or any other DTI) is contributing to bleeding.
5. If the PTT is greater than 40 and life threatening bleeding is present:
    a. Idarucizumab (Praxbind) 5 grams IV x1
6. Support with surgery, FFP, cryoprecipitate or platelets as needed if bleeding persists. A PTT may be rechecked if necessary to verify the activity of the idarucizumab.

Direct Thrombin Inhibitors: bivalirudin, argatroban:

1. Discontinue bivalirudin or argatroban
2. Check a STAT PTT (lab draw)
3. If the PTT is less than 40, it is unlikely that a direct thrombin inhibitor (DTI) is contributing to bleeding.
4. If the PTT is greater than 40 and life threatening bleeding is present:
    a. FEIBA (Factor VIII Inhibitor Bypassing Activity – "activated PCC")* 25 units/kg
5. Do NOT recheck a PTT after administration of FEIBA because the lab value is not effectively reversed, even if the bleeding ceases.
6. For failure to control bleeding:
    a. Repeat dose of IV FEIBA 25 units/kg
    b. May consider rFVIIa (NOVOSEVEN) 40 mcg/kg IV once

* Notes about FEIBA:

- The use of FEIBA (an "activated" PCC) may be associated with a higher risk of thrombosis compared to non-activated PCCs, especially in higher doses. Monitor closely for arterial and venous thrombosis.
- Monitoring: tests used to monitor hemostatic activity, such as aPTT, are not useful for monitoring response with anti-inhibitor coagulant complex. Dosing to normalize this value may result in DIC.
- Following reconstitution, infusion must be completed within 3 hours.
- Avoid concomitant use of FEIBA with Antifibrinolytic Agents

Injectable Factor Xa Inhibitor: fondaparinux

1. Discontinue fondaparinux
2. Give 3 factor, un-activated PCC (Profilnine)[1] 50 units/kg IV x one dose + 2 units of FFP
3. For failure to control bleeding:
    a. rFVIIa (NOVOSEVEN) 40 mcg/kg IV once

Oral Factor Xa Inhibitors: rivaroxaban & apixaban

1. Discontinue rivaroxaban or apixaban
2. Determine time of the last dose.
    a. If last dose of apixaban was within 6 hours, give charcoal (can reduce AUC by up to 27% at 6 hours).
    b. If rivaroxaban, activated charcoal may be useful for rivaroxaban within 2 hours of the last dose, but this has been less concretely established.
3. Check a STAT INR (lab draw)
4. If the INR is less than 1.5, it is ***unlikely*** that rivaroxaban or apixaban are contributing to bleeding.
5. Give 3 factor, un-activated PCC (Profilnine)[1] 50 units/kg IV x one dose + 2 units of FFP
7. Do NOT recheck an INR after administration of Profilnine because the lab value is not effectively reversed, even if the bleeding ceases.
6. For failure to control bleeding:
    a. Consider rFVIIa (NOVOSEVEN) 40 mcg/kg IV once

1. In a study of 3 vs. 4 factor PCC, the 3 factor PCC (Profilnine) increased endogenous thrombin generation better than 4 factor PCC. One postulated reason for this is that the 4 factor PCC contains heparin.

Warfarin: Reversal for Life Threatening Bleeding, Hemodynamic Instability or Emergency Surgery (within 4 hours)

1. Discontinue warfarin
2. Check a STAT INR (lab draw)
3. Give Vitamin K 2 mg IV now[1]
4. Assess for recent history of Heparin Induced Thrombocytopenia (Kcentra contains some heparin).

- *If a recent history of HIT is **absent** and INR is greater than 1.5:*
    a. Kcentra (4 factor PCC) IV once at 100 units/minute (usually 10 to 50 minutes)

INR	Kcentra dose
1.5 to 4	25 units/kg, maximum 2,500 units
4.1 to 6	35 units/kg, maximum 3,500 units
Greater than 6	50 units/kg, maximum 5,000 units

    b. Check a STAT INR (lab draw) 30 minutes after PCC is finished infusing.

- *If a recent history of HIT is **present** and INR is greater than 1.5:*
    a. If INR greater than 1.5, life threatening bleeding is present and a recent history of HIT is *present*, give 3 factor, un-activated PCC (Profilnine) IV x one dose + 2 units of FFP

INR	Profilnine dose
1.5 to 4	25 units/kg, maximum 2,500 units
4.1 to 6	35 units/kg, maximum 3,500 units
Greater than 6	50 units/kg, maximum 5,000 units

    b. Check a STAT INR (lab draw) 30 minutes after the Profilnine is finished infusing

5. Failure to control bleeding (and/or INR remains greater than 1.5):
    a. Give additional units of FFP as needed, recheck STAT INR 30 minutes after FFP is finished infusing

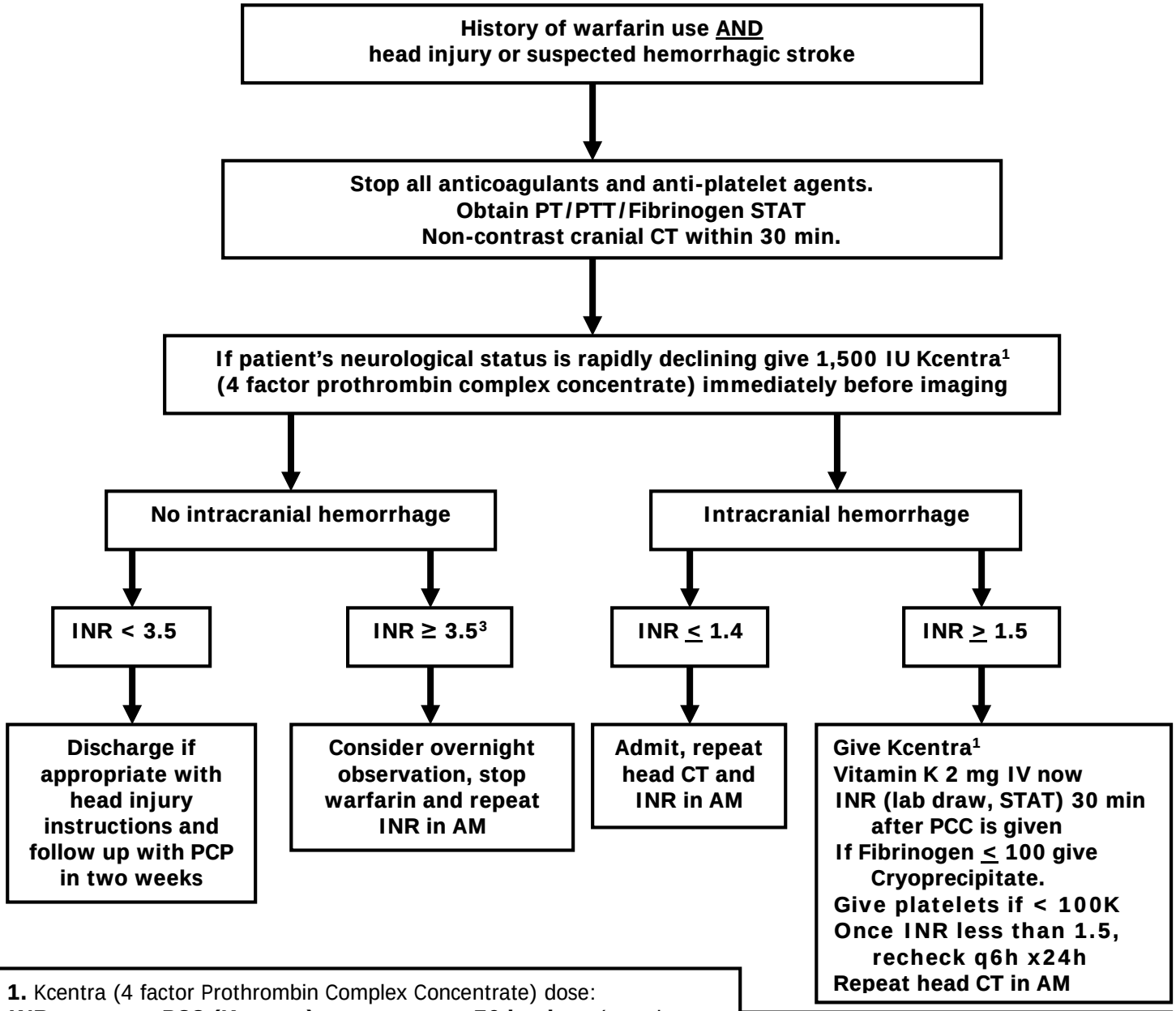
INR	FFP dose
1.4 to 2	2 to 4 units
2.1 to 3	4 to 6 units
Greater than 3.1	8 units

    b. Check platelets and fibrinogen and replace as needed
    c. For head injury, consider a dose of rFactor VIIa (NOVOSEVEN) 20 mcg/kg IV once
6. Repeat INR q6h until INR stable and within range x2 and not bleeding. May check more frequently if indicated.

1. 2 mg of Vitamin K is shown to reverse elevated INR values as well as 5 or 10 mg given IV.

Latest P&T Review: May 2016	**Next P&T Review:** May 2018
Changes Made: Review, minor revisions, changed to Kcentra for all warfarin reversal	

Algorithm for treatment of suspected intracranial hemorrhage in patients on warfarin therapy



1. Kcentra (4 factor Prothrombin Complex Concentrate) dose:

INR	PCC (Kcentra) Dose per Kg	70 kg dose (round to whole vial)
1 – 1.4	not recommended	not recommended
1.5 – 4	~25 IU/kg	~2,000 IU (~4 vials)
4.1 – 6	~35 IU/kg	~2,500 IU (~5 vials)
6.1 and over	~50 IU/kg	~3,500 IU (~7 vials)

1) Telemetry monitoring, pulse oximetry, and vitals Q15 minutes X 2 hours required ***> Limited to use in Critical Care setting <***
2) Patients with PE within 6 months should not be given PCC
3) Patients with INR over 10 should be given PCC only after discussion with trauma surgeon on call and pharmacist about concern for DIC
4) **Contains heparin:** patients with a history of HIT should not be given Kcentra – refer to Profilnine dosing for Life Threatening Bleeding

2. If PCC is given: check INR 30 minutes after end of infusion.
If FFP is given, check INR 30 minutes after the end of the FFP infusion.
If this INR is not less than 1.5, give FFP[4] and consider a dose of rFactorVIIa (NOVOSEVEN), 20 mcg/kg IV x1.

3. Patients with an INR greater than 9: Hold warfarin and consider Vitamin K 2 mg IV or PO (NOT subcutaneously)

4. Recommended initial dosing of FFP (Fresh Frozen Plasma)

INR	FFP
1.5 – 2.0	2 – 4 units
2.1 - 3.0	4 – 6 units
> 3.1	give 8 units

and recheck INR in 30 minutes

Give each unit over 5 - 15 min

Life Threatening Bleeding with Liver Failure or Cirrhosis (and no specific medication)

1. Check a STAT INR and platelets (lab draw)
2. Replace platelets as necessary to keep greater than 100,000/mm^3
3. Assess for hepato-renal syndrome
    a. If serum creatinine greater than 1.5, give DDAVP 0.3 mcg/kg IV x1
4. Give Vitamin K 2 mg IV_1
5. Give 3 factor, un-activated PCC (Profilnine) IV x one dose

INR	PCC Dose per Kg	70 kg patient dose
1.5 to 2	~ 15 IU/kg	~1050 IU (2 vials)
2.1 to 3	~ 25 IU/kg	~1750 IU (2 vials)
3.1 to 5	~ 30 IU/kg	~2100 IU (2 vials)
Greater than 5.1	~ 35 IU/kg	~2450 IU (2 vials)

6. Give 2 units of FFP
7. Check a STAT INR (lab draw) 30 minutes after the end of a Profilnine infusion or 1 hour after the end of a FFP infusion.
8. If INR remains greater than 1.5 and bleeding is not controlled, give additional FFP, consider dose below:
    a. INR: 1.5 to 2 2 to 4 units of FFP
    b. INR: 2.1 to 3 4 to 6 units of FFP
    c. INR: 3.1 or greater 8 units of FFP
9. Check a STAT INR 30 minutes after the end of the FFP infusion. Repeat INR q6h until INR stable and within range x2 and not bleeding. May check more frequently if indicated.
10. Failure to reduce the INR to less than 1.5: give 2 additional units of FFP and additional Vitamin K

Life Threatening Bleeding NOT Associated with a Particular Agent:

1. See Massive Transfusion Protocol

1. 2 mg of Vitamin K is shown to reverse elevated INR values as well as 5 or 10 mg given IV.

Latest P&T Review: May 2016	**Next P&T Review:** May 2018
Changes Made: Review, minor revisions, changed to Kcentra for all warfarin reversal	

Recombinant Factor VIIa (rFVIIa)

Restricted to the following indications:

For non-hemophilia use, rFactor VIIa is limited to the following indications:

- Non-traumatic intracranial bleeding (excluding subarachnoid hemorrhage)
    - Less than 4 hours from onset
- Isolated traumatic head injury with evidence of expanding bleeding
- Retroperitoneal bleeding (only after significant clotting factor replacement)
- Surgical patient rescue therapy (only after significant clotting factor replacement)
    - Includes cardiac surgery, aortic surgery, hepatic resection and spinal surgery
- Postpartum hemorrhage or post hysterectomy hemorrhage (only after significant clotting factor replacement)
- Severe multiple trauma (ongoing bleeding and coagulopathy despite surgical intervention and greater than 10 units of blood transfused within 6 hours)
- Hepatic failure with GI bleeding or a pending invasive procedure (only after significant clotting factor replacement)

Significant clotting factor replacement means:

- 6 units (or 20 ml/kg) of fresh frozen plasma OR
- 6 units of platelets x2 if platelet count is less than 50,000 OR
- 10 bags of cryoprecipitate x2 if fibrinogen is low OR
- Clotting factor replacement was not a feasible alternative because of time constraints

Dosing

- ICH unrelated to an anticoagulant: 20 mcg/kg (up to 100 kg) IV once
- ICH related to an anticoagulant, second line therapy: 20 mcg/kg (up to 100 kg) IV once
- Hemophilia: 90 mcg/kg IV once
- Re-dosing may be done only after consultation with the hematologist on call.

PCC Tipsheet

Salem Healthkeeps three different products that go by common name of "PCC" or "Prothrombin Complex Concentrates." The three are:

- Profilnine (3 factor PCC)
    - Name on the MAR: PCC for Urgent Surgery (Prothrombin Complex Concentrates Profilnine)
- Kcentra (4 factor PCC)
    - Name on the MAR: Prothrombin Complex Concentrates (Kcentra)
- FEIBA (4 factor "activated" PCC)
    - Name on the MAR: anti-inhibitor anticoagulant complex FEIBA – Activated PCC)

Profilnine (3 factor PCC) is used for urgent warfarin reversal for patients with HIT or heparin allergy. Profilnine should be:

- Given no faster than 10 mL per minute to avoid profound hypotension
- Given with IV Vitamin K (phytonadione) to keep the INR down for more than a few hours
- Given with 2 units of FFP to provide factor VII (which Profilnine lacks in a meaningful amount)
- An INR should be checked 30 minutes after the infusion is completed (for warfarin reversal)

Profilnine is the most economical (of the PCC products) "reversal" for warfarin-treated patients.

Kcentra (4 factor PCC) is used for warfarin reversal for patients wtih life-threatening bleeding or needs to be reversed urgently for surgery. Kcentra should be:

- Given over 10 to 30 minutes depending on size of the dose (100 units/min)
- Given with IV vitamin K (phytonadione) to keep the INR down for more than a few hours
- Given ***INSTEAD OF*** FFP because Kcentra contains factor VII and additional blood products should not be needed.
- Contains heparin (watch for HIT or "Heparin Allergies"
- An INR should be checked 30 minutes after the infusion is completed

Kcentra has FDA approval for warfarin reversal for life threatening bleeding, other PCCs do not.

FEIBA (4 factor PCC, includes activated factor VII) is used for direct thrombin inhibitor (DTI) reversal. The available, small amounts of data indicate that it is more useful than the other PCCs for medications such as argatroban or bivalirudin (ANGIOMAX) induced bleeding. FEIBA (for DTI-induced bleeding) should be:

- Given over 30 minutes
- Given ***WITHOUT*** Vitamin K or FFP: neither of these improves the action to reverse bleeding
- Given if the PTT is greater than 40 (a PTT less than 40 means that the DTI probably is not contributing to the bleeding)

An INR should NOT be checked after infusion: the drug should decrease bleeding but it will ***NOT*** correct the INR

Latest P&T Review: May 2016	**Next P&T Review:** May 2018
Changes Made: Review, minor revisions, changed to Kcentra for all warfarin reversal	