

## Session Title: Reversal strategies for patients with acute medical and intracranial bleeding

### Objectives

- Discuss the indications and clinical considerations for anticoagulation reversal in the acute care setting.
- Describe the clinical pharmacology of available anticoagulants and reversal agents.
- Evaluate potential agents and strategies for reversal of anticoagulants, including warfarin, unfractionated heparin, low molecular weight heparin, pentasaccharides, direct thrombin inhibitors, and direct factor Xa inhibitors.

**General Strategy:** Step 1 - D/C the drug; Step 2 - Antidote; Step 3 - Factor Replacement; Step 4 - Adjunctive therapy

### Recommended Readings

1. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage ([Frontera 2016](#))
2. Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants ([Conway 2017](#))
3. Laboratory testing in the era of direct or non-vitamin K antagonist oral anticoagulants ([Favaloro 2015](#))
4. Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants ([Tomaselli 2017](#))

### Direct Thrombin Inhibitors

1. Step 1 - D/C the drug
2. Step 2 - Antidote
  - a. Idarucizumab first studied in 110 healthy male volunteers 18-45 yrs ([Glund, Thromb Haemost 2015](#))
    - i. No effect on coagulation/endogenous thrombin potential (ETP) in absence of dabigatran
  - b. Randomized, placebo-controlled, double-blind phase I study to assess safety, tolerability, and efficacy of idarucizumab on reversal of dabigatran-induced anticoagulation ([Glund, Lancet 2015](#))
    - i. Volunteers aged 18-45 yrs randomized into 4 idarucizumab groups (1 g, 2 g, 4 g, 5 g)
    - ii. The diluted thrombin time (dTT), ECT, TT, aPTT, and ETP were assessed
    - iii. 47 male volunteers. Immediate and sustained reversal of dabigatran-associated increases in ECT, aPTT, and TT were noted with idarucizumab doses  $\geq 2$  gm
    - iv. Did not measure the effect of idarucizumab on bleeding patients
    - v. Funded by Boehringer Ingelheim
  - c. REVERSal Effects of Idarucizumab in Patients on Active Dabigatran (RE-VERSE AD™)
    - i. Methodology for prospective, phase 3 trial ([Pollack, Thromb Haemost 2015](#))
    - ii. Interim analysis published in 2015 ([Pollack, NEJM 2015](#))
      1. 51 pts had serious bleeding (group A) and 39 required urgent procedure (group B)
      2. No control group
      3. Idarucizumab seems to reverse laboratory markers of anticoagulation from dabigatran rapidly and completely, including dTT and ECT
        - a. Not all institutions have these assays available
      4. Dose that seems to work best is 5 gm given IV (two-2.5 gm infusions)
      5. Median investigator-reported time to cessation of bleeding was 11.4 hrs
      6. 21 of the 90 patients had 'serious adverse effects' including 5 thrombotic events (direct association with idarucizumab unclear)
      7. Key limitation: only 75% of patients had elevated thrombin times prior to idarucizumab = cohort may not have needed the drug for reversal
      8. Funded by Boehringer Ingelheim
    - iii. Full trial published in 2017 ([Pollack, NEJM 2017](#))

1. 503 patients (301 in Group A and 202 in Group B)
  2. Primary outcome: maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after administration of idarucizumab
  3. No control group
  4. Authors reported almost universal and complete binding of dabigatran as evidence by minimal unbound dabigatran concentrations after idarucizumab
  5. 9 patients required more than the 5 gm dose of idarucizumab
  6. 10% of patients in the full cohort had no laboratory evidence of dabigatran's presence prior to administration of idarucizumab (normal ECT and/or dTT).
  7. Large discrepancy between clinically relevant bleeding cessation times in the interim (11.4 hrs) versus full analyses (2.5 hrs).
    - a. It seems in the full analysis, >55% of Group A were excluded from time-to-bleeding assessment. Reasons for exclusion included no cessation of bleeding within 24 hours or the bleeding location could not be identified. This change in reporting favors idarucizumab.
  - d. Though idarucizumab reverses lab markers of dabigatran, it does not repair the damaged vessel. Cases of sustained bleeding after idarucizumab have been reported ([Alhashem et al. 2017](#); [Steele et al. 2017](#))
  - e. Approved 5 gm dose may not be sufficient in all cases, particularly in patients with renal failure who are unable to clear dabigatran. ([Simon et al. 2017](#))
  - f. Impaired renal function associated with increased exposure/decreased clearance of idarucizumab; dabigatran also cleared more slowly with decreased renal function ([Glund et al. 2017](#))
3. Step 3 - Factor Replacement
- a. Single-center, randomized, placebo-controlled, crossover study evaluated 4F-PCC ([Eerenberg 2011](#))
    - i. 12 healthy male volunteer received 150 mg of dabigatran twice a day for 2.5 days
    - ii. Patients received one additional dose and then infusion of 4F-PCC (50 U/kg) or placebo
    - iii. 4F-PCC did not reverse the prolongation of aPTT, ECT, and TT due to dabigatran
  - b. Randomized, crossover study ([Marlu 2012](#))
    - i. 10 healthy, white, male patients, ages 18-45 yrs administered dabigatran 150 mg X 1
    - ii. Blood samples drawn 2 hrs post-administration to represent peak anticoagulant activity
    - iii. 3 reversal agents tested were rFVIIa, aPCC, and 4F-PCC
    - iv. Although 4F-PCC increased ETP, only rFVIIa and aPCC corrected the altered lag-time
  - c. Healthy volunteers received dabigatran 150 mg orally every 12 hours for 5 days ([Arellano-Rodrigo 2015](#))
    - i. rFVIIa equal to 270 µg/kg, aPCC at 75 U/kg, and 4F-PCC at 50 IU/kg spiked into blood samples
    - ii. While rFVIIa or aPCC partially improved all the parameters, 4F-PCC did not modify the prolonged aPTT observed after dabigatran treatment
  - d. Prior to the availability of dabigatran's specific antidote (idarucizumab), 14 patients from a prospective cohort were treated with aPCC for major bleeding with 30-day follow-up ([Schulman et al. 2017](#))
    - i. Safety outcomes were arterial or venous thromboembolism (VTE) or death
    - ii. Comparison made with 28 historic cases treated with supportive care
    - iii. Effectiveness of aPCC was assessed as good in 9 (64%), moderate in 5 (36%), and poor in none
    - iv. No reported thromboembolic events and one death
  - e. Based on the available, higher quality data, **only aPCC, and possibly rFVIIa, may be effective in reversing anticoagulation parameter alterations secondary to dabigatran.**
    - i. All three ex-vivo studies enrolled healthy volunteers and tested against therapeutic levels of dabigatran. The studies attempted to use doses of factor similar to what would be used in actual patients, but may not be generalizable from ex-vivo extrapolation. Correction of

anticoagulation parameters may not translate into cessation of clinical bleeding and these treatments have been historically associated with thromboembolic complications.

4. Step 4 - Adjunctive therapy
  - a. Charcoal
    - i. Theoretically binds dabigatran
    - ii. Probably not helpful in GI bleeding, patient already has life-threatening bleeding
    - iii. May be helpful if patient overdoses and presents to hospital within the following 12 hours
  - b. HD/CVVH
    - i. Intermittent HD removes dabigatran effectively but is not always available and requires a hemodynamically stable patient ([Liesenfeld 2016](#)).
      1. Rebound in dabigatran concentration may occur upon cessation of HD. ([Chai-Adisaksopha et al. 2015](#))
    - ii. CVVHD does not reach comparable elimination rates and is not fast enough to prepare for urgent interventions in patients with high bleeding risks.
    - iii. Rebound dabigatran concentrations have also been reported after idarucizumab administration in the setting of severe renal failure. ([Stecher et al. 2017](#))

### Factor Xa Inhibitors

1. Step 1 - D/C the drug
2. Step 2 - Antidote
  - a. Andexanet alfa not yet approved in the U.S (phase III clinical trials). It is a modified recombinant human factor Xa decoy protein that sequesters factor Xa inhibitors to restore endogenous FXa activity.
  - b. In two randomized, double-blind, placebo-controlled parallel trials of healthy volunteers, ANNEXA-A and ANNEXA-R evaluated adults aged 50-75 years assigned apixaban or rivaroxaban, respectively. ([Siegal, NEJM 2015](#))
    - i. Subjects were given andexanet as either bolus only (400 mg for apixaban/800 mg for rivaroxaban) or bolus plus a 120-minute infusion (4 mg/min for apixaban or 8 mg/min for rivaroxaban).
    - ii. Andexanet decreased anti-FXa activity in both apixaban and rivaroxaban compared with placebo regardless of bolus and/or infusion regimen ( $p < 0.001$ ) for up to 2 hours
    - iii. No serious adverse events reported, though andexanet recipients did have non-neutralizing antibody development (17% compared with 2% placebo).
    - iv. Funded by Portola Pharmaceuticals (maker of andexanet)
  - c. Interim report of an ongoing multicenter, prospective, open-label, single-group study of patients with acute major bleeding ([Connolly et al. 2016](#))
    - i. Preliminary results of the Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXa Inhibitors (ANNEXA-4) investigated 67 patients with acute major bleeding who had received apixaban, rivaroxaban, edoxaban, or enoxaparin within 18 hours of enrollment
    - ii. Bleeding locations were GI (49%), intracranial (42%), and other (9%)
    - iii. Anti-FXa activity decreased in pts on rivaroxaban after andexanet bolus (89%, 95% CI 58-94%) and infusion (86%, 95% CI 55-93%). Anti-FXa activity decreased in pts on apixaban after andexanet bolus (93%, 95% CI 87-94%) and infusion (92%, 95% CI 85-94%).
    - iv. Clinically, excellent or good hemostasis was achieved in 79% (31 excellent, 6 good)
    - v. Unlike the ANNEXA-A and ANNEXA-R trials, patients did not experience any infusion-related reactions nor antibody development.
    - vi. 18% had thrombotic events (7 DVT, 5 strokes, 1 PE, 1 MI).
    - vii. Most safety events occurred between follow-up days 4 and 30.

- viii. No control group.
  - ix. Funded by Portola Pharmaceuticals
  - x. This study did not include patients on edoxaban or enoxaparin in their interim analyses; betrixaban was not FDA approved during this study period. For this reason, and for need of additional information on manufacturing practices, the [FDA did not approve the Biologics License Application in August of 2016](#).
- d. Ciraparantag noncovalently hydrogen binds to and inhibits target site binding of multiple anticoagulants, including FXa inhibitors, DTIs, and heparins. Currently in phase II trials. Further information expected with [placebo-controlled, single-blind study of rivaroxaban reversal with ciraparantag actively recruiting](#).
- i. In a preclinical in vitro study, ciraparantag did not reverse FXa activity unlike andexanet that had dose-dependent effects. Factor X and IX activity, aPTT, and thrombin generation potentiated by ciraparantag, suggesting potential procoagulant activity ([Lu et al. 2014](#))
  - ii. Randomized, double-blind, placebo-controlled, safety, tolerability, pharmacokinetic, and pharmacodynamic trial examined ciraparantag administration after single-dose edoxaban compared with ciraparantag alone. ([Ansell et al. 2017](#))
    - 1. Doses ranging from 100-300 mg restored fibrin diameters to baseline levels 30 minutes after ciraparantag; no evidence of procoagulant activity
3. Step 3 - Factor Replacement
- a. Randomized, placebo-controlled, crossover study of 12 healthy male volunteers - rivaroxaban dosed 20 mg BID significantly increased the PT and decreased the ETP. ([Eerenberg et al. 2011](#))
    - i. PT and ETP normalized after administration of 50 units/kg 4F-PCC and persisted 24 hours.
    - ii. In the 4F-PCC group, the rise in ETP over 24 hours to greater than 100 percent baseline ETP suggested that there may have been an excess of thrombin generation.
  - b. Single-center, randomized, double-blind, placebo-controlled crossover study. ([Cheung et al. 2015](#))
    - i. 6 healthy male volunteers administered apixaban 10 mg BID for 7 doses to reach steady state.
    - ii. 3 hours after the last apixaban dose, subjects randomized to receive 4F-PCC in doses of 25 units/kg or 37.5 units/kg or normal saline placebo.
    - iii. At 15 minutes after 4F-PCC administration, both doses increased ETP ( $p=0.06$  for 37.5 units/kg,  $p=0.03$  for 25 units/kg) and significantly decreased PT ( $p<0.01$  for both).
    - iv. These effects were sustained at 24 hours compared with placebo.
  - c. Randomized, crossover, ex vivo study of 10 healthy male volunteers ([Marlu et al. 2012](#))
    - i. rFVIIa at doses equating 20, 60, and 120 units/kg; aPCC at doses equating 20, 40, 80, and 160 units/kg; and 4F-PCC at doses equating 12.5, 25, and 50 units/kg after a single dose of rivaroxaban 20 mg.
    - ii. Both 4F-PCC and aPCC, but not rFVIIa, affected quantitative parameters to return ETP-AUC to near baseline and correct thrombin peak.
    - iii. Kinetic parameters TTP and LT were best affected by rFVIIa and aPCC.
    - iv. aPCC only agent to affect both quantitative (ETP-AUC, peak) and kinetic (TTP, LT) parameters
    - v. The higher concentrations of 4F-PCC and aPCC overcorrected the ETP-AUC from baseline and may suggest excess thrombin generation.
    - vi. Similar findings in an in vitro apixaban study ([Martin et al. 2015](#))
  - d. Single-center, ex vivo study of 6 healthy volunteers. ([Halim et al. 2014](#))
    - i. 2- to 4-times supratherapeutic maximal concentrations of edoxaban added to 15 whole blood sample aliquots per volunteer.
    - ii. After incubation, aPCC or rFVIIa at concentrations corresponding to therapeutic doses of 50 and 100 units/kg and 40 and 90 units/kg, respectively, were added to the aliquots.

- iii. Both aPCC and rFVIIa nearly normalized aPTT, PT, and extrinsic anti-FXa activity to baseline. Intrinsic FXa activity was slightly improved but not normalized.
  - e. **Given the paucity of high quality studies for coagulation factor use in patients on FXa inhibitors, either aPCC or 4F-PCC are reasonable to consider for these patients in the absence of antidotes.** aPCC and 4F-PCC doses between 25 units/kg and 50 units/kg may be sufficient.
4. Step 4 - Adjunctive therapy
    - a. Charcoal
      - i. Effective at reducing rivaroxaban absorption at least 8 hours post-dose ([Ollier et al. 2017](#))
      - ii. Probably not helpful in GI bleeding, patient already has life-threatening bleeding
      - iii. May consider if patient overdoses and presents to hospital within the following 8+ hours

## Warfarin

1. Step 1 - D/C the drug
2. Step 2 - Antidote
  - a. Vitamin K (phytonadione) remains a mainstay of treatment for reversing warfarin.
  - b. Vitamin K effects delayed (even IV); initial INR reduction with IV takes 6 to 8 hours ([Kalus 2013](#))
  - c. Vit K alone not sufficient for rapid reversal; ICH pts at risk of experiencing hematoma expansion early on after the initial bleed. ([Brott et al. 1997](#); [Kazui et al. 1996](#); [Huttner et al. 2006](#))
  - d. Recommended dose/route: 5-10 mg IV ([Hemphill et al. 2015](#); [Holbrook et al. 2012](#))
  - e. Infusion rate should not exceed 1 mg/minute to minimize the risk of anaphylactoid reactions; many institutions dilute a 10 mg IV vitamin K dose in 50 or 100 mL of 0.9% sodium chloride.
  - f. Oral onset time too long in emergent cases, subcutaneous associated with erratic and unpredictable absorption, and IM may cause bleeding and hematoma formation at the injection site. ([Lubetsky et al. 2003](#); [Crowther et al. 2002](#); [Watson et al. 2001](#))
3. Step 3 - Factor Replacement
  - a. Fresh Frozen Plasma
    - i. Fresh frozen plasma (FFP) is administered at doses ranging from 10-20 mL/kg for the reversal of warfarin-associated ICH and other conditions. ([Frontera et al. 2016](#); [Brophy et al. 2015](#))
    - ii. FFP provides exogenous source of all clotting factors and proteins found in blood
    - iii. FFP risks: transfusion-related acute lung injury, infusion reactions, hypocalcemia, infectious complications, and transfusion-associated circulatory overload. ([Pandey and Vyas 2012](#))
    - iv. INR of FFP estimated at 1.6; difficult for FFP alone to decrease patient's INR to  $\leq 1.5$
    - v. Administration takes up to several hours in standard clinical practice
    - vi. Concomitant vitamin K administration critical to correct INR
    - vii. FFP's utility further limited due to potential procurement delays (e.g., checking for blood compatibility, thawing) ([Lee et al. 2006](#); [Goldstein et al. 2006](#))
  - b. Four-Factor Prothrombin Complex Concentrate (4F-PCC)
    - i. Available in Europe since 1996; approved in U.S. in 2013; contains concentrated source of inactivated coagulation factors II, VII, IX, and X
      1. Faster INR reversal compared to FFP ([Goldstein et al. 2015](#); [Sarode et al. 2013](#))
      2. Package insert dosing of 4F-PCC for urgent VKA reversal recommends 25-50 units/kg of factor IX (maximum weight of 100 kg) based on the patient's body weight and INR
      3. Concomitant IV vitamin K 5-10 mg to maintain coagulation factor levels to prevent a rebound INR elevation ([Sin et al. 2016](#))
      4. Currently no robust safety/effectiveness evidence of repeat 4F-PCC dosing
      5. If INR  $\geq 1.4$  after 4F-PCC, consider further correction with FFP ([Frontera et al. 2016](#))
    - ii. 4F-PCC vs. FFP ([Sarode et al. 2013](#))

1. 202 patients randomized to receive 25-50 units/kg of 4F-PCC (n=98) or 10-15 mL/kg of FFP (n=104) for urgent VKA reversal in acute major bleeding
2. At 30 minutes after infusion, 4F-PCC was deemed superior to FFP in achieving an INR  $\leq 1.3$  (62.2% versus 9.6%; difference, 52.6%; 95% CI, 39.4 to 65.9)
- iii. 4F-PCC vs. FFP ([Steiner et al. 2016](#)) - INCH trial
  1. Randomized trial comparing 30 units/kg of 4F-PCC (n=27) with 20 mL/kg of FFP (n=23) for VKA reversal specifically in patients with ICH
  2. At 3 hours after start of treatment, more patients in 4F-PCC group achieved INR  $\leq 1.2$  when compared to the FFP group (66.7% versus 8.7%; OR, 30.6; 95% CI, 4.7 to 197.9).
  3. At 3 hours, mean hematoma expansion was lower in the 4F-PCC group (9.7 mL versus 23.7 mL; difference, 16.9 mL; 95% CI, 2.5 to 31.3).
  4. 5 deaths due to hematoma expansion within 48 hours of treatment (all FFP)
- iv. Pooled data from an international registry found equivalent adjusted risk of mortality in ICH patients who received either a 3- or 4-factor PCC (n=585) versus FFP (n=377) alone ([Parry-Jones et al. 2015](#))
- v. Multicenter retrospective cohort study of spontaneous ICH patients associated with VKA use (n=1176) found achievement of INR  $< 1.3$  within 4 hours was associated with lower rates of hematoma expansion (OR, 0.27; 95% CI, 0.15 to 0.43) ([Kuramatsu et al. 2015](#))
- vi. Fixed dosing (not validated in large clinical trials)
  1. Proposed benefits include cost-savings and minimizing delays. ([Gorlin et al. 2017](#))
  2. Doses of 1000, 1500, or 2000 units effective at INR correction. ([Klein et al. 2015](#); [Hirri and Green 2014](#); [Khorsand et al. 2012](#); [Khorsand et al. 2011](#); [Varga et al. 2013](#))
  3. One study in patients with intracranial bleeding demonstrated a fixed dosing strategy of 1000 units was not as effective in achieving an INR  $\leq 1.5$ . ([Abdoellakhan et al. 2017](#))
  4. Fixed weight-based doses of 25 units/kg and 30 units/kg may be effective. ([Appleby et al. 2017](#); [Steiner et al. 2016](#))
- c. Other Concentrated Coagulation Factor Products
  - i. 3F-PCC, activated prothrombin complex concentrate (aPCC), and recombinant activated factor VII (rFVIIa) not currently FDA approved for this indication.
  - ii. rFVIIa not recommended; aPCC and 3F-PCC have limited data and should only be considered in absence of 4F-PCC availability
4. Step 4 - Adjunctive therapy
  - a. Not many adjunctive options for warfarin reversal