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Society of Critical Care Medicine - Texas Chapter

STRATEGIES FOR ANTICOAGULATION REVERSAL FOR DIRECT ORAL ANTICOAGULANTS (DOAC)

Society of Critical Care Medicine (SCCM) Texas Chapter
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Making Cancer History®

DISCLOSURES

- Received funding for research from Daiichi Sankyo

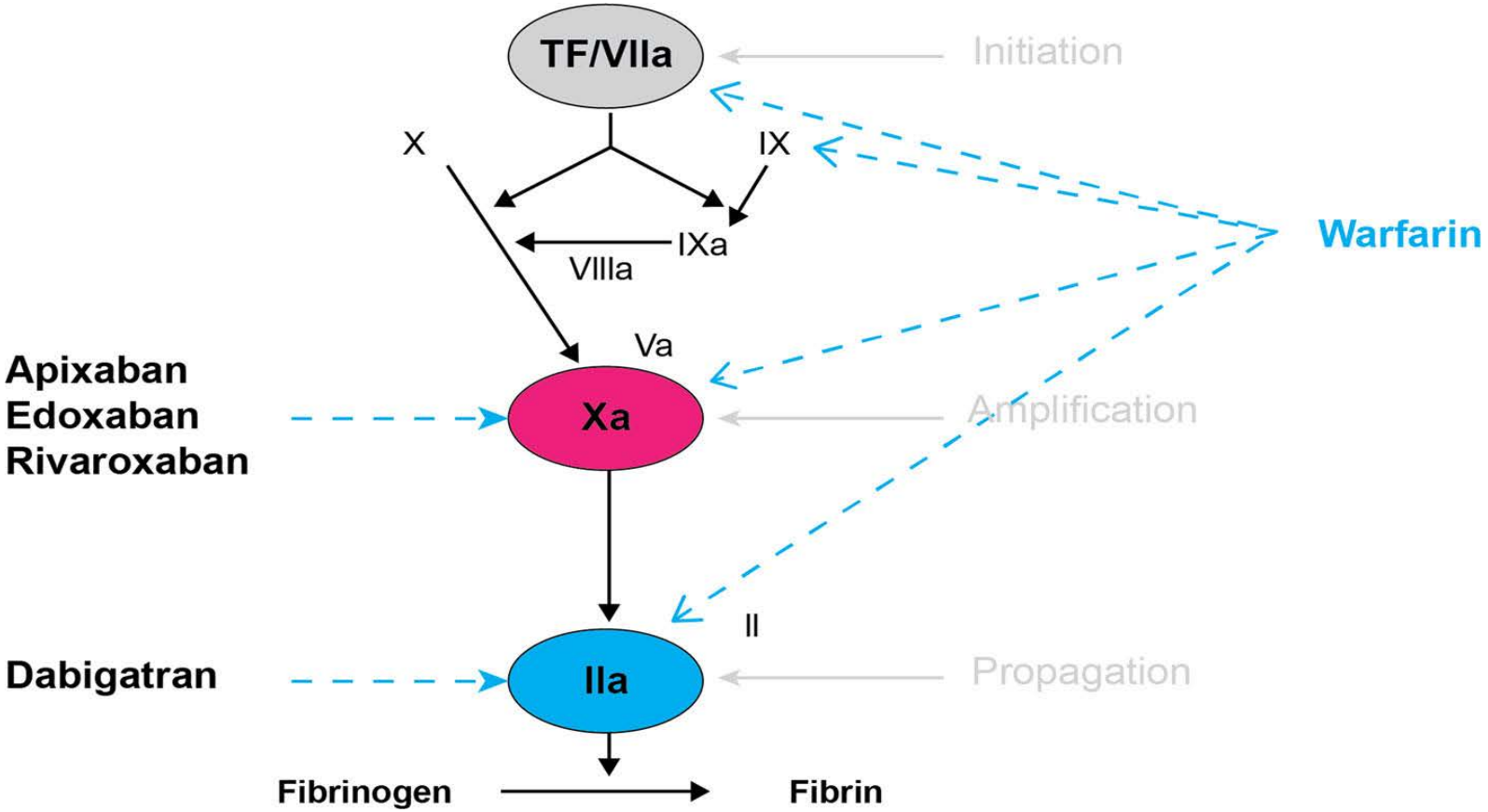
LEARNING OBJECTIVES

- Summarize clinical controversies surrounding the use of blood products for anticoagulation reversal.
- Explain the advantages and disadvantages associated with using blood products as the primary treatment approach for anticoagulation reversal.

OUTLINE

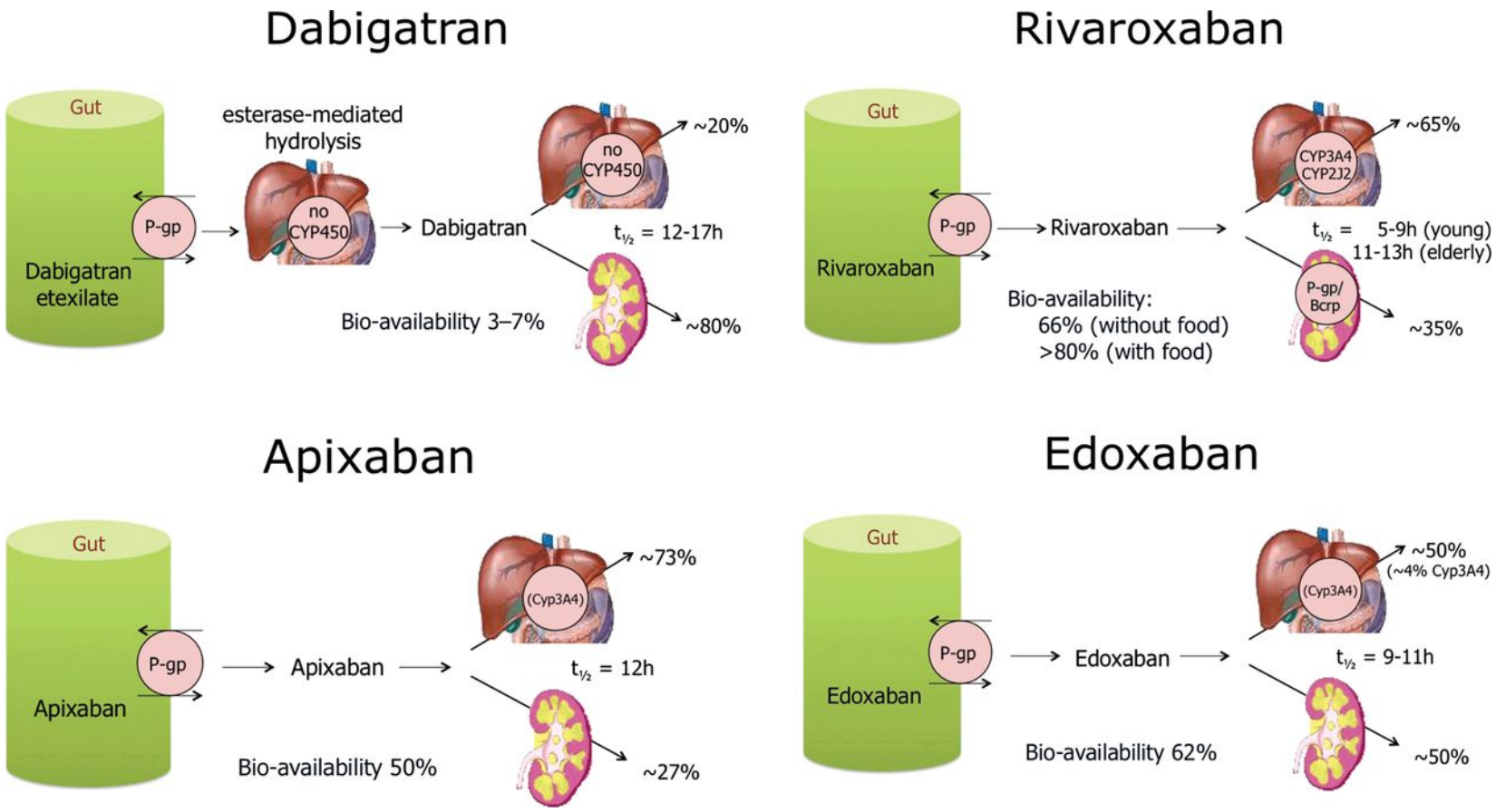
- DOAC: mechanism of action and pharmacokinetics
- Approved indications for the use of DOAC
- Anticoagulation reversal strategies
- Consensus guideline statements for the use of plasma products in DOAC reversal
- Review of clinical data on the use of prothrombin complex concentrates
- Case discussion
- Summary/rebuttal

DOAC: MECHANISM OF ACTION



Nutescu et al (2016). Pharmacology of anticoagulants used in the treatment of venous thromboembolism. Journal of Thrombosis and Thrombolysis

DOAC: PHARMACOKINETICS



P-gp — Inhibitors (↑exposure): ketoconazole, quinidine, amiodarone, verapamil.
Inducers (↓ exposure): Rifampin

CYP 3A4 — Inhibitors (↑exposure): ketoconazole, clarithromycin, ritonavir.
Inducers (↓ exposure): Rifampin, St. John's wort.

Adapted from Heidbuchel H et al. Europace 2013;15:625-651

APPROVED INDICATIONS FOR THE USE OF DOAC

- Primary thromboprophylaxis in knee/hip surgery: dabigatran, rivaroxaban, apixaban
- Primary thromboprophylaxis in hospitalized medically ill: betrixaban
- Non valvular atrial fibrillation: dabigatran, rivaroxaban, apixaban, edoxaban
- Venous thromboembolism treatment: dabigatran, rivaroxaban, apixaban, edoxaban

ANTICOAGULATION REVERSAL STRATEGIES FOR DOAC

- Specific antidotes:
  - Idarucizumab
  - Andexanet alfa
- Plasma and derived products
  - Fresh frozen plasma
  - Prothrombin complex concentrate (PCC)
    - FEIBA
    - 4-factor PCC
- Other hemostatic agents
  - Recombinant factor VII (rFVIIa)
  - Antifibrinolytics

ANTICOAGULATION REVERSAL STRATEGIES FOR DOAC: PCC

ACTIVATED PROTHROMBIN COMPLEX CONCENTRATE

- Anti-inhibitor coagulant complex approved for the control and prevention of bleeding in hemophilia A/B patients with inhibitors: “bypassing” agent
- Intravenous use after reconstitution
- Human plasma-derived: non activated factors II, IX, X
  activated factor VII
- Recommended dose: 50-100 units per kg

ANTICOAGULATION REVERSAL STRATEGIES FOR DOAC: PCC

4 FACTOR-PROTHROMBIN COMPLEX CONCENTRATE

- Human prothrombin complex approved for the urgent reversal of acquired coagulation factor deficiency by vitamin K antagonist (warfarin) in the setting of major bleeding or urgent invasive procedure
- Intravenous use after reconstitution
- Human plasma-derived: factors II, VII, IX, X
  protein C and S
  antithrombin III
  albumin
- Recommended dose: 25-50 units per kg (of factor IX)
- Maximum single dose: 5,000 units

CONSENSUS GUIDELINE STATEMENTS FOR THE USE OF PLASMA PRODUCTS

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INTRACRANIAL BLEEDING AND DOAC

Anti-Xa inhibitors:

- "We suggest administering a 4-factor PCC (50 U/kg) or activated PCC (50 U/kg) if intracranial hemorrhage occurred within 3–5 terminal half-lives of drug exposure or in the context of liver failure"

- "We suggest administering 4-factor PCC or activated PCC over rFVIIa because of the lower risk of adverse thrombotic events.

Direct thrombin inhibitors:

- We suggest administering aPCC (50 units/kg) or 4-factor PCC (50 units/kg) to patients with intracranial hemorrhage associated with direct thrombin inhibitors if idarucizumab is not available"

Frontera, Jennifer A., et al. "Guideline for reversal of antithrombotics in intracranial hemorrhage: executive summary. A statement for healthcare professionals from the Neurocritical Care Society and the Society of Critical Care Medicine." Critical care medicine 44.12 (2016): 2251-2257

MAJOR BLEEDING AND DOAC

- “In patients with dabigatran-associated major bleeding in whom a reversal agent is warranted, we suggest treatment with idarucizumab 5 g IV. If idarucizumab is not available, we suggest treatment with APCC 50 units/kg IV”

- “In patients with rivaroxaban-associated or apixaban-associated major bleeding in whom a reversal agent is warranted, we suggest treatment with andexanet alfa dosed according to the US FDA label. If andexanet alfa is not available, we suggest treatment with four-factor PCC 2000 units”

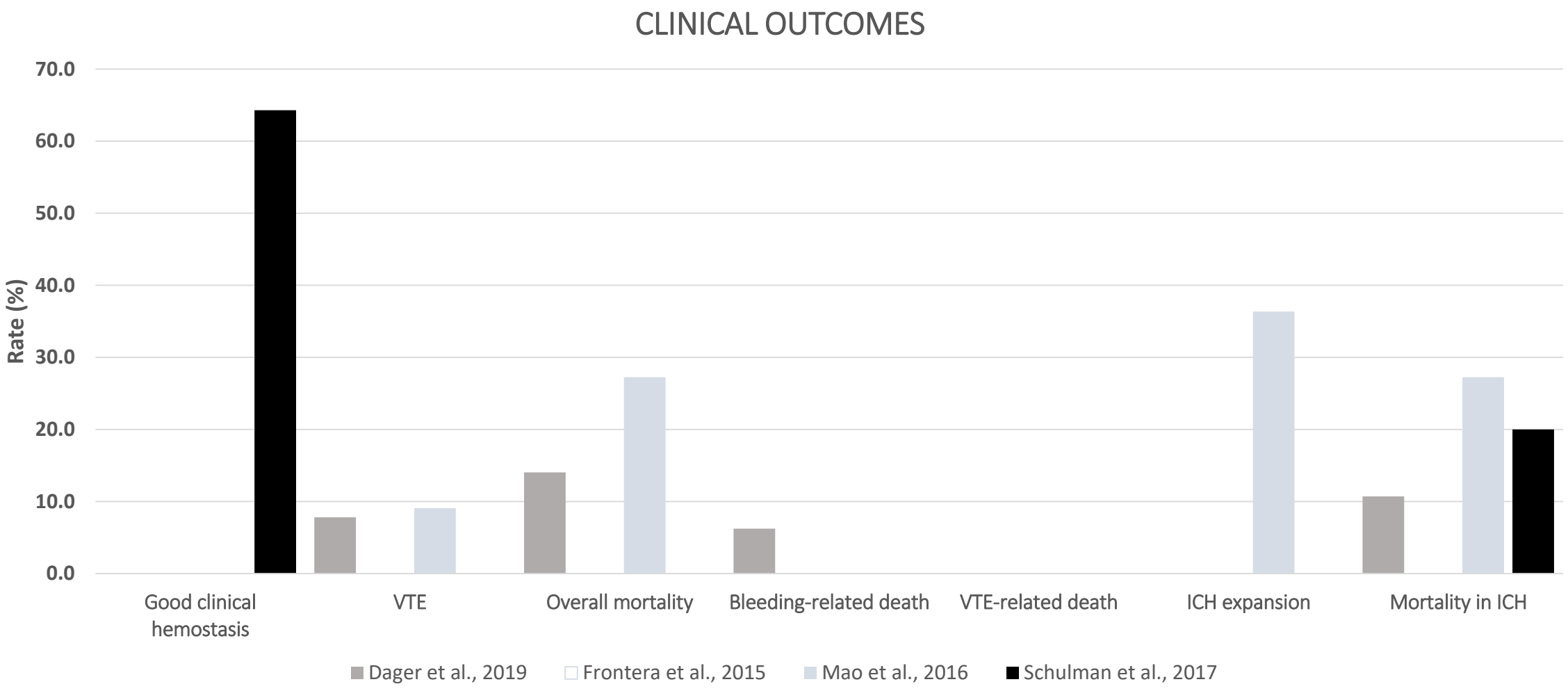
- “In patients with edoxaban-associated or betrixaban-associated major bleeding in whom a reversal agent is warranted, we suggest off-label treatment with either high dose andexanet alfa (800 mg bolus given at 30 mg/min followed by a continuous infusion of 8 mg/min for up to 120 min) or four-factor PCC 2000 units”

Cuker, Adam, et al. "Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum." American journal of hematology 94.6 (2019): 697-709

CLINICAL STUDIES USING ACTIVATED PROTHROMBIN COMPLEX CONCENTRATE IN DOAC REVERSAL

Reference	N	Clinical scenario	DOAC	Hemostatic agent	Laboratory parameter	Impact on laboratory parameter	Clinical outcome
Pernod et al., 2012	10	Healthy volunteers	Dabigatran 150 mg Rivaroxaban 20 mg	Novoseven 120 ug/kg aPCC (80 U/kg) 4-PCC (25 U/kg) * 2 hours after DOAC ingestion	Thrombin generation (CAT)	Partial correction	Not assessed
Dunkley et al., 2012	8	Healthy volunteers	Dabigatran	aPCC (50, 75, 100 U/kg)	Thrombin generation (CAT)	At 50 U/kg - restoration	Not assessed
Dager et al., 2019	64	Retrospective DOAC-bleeding (28/64 ICH)	Rivaroxaban (28) Apixaban (20) Dabigatran (16)	aPCC (20-50 U/kg) * 2 ICH received a second dose	Ecarin clotting assay Anti-Xa	Partial correction Heterogeneous report	VTE / Mortality * At 30 days
Mao et al., 2016	11	Retrospective DOAC-bleeding	Rivaroxaban (8) Apixaban (3)	aPCC (20 U/kg) (within 48 hours from DOAC or unknown time of last dose AND prolonged PTT)	INR/aPTT (12 hours post-aPCC)	INR < 1.5 (5/6) aPTT < 35” (4/4)	VTE/Bleeding expansion/ Mortality * At 30 days
Frontera et al., 2015	5	Prospective AF-ICH	Rivaroxaban (3) Apixaban (1) Dabigatran (1)	aPCC (50 U/kg) within 48 hours from DOAC (median time: 13 h)	Not reported	Not reported	Bleeding expansion (at 6h) Rankin Scale (3 months)
Schulman et al., 2017	32	Prospective nested cohort of major bleeding events in AF/VTE trials * 5 ICH	Dabigatran	aPCC (50 U/kg) with a repeat dose after 1 hour as needed (median time: 14h) * 4 patients required a second dose aPCC	aPTT Thrombin time	Not reported	Clinical hemostasis/VTE/ Mortality * At 30 days

CLINICAL OUTCOMES USING ACTIVATED PROTHROMBIN COMPLEX CONCENTRATE IN DOAC BLEEDING



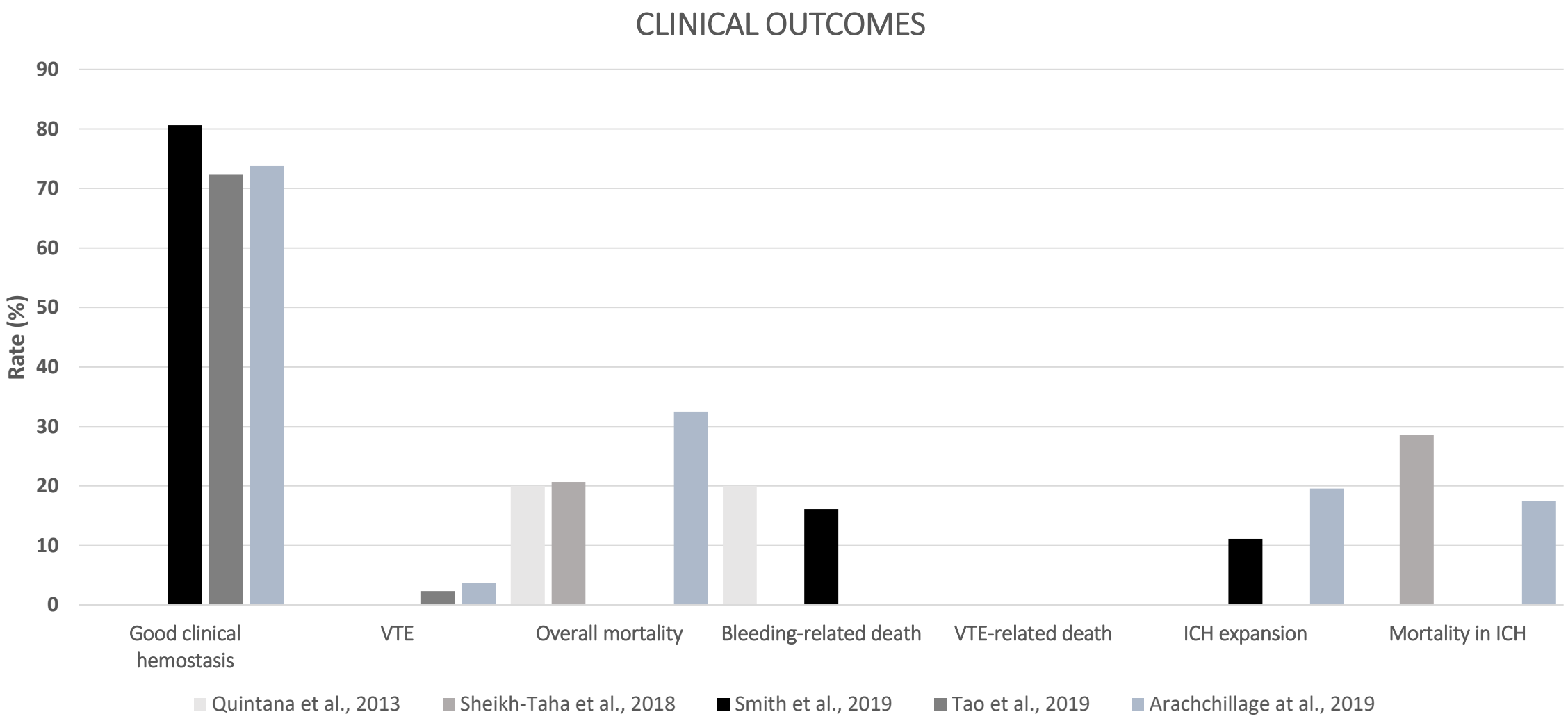
CLINICAL STUDIES USING 4 FACTOR-PROTHROMBIN COMPLEX CONCENTRATE IN DOAC REVERSAL

Reference	N	Clinical scenario	DOAC	Hemostatic agent	Laboratory parameter	Impact on laboratory parameter	Clinical outcome
Eerenberg et al., 2011	12	Healthy volunteers	Rivaroxaban 20 mg BID Dabigatran 150 mg BID	4-PCC (50 U/kg) (after 2 ½ days of DOAC)	PT (Rivaroxaban) Thrombin generation (ETP) aPTT (dabigatran) Ecarin clotting time Thrombin time	PT normalization ETP restored (rivaroxaban) Unchanged aPTT Thrombin time remain unmeasurable Ecarin clotting time unchanged	Minor bleeding (6/12)
Levi et al., 2014	35	Healthy volunteers	Rivaroxaban 20 mg BID	4-PCC versus 3-PCC versus control (4 hours after 5 days of DOAC)	PT aPTT Thrombin generation Calibrated anti-Xa	PT decrease within 30' (4-PCC) Unchanged aPTT Thrombin generation restored after 2-4h (AUC) by 4- and 3-PCC Unchanged anti-Xa	Bleeding events (3/35) VTE (0/35)
Barco et al., 2015	6	Healthy volunteers	Rivaroxaban 15 mg BID	4-PCC 37.5 U/kg versus 25 U/kg versus placebo (3 hours after 2 days of DOAC)	Thrombin generation (ETP) PT Calibrated anti-Xa	Modest increment in ETP PT decreased within 15' Unchanged anti-Xa * Effects of PCC 37.5 U/kg sustained at 24 hours	Minor bleeding (3/6)
Levy et al., 2017	145	Healthy volunteers	Rivaroxaban 20 mg BID	4-PCC (50 U/kg) versus tranexamic acid (1 gr IV-10') versus placebo (after 4 days of DOAC)	PT Thrombin generation	Partial PT correction with 4-PCC Thrombin generation restored * Observed only with PCC	Unchanged bleeding volume and duration after punch biopsy thigh (before DOAC and after PCC)
Cheung et al., 2015	6	Healthy volunteers	Apixaban 10 mg BID	4-PCC 37.5 U/kg versus 25 U/kg versus placebo (3 hours after 3 days of DOAC)	Thrombin generation (ETP) PT	Modest increment in ETP PT correction within 15' * Effects of PCC 37.5 U/kg sustained at 24 hours	Bleeding events (1/6)
Kraft et al., 2016	12	Healthy volunteers	Apixaban 5 mg BID	4-PCC (25 U/kg) (3 hours after 5 doses of DOAC)	Thrombin generation PT aPTT anti-Xa	Increment in peak thrombin and endogenous generation PT normalization aPTT and anti-Xa unchanged	Not reported

CLINICAL STUDIES USING 4 FACTOR-PROTHROMBIN COMPLEX CONCENTRATE IN DOAC BLEEDING

Reference	N	Clinical scenario	DOAC	Hemostatic agent	Laboratory parameter	Impact on laboratory parameter	Clinical outcome
Quintana et al., 2013	5	Retrospective acute GI bleeding	Dabigatran 110 mg BID * All treated for AF	4-PCC	aPTT	Unchanged	Bleeding cessation
Sheikh-Taha et al., 2018	29	Retrospective DOAC- major bleeding (21/29 ICH)	* 23/29 AF	4-PCC (50 U/kg)	PT	Not reported	Clinical hemostasis Mortality
Smith et al., 2019	31	Retrospective DOAC- major bleeding (18/31 ICH)	Apixaban (17) Rivaroxaban (14)	4-PCC (25-50 U/kg) (median time: 2 h post admission)	Not reported	Not reported	Clinical hemostasis Mortality Thrombotic events Cost *During hospital stay [4-10] days
Tao et al., 2019	43	Retrospective cases emergent DOAC- reversal (16/43 ICH)	Apixaban (22) Rivaroxaban (21) * AF (30/43)	4-PCC (25-50 U/kg)	PT aPTT	PT normalization (6/10)	Thrombotic events * Within 14 days post PCC
Arachchillage at al., 2019	80	Retrospective DOAC- major bleeding (46/80 ICH)	Apixaban (40) Rivaroxaban (40) * AF (65/80)	4-PCC (20-50 U/kg)	PT aPTT Calibrated anti-Xa	Not reported	Clinical hemostasis Thrombotic events Mortality * At 30 days post PCC

CLINICAL STUDIES USING 4 FACTOR-PROTHROMBIN COMPLEX CONCENTRATE IN DOAC BLEEDING



PRACTICAL CONSIDERATIONS FOR PREVENTION OF BLEEDING DURING DOAC THERAPY

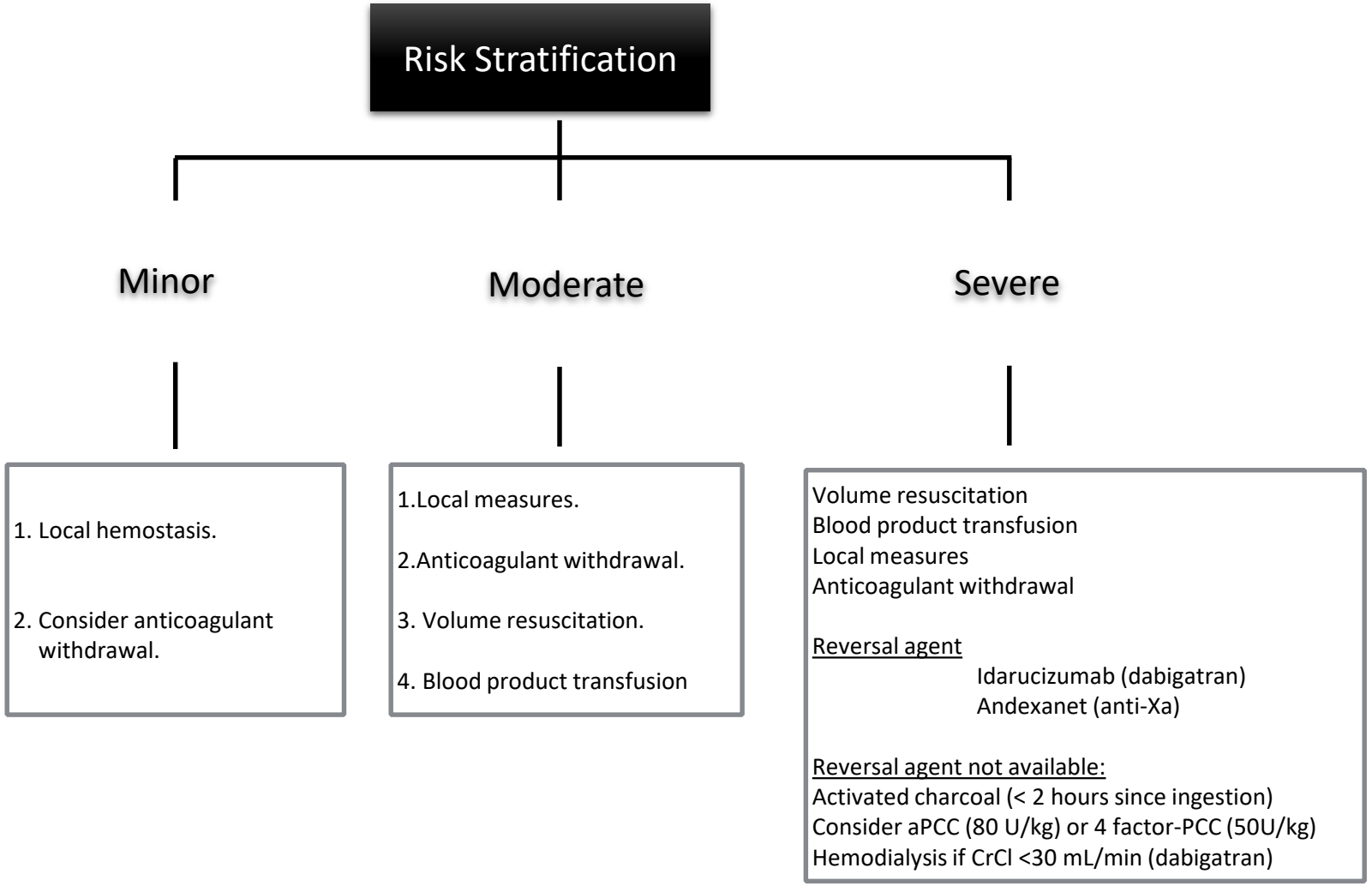
- Renal insufficiency
  Avoid use if Cr Cl < 30 ml/min
- Liver dysfunction
  Avoid in significant liver dysfunction (i.e.: advanced cirrhosis)
  Avoid if transaminases > 2 ULN
- Absorption and drug interactions
- Not recommended if upper GI malignancy, malabsorption, intractable nausea.
- Dose adjustment/avoid if concurrent modulators of CYP 3A4
- Dose adjustment if other concurrent P-glycoprotein substrates

PRACTICAL CONSIDERATIONS FOR PREVENTION OF BLEEDING DURING DOAC THERAPY

- Severe myelosupression and thrombocytopenia
  - Not recommended if platelet count < 100K/uL
  - Avoid if anticipated severe cytopenias, myeloablation

- High risk of bleeding patients
  - Untreated brain metastases (renal cell/melanoma)
  - Active GI / GU malignancies

PRACTICAL CONSIDERATIONS FOR MANAGEMENT OF BLEEDING DURING DOAC THERAPY



Adapted from Siegal et.al, BLOOD, 2014

STRATEGIES FOR ANTICOAGULATION REVERSAL FOR DOAC : SUMMARY/REBUTTAL

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Characteristic	PCC	Andexanet alfa
Availability	Readily available at most hospitals	Limited availability
Rate of Effective Management of Major Bleeding (95% CI)	75% (53% to 97%)	83% (75% to 89%)
Rate of Thromboembolic Complications (95% CI)	5% (1% to 9%)	11%
Cost	$1.27 per unit (USD) For 2000 units 4F-PCC $2,540	$3,300 per vial of 100 mg Low dose (9 vials) $29,700, high dose (18 vials) $59,400

Piran, Siavash, and Sam Schulman. "Treatment of bleeding complications in patients on anticoagulant therapy." Blood 133.5 (2019): 425-435
Connolly, S., M. Crowther, and T. J. Milling. "Interim report on the ANNEXA-4 study: andexanet for reversal of anticoagulation in factor Xa–associated acute major bleeding." American College of Cardiology 67th Annual Scientific Session and Expo 10 (2018): 12
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LEARNING ASSESSMENT QUESTION #1

- The following are associated with the incidence of bleeding complications during direct oral anticoagulant therapy, except:
  a) Upper gastrointestinal diseases, such as peptic ulcer disease and malignancy
  b) Concurrent use of p-glycoprotein inhibitors
  c) Concurrent use of cytochrome CYP3A4 inhibitors
  d) Lack of routine anticoagulant effect monitoring

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  c) Concurrent use of cytochrome CYP3A4 inhibitors
  d) Lack of routine anticoagulant effect monitoring

LEARNING ASSESSMENT QUESTION #2

- The use of coagulopathy reversal strategies is desirable in all bleeding scenarios during the use of direct oral anticoagulants
  a) True
  b) False

LEARNING ASSESSMENT QUESTION #2

- The use of coagulopathy reversal strategies is desirable in all bleeding scenarios during the use of direct oral anticoagulants
  a) True
  b) False

THANKS FOR YOUR ATTENTION

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