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Reversal of Anticoagulation in Major Bleeding: A Review of Guidelines, Controversies, and Implications for NP Practice

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Session Learning Objectives:

1. The listener will be able to identify and apply major society guidelines for evidence-based reversal strategies for common anticoagulants in the setting of major bleeding.

2. The listener will gain increased knowledge about the strength of evidence for reversal strategies and needs for ongoing research, especially regarding new reversal agents such as andexanet alfa, and regarding common methods for reversing DOACs with non-FDA indicated products.

3. The listener will gain increased knowledge about the risks and benefits of prescribing various oral anticoagulants to their patients and some of the factors involved in deciding when it is safe to restart anticoagulation after bleeding.

- Rapidly increasing use of DOACs, such as dabigatran/Pradaxa, apixaban/Eliquis, and rivaroxaban/Xarelto, which are easier to use and have some better data for bleeding risk compared to warfarin (Cuker et al; 2019; Momin et al, 2019)
- Major bleeding fatality rate 7.57% with DOACs, 11.05% with warfarin (Anderson, 2017)
- Cost, coverage, patient preference, and need for lab monitoring and diet restriction important factors in choosing agents

- New reversal agents and research in progress, big gaps in data
- Many trauma and neurosurgical patients take DOACs, have multiple comorbidities, need a strategy for reversal if indicated
- Weigh risks and benefits of rapid reversal with major bleeding (intracranial, critical site, life-threatening internal bleeding, massive transfusion, hemoglobin drop of 2; Tomaselli et al, 2017, ACC)

Society Guidelines for Reversal of Anticoagulation

- 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage, AHA/ASA (Greenberg et al, 2022)
- Neurocritical Care Society and Society of Critical Care Medicine (SCCM): Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage (Frontera et al, 2016), updates forthcoming, ENLS protocols incorporate elements.
- American College of Cardiology: Management of Bleeding in Patients Taking Oral Anticoagulants (Tomaselli et al, 2017, updated in Tomaselli et al, 2020), expert consensus.
- European Stroke Association Guideline on Reversal of Oral Anticoagulants in Acute Intracerebral Haemorrhage (Christensen et al, 2019).
- Reversal of direct oral anticoagulants: Highlights from the Anticoagulation Forum guideline (Hashik et al, 2021).

Highlights From the Guidelines

- Disclaimer: complex situations, weigh risks of reversal versus possible thrombosis or concurrent ischemia, DIC etc.
- Literature often is indirect, focused on laboratory values, not patient outcomes (Frontera et al, 2016).
- NCS/SCCM: limit hematoma expansion, improve outcomes
- American College of Cardiology (Tomaselli et al, 2017 and 2020): life-threatening bleeding or critical site. Local therapy, supportive, consider reversal.
- Guideline recommendations focus on normalizing coagulation, but limited data on outcome or mortality, few RCTs (Christensen et al, 2019).
- Recent and ongoing studies are comparing outcomes for andexanet alpha versus 4-factor prothrombin complex concentrate for reversal of DOACs

- VKA/warfarin:

1) Stop.
2) Consider concurrent thrombosis.
3) Vitamin K 10 mg IV with follow-up INR. Redose in 24-48 hours if INR over 1.4.
4) Prothrombin complex concentrates (PCCs) (Kcentra) for INR over 1.4 and ICH, weight-based and based on INR, avoid FFP if possible, serial INR testing. (Christensen et al, 2019 agree, but weak evidence. Tomaselli et al, 2020 agree).
5) Do not give recombinant FVIIa (NovoSeven)

PCC 25 times more concentrated factors than FFP, INR reversal within 15-20 minutes versus 6-24 hours, avoid volume overload and transfusion reactions, but higher thrombotic risk and cost (Christos et al, 2016).

- Direct Factor Xa Inhibitor Reversal (apixaban, rivaroxaban): Based on clinical situation, not labs.

1) Stop.
2) Last dose?
3) Activated charcoal 50g within 2 hours, if safe.
4) Four-factor PCC or Activated PCC (FEIBA), 50 units/kg, if within 3-5 half lives or with liver failure (low evidence).
5) PCC over recombinant FVIIa due to thrombosis risk.

- 2022 ICH guideline from ASA: Andexanet alfa is “reasonable,” while aPCC or four-factor PCC “may be considered.” NCC Guideline dated, with approval of specific reversal agent Andexxa. Christensen et al, 2019, and Tomaselli et al, 2020, recommend Andexxa, if available, over PCC or aPCC; reasonable to give PCC or aPCC if Andexxa not available (low evidence). Christensen et al, 2019, recommend against FFP (low evidence).

- Direct Thrombin Inhibitor Reversal (dabigatran):

1) Stop.
2) Time/degree of exposure.
3) Reverse based on degree of bleeding, not labs.
4) Charcoal within 2 hours.
5) Idarucizumab/Praxbind 5g IV in two divided doses within 3-5 half-lives if no renal failure.
6) aPCC or PCC if Praxbind not available.
7) Consider dialysis.
8) Recommend against rFVIIa or FFP

- 2022 ICH guideline from ASA says idarucizumab is “reasonable.” When not available, aPCC of PCC “may be considered.” Christensen et al, 2019, agree with preferential use of idarucizumab, despite limited evidence for clinical endpoints, low evidence. Tomaselli et al, 2020, also agree.

- REVERSE-AD study: median 2.5 hours to stop of bleeding, normal periprocedural bleeding in 93%. 6% thrombosis, mostly in patients not restarted on anticoagulation (Anderson, Cifu, 2017). Most patients effect within minutes. Monoclonal antibody binds dabigatran (Christos et al, 2016). FDA approved 2015. FDA approved for use prior to urgent procedures. No data for aPCC prior to procedure (Cuker et al, 2019).

- Unfractionated Heparin Reversal:

1) Stop.
2) Urgent reversal if full-dose infusion.
3) IV protamine sulfate, dosing based on units of heparin in last 2-3 hours, 1mg for 100 units, max 50mg, redosing based on aPTT

- LMWH (enoxaparin/Lovenox, therapeutic): protamine sulfate 1mg per 1mg if within 8 hours, 0.5mg per 1mg within 8-12 hours, redosing based on response, consider rFVIIa if protamine contraindicated.

- Pentasaccharides Reversal (Fondaparinux): aPCC (FEIBA), 20 units/kg, if therapeutic level

- Antiplatelet Agent Reversal:

1) Stop.
2) No platelets unless neurosurgical procedure and on ASA or ADP inhibitor (clopidogrel/Plavix).
3) No platelets if documented normal platelet function.
4) Consider desmopressin/DDAVP 0.4mcg/kg IV once

- Lab testing challenging, specialized assays often not available in real time. Point-of-care testing under development (Kuramatsu et al, 2019).
- Minimum DOAC level contributing to bleeding risk is unknown. Table with suggested tests and interpretation in Tomaselli et al, 2020. Clinical situation will require judgement.
- Dabigatran: normal thrombin time (TT) suggests insignificant drug level, as does ecarin clotting time (ECT). Normal activated partial thromboplastin time (aPTT) usually means insignificant level.
- Apixaban, rivaroxaban: Negative anti-factor Xa assay usually means insignificant level. Normal prothrombin time (PT) or aPTT does NOT exclude significant level. Prolonged PT suggests significant level.

- Expert opinion, best available evidence, significant knowledge gaps. Christensen et al, 2019, gives nice overview of evidence levels.
- General measures: Resuscitation, local hemostasis, correct hypothermia and acidosis, IR/GI/surgical procedures, restrictive transfusion, platelets (over 50), fibrinogen (over 100), correct ionized calcium level, consider TXA within 3 hours, viscoelastic testing, DDAVP (see Tomaselli et al, 2020).
- Follow institutional protocol, consult trauma guidelines also.
- Interprofessional teams needed. Have a plan!

- Restarting Anticoagulation: Reassess indication. CHA2DS2-VASc score for paroxysmal afib. First time provoked DVT over 3 months ago? Bioprosthetic valve over 3 months ago?
- Involve other disciplines, patient, caregivers. High thrombotic risk, consider early anticoagulation after stabilization, 1-3 days, with monitoring and short-acting agents such as heparin.
- Timing not systematically studied in ICH. Guidelines recommend at least 4 weeks. Surgeon dependent.
- Surgical procedures, 24-72 hours based on risk. Limited data.
- See detailed discussion in Tomaselli et al, 2020.

Andexxa by Portola

- Andexanet alfa/Andexxa is decoy target that binds factor Xa inhibitors, such as apixaban and rivaroxaban.
- FDA approved in 2018 for life-threatening or uncontrolled bleeding in patients taking apixaban or rivaroxaban.
- Great controversy among clinicians and researches, active literature development, guidance from societies and interest groups.

- Not available at many major hospitals, including trauma centers.
- Controversial research and very high cost.
- Only available specific reversal agent for factor Xa inhibitors.
- Annexa-4 study (Connolly et al, 2019): 352 patients with acute major bleeding, given bolus of andexanet alfa plus 2-hour infusion, measured anti-Xa activity and excellent or good hemostasis at 12 hours after infusion. Short half life.

- Mean age 77 years, mostly with cardiovascular disease. 64% intracranial, 26% gastrointestinal bleeding.
- Apixaban: 92% reduction in anti-Xa activity, rivaroxaban: 92% reduction in anti-Xa activity.
- Excellent or good hemostasis in 82% of 249 patients.
- Single-group cohort study for safety and efficacy, multicenter, prospective, open-label.

- Extension studies ongoing in Germany and Japan.
- Dosing based on which drug and time since ingestion.
- Death in 30 days 14%, thrombotic event 10%.
- Reactions: Thrombotic events. Increased risk or due to underlying condition? Increased thrombin generation (Momin et al, 2019; Siddiqui et al, 2019)?
- No thrombotic events after oral anticoagulation restarted (Connolly et al, 2019).

- Praxbind for dabigatran: 4.8% thrombotic events at 30 days, 1/3 after resumed anticoagulation. (Cuker et al, Anticoagulation Forum). Complicated factors, populations, different intrinsic risks, studies not comparable (Milling, 2019).
- Meta-analysis of PCC for Xa inhibitor reversal reported thrombotic events in 4% of 240 patients, but quality was low (Smith et al, 2019).

- Limitation of Annexa-4 study: no randomized control group due to ethical and logistical challenges with placebo. Ethical challenge to randomize patients to certain harm (Radecki et al, 2019).
- FDA approved randomized trial ongoing, with comparison with off-label agents used in current standard of care, which is based on very limited data (Radecki et al, 2019).
- Vestal (2021), found better reversal 64.7% vs 54.8%) and lower mortality (30% vs 45.2%) with andexxanet alfa compared with 4F-PCC in retrospective data for 56 ICH patients
- Dobesh et al (2023) also found significant reduction in mortality in ICH and GI bleeds with use of andexxanet alfa vs 4F-PCC in an observational cohort study involving 4395 patients

- Comparison: No prospective studies with PCC in dabigatran-associated bleeding. Very limited data on use of aPCC (Cuker et al).
- Some in vitro human data in healthy volunteers, as well as animal studies, suggest normalized coagulation testing with PCC and aPCC in patients taking rivaroxaban or apixaban (Christos et al, 2016).
- A few studies have evaluated safety and efficacy of PCCs for DOAC reversal, with some evidence for effective hemostasis, mostly retrospective data. One meta-analysis noted difficulty in asserting whether PCCs were more effective than cessation of DOAC alone (discussion in Milling et al, 2020).

- PCCs evaluated for patients with major bleeding taking rivaroxaban or apixaban in two small prospective cohort studies. Hemostasis effective in 69% in 84 Swedish patients. Hemostasis good in 65% in 66 Canadian patients, 8% thrombotic events in 30 days (Cuker et al, 2019).
- A small retrospective American study also found benefit in PCC for patients with major bleeding with apixaban or rivaroxaban, with clinical hemostasis reported at 72.4% of 29 patients (Sheikh-Taha, 2018).
- Another American retrospective observational study reported 80.6% effective hemostasis in 31 patients with major bleeding. Lack of high-quality evidence (Smith et al, 2019).
- Faulkner et al, 2020, metaanalysis, suggest PCC effective for anticoagulation reversal for neurosurgical procedures, but relies on retrospective data and underpowered to address DOACs.

- Cost of low dose Andexxa is about $27,500. High dose is $49,500.
- Kcentra cost is about $14,500 for 100-kg patient (Momin et al, 2019).
- New Technology Add-On payments available through Centers for Medicare and Medicaid Services, up to $14,062.50 for Medicare inpatient cases (Cuker et al, 2019).
- Reversal is not indicated routinely in absence of major bleeding. Consider establishing anti-thrombosis stewardship team for DOAC reversal. Avoid delays by developing very clear guidelines, based on newest evidence (Cuker et al, 2019).
- Cannot ignore the presence of specific reversal agents!

Future Directions and Discussion

- Ethical considerations with cost and availability of reversal agents, clear guidelines can help remove emotion.
- Systematic management, with cost analysis, logistics, education, billing, ongoing evidence review, tracking (Cuker et al, 2019).
- Need specific studies on human trauma patients and use of Andexxa. Very promising increase in survival in porcine polytrauma model study (Grottke et al, 2019).
- Limited literature on “real-world” experience for both idarucizumab and andexanet alfa (Chaudhary et al, 2020).

- Calls for randomized, prospective comparison of Andexxa and PCC regarding hemostasis and thrombosis risk (Blow et al, 2019), FDA approved study in progress.
- Some retrospective comparison studies available, with some suggestion PCC is a safe and effective alternative to andexanet alfa, but hard to compare data and low-quality evidence (Barra et al, 2020; Highsmith et al, 2020; Lipari et al, 2020; Ammar et al, 2021).
- Peled et al, 2020, argue PCC is current standard of care, despite lacking direct FDA indication, for DOAC reversal, pending more data to claim superiority of Andexxa.
- Data needed on thrombosis risk with all reversal agents.
- Need for data on resuming anticoagulation after Andexxa treatment (Tomoda, 2019). Also applies to other anticoagulants.

- Aripazine/Ciraparantag binds direct and indirect fXa and thrombin inhibitors, early stages of research, unclear future (Tomaselli et al; 2017; Christos et al, 2016; Kuramatsu et al, 2019).
- There is an ongoing international prospective, observational study, comparing mortality in patients on DOACs or warfarin with urgent surgery or major bleeding. Does not include targeted intervention comparison (Ellington, 2019).
- A small multicenter RCT is enrolling DOAC patients for TXA administration. The CRASH-3 trial in traumatic brain injury may provide better data on TXA in ICH with DOACs (Kuramatsu et al, 2019).

- Questions or ideas?
- What should your health system do about Andexxa?
- Is your health system participating in research on these evolving and controversial topics?
- How do these guidelines and studies affect choices and timing of anticoagulation in the outpatient setting?

Thank You!

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